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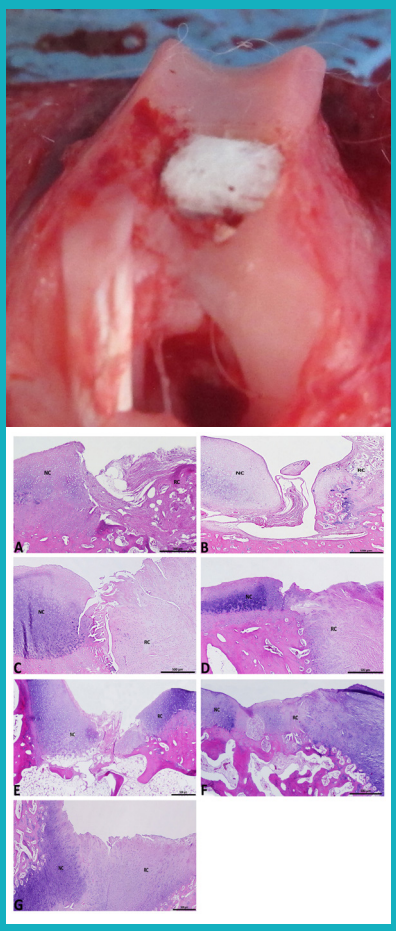

- ***Comparison of Small-diameter-hole and Traditional Microfracture in Cartilage Repair and the Effect of Adding a Hyaluronic Acid-based Acellular Matrix Scaffold: An Animal Study***
  Vahdet UÇAN, Fatih YILDIZ, Nuh Mehmet ELMADAĞ, Gökçer UZER, Yunus GÜZEL, Olgu Enis TOK, Mukaddes EŞREFOĞLU; İstanbul, Ordu, Turkey
- ***Development and Validation of an In Vitro Dissolution Method Based on HPLC Analysis for L-Dopa Release From PLGA Nanoparticles***
  Sema ARISOY, Özgün SAYINER, Tansel ÇOMOĞLU; Ankara, Turkey
- ***The Effects of Thermo-mechanical Aging on Microleakage in Composite Restorations Polymerized Using One New Generation and Two Conventional Led Light Curing Units***
  Nazmiye DÖNMEZ, Yeşim ŞEŞEN USLU, Şeyda HERGÜNER SİSO, Ali TOPRAK; İstanbul, Turkey
- ***The Efficacy of Eltrombopag Treatment in Patients who developed Platelet Engraftment Failure after Allogeneic Stem Cell Transplantation: A Single Center Experience***
  Ali ESER, Ayşen TİMURAĞAOĞLU; İstanbul, Turkey
- ***Report of a Case of Signet Ring Carcinoma Presenting as Gastric Mucosal Thickening: A Diagnostic Dilemma***
  Cumali KARATOPRAK, Adem AKÇAKAYA, Hakan ŞENTÜRK, Ganime ÇOBAN, Nurhan ŞAHİN, Hacı Mehmet TÜRK; İstanbul, Turkey

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AIMS AND SCOPE

Bezmialem Science is an independent, unbiased, international online journal that publishes articles in all branches of medicine in accordance with the double-blind peer-review process. The print version of the journal is not available and it is only accessible at www.bezmialemscience.org. The manuscripts published on this web page can be read free of charge and files can be downloaded in PDF format. Four issues are released per year, in January, April, July and October. Publication language is Turkish and English.

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Scientific or Technical Report: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

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Manuscripts accepted for publication, not published yet: Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med In press 1997.

Epub ahead of print Articles: Aksu HU, Ertürk M, Gül M, Uslu N. Successful treatment of a patient with pulmonary embolism and biatrial thrombus. Anadolu Kardiyol Derg 2012 Dec 26. doi: 10.5152/akd.2013.062. [Epub ahead of print]

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BEZMIALEM VAKIF UNIVERSITY 1845

BEZMİÂLEM science

CONTENTS

Commentary

1 Problems of Healthcare Professionals in COVID-19 Pandemic

Prof. Dr. Adem AKÇAKAYA; İstanbul, Turkey

Original Articles

3 Effect of Repeated Movements on Motion Perception and Motor Learning of Dominant and Non-dominant Upper Extremity of Healthy Individuals

Deniz KOCAMAZ, Songül ATASAVUN UYSAL, Elif DİNLER, Tuğba BADAT, Begümhan TURHAN, Yavuz YAKUT; Gaziantep, Ankara, Turkey

9 Development and Validation of an *In Vitro* Dissolution Method Based on HPLC Analysis for L-Dopa Release From PLGA Nanoparticles

Sema ARISOY, Özgün SAYINER, Tansel ÇOMOĞLU; Ankara, Turkey

20 Spectrophotometric Determination of Erdosteine at Capsule Dosage Forms

Cem ÖNAL, Demet DİNÇEL; İstanbul, Turkey

25 Cyclic Fatigue Resistance of Biorace Nickel-titanium File with Variable Taper after Immersion in Sodium Hypochloride

Burçin ARICAN, Ayfer ATAV ATEŞ; İstanbul, Turkey

29 Pancreatic Tumors in Children

Hasan Özkan GEZER, Abdülkerim TEMİZ, Semire EZER, Emine İNCE, Nalan YAZICI, Şenay DEMİR, Bermal HASBAY, Pelin OĞUZKURT; Adana, Turkey

35 Analysis of Personal, Environmental, and Occupational Factors Affecting the Activity Performance of Disabled Drivers

Orkun Tahir ARAN, Hülya KAYIHAN; Ankara, İstanbul, Turkey

41 A Liquid Chromatographic Analysis of Gemifloxacin in Pharmaceutical Preparations Using 4-bromomethyl-7-methoxycoumarin Reagent

Cem ÖNAL; İstanbul, Turkey

46 Effect of Birth Ball Exercising for the Management of Childbirth Pain in Turkish Women

Demet AKTAŞ, Sevil KOLSUZ, Mukadder ERTUĞRUL, Elif Gizem BEŞİRLİ, Fatma Reyyan GÜNDOĞAN; Çankırı, Zonguldak, Ankara, Turkey

BEZMIALEM VAKIF UNIVERSITY 1845

BEZMİÂLEM science

CONTENTS

53 Comparison of Mother-Infant Relationship in Turkish Primiparous Women in Accordance with Vajinal Birth and Cesarean Section

Elif Zahide ÇELEBİ, Filiz OKUMUŞ; İstanbul, Ankara, Turkey

61 Turkish Version of the Multidimensional Index of Life Quality in Patients with Acute Coronary Syndrome

ŞEYMA DEMİR, ZEYNEP ÖZER; Bolu, Antalya, Turkey

68 Effect of Mouthrinses on Water Sorption and Solubility of Flouride-Releasing Restorative Materials

Neslihan ÖZVEREN, Ezgi BALTACI, Sinem BATUR KARA; Edirne, Turkey

75 Prevalence of Pressure Injuries and Risk Factors in Long-Term Surgical Procedures

Cemile AKAN, Yazile YAZICI SAYIN; İstanbul, Turkey

84 Comparison of Small-diameter-hole and Traditional Microfracture in Cartilage Repair and the Effect of Adding a Hyaluronic Acid-based Acellular Matrix Scaffold: An Animal Study

Vahdet UÇAN, Fatih YILDIZ, Nuh Mehmet ELMADAĞ, Gökçer UZER , Yunus GÜZEL, Olgu Enis TOK, Mukaddes EŞREFOĞLU; İstanbul, Ordu, Turkey

91 The Effects of Thermo-mechanical Aging on Microleakage in Composite Restorations Polymerized Using One New Generation and Two Conventional Led Light Curing Units

Nazmiye DÖNMEZ, Yeşim ŞEŞEN USLU, Şeyda HERGÜNER SİSO, Ali TOPRAK; İstanbul, Turkey

98 The Efficacy of Eltrombopag Treatment in Patients who developed Platelet Engraftment Failure after Allogeneic Stem Cell Transplantation: A Single Center Experience

Ali ESER, Ayşen TİMURAĞAOĞLU; İstanbul, Turkey

106 Comparison of Dosage Loss Between Medications Crushed with Two Different Methods by Two Nurses: An *In Vitro* Study

Betül TOSUN, Nursemin ÜNAL, Nurten ÖZEN3, Filiz ATALAY; Gaziantep, Ankara, İstanbul, Turkey

Review

112 A Current View of Care of High Risk Pregnancy

Büşra YILMAZ, Ümran OSKAY; İstanbul, Turkey

Case Report

120 Report of a Case of Signet Ring Carcinoma Presenting as Gastric Mucosal Thickening: A Diagnostic Dilemma

Cumali KARATOPRAK, Adem AKÇAKAYA, Hakan ŞENTÜRK, Ganime ÇOBAN, Nurhan ŞAHİN, Hacı Mehmet TÜRK; İstanbul, Turkey

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EDITORIAL

Dear Readers;

The year 2020, which we started with the hope of a year full of new hopes and beauties, has been a difficult year for our country and the world. For this reason, the beginning of the year 2021 came with a bit of disappointment and worries about whether the troubles would end. I think we have achieved many successes on behalf of our journal under these difficult conditions, despite all the intensity and worldwide negativities.

The COVID-19 pandemic, which changed the face of the world, caused us to make changes in our journal, our efforts and our goals. We deeply felt the difficulties experienced by all healthcare professionals during this period. When we took a look at what we did last year, we switched our entire publishing format to English and the language of journal on our website became English. This year, we released three supplements, one of which contained the abstracts presented at our student congress, and two of them were for COVID-19. We had to increase the number of 1 supplement to 3 supplements, which we planned for the treatment options and drug applications used in COVID-19, due to the intense interest in the subject and a large number of valuable articles. We published 2 of them in 2020. We will publish the third in the first months of 2021. I would like to mention the efforts of our assistant editor, Fatemeh Bahadori, who assumed the duty of guest editor in this process and thank him for her efforts. I would also like to thank our Chairman of the Board of Trustees, Mr. Ahmet Akça and our Rector Rümeyza Kazancıoğlu, who supported us in solving financial problems.

I would like to mention two things that make us happy and that we can evaluate as our success. First of all, the number of clicks on our website and reading of our publications has increased approximately 5 times this year. I would like to state that the indexes we have participated in recently and the fact that our publication language is English has contributed to this result. Second, the number of studies submitted to our journal increased by 100% in 2020. Since the number of articles we could publish was limited, we had to reject some valuable articles submitted by you. Due to this interest, we decided to increase the number of articles we published in each issue this year and to meet your demands to some extent. Another change is that we will publish your articles according to the diversity of issue based on the requests received and the decision of our editorial board. We had published your articles according to the order of acceptance of the publication until this year. This means that the publication of the questionnaire, reliability and validity studies may therefore be delayed a bit. I would like to thank you, our dear readers, for providing us this momentum and increase.

Another innovation we have planned for this year is to add a new section titled "COMMENT", where articles will take place on a topic chosen by the Chief Editor, which includes current issues and innovations. In this issue, we set the title of the first article as **"Problems of Healthcare Professionals in the COVID-19 Pande**mic" in memory of the healthcare professionals who showed unique heroism and lost their lives during the pandemic process. As it is known in the fight against COVID-19, the healthcare professionals fighting on the front have struggled very seriously. Many of them died. I wish mercy from Allah to our healthcare professionals who lost their lives, and patience to their families and relatives. Healthcare professionals continue to struggle with many problems in the ongoing process. With our sense of gratitude for their memory, we will discuss the problems they have experienced and the problems that are still being experienced, inspired by a meeting on this subject. I think you will read the topic **"Problems of Healthcare Professionals in COVID-19 Pandemic"** with interest.

I would like to mention the articles that stand out in this issue by expressing my happiness to bring you together with our articles that are increasing day by day. The experimental study by Uzer G et al., entitled "Comparison of Small-diameter-hole and Traditional Microfracture in Cartilage Repair and the Effect of Adding a Hyaluronic Acid-based Acellular Matrix Scaffold: An Animal Study"; the method study by Arısoy S et al., entitled "Development and Validation of an In Vitro Dissolution Method Based on HPLC Analysis for L-Dopa Release From PLGA Nanoparticles"; the dentistry study by Dönmez N et al., entitled "The Effects of Thermo-mechanical Aging on Microleakage in Composite Restorations Polymerized Using One New Generation and Two Conventional Led Light Curing Units"; the study by Eser A et al., entitled "The Efficacy of Eltrombopag Treatment in Patients who developed Platelet Engraftment Failure after Allogeneic Stem Cell Transplantation: A Single Center Experience"; and the study by Karatoprak et al., entitled "Report of a Case of Signet Ring Carcinoma Presenting as Gastric Mucosal Thickening: A Diagnostic Dilemma" were the articles at the forefront.

I would like to thank Assoc. Prof. Dr. Nükhet Kütük for her support so far, who left us, while welcoming our friends who attended our editorial board in the new year. I would like to thank both our assistant editors and referees, who achieved a 20% shortening in our publication evaluation process despite our increasing number.

Dear Readers,

I congratulate you on your new year and wish it to be useful for our country and our world. May everything be as you wish, to meet you in our next issue.

Best regards,

Prof. Dr. Adem AKÇAKAYA
Editor-In-Chief

Commentary

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Problems of Healthcare Professionals in COVID-19 Pandemic

COVİD-19 Pandemisinde Sağlık Çalışanlarının Sorunları

Prof. Dr. Adem AKÇAKAYA

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Introduction

As is known, the Coronavirus disease-19 (COVID-19) pandemic has started in China in November-December 2019 and then spread to the whole world (1). It was declared as an international public health emergency by The World Health Organization (WHO) on January 30, 2020, and later described as a pandemic (2). The disease has spread all over the world in a very short time. Of the patients, 28.5% were in Asia, 24.1% in North America, 23.7% in Europe, 19.8% in South America, and 3.7% in Africa. In our country, the first patient was announced in March, and the first death on March 18.

The analysis conducted by Amnesty International in September 2020 revealed that at least 7,000 healthcare workers worldwide died due to COVID-19. In this report, the countries with the highest number of health worker deaths were recorded in Mexico and the USA. Turkey was ranked 16th on the list. The rate of infection was found to be the highest in the health workers working in inpatient wards of hospitals. This finding showed that healthcare workers in the wards have a higher risk in terms of biosecurity measures than healthcare workers in units such as intensive care unit or emergency services.

As of January 14, 2021, the number of patients infected with the coronavirus in Turkey was 2,364,801, the number of patients recovered was 2,236,938 so far and the number of patients who died was 23, 495. A total of 26,899,442 tests were carried out to date. As of January 1, 2021 Turkey was ranked 7th among 193 countries in terms of the number of patients and ranked 18th in terms of the number of deaths (3). Despite the number of patients was high, considering the mortality rates among health workers and in the society, it could be concluded that Turkey managed the process successfully. The early implementation of the scientific committee and the guides that were created early were effective in this result. However, the existing problems of healthcare workers, who have played a major role in this success, have increased exponentially.

In Turkey, a medical army consisting of 540,000 soldiers including about 165,000 physicians, 200,000 nurses, and 175,000 other health professionals fights against the pandemic (4). Health professional organizations in Turkey and the world state that healthcare professionals are infected with COVID-19 at a rate of approximately 10 times more than other components of the society. According to the data of the Turkish Medical Association, 282 healthcare workers died because of COVID-19 since the beginning of the pandemic (5). The number of physicians who died while on active duty during the COVID-19 pandemics in Turkey in 2020, was 98.

Physicians and healthcare professionals working in difficult conditions away from their families had to struggle with different problems in the working environment depending on their branch and place of work. In this article, the issues mentioned in a session at the WIHU'20 COVID-19 congress where the problems of healthcare professionals were addressed, will be mentioned, and the problems experienced by healthcare professionals in this process will be discussed.

Addressing the problems of Emergency Service Workers in the pandemic, emergency medicine specialist Dr. Nedim Uzun said in his speech that: "Although the problems of emergency healthcare workers are largely the same as before the pandemic,

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these problems have become more pronounced during the pandemic process. The fight against the pandemic has been tried to be carried out largely through emergency service employees. Emergency room workers are the ones most exposed to the virus load due to the first encounter COVID-19 and due to heavy working conditions. As a result, the increasing violence in health, the deterioration of our physical and mental health, and the insufficient financial and spiritual support in return cause burning out of emergency service workers. Primary health care services need to be made more active and the pandemic burden should be distributed fairly".

In her speech, Dr. Hina J Shahid, a family physician and the head of the Muslim Physicians Association, who participated as a speaker from the UK, stated that: "As a result of factionalism, racism, and Islamophobia in the UK, COVID-19 has a disproportionate impact on Muslim healthcare workers. We have difficulties in accessing personal protective equipment. It is remarkable that healthcare workers are more likely to get sick compared with the society, and that the mortality rate of minorities among healthcare workers is higher".

Speaking on behalf of the nurses and the union, Nurse Muhterem Şahin stated in her speech that they had problems in financial, moral and personal rights, and that working conditions were very difficult and tiring, and that healthcare workers could not get the value they deserved.

Speaking on behalf of the infectious diseases specialists who have undertaken the most duties in the pandemic, Dr. Sibel Bollukçu said that considering the fact that COVID-19 resulted in a multisystemic involvement in patients, the approach should also be multidisciplinary, and that in the light of the guidelines set up by the ministry in our country, it was unnecessary to ask for consultation from infectious diseases specialists in outpatient and inpatient clinics, and that additional work such as off-label drug approval increased the intensity of the physicians of that branch who needed to work actively in the field ".

Speaking on behalf of non-governmental organizations, Dr. Ercan Kurnaz said, "In private health institutions and clinics, healthcare workers suffer financial difficulties due to occupation loss during the pandemic process, they cannot get their salaries and cannot afford their routine expenses, the workload of primary healthcare workers has increased, and their mental health is affected due to the high level of stress and psychological distress experienced by healthcare professionals".

Explaining the problems experienced in intensive care units, Associate Prof. Dr. Hayrettin Daşkaya stated that the pandemic should not be perceived as a health problem only, that social and economic conditions and the level of individual resistance affected the course of the disease, those possible problems would be predicted in advance with close observation of the field, that it should not be forgotten that all the work and the struggling were for humans, and that it was very important for healthcare workers to protect themselves in this process.

The pandemic continues in 2021. Phase studies of vaccines, which were initiated with hopes, were completed and vaccination was started in many countries, especially in our country. However, concerns about mutations and problems that may arise in the antibody generation process of vaccines continue to exist.

The pandemic had a multifaceted effect on the social life, economy, education, briefly all vital areas in the countries and caused changes in individual life. Healthcare professionals have suffered and continue to experience serious grievances in this struggle because they are the group with the heaviest burden and having the highest rate of mortality. Physicians experienced victimizations and injustices in their personal rights, life sphere, assignments, and distribution of workload, according to the institution, branch and country they worked. In addition to their lives, physicians had to struggle with economic losses and, rarely, with racism and discrimination in some countries.

How long this process will continue is unpredictable despite recent developments. All healthcare workers, especially physicians, should be given financial and moral personal rights. Their working conditions should urgently be improved, the moral value they deserve should be given, support for healthcare workers in line with their religious and cultural needs should be increased, and safe employment should be ensured. Inequalities in the work environment, injustice in access to vaccines, tests, and personal protective equipment, and discrimination should be ended, and a fraternal work environment should be created, regardless of branch, race, gender and religion.

* Editor-In-Chief of The Bezmialem Science, Head of the Department of General Surgery of the Bezmialem Vakıf University, President of Physicians Rights Association.

References

1. https://www.istabip.org.tr/koronavirus/Haberler/5986/COVID-19-pandemisinde-istanbul-kamu-hastaneleri-anketi-degerlendirmesi (14 Ocak 2021)
2. Akbaş MN, Akçakaya A. COVID-19 and Phytotherapy. Bezmialem Science 2020;8:428-37.
3. https://tr.wikipedia.org/wiki/T%C3%BCrkiye%27de_COVID-19_pandemisi(14 Ocak 2021)
4. Sant'Ana G, Imoto AM, Amorim FF, Taminato M, Peccin MS, Santana LA, et al. Infection and death in healthcare workers due to COVID-19: a systematic review. Acta Paul Enferm. 2020;33: eAPE20200107.
5. https://www.bbc.com/turkce/haberler-turkiye-55409530 (22 Aralık 2020)

Original Article

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Effect of Repeated Movements on Motion Perception and Motor Learning of Dominant and Non-dominant Upper Extremity of Healthy Individuals

Sağlıklı Gençlerde Üst Ekstremite Dominant ve Non-dominant Tarafta Tekrarlı Hareketin Hareket Algısı ve Motor Öğrenmeye Etkisi

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ABSTRACT

Objective: Hand dominancy can be observed as right, left, or the usage of bilateral hands. Majority of the Turkish population are right-hand dominant. This study aimed to examine and interpret the motion perception and motor learning of the dominant and non-dominant upper extremity.

Methods: A total of 146 right-hand dominant university students participated in this study. The mean age of participants was 23.0±1.99, wherein 80 were female (54.79%) and 66 were male (45.21%). Hand preference was evaluated by the Edinburgh Hand Preference Questionnaire. Participants were positioned at the table edge with the hip, knee, and elbows at 90 degrees flexion. Measurements were made on a special platform. Participants were asked to place the glass at the center point, with a 25 cm distance from the rangefinder, and their eyes closed. Measurements were repeated 3 times on both dominant and non-dominant sides. The distance and deviation rate from the center point were recorded in cm with the laser rangefinder. Statistical Package for the Social Sciences 21.0 program was used in the analysis.

Results: According to the Edinburg Hand Preference Questionnaire, 42 of participants (28.76%) were strong right dominant, 95 (65.06%) were weak right dominant, and 9 (6.18%) were weak left dominant. The mean of distance from the central point for three measurements during the activity of glass placing were 2.56±1.91 cm on the dominant side and 2.57±1.86 cm on the non-dominant

ÖZ

Amaç: El dominansı; sağ dominant, sol dominant veya bilateral el kullanılması şeklinde görülmektedir. Sağ dominant bireylerin çoğunlukta olduğu toplumumuzda dominant ve non-dominant tarafta tekrarlı hareketlerin hareket algısı ve motor öğrenmeye etkisinin incelenmesi ve yorumlanabilmesi amacıyla bu çalışma planlanmıştır.

Yöntemler: Çalışmaya yaş ortalaması 23.0±1,99 yıl olan, 80'i kadın (%54,79), 66'sı erkek (%45,21) olmak üzere 146 gönüllü sağ eli dominant olan üniversite öğrencisi katıldı. El tercihi Edinburg El Tercih Anketi ile değerlendirildi. Bireyler kalça, diz ve dirsekler 90^0 fleksiyonda olacak şekilde masa kenarında pozisyonlandı. Ölçümler özel platform üzerinde yapıldı. Bireylerden, gözler kapalı iken, uzaklık ölçerden 25 cm mesafedeki merkez noktaya bardağı yerleştirmesi istendi. Ölçümler 3 kez dominant ve non-dominant tarafta tekrarlandı. Merkez noktaya uzaklık ve sapma miktarı lazerli uzaklık ölçer ile cm cinsinden kaydedildi

Bulgular: Edinburg El tercih anketine göre bireylerin 42'ı (%28,76) kuvvetli sağ dominant, 90'ı (%65,06) zayıf sağ dominant, 9'u (%6,18) zayıf sol dominanttı. Bardak yerleştirme aktivitesi sırasında merkez noktadan uzaklıkların üç ölçüm için ortalaması dominant tarafta 2,56±1,91 cm, non-dominant taraf için ise 2,57±1,87 cm'di. Dominant ve non-dominant el açısından merkez noktadan uzaklık ölçümleri açısından anlamlı fark bulunmadı (p>0,05). Ancak

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side. No significant difference was observed in terms of distance from the center point in dominant and non-dominant hand ($p>0.05$). However, when results of the deviation from the center of three measurements were examined in the dominant side, according to the deviation distance, the first measurement was found closer to the center point than the second and third measurement results ($p<0.05$).

Conclusion: It is thought that the first measurement results are closer to the center with the effect of visual memory at the dominant and non-dominant sides, but in the second and third repetitions, it is thought that the deviation from the center is due to the short term memory, kinesthesia, and motor learning ability which could not be coded correctly.

Keywords: Dominant side, non-dominant side, motor learning, visual memory, right-hand dominance, left-hand dominance

dominant tarafta ardı ardına yapılan üç ölçümün merkezden sapma mesafesi sonuçları incelendiğinde birinci ölçüme dair sapmanın, ikinci ve üçüncü ölçüm sonuçlarına göre merkez noktaya daha yakın olduğu tespit edildi ($p<0,05$).

Sonuç: Dominant ve non-dominant taraf ölçüm sonuçlarına göre görsel hafızanın etkisi ile ilk ölçüm sonuçlarının merkeze daha yakın olduğu, ikinci ve üçüncü tekrarda kısa süreli hafıza, kinestezi ve doğru kodlanamayan motor öğrenme becerisi nedeniyle merkez noktadan uzaklaşıldığı düşünülmektedir.

Anahtar Sözcükler: Dominant taraf, non-dominant taraf, hareket algısı, motor öğrenme, sağ el dominansı, sol el dominansı

Introduction

Motor control is a result of motor learning provided by the dominant hemisphere. During motor learning and motor control, the primary motor cortex provides individual or synergistic movements of the extremity muscles when the motor cortex is stimulated. The premotor cortex is responsible for motor movements learned for a general function and posture task for movements. Another important feature of the premotor cortex is that it has mirror neurons in its silent activation. These neurons observe the movement, and release the same movement. Similarly, it is important in mental imaging, activation in mirror neurons under the premotor cortex and parietal cortex, motor perception, motor learning, empathy, imitation, and learning new motor movements. The parietal cortex is also related to the feeling of discrimination. Brodmann areas, ranking between 3-2-1, are particularly related to somatosensory senses. Thalamic fibers are also origin from areas 3a and 3b. Areas 2 and 3a have an important role in proprioception and kinesthesia (1).

Cerebral lateralization is the capacity of a hemisphere (usually left) to provide more control of the contralateral side of the body compared to the other hemisphere. In this way, the contralateral side movements occur to be more accurate, rapid, and coordinated (2). The left hemisphere, which provides sensory and motor functions on the right side of the body, is the center of intellectual abilities. The right hemisphere, which controls the left side of the body, is responsible for the analysis of complex structures, holistic approach, determination of direction, and shapes of objects. Although both right and left sides of the body are used during different activities, one half of the brain dominates specialized and skill-related activities (3). It is essential to acquire skills with the use of dominant sides, to keep the gained skills in the short term memory, and to ensure its permanence. In this way, information is transferred to long-term memory, and motion perception develops (4).

Studies have shown that dominant hand use is associated with fine motor skills. In addition, studies have shown significant differences between dominant and non-dominant hand regarding asymmetry, number of hits, and completion time (5). Strength of hand grip and motion perception is associated with muscle strength in the upper extremity. Studies have shown that hand gripping force and load distribution have a significant effect on the hand function. The importance of thumb, ring finger, and palms in determining the motion perception and the grip in the dominant hand was emphasized (6,7). In the literature, studies conducted with university students suggested that somatosensory stimuli changes brain activation and long-term memory skills (8).

Obviously, data on literature is needed which includes not only the use of dominant upper extremity in healthy individuals depending on parameters such as muscle and grip strength, age, height, body mass index, and gender but also vary from the reaction time to motion perception and distance determination in young adults according to auditory stimuli (6).

In light to this information, we can say that short-term memory is more effective in just experienced movements. Factors such as repeated movement and planning of motion may take a part in motor learning and control. The hypothesis of this study is that repeated movements are effective on motion perception and motor learning of the upper extremity.

Method

Ethical Approval

This study was carried out at Hasan Kalyoncu University, Physical Therapy and Rehabilitation Department of Health Science Faculty. Ethical approval was obtained from the Local Ethics Committee, for the study on March 21, 2017 with the decision number 2017-02. The study was carried out in accordance with principles defined in the Declaration of Helsinki. Participants were informed about the study, and the informed consent form was signed.

Participants

A total of 146 students aged between 18 and 30 years, who are right-handed writers participated in this study. Those who are older than 30 years old, left-handed writers and those who use

bilateral hands during writing were excluded. Age and gender information of participants were recorded.

Apparatus and Procedure

In this study, participants were positioned at the table edge with the hip, knee, and elbows at 90-degree flexion. Measurements were made on a special platform. Figure 1 shows the experimental setup. The platform was designed to allow the upper extremity movement up to 180 degrees and to place two laser rangefinder. Both right and left forearms were resting on the table. In the study, a distance of 25 cm from each laser rangefinder was determined as the center point, and two matted glasses were placed. Participants were informed about the center point and the desired activity with their eyes open. Participants were asked to experience places on the platform, where the glasses are, while their eyes were opened. First, they were asked to keep the glass in its place, then to raise the glass once, and leave it to the same center point again. During evaluations, participants were asked to take the glass passed from different distances and put it on the center point. During the activity, glasses were passed from different arm angles. Measurements were repeated 3 times in the dominant and then the non-dominant side. The distance from the center point and the deviation rate were recorded in cm with the laser rangefinder. All evaluations were performed in a quiet hall with at least two physiotherapists who were among the authors of the study.

The hand preference of individuals was determined by the Edinburg Hand Preference Questionnaire, which was modified by Geschwind and Behan. Questions in this survey were related to simple daily functions. The hand preference of participants was asked while writing, painting, ball and stone throwing, scissoring, tooth brushing, holding a knife while slicing bread, holding a fork without a knife, rowing (bottom hand), hammer holding, holding a match, and opening a lid. Answers ranged between "always right," "usually right," "with bilateral hands," "left," and "always left," and for answers respectively +10, +5, 0, -5, and -10 points were given (9). The value from +100 to -100 was called the Geschwind score (GS). Negative scores refer to left-handedness whereas positive scores refer to right-handedness. In GS, the hand preference score ranges between -80 and -100 suggests strong left-dominant, between -20 and -70 suggests weak left-handedness, and between -15 and 15 refers to two-handedness. Score ranges from 20-75 suggests weak right-dominant and 80-100 refers to strong right-dominant (10).

Figure 1. Evaluation platform

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences 21.0 (SPSS Inc., Chicago, USA). The distance from the laser rangefinder was calculated as mean ± standard deviation (X ± SD). The deviation from the center point was calculated as the difference ± SD (D ± SD) in dominant and non-dominant sides. The correspondence of variables to the normal distribution was examined by visual (histogram and probability graphs) and analytical methods (Shapiro-Wilks test). Paired Sample t-test was used to compare the difference between dominant and non-dominant sides. The margin of error was accepted as $p<0.05$.

Results

In this study, we examined effects of repeated movements on the motion perception and motor learning of the dominant and non-dominant upper-extremity in healthy individuals.

Characteristics of Participants

A total of 146 right-hand dominant volunteers participated, wherein 80 were females (54.79%) and 66 were males (45.21%) with mean age of 23.0±1.99. All participants were university students. According to the Edinburgh Hand Preference Questionnaire, 42 of participants (28.76%) were strong right-handed, 95 (65.06%) were weak right-handed, and 9 (6.18%) were weak left-handed.

Distance from the Laser Rangefinder and Deviation from the Center Point

In the motion perception and motor learning of the dominant and non-dominant side evaluation, 3 repeated measurements were performed while their eyes were closed. No significant differences were noted in all measurements in terms of gender ($p>0.05$).

The mean and standard deviation of the distance from the laser rangefinder and the deviation from the center point for three measurements during the activity of placing the glass are shown in Table 1 for the dominant and non-dominant sides. No significant differences we noted between the dominant and non-dominant sides ($p>0.05$) (Table 1).

No differences were noted between the dominant and non-dominant sides in terms of deviation differences from the center point with their eyes closed (Table 2, $p>0.05$).

In non-dominant side, deviation from the center point was also similar. But in dominant side measurements, the deviation from the center point of the first evaluation was closer than the second and third evaluations. (Table 2, $p<0.05$). No difference was noted between the second and third evaluations of dominant hands (Table 2, $p>0.05$).

Discussion

In this study, repeated movements on motion perception and motor learning of the upper extremity dominant and non-dominant side in healthy young individuals with right-hand dominancy was evaluated on a specially developed platform. It is determined that the distance from the laser rangefinder and deviation from the center point for three measurements during the activity of placing glass were similar at dominant and non-dominant sides.

In literature it is determined that in studies which evaluate motion perception and learning, right-dominant individuals were preferred. When studies were examined in terms of average ages, it was seen that young individuals could better adapt to the study design, and these adaptations could be perceived more easily in terms of cognition (11,12). In this study, right-dominant individuals were preferred in accordance with the literature. Our results did not differ between genders, thus gender comparisons were not made in our sample.

Hemispheric lateralization is mainly parallel to hand dominancy (13). Hand dominancy may change over time due to environmental factors such as educational and cultural influences, but the hemispheric dominance is constant (14,15). Although results of the Edinburgh Hand Preference Questionnaire used for the determination of hand dominancy in our study were in parallel with the hemispheric dominance, the hemispheric dominance with this measurement method could not be determined precisely and accurately. In addition, in this questionnaire, the dominant hand preference is determined by hand use in daily life, the determination of hand preference as strong and weak suggests that hemisphere dominance may change. We attributed this to the fact that people may be affected by the environment in determining hand choices. Furthermore, other methods could be used to determine hemispheric dominancy. Results of this study were evaluated according to the literature with consideration of the hand dominancy. Only the right-hand dominant individuals were included in this study due to less frequent left-hand dominant individuals in Turkish population. We think that results of studies comparing the right and left-hand dominant individuals may contribute to the evaluation of motion perception and learning.

The coordination of the musculoskeletal system is ensured by the coordinated work of sensory and motor areas in the cortex. The left and right brain hemispheres are responsible for controlling the contralateral side of the body through commissural fibers.

Table 1. The distance from the laser rangefinder on dominant and non-dominant sides (mean ± standard deviation) (cm)

	1st measurement		2nd measurement		3rd measurement		
	X	SD	X	SD	X	SD	p
DDs	25.91	2.57	26.22	3.15	26.41	3.14	0.055*
DNDs	26.24	2.64	26.59	3.12	26.36	3.06	0.074
Ddr	2.32	1.65	2.69	1.95	2.63	2.13	0.731
NDdr	2.35	1.71	2.64	1.93	2.69	1.99	0.817

p<0.05 is statistically significant.
X: Mean, SD: Standard deviation, Ds: Distance from laser rangefinder on dominant side, NDs: Distance from laser rangefinder on non-dominant side, Ddr: Dominant hand deviation rate, NDdr: Non-dominant hand deviation rate

Table 2. Comparison of deviation differences between measurements on dominant and non-dominant sides (deviation ± standard deviation) (cm)

Evaluations	D	SD	T	p
Ds 1-NDs 1	0.02	2.59	-0.096	0.924
Ds 2-NDs 2	0.08	3.22	-0.286	0.776
Ds 3-NDs 3	0.04	3.60	0.147	0.883
Ds 1-Ds 2	0.40	1.95	1.961	0.035*
Ds 1-Ds 3	0.49	2.35	-2.175	0.020*
Ds 2-Ds 3	0.19	2.27	-1.607	0.066
NDs 1-NDs 2	0.25	2.30	1.286	0.200
NDs 1-NDs 3	0.13	2.84	-0.534	0.594
NDs 2-NDs 3	0.27	2.25	-1.887	0.059

*p<0.05 is statistically significant. Paired sample t-test.
D: Difference, SD: Standard deviation, Ds: Dominant side, NDs: Non-dominant side

Although different discriminators have been mentioned in the concept of cerebral dominancy, hand preference has been one of the most studied subjects by clinical and preclinical sciences as a symptom of motor dominancy. Ocklenburg and Gunturkun (14). investigated the relationship between hand preference and gender with the university students, their study stated that participants generally preferred their right hands in jobs that require skill, and it would be appropriate to evaluate the anatomically symmetrical brain hemispheres in terms of functionality. In this, we planned to evaluate repeated movements on motion perception and motor learning of healthy young individuals, and it was concluded that hand dominancy was not a distinguishing factor in terms of motion perception, motor learning, and functionality. Similar effects were observed with the non-dominant side with their eyes closed.

In literature, it is observed that special platforms with sensors are preferred in studies where motor control is examined. Mathew et al. (11) investigated handedness and motor control in their study. They stated that dominancy is not a predictive factor in the determination of motor control. We have used a special platform for measurements. It is determinate that the distance from the laser rangefinder and deviation from the center point for three measurements during activity of placing glass were similar at dominant and non-dominant sides. In group comparisons, a difference was only noted on the dominant side. The first measurement results for the dominant side were closer to the center point, the second measurements deviated from the center point, and the third measurement has less deviation from the center point than that of the second measurements. It is thought that the first measurement results are the effect of visual memory at the dominant and non-dominant side, but in the second and third repetitions, it is thought that the deviation from the center is due to the short term memory, kinesthesia, and motor learning ability which could not be coded correctly. Therefore, more detailed studies explaining the motion perception and motor learning explaining the comparative results of the right- and left-hand dominancy are necessary.

In light of this information, it is clear that hand dominancy is not a predictive factor for motor control and motor learning. We thought that these may be related to gender, education level, social, and cultural level as well as its use during daily life activities.

The declarative memory, which is the sub-group of long-term memory, is defined as the idea and schematization of the information which is conscious. Motions and skills occur unconsciously in the other subgroup of long-term and procedural memory. While learning a motor activity, the first thing to do is to formulate ideas, and the memory progresses from the declarative to the procedural (16). In the light of the information of the cortex and sub-cortex structures, it is the memorization of the coded motion with the repetition of the planned motor movement and with the relationship with basal ganglia and cerebellum. As a result of evaluations, the deviation in the first measurements of the dominant side was found to be similar, and the deviation from the center point in the second and third measurements was found to be higher. These findings can be explained by the relationship between motor learning, motor control, and memory. This situation can be interpreted as participants acted by focusing more on the activity, and by formulating ideas during the first evaluation and in the following evaluations, they acted under the influence of procedural memory.

Study Limitations

The limitation of the study includes the absence of auditory impulse for confusion during measurements. All measurements were performed in a silent room. Different age groups could be included in future studies, and differences between age groups could be examined.

Conclusion

In the study, which examined the motion perception and motor control of the dominant and non-dominant upper extremity in healthy young individuals, it was stated that hand dominancy not a main determinant. Repeated movements, visual information, short-term memory, and correct coding could affect the motor ability.

This study also updates the old literature on this subject. A need for further studies in this field is seen by including the right- and left-hand dominant individuals, and evaluating visual and auditory interference during movements.

Ethics

Ethics Committee Approval: This study was carried out at Hasan Kalyoncu University, Physical Therapy and Rehabilitation Department of Health Science Faculty.

Informed Consent: Participants were informed about the study, and the informed consent form was signed.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: D.K., Y.Y., Design: D.K., Y.Y., Data Collection or Processing: D.K., E.D., T.B., Analysis or Interpretation: S.A.U., B.T., Y.Y., Literature Search: D.K., S.A.U., E.D., T.B., B.T., Y.Y., Writing: D.K., S.A.U., E.D., T.B., B.T.

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References

1. Vuoksimaa E, Koskenvuo M, Rose RJ, Kaprio J. Origins of handedness: A nationwide study of 30 161 adults. Neuropsychologia 2009;47:1294-301.
2. Teixeira L, Silva MV, Carvalho M. Reduction of lateral asymmetries in dribbling: The role of bilateral practice. Laterality 2003;8:53-65.

3. Yıldırım S, Dane Ş. Serebral lateralizasyon ve el tercihi. EAJM 2007;39:45-8.
4. Yonelinas AP. The hippocampus supports high-resolution binding in the service of perception, working memory and long-term memory. Behav Brain Res 2013;254:34-44.
5. Sebastjan A, Skrzek A, Ignasiak Z, Sławińska T. Age-Related changes in hand dominance and functional asymmetry in older adults. Plos One 2017;e0177845.
6. Cai A, Pingel I, Lorz D, Beier JP, Horch RE, Arkudas A. Force distribution of a cylindrical grip differs between dominant and nondominant hand in healthy subjects. Arch Orthop Trauma Surg 2018;138:1323-31.
7. Narin S, Demirbüken İ, Özyürek S, Eraslan U. Dominant el kavrama ve parmak kavrama kuvvetinin önkol antropometrik ölçümlerle ilişkisi. DEÜ Tıp Fakültesi Dergisi 2009;23:81-5.
8. Göktepe G. Effect of bilateral somatosensory stimulus on oscillatory brain activity and long term memory. Orta Doğu Teknik Üniversitesi 2017.
9. Oldfield RC. The assessment and analysis of handedness: The Edinburgh Iventory. Neuropsychologia 1971;9:97-103.
10. Tan U. The distribution of the Geschwind scores to familial left-handedness. Int J Neurosci 1988;42:85-105.
11. Mathew J, Sarlegna FR, Bernier PM, Danion FR. Handedness matters for motor control but not for prediction. eNeuro 2019;6:ENEURO.0136-19.2019.
12. Di Tore PA, Schiavo R, D'Isanto, T. Physical education, motor control and motor learning: Theoretical paradigms and teaching practices from kindergarten to high school. Journal of Physical Education and Sport 2016;16:1293-7.
13. Akça F, Çekin R, Ziyagil MA. Genç erkeklerde el dominansının hedefli yüksek atış performansına etkisi. CBÜ Bed Eğt Spor Bil Dergisi 2015;10:1-8.
14. Ocklenburg S, Gunturkun O. Hemispheric asymmetries: the comparative view. Front Psychol 2012;3:5.
15. Aliosmanoğlu B, Köçkar Ç. Üniversite öğrencilerinde el tercihinin ve dominant gözün bazı hastalıklar ile ilişkisi. Eur J Basic Med Sci 2014;4:53-7.
16. Jones G, Macken B. Long-term associative learning predicts verbal short-term memory performance. Memory & Cognition 2018;46:216-29.

Original Article

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Development and Validation of an *In Vitro* Dissolution Method Based on HPLC Analysis for L-Dopa Release From PLGA Nanoparticles

Optimize Edilen HPLC Yöntemi ile L-Dopa Yüklü PLGA Nanopartiküllerinden Etkin Madde Salımının Farklı *İn Vitro* Çıkış Yöntemleri ile Değerlendirilmesi

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ABSTRACT

Objective: In the past decade, dissolution testing has emerged as a valauble tool for the characterization of drug product performance in the field of pharmaceuticals. During the development of new formulations, dissolutions tests assist in the evaulation of any changes in the formulation arising during manufacturing process, thereby assuring product quality and performance post manufacturing.

Methods: In the present study, a simple high performance liquid chromatography (HPLC) method was developed and validated to quantitate the release of L-Dopa from poly (D, L-lactic-co-glycolic acid) (PLGA) nanoparticles. The chromatographic separation was performed with a reversed-phase C18 column, using acetonitrile-water containing 0.05% trifluoroacetic acid (5:95, v/v) as a mobile phase at 280 nm. The developed method was validated for its specificty, linearity, accuracy, and precision according to the ICH guidelines.

Results: The developed method was shown to be linear (r2 ≥ 0.995) in the concentration range of 125-40 µg/mL. The mean % recoveries were found to be 102.59-98.70%, indicating an agreement between the true value and the detected value. Solution stability was guaranteed by the addition of an antioxidant. The analytical method was shown to be suitable for the evaluation of release of

ÖZ

Amaç: Farmasötik alanda çözünme hızı testleri, ilaç ürün performansını karakterize etmek için önemli parametrelerdendir. Üretim sürecinden sonra ürün kalitesini ve performansını sağlamak için, formülasyondaki değişiklikler, yeni formülasyonların geliştirilmesi sırasında çözünme testleriyle değerlendirilebilir.

Yöntemler: Bu çalışmada, poli (D, L-laktik-ko-glikolik asit) (PLGA) nanopartiküllerinden salınan L-Dopa miktarının belirlenmesi için yüksek basınçlı sıvı kromatografisi (HPLC) yöntemi geliştirilmiş ve onaylanmıştır. 280 nm hareketli faz olarak %0,05 trifloroasetik asit (5:95, h/h) içeren asetonitril-su kullanılarak, ters fazlı C18 kolonu ile kromatografik ayırma yapılmıştır. Geliştirilen yöntem, özgünlüğü, doğrusallığı, doğruluğu ve kesinliği için ICH kurallarına göre doğrulanmıştır.

Bulgular: Yöntemin 1,25-40 µg/mL konsantrasyon aralığında doğrusal (r2 ≥0,995) olduğu gösterilmiştir. Ortalama % geri kazanım, %102,59-%98,70 arasında olup, gerçek değer ile tespit edilen değer arasında bir korelasyon olduğu belirlenmiştir. Antioksidan ilavesiyle çözelti stabilitesi sağlanmıştır. Analitik yöntemin nanopartiküllerden salınan L-Dopa'nın değerlendirilmesi için uygun olduğu gösterilmiştir. Örnek ve ayırma (SS) ve diyaliz membranı (DM) yöntemleri kullanılarak *in vitro* salım çalışmaları

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L-Dopa from PLGA nanoparticles. *In vitro* release of L-Dopa was studied using sample and separate (SS) and dialysis membrane (DM) methods. To compare SS and DM methods, difference ($f1$) and similarity ($f2$) factors were calculated. No significant differences were recorded in the release kinetics of L-Dopa from nanoparticles using both methods ($f1$ <15 and $f2$ >50).

Conclusion: Dissolution test methods were compared and procedure for an analytical method based on HPLC was optimizated and validated for the dissolution of L-Dopa loaded nanoparticles.

Keywords: Analytical validation, L-Dopa, PLGA nanoparticles, *in vitro* drug release, sample and seperation method, dialysis membrane method

yapılmıştır. SS ve DM yöntemlerinin karşılaştırılmasında farklılık ($f1$) ve benzerlik ($f2$) faktörleri kullanılmıştır. Nanopartiküllerden L-Dopa'nın salım kinetiğindeki fark her iki yöntem için de anlamlı bulunmamıştır ($f1$ <15 ve $f2$ >50).

Sonuç: Bu çalışmada, L-Dopa yüklü nanopartiküllerden etkin madde salımının değerlendirilmesi için stabilite testleri de dahil olmak üzere bir çözünme testi yöntemleri karşılaştırılmış ve salınan L-Dopa miktarının tespiti için HPLC yöntemi optimize edilmiş ve valide edilmiştir.

Anahtar Sözcükler: Analitik validasyon, L-Dopa, PLGA nanopartikül, *in vitro* ilaç salımı, örnek ve ayırma yöntemi, diyaliz membran yöntemi

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder with a global prevalence of 1-3% in the population with age above 65 years. Clinical pathology of PD involves progressive loss of dopaminergic neurons, particularly in nigro-striatal area and its surrounding pathways. This loss of dopaminergic neurons affects movement and facial expressions in the affected patients (1,2). Conventional treatment for PD involves administration of L-Dopa, a dopamine precursor. However, L-Dopa therapy is associated with certain limitations. These include fluctuations in L-Dopa levels in the plasma owing to erratic gastric emptying and intermittent oral intake (3), poor relative bioavailability (~5-15%), and availability of <1% of the administered dose in the brain (4-7).

In the past few decades, several polymeric nanoparticles prepared using natural or synthetic polymers have been developed and explored to allow safe and enhanced delivery of drugs like L-Dopa to the targeted site. Among these, nanoparticles obtained from biodegradable and biocompatible polymers such as poly-lactic-co-glycolic acid (PLGA) or poly (glycolic acid) have been used most commonly. In general, nanoparticles are preferred for drug administration owing to their high chemical and biological resistance and ability to carry both hydrophilic and lipophilic substances in their active form. In addition, these nanoparticles can be administered in the body via different routes.

Since nanoparticles release small amounts of encapsulated drugs as a function of time, the analytical methods used to study *in vitro* release of drugs must be highly sensitive to quantify drug concentrations in the dissolution medium. Testing methods used to study *in vitro* release for nanoparticles based delivery systems can be broadly divided into three categories, membrane diffusion methods [such as dialysis method (DM)], sample and separation methods (SS), and continuous flow methods. Among these, DM is used most commonly to evaluate *in vitro* release of drugs from nanoparticles, followed by SS. In the present study, DM was used as reference method and SS was used as test method.

Among the currently available analytical methods, HPLC is the most commonly used method employed for the characterization of various pharmaceutical molecules. HPLC-diode array detector (DAD) offers a quick, sensitive, and accurate method for the separation and identification of drugs in pharmaceutical nanoparticulate formulations (8,9). Although several researchers have investigated *in vitro* release of drugs from nanoparticles, no HPLC method has been established for the simultaneous determination of L-Dopa. No studies have been reported for the use of DM and SS methods for the quantification of the amount of L-Dopa released from nanoparticles in dissolution medium. Besides this, in most of the reported studies used L-Dopa solutions at low pH as standard solution (10-13).

Nanoparticles were specially designed to ensure delivery of L-Dopa to brain by endocytosis when administered nasally. To represent dissolution profile of L-Dopa released from the nanoparticles, two buffered solutions mimicking pH conditions present in the endolysosomal compartment (pH 4.5) and brain (pH 7.4) were used (14). Several previous studies have reported evidences for the stability of L-Dopa in acidic conditions (10,12,13,15). The present study aimed to develop and optimize an analytical method to determine the levels of L-Dopa in different media having a higher pH as compared to the acidic media reported earlier for L-Dopa.

In the present study, a double emulsion-solvent evaporation method was used to prepare PLGA nanoparticles, wherein methylene chloride, polyvinyl alcohol, and PLGA were used as organic solvent, surfactant, and polymer, respectively. In order to determine the release profile of L-Dopa from PLGA nanoparticles, SS and DM methods were compared. In general, it is believed that *in vitro* release method reflects the changes in the manufacturing procedure that in turn affects the performance of the drug entrapped in the nanoparticles. Thus, *in vitro* dissolution test methods used in the study were compared and HPLC method was further validated to ensure the robustness of the developed analytical method. The study also included stability tests for the L-Dopa released from the PLGA nanoparticles.

Method

Instrumentation

For HPLC studies, Agilent 1100 series integrated HPLC system with DAD, pump, auto-sampler, and degasser unit was used. Reversed phase HPLC analysis was carried out using a 250x4.6 mm, 5 µm reversed-phase C18 HPLC column obtained from Macherey-Nagel. For *in vitro* drug release studies, orbital shaker and ultra centrifuge (Sigma® 30KS) purchased from Sigma were used.

Reagents and Materials

L-Dopa was a kind gift from ILKO Pharmaceuticals (Ankara, Turkey). Deionised water used in the study was obtained from a Millipore water supplier. Trifluoroacetic acid (TFA), NaCl, Na_2HPO_4, KH_2PO_4, acentonitrile (HPLC grade), and Tween 80 were procured from Merck. For HPLC analysis, the mobile phase was filtered through a 0.45 µm membrane filter (Millipore, Barcelona) and degassed using an ultrasonic bath, prior to use. Cellulose dialysis tubing (14,000 MWCO), polypropylene co-polymer centrifuge tubes, and polyvinyl alcohol (PVA) were purchased from Sigma-Aldrich.

Chromatographic System and Conditions

First, the wavelength for absorption maxima for the drug was selected based on its UV spectrum. L-Dopa was characterized by a absroption maxima at 280 nm which was further used for HPLC analysis. Mobile phase for HPLC analysis comprised of TFA solution (0.05% v/v, pH 3) and acetonitrile at 95:5 (v/v). For chromatographic separation, 250x4.6 mm, 5 µm C18 reversed-phase HPLC column was used. A flow rate of 1 mL/min and run time of 7 minutes with 10 µL injection volume were used for HPLC analysis (1). The method used in the present study was developed and validated as per the considerations of the ICH guideline Q2 (R1) that involved several parameters including specificity, linearity, detection and quantification limits, repeatability and intermediate precision, accuracy, and stability (16).

Preparation of Reagents

Suitable analytical procedures should be used to define the amount of L-Dopa used during dissolution test. Two stock solutions of L-Dopa at concentration of 100 µg/mL were prepared by dissolving a suitable amount of L-Dopa in buffered solutions at pH 4.5 and pH 7.4. Prior to use, all solutions were sonicated for 30 min. For each stock solution, 6 diluted samples in the concentration range of 1.25-40 µg/mL (ppm) (1.25, 2.5, 5, 10, 20, and 40 µg/mL) were prepared from the stock solutions. The stability of L-Dopa in the diluents (phosphate buffer solution at pH 4.5 and pH 7.4) was investigated for a period of 48 hours at different tempratures (4 ºC, 25 ºC, and 37 ºC) in both the presence and absence of ascorbic acid.

Preparation of Nanoparticles

L-Dopa loaded nanoparticles were prepared using a double emulsion solvent evaporation method with PVA as a stabilizer. Briefly, L-Dopa and PLGA were first dissolved in dichloromethane (DCM). Further, distilled water was added to the resulting solution and mixed using an ultrasonic homogenizer to form a primary water-in-oil (W/O) emulsion. Following this, the primary emulsion was emulsified in PVA solution with homogenization to form a double water-in-oil-in-water (W_1/O/W_2) emulsion. The resulting double emulsion was stirred using a magnetic stirrer at a constant rate at room temperature (25 °C) to evaporate the organic solvent. The resulting nanoparticle suspension was further incubated at 4 °C overnight to ensure hardening of the PLGA matrix by allowing DCM to fully partition to the external aqueous phase. The nanoparticles were recovered by ultracentrifugation. The supernatant was carefully removed and pellet containing nanoparticles was washed twice with distilled water to remove free drug and excess surfactant. The sample was further subjected to lyophilization.

Dissolution Test Development

Dissolution Medium

The term "sink condition" is generally defined as the ability of the dissolution medium to dissolve at least three times the amount of drug present in the dosage form. Percentage of drugs released from the nanoparticles should be detected using the developed analytical method. Selection of the most suitable media conditions is based upon the stability of the analyte in the test medium and its application in terms of *in vivo* performance. Since the nanoparticles were specifically designed to deliver L-Dopa to brain via endocytosis using a nasal route of administration, the *in vitro* release of L-Dopa from PLGA nanoparticles was studied at pH 4.5 to mimic the endolysosomal pH and at pH 7.4 to mimic the brain pH (17). Phosphate buffer solution at pH 4.5 was prepared by dissolving 6.8 g potasium dihydrogen phosphate in 1 L distilled water containing 2 % Tween 80 (v/v) and 0.1 % (w/v) ascorbic acid (aa). Phosphate buffer solution at pH 7.4 was prepared by dissolving 2.38 g disodium hydrogen phosphate, 0.19 g potassium dihydrogen phosphate, 8 g sodium chloride, 2% Tween 80, and 0.1% aa in 1 L distilled water. In the present study, 2% (w/v) Tween 80 was used to enhance the solubility of L-Dopa in aqueous solution and 0.1% (w/v) aa was added to protect L-Dopa from oxidation during the assay (18).

Method devolopment

In Vitro Drug Release (SS Method)

L-Dopa loaded nanoparticles weighed to contain 45 µg L-Dopa were suspended in 5 mL of buffered solution. The nanoparticle suspensions were transferred to tubes and incubated in an orbital shaker bath at 37±0.5 °C with rotation at 100 rpm. The tubes were removed from the water bath at 30, 60, 120, and 240 minutes, and centrifuged at 2000 rpm for 20 min. The supernatant was carefully removed and used for further analyis. The nanoparticle pellets were resuspended in 5 mL of fresh buffer (pH 4.5) and placed back in the shaker bath. The supernatant was used to determine the concentration of L-Dopa. All experiments were perfomed in triplicates and results were expressed as mean ± variation.

In Vitro Drug Release (DM Method)

L-Dopa loaded nanoparticles containing 45 µg L-Dopa were suspended in 0.5 mL of buffered solution and inserted in a dialysis bag. The dialysis bag was placed in 4.5 mL (total 5 mL) of buffered solution at pH 4.5. This was further incubated at 37±0.5 °C in an orbital shaker bath at 100 rpm. To evaluate drug release as a function of time, 1 mL sample aliquots were collected at 30, 60, 120 and 240 minutes and replaced with 1 mL fresh buffer (pH 4.5). Drug concentrations in the aliquots were determined using the above mentioned analytical method. All experiments were performed in triplicates and results were expressed as mean ± variation.

Statistical Calculations

All results are reported as mean ± standard deviation of replicates. For drug release (%) at different time intervals, two tailed t-test was performed using Prism Software Version 6.0, where differences were considered to be significant with $p<0.05$. Microsoft Office Excel® was used to calculate $f1$ and $f2$ factors.

Results

The present study involved development of a HPLC based analytical method to determine time dependent release of L-Dopa from PLGA nanoparticles synthesized using a double emulsion solvent evaporation method. For reversed-phase HPLC analyis, mobile phase comprised of TFA solution (0.05% v/v) at pH 3 and acetonitrile at ratio of 95:5 (v/v). The chromatographic separation was carried out using a 250x4.6 mm, 5 µm C18 HPLC column. The flow rate for HPLC analysis was kept at 1 mL/min with run time of 7 minutes and 10 µL injection volume. No interfence was observed after injection of L-Dopa solution, placebo, and nanoparticles.

The regression equations for the calibration curve were found to be y=5.7424x+2.1421 (Figure 3) and y=7.4159x+9.5333 (Figure 4) for phosphate buffer solution at pH 4.5 and phospate buffer saline solution at pH 7.4, respectively. The regression coefficient r^2 was calculated to be 0.9998 and 0.995 for buffered solutions at pH 4.5 and pH 7.4, respectively. Linearity data calculated using Prism Software Version 6.0 are summarized in Table 1. Repeatability analysis for buffered solutions at pH 4.5 and pH 7.4 were characterized by relative standard deviation (RSD) % of 3.07-0.03% and 0.83-0.01%, respectively. For inter day assays, buffer at pH 4.5 was found to have precision with RSD % of 1.44-0.01% while buffer at pH 7.4 showed precision of RSD % 1.00% and 0.01%. The mean % recoveries for buffered solutions at pH 4.5 and pH 7.4 were calculated to be in the range of 102.59-98.70 and 101.92-100.00, respectively. L_D and L_Q values were found to be 0.0408 and 0.1235 µg/mL, respectively, for buffer at pH 4.5. For buffer at pH 7.4, L_D and L_Q values were 0.0636 and 0.1928 µg/mL, respectively. When the analysis was performed as function of temperature over a period of 48 hours, the amount of remaining L-Dopa was found to be 97.46% at 4 °C, 95.54% at 25 °C, and 89.63% at 37 °C for buffer at pH 4.5 in presence of ascorbic acid. In comparison to this, the remaining L-Dopa in buffered solution at pH 7.4 in the presence of aa over a period of 48 hours was calculated to be 103.21% at 4 °C, 88.21% at 25 °C, and 75.85% at 37 °C.

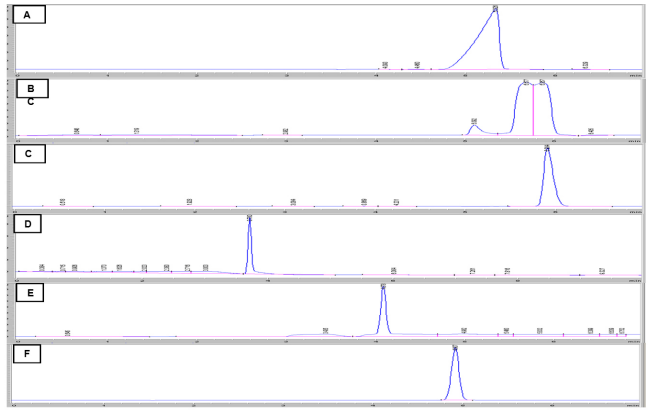
The differences in release rate were evaluated for SS and DM method. $f1$ was found to be 6.02 and $f2$ was 95.38. No differences were observed in the test and reference methods for all the time intervals for which drug release (%) was studied ($p=0.853$; $p<0.05$).

Discussion

Optimization of the Chromatographic Method

The HPLC method developed in the present study to determine the release of drugs provided a reliable quality control analysis. The wavelength selection for HPLC analysis was done on the basis of absorption maxima obtained for three different concentrations of L-Dopa solutions according to the acquired ultraviole (UV) spectra. A wavelength of 280 nm was selected for HPLC analysis because it provided high sensitivity, required for the quantitation of significantly low concentations of the drug present in the dissolution samples.

The detection of L-Dopa required an adequate mobile phase comprising of a suitable ratio of polar to non-polar solvent. For an acceptable chromatographic separation, several parameters including pH of the mobile phase and percentage of organic modifier were tested. HPLC analysis was conducted at a flow rate of 1 mL/min with a run time of 7 minutes and 10 µL injection volume. L-Dopa at a concentration of 10 ppm was injected into the system. The chromatograms obtained for the HPLC analysis showed that the use of acidic mobile phase with reversed-phase C18 column provided high solubility for L-Dopa resulting in



	Chromotographic conditions	Retention (time minute)	Symetry of peak	pH of TFA
A	T FA - acetonitrile (95 - 5)(v/v)	5.3	5.514	7.6
B	TFA - acetonitrile (90 - 10)(v/v)	-	-	7.6
C	TFA - acetonitrile (95 - 5)(v/v)	5.9	0.666	2,3
D	TF A - acetonitrile (90 - 10)(v/v)	4.1	0.61	2,3
E	TFA - acetonitrile (97 - 3)(v/v)	3.7	0.784	2,3
F	TFA - acetonitrile (95 - 5)(v/v)	4.9	1.058	3

Figure 1. Preliminary chromatogram for HPLC analysis performed on a C18 reverse phase column

HPLC: High performance liquid chromatography

symmetric and sharp peaks. As shown in Figure 1, TFA solution was determined as acidic buffer solution for HPLC analysis.

For the mobile phase used in HPLC analysis, when the ratio of acetonitrile to 0.05 % (v/v) TFA solution in water was changed from 10:90 (v/v) to 5:95 (v/v) a sharp peak for the active substance was obtained. Following this, a ratio of 2.5:97.5 (v/v) for acetonitrile to 0.05% (v/v) TFA solution was also tested for mobile phase to allow for better separation. However, peak of L-Dopa couldn't be determined at this ratio in contrast to our previous experiments. In order to protect the column's integrity, pH for 0.05% (v/v) TFA solution was adjusted to pH 3 using 0.1 N HCl solution and thus the resulting peak tailing was acceptable (Figure 1).

For the sample peak, symmetry factor was found to be 1.058 which was within the limit of <1.5 as established for various pharmacopoeias (Figure 1). Therefore, all the HPLC analysis performed in the study were carried out using a 250x4.6 mm, 5 µm C18 HPLC column with a flow rate of 1 mL/min, run time of 7 minutes, 10 µL injection volume, 25 °C column temperature, and mobile phase comprising of acetonitrile and 0.05% (v/v) TFA solution at 5:95 (v/v) (pH 3) (1).

Nanoparticles used in the study were specifically designed to be transported to brain via nasal route by means of endocytosis. To evaluate the dissolution profile of L-Dopa from PLGA nanoparticles, two buffered solutions at pH 4.5 and pH 7.4 were used to mimic pH of endolysosomal compartment and brain, respectively (14). As mentioned earlier, several studies have previously established the stability of L-Dopa in acidic conditions (10,12,13,15). Therefore, present study focussed on developing and optimizing a HPLC based analytical method to determine the amount of released L-Dopa in different media conditions having pH values higher than those reported in previous studies. In addition to this, buffered solutions at pH 4.5 and pH 7.4 with and without L-Dopa were also injected and analyzed using the same method to check for any interference in the peaks. As shown in Figure 2, no interference was observed (Figure 2).

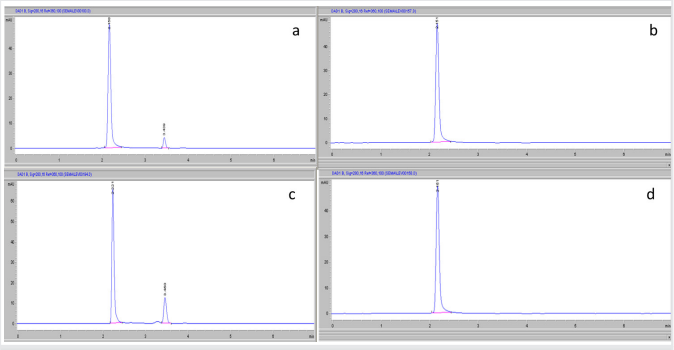


Figure 2. a) Chromatogram of L-Dopa in buffered solution at pH 4.5, b) Chromatogram of buffered solution at pH 4.5, c) Chromatogram of L-Dopa in buffered solution at pH 7.4, and d) Chromatogram of buffered solution at pH 7.4

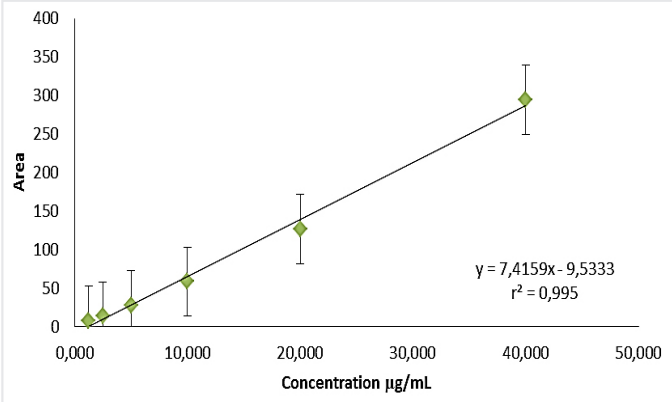


Figure 4. Calibration curve of L-Dopa in buffered solution at pH 7.4 obtained using HPLC based analytical method (n=3)

HPLC: High performance liquid chromatography

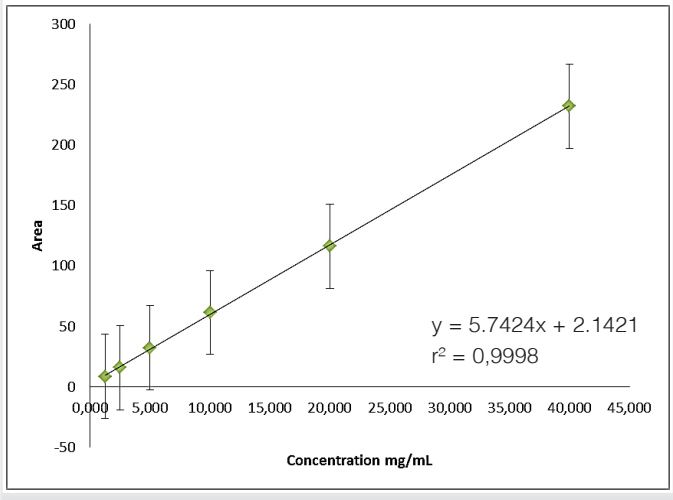


Figure 3. Calibration curve of L-Dopa in buffered solution at pH 4.5 obtained using HPLC method (n=3)

HPLC: High performance liquid chromatography

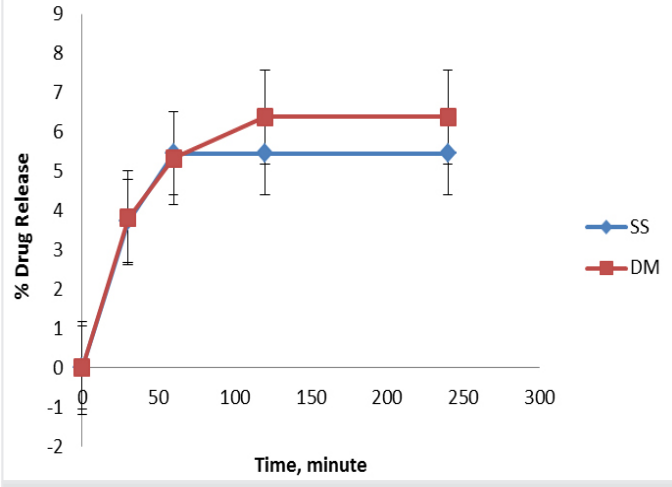


Figure 5. Comparative release profile of L-Dopa from nanoparticles obtained using DM and SS methods (n=3)

DM: Dialysis method, SS: Separation methods

Method Validation

In the present study, the analytical method was developed and validated according to the ICH guideline Q2 (R1) (16). The developed method was validated for various characteristics including linearity, accuracy, precision, specificity, stability, and detection limit and quantification limit. The method thus established was further utilised to quantitate the amount of the drug released from L-Dopa loaded nanoparticles.

Linearity

For the evaluation of linearity, standard solutions at different concentrations of L-Dopa were used. ICH guidelines suggest use of a minimum of five concentration levels for linearity studies. In the present study, linearity for L-Dopa was determined over a range of 1.25-40 µg/mL at six different concentrations. All the analysis were performed in triplicates (n=3) (16). For each concentration, samples were analysed six times, and the resulting peak areas were documented and analysed. The results for the regression analysis are shown in Figures 3 and 4. A good linear relationship ($r^2 \geq 0.995$) was observed between the concentrations and their respective peak areas as provided by the detector (Figures 3 and 4). The regression coefficient r^2 values ≥0.995 are considered to be acceptable according to the ICH guidelines (16). Generally, correlation intercept is calculated to evaluate the acceptability of the linearity of the data. In fact, for better analysis of the data, slope of line should also be calculated (Table 1) (8). All these results showed that all calibration curves were characterized by suitable linearity according to ICH guidlines (16).

Precision

The values for the absolute differences between the mean assay results for the developed method were obtained using repeatability and intermediate precision tests. All these values met the acceptance criteria of RSD %, RSD <2.0. In general, repeatability establishes the precision of multiple sampling under the same operating conditions over a short interval of time. In comparison to this, precision establishes variations arising from the same laboratory under variable operating conditions, for example different days, analysts or equipment. Thus, all these results suggest that the developed method was reproducible and precise (19).

Repeatability

Repeatability proves precision of the method under same operational conditions over a short period of time. Repeatability also refers to intra-assay sensitivity. In the present study, low (1.25 µg/mL), medium (5 µg/mL), and high (20 µg/mL) concentrations of L-Dopa used in the calibration curve were analyzed to determine mean, standard deviation (SD), and RSD (n = 6). As per the standard guidelines, RSD % for standard peak must be < 2.0 (20). As shown in Tables 2 and 3, the developed method met the standart requirements of this analytical validation parameter for medium (5 µg/mL) and high (20 µg/mL) concentrations of the drug (20). In case of L-Dopa concentration of 1.25 µg/mL, which represents the lower concentration, % RSD was >2.0. However, there are several studies that extend the limits for % RSD to 5-6% (8). Since the concentration of 1.25 µg/mL represents the lowest point of the calibration curve, so extension of limits might be suitable for this method.

Intermediate Precision

The variations in terms of analyst for the developed method were determined using replicate injections of the above mentioned concentrations and analyzed using different analysts on the same day (Tables 4 and 5). Intermediate precision was performed using

Table 1. Linearty data for analytical method

Values	pH 4.5	pH 7.4
Slope	5.742	7.416
Standard deviation of slope	0.02059	0.1312
Confidence interval 95%	5.699-5.786	4.679-0.896
Correlation coefficient	0.9999	0.9975
Regression coefficient	0.9998	0.9950
Intercept	2.142	-9.533
Standard deviation of Intercept	0.3595	2.473
Confidence interval of intercept	1.390-2.895	-14.777- -4.290

Table 2. Repeatability analysis for the assay performed in buffered solution at pH 4.5 (n=6)

1.25 µg/mL		5 µg/mL		20 µg/mL	
Area	**Concentration µg/mL**	**Area**	**Concentration µg/mL**	**Area**	**Concentration µg/mL**
Average	1.24863	**Average**	5.12961	**Average**	19.73933
SD	0.04	SD	0.03	SD	0.13
RSD	3.07	RSD	0.50	RSD	0.68

SD: Standard deviation, RSD: Relative standard deviation

RSD % of six repeated assays on samples at three concentration levels. RSD % values were found to be in the range of 1.44-0.1% for all concentration levels and pHs studied. For intermediate precision, RSD % value should not exceed 2.0% The results summarized in Tables 4 and 5 show that the developed method met the requirements set for this analytical validation parameter (16).

Accuracy

The accuracy was determined in terms of recovery of known amounts of L-Dopa. For testing the accuracy of analytical methods, three concentrations (1.25, 5, and 20 µg/mL representing low, medium, and high concentrations, respectively) of the drug, covering the linear range of analytes, were prepared by diluting the stock solutions. The mean % recoveries were found to be in the range of 101.92-98.70%, thus implying an agreement between the true value and the found value (Tables 6 and 7). All these results indicate that the developed method met the requirements for method verification according to ICH guidelines (16).

Specificity

Specificity of an analytical method can be defined as the ability to assess an analyte unequivocally in the presence of expected components. This definition has a descriptive effect on the identity of an analyte. In our study, the specificity tests were performed using three different polymers for nanoparticle preparation and L-Dopa in two different media conditions. It was decided that the HPLC method was specific for the determination of L-Dopa according to the data summarized in Table 8. L-Dopa samples were injected five times and similar retention times were observed in all cases. All the nanoparticles prepared using different polymers were injected with or without L-Dopa. No interference was observed between the peaks of nanoparticles and L-Dopa. Thus, the described HPLC method was specific for buffered solution at pH 7.4 buffer and selective for buffered solution at pH 4.5.

Table 3. Repeatability analysis for the assay performed using HPLC based analytical method with buffered solution at pH 7.4 (n=6)

1.25 µg/mL		5 µg/mL		20 µg/mL	
Area	**Concentration µg/mL**	**Area**	**Concentration µg/mL**	**Area**	**Concentration µg/mL**
Average	1.31923	**Average**	5.00051	**Average**	18.49404
SD	0.01	**SD**	0.04	**SD**	0.10
RSD	0.56	**RSD**	0.83	**RSD**	0.53

SD: Standard deviation, RSD: Relative standard deviation, HPLC: High performance liquid chromatography

Table 4. Precision analysis of the assay performed using HPLC based analytical method with buffered soltuion at pH 4.5 (n=6)

	1.25 µg/mL		5 µg/mL		20 µg/mL	
	1. day	**2. day**	**1. day**	**2. day**	**1. day**	**2. day**
Average	1.2128	1.19172	5.12961	4.89316	20.6562	20.6382
SD	0.01	0.02	0.03	0.05	0.77	0.02
RSD	1.44	1.58	0.5	1	0.66	0.1

SD: Standard deviation, RSD: Relative standard deviation, HPLC: High performance liquid chromatography

Table 5. Precision analysis for the assay performed using HPLC based analytical method with buffered soltuion pH 7.4 (n=6)

	1.25 µg/mL		5 µg/mL		20 µg/mL	
	1. day	**2. day**	**1. day**	**2. day**	**1. day**	**2. day**
Average	1.22944	1.17172	5.00051	4.8931600	19.49404	19.63820
SD	0.01	0.02	0.04	0.05	0.10	0.02
RSD	0.54	0.85	0.83	1.00	0.53	0.11

SD: Standard deviation, RSD: Relative standard deviation, HPLC: High performance liquid chromatography

Table 6. Accuracy analysis for the assay performed using HPLC based analytical method with buffered soltuion at pH 4.5 (n=6)

1.25 µg/mL		5 µg/mL		20 µg/mL	
Experimental concentration	**% Recovery**	**Experimental concentration**	**% Recovery**	**Experimental concentration**	**% Recovery**
Average	99.89	**Average**	102.59	**Average**	98.70
SD	1.06	**SD**	0.51	**SD**	0.67
RSD	1.07	**RSD**	0.50	**RSD**	0.68

SD: Standard deviation, RSD: Relative standard deviation, HPLC: High performance liquid chromatography

Stability

The stability of L-Dopa in aqueous solution was evaluated to verify any spontaneous degradation of the samples during preparation (21). The aqueous solutions of L-Dopa were found to be unstable. However, aqueous solutions have been previously shown to be stable in the presence of high concentrations of acidic substances. Stability of L-Dopa remained uneffected in the presence of light. The storage condition for the active substance was specified to be at 2-8 °C. In addition to this, the oxidation of L-Dopa can be avoided in the presence of antioxidants. Therefore, information was obtained for the stability of L-Dopa in the presence of aa in the body and during the validation and formulation studies (3,18,22). Stock solution of L-Dopa at 0.4 mg/mL concentration was prepared using buffered solutions at pH 4.5 and pH 7.4. The solutions were mixed and vortexed until solid particles disappeared. The samples were further divided into aliquots of 3 mL. The stability of the solutions containing ascorbic acid was extended up to 48 hours. No oxidation was observed in the solutions containing aa at 4 °C. Thus, all these results suggest that aa should be added as a preservative in the dissolution medium during dissolution studies. No interference was recorded between the peaks of L-Dopa and ascorbic acid. The results of stability studies are summarized in Tables 9 and 10.

Table 7. Accuracy analysis for the assay performed using HPLC based analytical method with buffered soltuion pH 7.4 (n=6)

1.25 µg/mL		5 µg/mL		20 µg/mL	
Experimental concentration	**% Recovery**	**Experimental concentration**	**% Recovery**	**Experimental concentration**	**% Recovery**
Average	101.92	**Average**	100.00	**Average**	100.01
SD	0.74	**SD**	0.81	**SD**	0.83
RSD	0.56	**RSD**	0.81	**RSD**	0.83

SD: Standard deviation, RSD: Relative standard deviation, HPLC: High performance liquid chromatography

Table 8. The results of specificity analysis for HPLC method developed for L-Dopa

	pH 4.5		pH 7.4	
	Time (minute)	**Area**	**Time (minute)**	**Area**
L-Dopa	4.2	42.7	3.93	39.9
Resomer RG 503 H nanoparticles	2.3	10	0	0
Resomer RG 756H nanoparticles	2.3	8.6	0	0
Resomer RG 756H nanoparticles	2.4	9.4	0	0

HPLC: High performance liquid chromatography

Tablo 9. Results for stability study of L-Dopa in buffered solution at pH 4.5 (aa = ascorbic acid)

	pH 4.5					
	aa added			aa not added		
Hours	**0**	**24**	**48**	**0**	**24**	**48**
Temperature	**% drug content**			**% drug content**		
4 °C	100.00	100.01	97.46	100.00	100.17	68.37
25 °C	100	99.27	95.54	100.00	100.02	60.64
37 °C	100	100.29	89.63	100.00	100.05	55.89

Tablo 10. Results for stability study of L-Dopa in buffered solution at pH 7.4 (aa = ascorbic acid)

	pH 7.4					
	aa added			aa not added		
Hours	**0**	**24**	**48**	**0**	**24**	**48**
Temperature	**% drug content**			**% drug content**		
4 °C	100.00	100.07	103.21	100.00	98.55	87.96
25 °C	100.00	104.20	88.21	100.00	86.47	70.70
37 °C	100.00	99.96	75.85	100.00	88.78	67.95

Limit of Detection (L_D) and Limit of Quantification (L_Q)

Limit of detection (L_D) represents the lowest concentration level in a peak area where signal level is atleast three fold of the baseline-to-noise. Limit of quantification (L_Q) represents the lowest concentration level that can be precisely provided by a peak area with a given signal-to-noise. Calibration curve was calculated using L-Dopa concentrations in the range of 1.25-40 μg/mL. The following equations were used:

Detection limit (L_D) =3.3 a/s;

Quantification limit (L_Q) =10 a/s;

where "a" is the standard deviation of y-intercept of regression lines and "s" is the slope of the calibration curve. For L_D and L_Q, no defined limit is available in the literature and these are specific for each method. As shown in Table 12, the results met the requirements for *in vitro* dissolution tests (23).

***In Vitro* Drug Release**

In order to design a suitable dissolution medium for a poorly soluble drug, the first method involves increasing the volume of aqueous sink conditions or decreasing the amount of dissolved drug. The second approach is based upon the addition of anionic or non-ionic surfactans and solubilization of the drug by co-solvents up to 40%. In another approach, pH is altered to obtain a better sink condition. The last two approaches are less cumbersome and have been employed more widely in dissolution tests in the pharmaceutical industry. To enhance the solubility of L-Dopa 2% Tween 80 was added to the dissolution medium. In addition to this, ascorbic acid was also used in the mediums to protect L-Dopa against oxidation during *in vitro* release.

The cumulative amount of L-Dopa released from polymeric material was plotted as a function of time. As shown in Figure 4, only 5-6% of the drug content was released from the nanoparticles as evaluated for both methods. In order to achieve sink conditions, L-Dopa concentrations shouldn't exceed 20% of its saturation solubility in dissolution medium which was maintained in the the present study. Thus, inhibited release of L-Dopa was not contributed by insufficient sink conditions. In addition, it did not arise owing to inadequate loading of nanoparticles either (amount of released drug as a function of the encapsulated drug substance). Interactions between L-Dopa and PLGA prevented complete dissolution. Moreover, 5-6% of the drug content was suitable enough for the dicussion of the two methods. *In vitro* release profiles of the test formulations were similar to the reference formulation. In literature, it is mentioned that release rate of the encapsulated drug is progressively higher in SS method as compared to DM (Figure 5) (24). This might be contributed by the differences in the hydrodynamics of the system as the nanoparticles are present in the dialysis bag in one methode while in the other formulation is dispersed in a flask (25).

The similarity factor ($f2$) is a measurement of the similarity in the percent (%) dissolution between the two profiles (26). The difference factor ($f1$) is proportional to the average difference between the two profiles. FDA guidelines recommend that $f1<15$ and $f2>50$ are indicative of equivalence in dissolution profiles (27).

$$f2 = 50 \times \log [1 + (1/n) \Sigma^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \times 100)$$

$$f1 = [\Sigma^{n}_{t=1} (R_t - T_t) / \Sigma^{n}_{t=1} R_t] \times 100$$

As shown in Table 12, no signicant differences were obtained in the release kinetics of L-Dopa as studied using both methods ($f1<15$ and $f2>50$) (24,28). A two tailed t-test was used to compare the dissolution profiles. No differences were observed in the drug release (%) for the test and reference methods at all time intervals ($p=0.853$; $p<0.05$).

Table 11. Limit of detection (L_D) and Limit of quantification (L_Q) for HPLC analysis

	L_D	L_Q
pH 4.5	0.0408	0.1235
pH 7.4	0.0636	0.1928

HPLC: High performance liquid chromatography

Conclusion

The analytical methods developed and validated in the present study were found to be simple, sensitive, accurate, and precise. The results of the study indicated that the developed methods are suitable for dissolution studies as well as routine quality control analysis of L-Dopa present in nanoparticulate formulations. DM and SS methods were characterized by similar *in vitro* release

Table 12. Values for f_1 and f_2 factors for the dissolution profile obtained using DM as reference and the SS as test model (n=3)

	SS method	DM method
Time (minute)	Test model, drug release (%)	Reference model, drug release (%)
30	3.73±0.03	3.81±0.01
60	5.45±0.02	5.33±0.05
120	5.45±0.02	6.38±0.01
240	5.45±0.02	6.38±0.01
	f_1	**6.02**
	f_2	**95.38**

DM: Dialysis method, SS: Separation methods

profiles, with acceptable precision (<10% SD). SS method showed faster release from formulations as compared to those observed using dialysis bag (Table 12). No significant differences were reported between DM and SS methods used for release kinetics study ($f1<15$ and $f2>50$). For further studies, the optimal method with *in vivo* relevance needs to established keeping into consideration *in vivo* to *in vitro* corelation.

Ethics

Ethics Committee Approval: *In vitro* study.

Informed Consent: *In vitro* study.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Data Collection or Processing: S.A., Ö.S., Analysis or Interpretation: T.Ç., Literature Search: S.A., Ö.S., Writing: S.A., T.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Zhou YZ, Alany RG, Chuang V, Wen J. Optimization of PLGA nanoparticles formulation containing L-DOPA by applying the central composite design. Drug Dev Ind Pharm 2013;39:321-30.
2. Sharma S, Lohan S, Murthy R. Formulation and characterization of intranasal mucoadhesive nanoparticulates and thermo-reversible gel of levodopa for brain delivery. Drug Dev Ind Pharm 2014;40:869-78.
3. Luinstra M, Grasmeijer F, Hagedoorn P, Moes JR, Frijlink HW, de Boer AH. A levodopa dry powder inhaler for the treatment of Parkinson's disease patients in off periods. Eur J Pharm Biopharm 2015;97(Pt A):22-9.
4. Vasa DM, Buckner IS, Cavanaugh JE, Wildfong PL. Improved Flux of Levodopa via Direct Deposition of Solid Microparticles on Nasal Tissue. AAPS Pharm Sci Tech 2017;18:904-12.
5. Pahuja R, Seth K, Shukla A, Shukla RK, Bhatnagar P, Chauhan LKS, et al. Trans-blood brain barrier delivery of dopamine-loaded nanoparticles reverses functional deficits in parkinsonian rats. ACS Nano 2015;9:4850-71.
6. Nedorubov A, Pavlov A, Pyatigorskaya N, Brkich G, Aladysheva Z. HPLC-MS/MS Method Application for the Determination of Pharmacokinetic Parameters of Intranasal Delivered L-DOPA in Rats. J Pharm Sci Res 2018;10:2489-92.
7. Gambaryan P, Kondrasheva I, Severin E, Guseva A, Kamensky A. Increasing the Efficiency of Parkinson's Disease Treatment Using a poly (lactic-co-glycolic acid)(PLGA) Based L-DOPA Delivery System. Exp Neurobiol 2014;23:246-52.
8. Souza PRdSe, Carvalho JMd, Albert ALM, Moreira JC, Leandro KC. Development and validation of a method for the determination of valproic acid in pharmaceutical formulations by high performance liquid chromatography with diode array detection (HPLC-DAD). Vigilância Sanitária em Debate 2013;1.
9. Fuster J, Negro S, Salama A, Fernández-Carballido A, Marcianes P, Boeva L, et al. HPLC-UV method development and validation for the quantification of ropinirole in new PLGA multiparticulate systems: Microspheres and nanoparticles. Int J Pharm2015;491:310-7.
10. Raut PP, Charde SY. Simultaneous estimation of levodopa and carbidopa by RP-HPLC using a fluorescence detector: its application to a pharmaceutical dosage form. Luminescence 2014;29:762-71.
11. Konduru N, Madhuri G. STABILITY INDICATING METHOD OF CARBIDOPA AND LEVODOPA ASSAY IN CARBIDOPA, LEVODOPA AND ENTACAPONE FILM COATED TABLETS BY RP-HPLC.
12. Dhawan R, Ravi S, Subburaju T. Compatibility and stability studies of levadopa, carbidopa, entacapone and natural bioenhancer mixture. IJPAR 2014;3:474-81.
13. Reddy BJC, Sarada NC. A Simple Validated Stability Indicating RP-HPLC Method for the Determination of Three Antiparkinsonism Compounds in Oral Contraceptive Tablet Formulations. Int Jornal ChemTech Research 2017;10:636-46.
14. Gao X, Tao W, Lu W, Zhang Q, Zhang Y, Jiang X, et al. Lectin-conjugated PEG–PLA nanoparticles: preparation and brain delivery after intranasal administration. Biomaterials 2006;27:3482-90.
15. Junnotula V, Licea-Perez H. Development and validation of a simple and sensitive method for quantification of levodopa and carbidopa in rat and monkey plasma using derivatization and UPLC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 2013;926:47-53.
16. ICH. Q2(R1) Validation Of Analytical Procedures: Text And Methodology. 2005.
17. Piazza J, Hoare T, Molinaro L, Terpstra K, Bhandari J, Selvaganapathy PR, et al. Haloperidol-loaded intranasally administered lectin functionalized poly (ethylene glycol)–block-poly (D, L)-lactic-co-glycolic acid (PEG–PLGA) nanoparticles for the treatment of schizophrenia. Eur J Pharm Biopharm 2014;87:30-9.
18. Pappert EJ, Buhrfiend C, Lipton JW, Carvey PM, Stebbins GT, Goetz CG. Levodopa Stability in Solution: Time Course, Enviromental Effects, and Practical Recomendations for Cl,n,cal Use. Mov Disord 1996;11:24-6.
19. Bhatnagar P, Vyas D. Stability Indicating HPLC Method for Simultaneous Estimation of Entacapone, Levodopa and Carbidopa in Pharmaceutical Formulation. J Chromatogr Sep Tech 2015;6:7.
20. Ermer J, Miller JHM. Method validation in pharmaceutical analysis: A guide to best practice: John Wiley & Sons; 2006.
21. Mendez AS, Steppe M, Schapoval EE. Validation of HPLC and UV spectrophotometric methods for the determination of meropenem in pharmaceutical dosage form. J Pharm Biomed Anal 2003;3:947-54.
22. Ravani L, Sarpietro MG, Esposito E, Di Stefano A, Sozio P, Calcagno M, et al. Lipid nanocarriers containing a levodopa prodrug with potential antiparkinsonian activity. Mater Sci Eng C Mater Biol Appl 2015;48:294-300.
23. Mehta J, Patidar K, Patel P, Kshatri N, Vyas N. Development & validation of an in vitro dissolution method with HPLC analysis for misoprostol in formulated dosage form. Anal Methods 2010;2:72-5.

24. D'Souza SS, DeLuca PP. Methods to assess in vitro drug release from injectable polymeric particulate systems. Pharm Res 2006;23:460-74.
25. D'Souza SS, DeLuca PP. Development of a dialysis in vitro release method for biodegradable microspheres. AAPS PharmSciTech 2005;6:E323-E8.
26. Gonjari DI, Karmarkar AB, Hosmani AH. Evaluation of in vitro dissolution profile comparison methods of sustained release tramadol hydrochloride liquisolid compact formulations with marketed sustained release tablets. Digest Journal of Nanomaterials and Biostructures 2009;4(4):651-61. Epub 2009.
27. FDA. Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997.
28. Shazly G, Nawroth T, Langguth P. Comparison of Dialysis and Dispersion Methods for In Vitro Release Determination of Drugs from Multilamellar Liposomes. Dissolut Technol 2008.

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Spectrophotometric Determination of Erdosteine at Capsule Dosage Forms

Erdostein'in Kapsül Dozaj Formlarında Spektrofotometrik Olarak Analizi

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ABSTRACT

Objective: Two simple, rapid and sensitive methods were developed for determination of Erdosteine (ERD) in pure form as well as in their pharmaceutical formulations.

Methods: The methods were based on formation of colored charge transfer complexes with ERD with chloranil (CA) and 7,7,8,8-tetracyanoquinodimethane (TCNQ). The obtained charge-transfer complexes were measured at 454 and 843 nm for CA and TCNQ methods, respectively. Optimization of different experimental conditions were investigated.

Results: Beer's plots were obeyed in a general concentration range of 10-500 μg mL^{-1} and 20-600 μg mL^{-1} for CA and TCNQ methods, respectively. The validity of methods in terms of specificity, linearity, accuracy, precision, limit of detection and limit of quantitation were evaluated.

Conclusion: The methods were applied successfully in the determination of ERD in capsule dosage forms. Developed new spectrophotometric methods have been found to be very practical and practical. The lack of complex sample preparation increases the applicability of the method.

Keywords: Erdosteine, charge transfer complex, TCNQ, CA, spectrophotometry, validation, pharmaceutical formulation

ÖZ

Amaç: Erdostein'in (ERD) farmasötik formülasyonlarında tayini için iki basit, hızlı ve hassas yöntem geliştirilmiştir.

Yöntemler: Metotların esası, kloranil (CA) ve 7,7,8,8-tetrasiyanokinodimetan (TCNQ) ile ERD arasında renkli yük transfer komplekslerinin oluşturulmasına dayanmaktadır. Maksimum dalga boyları CA ve TCNQ yöntemleri için sırasıyla 454 ve 843 nm'de ölçülmüştür. Deney koşullarının optimizasyonu araştırılmıştır.

Bulgular: Beer kuralı, CA ve TCNQ metotları için sırasıyla 10-500 μg mL^{-1} ve 20-600 μg mL^{-1} konsantrasyon aralığında bulundu. Yöntemler özgünlük, doğrusallık, doğruluk, kesinlik, gözlenebilme sınırı, tayin sınırı gibi validasyon parametreleri açısından değerlendirildi.

Sonuç: Metodlar ayrıca ilaç içeren kapsüllerde ERD'nin tayininde de başarıyla uygulandı. Geliştirilen yeni spektrofotometrik metotların oldukça pratik ve uygulanabilir olduğu belirlenmiştir. Örnek hazırlama aşamasında karmaşık numune hazırlama işlemlerine gereksinim duyulmaması yöntemin uygulanabilirliğini artırmaktadır.

Anahtar Sözcükler: Erdostein, yük transfer kompleksi, TCNQ, CA, spektrofotometri, validasyon, farmasötik formülasyon

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Introduction

Erdosteine (ERD), a potent mucolytic agent, shows pharmacological activity by lowering the viscosity of mucus in the respiratory system and thus reducing the ability of the bacteria to adhere to the cellular membrane. ERD has anti-inflammatory properties in the bronchial airways and scavenges free radical compounds from the airways. Chemical structure of ERD consists of thiolactone and carboxyl group. Its chemical formula is 2- [2-oxo-2 - [(2-oxothiolan-3-yl) amino] ethyl] sulfanylacetic acid (Figure 1) (1-3).

Various analytical methods such as UV spectrophotometric method (4-8) and high performance liquid chromatography (9-14) have been found in the literature for the determination of ERD from pharmaceutical preparations and biological fluids. In this study, two spectrophotometric methods were proposed to determine the amount of ERD in pharmaceutical preparations using easily accessible materials and equipment. In the proposed methods, CA and tetracyanoquinodimethane (TCNQ) reagents were reacted with ERD to form charge transfer complexes (CT complexes). For quantitative analysis of pharmaceutical compounds in pharmaceutical dosage forms, the use of CA and TCNQ reagents to obtain CT complexes is preferred because they do not require a buffer, they are fast, precise and cost-effective (15-18). Therefore, in this study, we considered it appropriate to develop two methods for the analysis of ERD using these two markers, and these developed methods were successfully applied in the analysis of ERD in pharmaceutical formulations.

Method

Devices

Spectrophotometric measurements were performed using a Hitachi spectrometer Model U-2900 equipped with a xenon lamp and 1 cm quartz cells.

Reagents and Solutions

ERD was obtained from EnzyChem Lifesciences (Korea), TCNQ Fluka (Neu-Ulm, Germany) and CA Merck (Darmstadt, Germany). The pharmaceutical preparation (ERDOSTIN® 300 mg) was obtained from the pharmacy. All chemicals and reagents were used for analytical purity.

Stock Solutions

Stock solutions of ERD were prepared in methanol to make up 1 mg/mL. Solutions of 0.2% (w/v) for TCNQ and 0.2% (w/v) for CA were prepared in acetonitrile. The solutions were determined to be stable for 1 week at 4 °C.

General Analysis Method

ERD stock solution in volumes of 0.050-2.5 mL and 0.100-3.0 mL was added to 5 mL calibrated flasks for CA and TCNQ methods, respectively. The volume of the stock solutions in each flask was brought to 2.5 mL with acetonitrile for the CA method and 3.0 mL for the TCNQ method, and 0.75 mL CA and 1 mL TCNQ reagents were added to them. The reaction mixture was heated at 80 °C for 5 min for the TCNQ method and then stood at room temperature for 5 min for CA. After the cooling process, it was diluted to 5 mL with methanol and its absorbance was measured against the blank test at 454 and 843 nm for CA and TCNQ methods, respectively. Calibration charts were prepared by measuring the absorbance against the ERD concentration.

Analysis Method for Capsules

The amount equivalent to 300 mg ERD was weighed and dissolved in 125 mL of methanol. Then it was extracted in a mechanical mixer for 20 minutes and in an ultrasonic bath for 20 minutes. The volume was made up to 250 mL and then filtered through filter paper. The filtrate was diluted with methanol and studied as in the preparation of the calibration curve. The amount of substance in the capsule was measured using the calibration graph and the corresponding regression equation.

Results

The maximum absorption of the CT complexes obtained as a result of the reaction formed by ERD with CA and TCNQ reagents was observed at 454 and 843 nm, respectively (Figure 2).

Optimum conditions such as reaction time, temperature, type of solvent, amount of reagents used and reaction stoichiometry were also investigated for the reaction, which were explained in detail below.

Choosing the Most Suitable Solvent

Various solvents commonly used in analytical procedures including acetonitrile, chloroform, methanol, acetone, ethanol, 1,4-dioxane and methylene chloride were used to determine

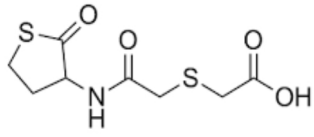

Figure 1. Chemical structure of Erdosteine

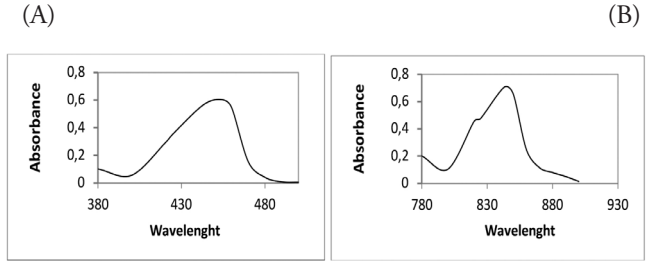

Figure 2. (A) Absorption spectrum of ERD-CA complex against blank solution (400 µg mL-1) (B) Absorption spectrum of ERD-TCNQ complex against blank solution (600 µg mL-1)

CA: Chloranil, TCNQ: Tetracyanoquinodimethane, ERD: Erdosteine

the most suitable solvent. It was observed that the most suitable solvent was obtained by using methanol.

Reagent Concentration

The optimum reagent concentration was investigated by changing the concentrations of TCNQ and CA reagents and keeping the ERD concentration constant. As shown in the figure, the optimum reagent amount was 0.75 mL CA [0.2% (w/v)] and 1.0 mL TCNQ [0.2% (w/v)] (Figure 3).

Reaction Time

The time required to complete the reaction between ERD and CA and TCNQ was studied spectrophotometrically at room temperature and 60-80 °C, respectively. A reproducible color development was achieved in 5 minutes for CA and TCNQ, respectively, at room temperature and 80 °C. The color reaction resulting from the CT complexes was observed stably for 12 hours (Figure 4).

Reaction Stoichiometry

Job's continuous change method was used for the reaction stoichiometry (19). According to the results, the equivalent molarity of ERD and reagents was defined as the 1:1 ratio (compound/reagent).

Method Validation

The proposed analytical methods were validated according to the ICH guideline Q2 (R1) (20). Calibration curves were generated for all methods under the above conditions. Regression equation, correlation coefficients, Beer's law limits, limit of observability (LOD) and determination limit (LOQ) data for each method are given in Table 1.

According to the results obtained, a linear correlation between 10-500 μg mL^{-1} and 20-600 μg mL^{-1} was observed for CA and TCNQ methods, respectively.

The formula of LOD/LOQ = κSDa/b was used to calculate LOD or LOQ. Here the value of is 3 for LOD and 10 for LOQ. SDa indicates the standard deviation of the scale curve intersept and b is the slope. The results are shown in Table 1.

Sensitivity values of intra-day and inter-day were examined at 50, 100 and 500 μg/mL for the TCNQ and CA method (n=5 for each) for 5 consecutive days. The % RSD values for the inter-day precision % and the inter-day precision results for all

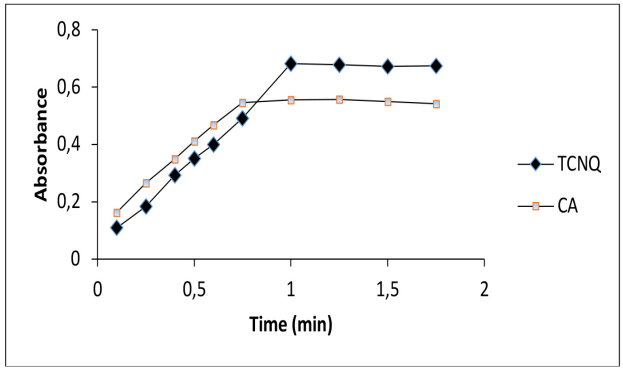

Figure 3. Effect of volumes of CA (0.2%, w/v) and TCNQ (0.2%, w/v) reagents on the formation of the reaction product of ERD with CA and TCNQ

CA: Chloranil, TCNQ: Tetracyanoquinodimethane, ERD: Erdosteine

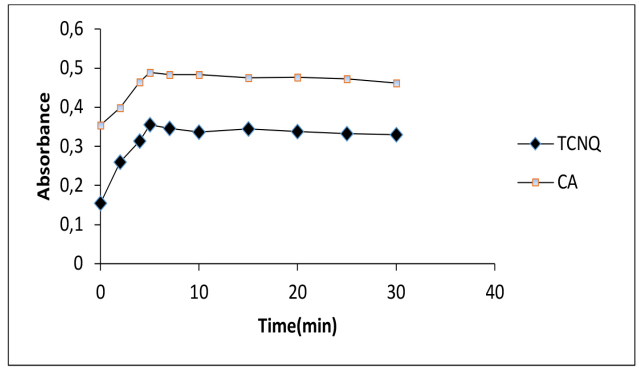

Figure 4. Effect of temperature and heating time on reaction of TCNQ (at 80 °C) and CA (at room temperature) reagents with ERD

CA: Chloranil, TCNQ: Tetracyanoquinodimethane, ERD: Erdosteine

Table 1. Validation parameters

	CA reagent	TCNQ reagent
Linear range[a] (μg mL^{-1})	10-500	20-600
Regression equation[b]		
Slope ± SD	0.0016±0.000008	0.0013±0.000015
Intersept ± SD	0.0711±0.00032	0.0612±0.00014
Correlation coefficient, r	0.9997	0.9995
LOD (μg mL^{-1})	0.00034	0.00074
LOQ (μg mL^{-1})	0.0011	0.0025
Precision		

[a]Average of 6 studies
A=mC+b [C: Concentration (μg mL^{-1}) and A: Absorption at λ_{max})
SD: Standard deviation, CA: Chloranil, TCNQ: Tetracyanoquinodimethane, LOD: Limit of obsercability detection, LOQ: Limit of quantification

proposed methods provided good reproducibility. Results are given in Table 2. The accuracy of the developed methods was examined using the standard addition technique. Pure analyte was mixed with standard solutions at 3 different concentration levels on the sample solution and analyzed. The results obtained are presented in Table 3. It was observed that the average recovery percentages calculated were 100.31% for CA and 100.82% for TCNQ, proving the method to be of high accuracy (Table 2). The methods developed were been successfully applied in the analysis of the drug substance in pharmaceutical preparations, and according to these results, no interference from additives and excipients was observed. The results are given in Table 4. Small changes were made to the method developed to test the robustness of the method and the effect of these changes on the method was examined. For this, changes in TCNQ and CA reagent concentrations (%, w/v ±0.05) and reaction times (optimum time ±0.5 min) were made, and when the results were examined in terms of recovery and RSD values, it was observed that there was no significant difference.

Table 2. Precision results

Precision results	Added concentration (μg mL^{-1})	Concentration found (μg mL^{-1}) (mean ± SD[c])	RSD (%)
intra-day			
CA reagent	50	50.01±0.28	0.56
	100	100.28±0.87	0.87
	500	501.64±1.43	1.43
TCNQ reagent	50	50.04±0.37	0.74
	100	99.97±0.92	0.92
	500	503.36±1.65	0.33
inter-day			
CA reagent	50	50.16±0.56	1.12
	100	101.97±1.34	1.31
	500	502.64±1.83	0.35
TCNQ reagent	50	50.29±0.47	0.93
	100	101.31±1.34	1.32
	500	503.37±2.2	0.44

SD: Standard deviation, CA: Chloranil, TCNQ: Tetracyanoquinodimethane, RSD: Relative standard deviation

Table 3. Recovery results

Method developed	Concentration taken[a] (μg mL^{-1})	Added concentration (μg mL^{-1})	Concentration found[b] (μg mL^{-1}) (mean ± SD[c])	Recovery (%)	RSD (%)
CA reagent	100	10	109.36±1.12	99.42	1.02
		200	301.28±2.74	100.43	0.91
		400	505.39±3.86	101.08	0.76
TCNQ reagent	100	20	120.68±1.24	100.57	1.03
		200	303.87±3.01	101.29	0.99
		500	603.54±4.27	100.59	0.71

[a]ERDOSTIN® 300 mg, [b]n=5, [c]Standard deviation, SD: Standard deviation, RSD: Relative standard deviation, TCNQ: Tetracyanoquinodimethane

Table 4. Analysis of capsules containing 300 mg erdosteine (n=5)

	When Using CA reagent (mean ± SD[c])	When Using TCNQ reagent (mean ± SD[c])
Mean ± SD	302.08±3.28	300.94±2.64
Recovery (%)	100.69	100.31
RSD (%)	1.09	0.88

[a]ERDOSTIN® 300 mg
[b]n=5
[c]Standard deviation, SD: Standard deviation, CA: Chloranil, TCNQ: Tetracyanoquinodimethane

Conclusion

As a result, the new spectrophotometric methods developed are very practical and applicable. Not requiring complicated sample preparation processes before hand increases the applicability of the method. The developed methods enable the analysis of ERD in pharmaceutical preparations with high accuracy and precision. This method can be used in routine analysis of the drug.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: C.Ö., Design: C.Ö., Data Collection or Processing: C.Ö., D.D., Analysis or Interpretation: C.Ö., D.D., Literature Search: D.D., Writing: C.Ö., D.D.

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References

1. Dechant KL, Noble S. Erdosteine. Drugs 1996;52:875-81.
2. Fumagalli G, Balzarotti C, Banfi P, Decò P, Ferrante L, Zennaro M. Erdosteine: A new molecule with mucolytic activity. Clinical and instrumental evaluation in patients with acute exacerbated chronic bronchopneumopathies. Italian J Chest Diseases 1988;42:299-308.
3. Marchioni CF, Moretti M, Muratri M, Casadei MC, Guerzoni P, Scuri R, et al. Effects of Erdosteine on Sputum Biochemical and Rheologic Properties- Pharmacokinetics in Chronic Obstructive Lung Disease. Lung 1990;168:285-93.
4. Nanda RK, Gaikwad J, Prakash A, Ghosh VK, Nagore DH. Estimation of Cefixime and Erdosteine in its Pharmaceutical Dosage Form by Spectrophotometric Method. Asian J Research Chem 2009;2:404-6.
5. Mistry N, Shah P, Chaudhari D, Baria B, Gandhi T. Simultaneous Estimation of Erdosteine, Guaiphenesin and Terbutaline Sulphate in Syrup Formulation by Two UV Spectrophotometric Methods. Indian Drugs 2017;54:46-51.
6. Moustafa NM, Badawey AM, Lamie NT, Abd El-Aleem AB. Stability-Indicating Methods for the Determination of Erdosteine in the Presence of its Acid Degradation Products. J AOAC Int 2014;97:86-93.
7. Nanda RK, Gaikwad J, Prakash A. Estimation of tamsulosin and tolterodine in its pharmaceutical dosage form by spectrophotometric method. Int J Pharm Tech Res 2009;1:420-3.
8. Dhoka MV, Gawande VT, Joshi PP, Gandhi SV, Patil NG. Simultaneous estimation of Cefixime and Erdosteine in capsule dosage form by spectrophotometric method. Hindustan Antibiot Bull 2009;51:29-32.
9. Muramatsu N, Toyo'oka T, Yamaguchi K, Kobayashi S. High-performance liquid chromatographic determination of erdosteine and its optical active metabolite utilizing a fluorescent chiral tagging reagent, R-(–)-4-(N,N-dimethylaminosulfonyl)-7-(3-aminopyrrolidin-1-yl)-2,1,3-benzoxadiazol. J Chromatogr B Biomedical Sciences and Applications 1998;719:177-89.
10. Madhura VD, Vandana TG, Pranav PJ. Simultaneous estimation of cefixime trihydrate and erdosteine in pharmaceutical dosage form by using reverse phase-high performance liquid chromatography. Int. J Chem Tech Res 2010;2:79-87.
11. Ayre AP, Pawar HA. Stability-Indicating RP-HPLC Method for Estimation of Erdosteine and its Degradation Products in Pharmaceutical Dosage Form. Journal of Pharmaceutical and Bioanalytical Science 2012;1:2-7.
12. Khan MG, Jain PS, Shirkhedkar AA, Fursule RA, Kale NK, Surana SJ. Stability indicating HPLC determination of Erdosteine in bulk drug and pharmaceutical dosage form. J Pharm Bio Science 2013;3:105-9.
13. Kim HY, Chang KY, Lee HJ, Han SB, Lee KR. Sensitive determination of erdosteine in human plasma by use of automated 96-well solid-phase extraction and LC-MS/MS. J Pharm Biomed Analysis 2004;34:661-9.
14. Liu D, Wang Y, Tang YB, Chen XY, Zhong DF. Quantification of erdosteine in the low-volume of dog plasma by liquid chromatography tandem mass spectrometry. Chemical Research in Chinese Universities 2007;23:736-41.
15. Foster R. Organic Charge-Transfer Complexes, Academic Press, New York, 1969.
16. Zhao FL, Xu BZ, Zhang ZQ, Tong SY. Study on the charge-transfer reaction between 7,7,8,8-tetracyanoquinodimethane and drugs. J Pharm Biomedical Analysis 1999;21:355-60.
17. Al-Majed AA. Spectrophotometric estimation of D-penicillamine in bulk and dosage forms using 2,6-dichloroquinone-4-chlorimide (DCQ). J Pharm Biomedical Analysis 1999;21:827-33.
18. Mulliken RS, Person WB. Molecular Complexes. Journal of Molecular Structure 1969;10:155.
19. Job P. Formation and Stability of Inorganic Complexes in Solution. Annales de Chimie 1928;9:113-203.
20. ICH, In: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Validation of Analytical Procedures: Text and Methodology Q2 (R1), 2005.

Original Article

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Cyclic Fatigue Resistance of Biorace Nickel-titanium File with Variable Taper after Immersion in Sodium Hypochloride

Sodyum Hipokloritin Farklı Taperlardaki Biorace Nikel Titanyum Eğesinin Döngüsel Yorgunluk Direncine Etkisinin Değerlendirilmesi

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ABSTRACT

Objective: This study aimed to evaluate the effect of sodium hypochlorite on the cyclic fatigue resistance of BioRace (BR) files according to taper.

Methods: BR 25.04 and 25.06 files were divided into the following groups: group 1, 20 BR 25.04 with no immersion in NaOCl; group 2, 20 BR 25.04 with immersion in 5.25% NaOCl at 37 °C ±1 °C for 5 min; group 3, 20 BR 25.06 with no immersion; and group 4, 20 BR 25.06 with immersion in 5.25% NaOCl at 37 °C ±1 °C for 5 min. The instruments were applied to a stainless-steel artificial root canal of 60° curvature and 5-mm radius. The time to failure (TTF) in seconds and number of cycles to failure (NCF) were recorded.

Results: The cyclic fatigue resistance of BR 25.04 was significantly higher than that of BR 25.06. The TTF and NCF values were significantly higher in group 1 than in groups 2 and 3 and in group 2 than in group 4. However, neither value differed significantly between groups 3 and 4 (p>0.05).

Conclusion: Taper and sodium hypochlorite affected the cyclic fatigue resistance of BR.

Keywords: BioRace, cyclic fatigue resistance, sodium hypochlorite, taper

ÖZ

Amaç: Bu çalışmanın amacı sodyum hipokloridin farklı taperlara sahip olan BioRace (BR) döner alet sisteminin döngüsel yorgunluğuna etkisini değerlendirmektir.

Yöntemler: BR 25,04 ve BR 25,06 enstrümanlarının döngüsel yorgunlukları, farklı koşullarda test edildi. Grup 1, BR 25,04 nolu eğe hiç bir solüsyonda bekletilmeden; grup 2: BR 25,04 %5,25 NaOCl solüsyonunda 37 °C ±1 °C'de 5 dakika bekletilerek; grup 3: BR 25,06 hiç bir solüsyonda bekletilmeden; grup 4: BR 25,06 %5,25 NaOCl solüsyonunda 37 °C ±1 °C'de 5 dakika bekletildikten sonra 60° kurvatür açılı and 5 mm kurvatür yarıçaplı paslanmaz çelik bloktan üretilmiş eğimli olukta test edildi. Her bir eğenin kırılana kadarki döngü sayısı (NCF) ve kırılana kadarki süresi (TTF) saniye cinsinden kaydedildi. Elde edilen veriler istatistiksel analizler ile değerlendirildi.

Bulgular: BR 25,04 eğesinin döngüsel yorgunluk direnci, BR 25,06'dan istatistiksel olarak daha yüksektir. TTF ve NCF değerleri grup 1 > grup 2 , grup 1 > grup 3 , grup 2 > grup 4 şeklinde bulundu. Buna karşılık, grup 3 ve grup 4 arasında istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: Bu çalışmanın sınırları doğrultusunda BR ensturmanlarının taperı ve sodyum hipokloritte bekletilmesi aletin döngüsel yorgunluğuna etki etmektedir.

Anahtar Sözcükler: BioRace, döngüsel yorgunluk direnci, sodyum hipoklorit, taper

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Introduction

File failure during root canal instrumentation is challenging (1). Fracture of nickel-titanium (Ni-Ti) files can be caused by torsional stress or cyclic fatigue. Cyclic fatigue can occur when a file is exposed to repeated compression and tension (2,3). To reduce the frequency of fracture, new instruments manufactured from advanced alloys have been developed.

BioRace instruments (BR; FKG, La Chaux-de-Fonds, Switzerland) are manufactured from conventional austenite Ni-Ti and include six rotary instruments with electropolished surfaces, safety tips, triangular cross-sections with alternating cutting edges (4,5), and tapers of 0.02 to 0.08 (6).

Several factors influence the cyclic fatigue resistance of endodontic instruments, such as the manufacturing process, rotation type, operational speed, metal surface treatment, and immersion in disinfection solution (2-4,7). NaOCl solution is used for irrigation during endodontic procedures, and Ni-Ti instruments come into contact with this solution during root canal instrumentation and disinfection (8,9), which corrodes the instruments and does affect their cyclic fatigue resistance (2,10-12). However, contradictory results have been reported, which are likely due to differences in conditions (9-12).

To our knowledge, no study has investigated the effect of taper and NaOCl on the cyclic fatigue resistance of a file. Thus, this study aimed to evaluate the effect of NaOCl and taper on the cyclic fatigue resistance of BR Ni-Ti instruments. The null hypotheses were as follows:

1. The cyclic fatigue resistance of the file is not affected by its taper.

2. The cyclic fatigue resistance of the file is not affected by immersion in NaOCl solution.

Method

In this study, we tested the cyclic fatigue resistance of 40 BR 3 (25.04) and 40 BR 4 (25.06) Ni-Ti files in an artificial curved canal after immersion in NaOCl. The instruments were inspected under a surgical microscope (M320, Leica Microsystems, Wetzlar, Germany) at 20x magnification for defects and deformities. None of the instruments was discarded.

The files were randomly divided into the following groups (n=20 each): group 1, BR 3 with no immersion; group 2, BR 3 with immersion in 5.25% NaOCl at 37 °C ±1 °C for 5 min; group 3, BR 4 with no immersion; and group 4, BR 4 with immersion in 5.25% NaOCl at 37 °C ±1 °C for 5 min. The working part of the instrument was statically immersed in NaOCl and rinsed in 10 mL of distilled water. Then, the 16-mm working part of the instrument (curvature 60°, radius 5 mm) was applied to the stainless-steel artificial root canal (width 1.5 mm, depth 3.0 mm). The center of the curvature was 5 mm from the tip of the instrument, and the curved segment of the canal was 5 mm long. To reduce friction, synthetic oil was applied to the canal. The instruments were rotated freely inside the canal using an X Smart endodontic motor at 600 rpm and 1 N/cm until fracture occurred (Figure 1). To mimic physiological conditions, continuous irrigation with distilled water at 37 °C was performed.

Statistical Analysis

The time to failure (TTF; in seconds) was recorded both visually and audibly. The number of cycles to failure (NCF) was calculated by multiplying the time(s) to failure by the number of rotations or cycles per second, regardless of the direction of rotation (13). Data were subjected to the Shapiro-Wilk test to verify the assumption of normality. One-way analysis of variance and Tukey's multiple-comparison test were performed using NCSS™ 2007 software (NCSS, Kaysville, UT) with a significance level of 0.05. TTF and NCF values were subjected to Weibull reliability analysis to calculate the probability of survival.

Results

The mean NCF and TTF values are shown in Tables 1 and 2. The mean TTF of the BR 25.04 groups (groups 1 and 2) was greater than that of the BR 25.06 groups (groups 3 and 4). The resistance to cyclic fatigue of the BR instrument with a 0.06 taper was not significantly affected by immersion in NaOCl. However, static immersion in NaOCl for 5 min significantly reduced the cyclic fatigue resistance of the instrument with a 0.04 taper. The TTF and NCF values were significantly higher in group 1 than in groups 2 and 3 and in group 2 than in group 4. However, neither value differed significantly between groups 3 and 4 ($p>0.05$).

Weibull reliability plots with probability of survival values are shown in Figure 1, and the Weibull modulus, R^2, and number of cycles to 99% survival are presented in Table 2. The predicted TTFs for groups 1, 2, 3, and 4 were 43.24, 34.36, 25.38, and 26.62 s, respectively. The predicted number of cycles to 99% survival in groups 1, 2, 3, and 4 was 206.83, 186.68, 127.81, and 110.28, respectively.

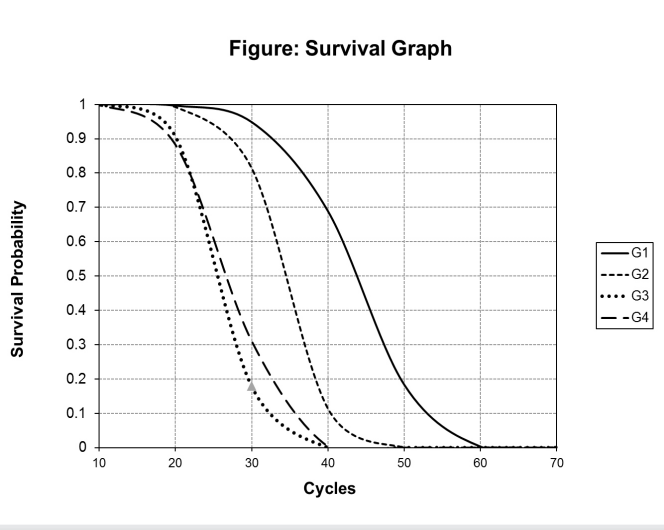

Figure 1. Probability of Survival Values of Groups (NCF, number of cycles to failure)
NCF: Number of cycles to failure

Discussion

We evaluated the effect of NaOCl on the cyclic fatigue resistance of a BR Ni-Ti instrument with different tapers. The null hypotheses that taper (BR) and immersion in NaOCl would not affect the cyclic fatigue resistance were rejected.

The cyclic fatigue resistance of a file decreases with increasing metal volume (14). In this study, files of one tip size but different tapers were tested to exclude the influence of other variables such as alloy type, cross section, and kinematics (7,15). Compared with BR 4 (0.06 taper), BR 3 (0.04 taper) had better cyclic fatigue resistance and NCF value regardless of immersion in NaOCl. This is in agreement with prior reports (16,17).

There is no universally accepted method for testing the cyclic fatigue resistance of endodontic instruments. Although the use of human teeth would be representative, it is impossible to standardize the tooth morphology (18). For this reason, artificial root canals are used to test cyclic fatigue resistance. Given the difficulty of shaping curved canals in the endodontic clinic, previous *in vitro* studies used 45°, 60°, 75°, and 90° curved canals of 5-mm radius (2,13,18). In this study, based on Pruett's method, a stainless-steel artificial root canal of 60° curvature and 5-mm radius was selected (19).

Endodontic instruments come into contact with NaOCl during root canal instrumentation and disinfection (12). Past studies of the effect of corrosion by NaOCl on the cyclic fatigue resistance of Ni-Ti instruments have yielded contradictory results (2,10). This could be caused by differences in the immersion time (1 min to 48 h), immersion type (static or dynamic), test protocol, instrument, heating (21 °C-60 °C), and concentration (9-12). Berutti et al. (10) evaluated the effect of hot NaOCl on a Protaper instrument using a 5-min contact time, and corrosion reduced its cyclic fatigue resistance. Saber et al. (18) investigated the effect of instrument material, taper, and degree of root canal curvature on the cyclic fatigue of the ProFile GT and Profile GT Series X. Instrument taper affected the cyclic fatigue resistance of both instruments. Topçuoğlu et al. (20) reported that immersion in 5% NaOCl for 5 min significantly decreased the cyclic fatigue resistance of several retreatment files with large metal volume. Elnaghy and Elsaka reported that the cyclic fatigue resistance of WaveOne Gold and Reciproc was considerably decreased by immersion in saline and NaOCl at 37 °C (2). However, Pedulla et al. (12) found that static or dynamic immersion in NaOCl for 1 or 5 min did not reduce the cyclic fatigue resistance of Ni-Ti instruments. Herein, we focused on the effects of taper and immersion time using a protocol based on that of Pedulla et al. (12). The 16-mm working part of the instrument was immersed in NaOCl at 37 °C ±1 °C to simulate *in vivo* conditions. In this way, galvanic corrosion phenomena caused by differences in the shape of the shaft and the working part of the instrument were eliminated (10). We used 5-min contact with NaOCl to simulate clinical practice (12).

Weibull analysis enables evaluation of the probability of instrument survival and prediction of the time and number of cycles to 99% survival. Higher Weibull modulus values indicate better reliability (21). BR 4 with immersion in NaOCl (group 4) had the lowest Weibull modulus and the fewest cycles (11.03) and shortest time (110.28 s) to 99% survival. BR 3 (no immersion) had the largest number of cycles to 99% survival (20.68) (Table 2).

Table 1. Comparison of time to fracture of groups with mean ± standard deviation (statistical level at p≤0.05)

	No immersion	Immersion in NaOCl	p value
	Mean ± SD	**Mean ± SD**	
25.04 BioRace (BR3)	Group 1: 43.24 (7.37)	Group 2: 34.35 (4.73)	0.001
25.06 BioRace (BR4)	Group 3: 25.88 (4.02)	Group 4: 26.62 (5.28)	0.668
p value	0.000	0.000	

SD: Standard deviation

Table 2. Sample size, NCF, Time to Fracture, Weibull Calculations Weibull calculations included Weibull modulus, coefficient of determination (R^2), and predicted cycles for %99 survival and time

	TTF (sec) Mean ± SD	NCF Mean ± SD	Weibull modulus	R2	Predicted cycles for % 99 survival	Predicted time (sec) for % 99 survival
G1	43.24	432.40	6.24	0.92	20.68	206.83
G2	34.36	343.60	7.54	0.90	18.67	186.68
G3	25.88	258.80	6.52	0.84	12.78	127.81
G4	26.62	266.20	5.22	0.94	11.03	110.28

SD: Standard deviation, NCF: Number of cycles to failure

Conclusion

Taper and NaOCl affected the cyclic fatigue resistance of BR files. As the taper of the BR file increased, the cyclic fatigue resistance decreased. In contrast, immersion in NaOCl decreased the cyclic fatigue resistance of BR instruments with a 0.04 taper but had no effect on those with a 0.06 taper.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: For this type of study, formal consent is not required.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A.Ö., Concept: B.A.Ö., A.A.A., Design: B.A.Ö., A.A.A., Data Collection or Processing: A.A.A., Analysis or Interpretation: B.A.Ö., A.A.A., Literature Search: B.A.Ö., A.A.A., Writing: B.A.Ö.

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References

1. Cheung GSP. Instrument fracture: mechanisms, removal of fragments and clinical outcomes. Endod Topics 2007;16:1-26.
2. Elnaghy AM, Elsaka SE. Effect of sodium hypochlorite and saline on cyclic fatigue resistance of WaveOne Gold and Reciproc reciprocating instruments. Int Endod J 2017;50:991-8.
3. Ertuğrul IF, Orhan EO. Cyclic fatigue and energy dispersive X-ray spectroscopy examination of the novel ROTATE instrument. Microsc Res Tech 2019;1-7.
4. Lopes HP, Elias CN, Vieira VT, Moreira EJ, Marques RV, de Oliveira JC, et al. Effects of electropolishing surface treatment on the cyclic fatigue resistance of BioRace nickel-titanium rotary instruments. J Endod 2010;36:1653-7.
5. Freire LG, Gavini G, Branco-Barletta F, Sanches-Cunha R, dos Santos M. Microscopic computerized tomographic evaluation of root canal transportation prepared with twisted or ground nickel-titanium rotary instruments. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011:112;143-8.
6. FKG. BioRace brochure. Available at: https://www.fkg.ch/sites/default/files/fkg_br_brochure_an_lowr.pdf. Accessed at 20.11.2019.
7. Gambarini G, Grande NM, Plotino G, Somma F, Garala M, De Luca M, et al. Fatigue resistance of engine-driven rotary nickel- titanium instruments produced by new manufacturing methods. J Endod 2008:34;1003-5.
8. O'Hoy PY, Messer HH, Palamara JE. The effect of cleaning procedures on fracture properties and corrosion of NiTi files. Int Endod J 2003;36:724-32.
9. Darabara M, Bourithis L, Zinelis S, Papadimitriou GD. Susceptibility to localized corrosion of stainless steel and NiTi endodontic instruments in irrigating solutions. Int Endod J 2004;37:705-10.
10. Berutti E, Angelini E, Rigolone M, Migliaretti G, Pasqualini D. Influence of sodium hypochlorite on fracture properties and corrosion of ProTaper Rotary instruments. Int Endod J 2006;39:693-9.
11. Haikel Y, Serfaty R, Wilson P, Speisser JM, Allemann C. Mechanical properties of nickeltitanium endodontic instruments and the effect of sodium hypochlorite treat- ment. J Endod 1998;24:731-5.
12. Pedulla E, Grande N, Plotino G, Pappalardo A, Rapisarda E. Cyclic Fatigue Resistance of Three Different Nickel-Titanium Instruments after Immersion in Sodium Hypochlorite. J Endod 2011;37:1139-42.
13. Kim HC, Kwak SW, Shun-Pan Cheung G, Ko DH, Chung S, Lee W. Cyclic Fatigue and Torsional Resistance of Two New Nickel-Titanium Instruments Used in Reciprocation Motion: Reciproc Versus WaveOne. J Endod 2012;38:541-4.
14. Sattapan B, Nervo GJ, Palamara JE, Messer HH. Defects in rotary nickel-titanium files after clinical use. J Endod 2000;26:161-5.
15. Karataş E, Arslan H, Büker M, Seçkin F, Çapar ID. Effect of movement kinematics on the cyclic fatigue resistance of nickel-titanium instruments. Int Endod J 2016;49:361-4.
16. Schrader C, Peters OA. Analysis of torque and force with differently tapered rotary endodontic instruments in vitro. J Endod 2005;31:120-3.
17. Barbosa F, gomes J, De araújo M. Influence of previous angular deformation on flexural fatigue resistance of K3 nickel- titanium rotary instruments. J Endod 2007;33:1477-80.
18. Saber SMS, Seeda MMA, Hassanien E. The effect of instrument material, taper and degree of root canal curvature on cyclic fatigue of rotary nickel-titanium instruments. ENDO (Lond Engl) 2013;7:59-64
19. Pruett JP, Clement DJ, Carnes DL. Cyclic fatigue testing of nickel titanium instruments. J Endod 1997;23:77-85.
20. Topçuoğlu HS, Pala K, Aktı A, Düzgün S, Topçuoğlu G. Cyclic fatigue resistance of D-RaCe, ProTaper, and Mtwo nickel–titanium retreatment instruments after immersion in sodium hypochlorite. Clin Oral Invest 2016;20:1175-9.
21. Nguyen HH, Fong H, Paranjpe A, Flake NM, Johnson JD, Peters OA. Evaluation of the resistance to cyclic fatigue between ProTaper Next, ProTaper Universal, and Vortex Blue rotary instruments. J Endod 2014;40:1190-3.

Original Article

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Pancreatic Tumors in Children

Çocuklarda Pankreas Tümörleri

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ABSTRACT

Objective: Pancreatic tumors in children are exceedingly rare and hence present diagnostic and therapeutic challenges to pediatric surgeons. In this study, we aimed to present our experiences and treatment outcomes related to these rare tumors.

Methods: The clinical data, laboratory investigations, radiological imaging, and the pathology and surgical details of patients with pancreatic tumors who were diagnosed between 2005 and 2019 were retrospectively reviewed.

Results: A total of 9 patients (5 men) were included in the study. The most common symptom at the time of presentation was vague abdominal pain. A pancreatic tumor was detected incidentally in 4 patients. All tumors were non-functional primary tumors. Histopathological diagnosis of these tumors were solid-pseudopapillary tumors (n=3), congenital pancreatic cysts (n=3), pancreatoblastoma (n=1), rhabdomyosarcoma (n=1), and an undifferentiated carcinoma (n=1). In addition, 8 patients were treated surgically (through tumor excision, central pancreatectomy + distal pancreaticojejunostomy, distal pancreatectomy, and cystogastrostomy). Two deaths from tumor dissemination were recorded. The patients were followed-up at a mean duration of 72 months (range: 6-120 months).

Conclusion: Pediatric pancreatic tumors are rare and are usually benign in nature. They present symptoms that are often nonspecific. In non-metastatic cases, surgical tumor removal is the preferred method for the treatment. For most tumors, surgical resection is

ÖZ

Amaç: Çocuklarda son derece nadir görülen pankreas tümörlerinin tanı ve tedavisi pediatrik cerrahlar için halen zorluklar barındırmaktadır. Bu çalışmamızda pankreas tümörleri ile ilgili deneyimlerimizi ve tedavi sonuçlarımızı sunmayı amaçladık.

Yöntemler: 2005 ve 2019 yılları arasında, pankreas tümörü tanısı konulan, 0-18 yaş arası çocukların dosyaları geriye dönük olarak incelendi. Klinik, laboratuvar, radyolojik görüntüleme tetkikleri, patoloji ve ameliyat verileri elde edildi.

Bulgular: Çalışmamızda 5'i erkek toplam 9 hasta değerlendirildi. Hastaların en sık başvuru şikayeti karın ağrısıydı. Dört hastada ise pankreas tümörü tesadüfen tespit edildi. Tespit ettiğimiz tüm tümörler pankreasın fonksiyonel olmayan primer tümörleriydi. Tümörlerin histopatolojik tanıları ise solid-psödopapiller tümör (n=3), konjenital pankreas kisti (n=3), pankreatoblastoma (n=1), rabdomiyosarkom (n=1) ve undifferansiye karsinom (n=1) idi. Tümör eksizyonu (enükleasyon) (n=5), santral pankreatektomi + distal pankreaticojejunostomi (n=1), distal pankreatektomi (n=1), ve kistogastrostomi (n=1) gibi yöntemler ile sekiz hasta cerrahi olarak tedavi edildi. Tümörün yaygınlığından iki hasta kaybedildi. Hastalar ortalama 8 yıl (6 ay-10 yıl) takip edildi.

Sonuç: Nadir görülen çocukluk çağı pankreas tümörleri, genellikle iyi huyludurlar. Başvuru nedeni sıklıkla hastalığa özgül olmayan semptomlardır. Metastatik olmayan olgularda, tümörün çıkarılması hastaların tedavisinde öncelikli olarak tercih edilmesi gereken yöntemdir. Tümörler çoğunlukla pankreasın gövde veya kuyruk

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the optimal treatment that may be successfully performed with low morbidity rate when the lesion is either in the body or in the tail of the pancreas. The long-term outcomes with this approach are generally good.

Keywords: Pancreatic, pediatric, neoplasm, cancer, surgery

kısmında yerleştiğinden cerrahileri yüz güldürücüdür ve düşük morbidite ile sonuçlanır. Tam olarak tümörün çıkarılabildiği olgularda uzun vadeli sonuçlar genellikle iyidir.

Anahtar Sözcükler: Pankreas, pediatrik, neoplazm, kanser, cerrahi

Introduction

Pancreatic tumors are extremely rare in children and young adults. Although solid-pseudopapillary tumors (SPT) are more common in adolescence, pancreatoblastoma (PBs) remain the most commonly encountered tumors in the first decade of life (1,2). Other less common tumors, such as neuroblastoma, neuroendocrine tumors, acinar cell carcinoma, rhabdomyosarcoma (RMS), lymphoma, and hemangioendothelioma have also been reported (1,3). The incidence of pediatric pancreatic tumors, irrespective of their histology, has increased over the past 3 decades, with the advancements in the imaging methodologies. However, no significant changes have been reported in therapeutic approaches during this time period (1,4). Surgery remains the cornerstone of any curative approach, with the exception of lymphoma, although the associated morbidity rates are 30%-40% (5). Pancreatic tumors in children continue to be challenging for pediatric surgeons, often due to insufficient experience in the management of such patients (6). The aim of the present study was to review our institutional experiences of pancreatic tumors in children, with a particular focus on tumor presentation, diagnosis, treatment, and outcomes.

Method

Our local ethics committee approved this study (project no: KA19/377). All patients and their families were fully informed about the study and they consented to their participation. This retrospective study included 9 patients with pancreatic tumors identified from the histopathology reports at the Department of Pediatric Surgery, Başkent University and the Faculty of Medicine between 2005 and 2019. The clinical features, diagnostic methods, and the treatment and results were accordingly recorded.

Results

Nine patients (4 girls, 5 boys) of median age at the time of surgery of 11 years (age range: 1-17 years) were identified from the medical charts and notes. The patient data (i.e., age, sex, presenting symptoms, tumor location, tumor nature and number, tumor size (cm), tumor type, treatment/in the order of time, and outcomes) are summarized in Table 1.

A 15-year-old male patient (case #1) was investigated in the external center for abdominal pain. His magnetic resonance imaging (MRI) revealed a heterogeneous mass of approximately 14.3x10.2 cm in diameter at the lateral segment of the left lobe of the liver. A needle biopsy was performed, and the subsequent pathology revealed a hepatoblastoma. The patient was referred to the pediatric oncology department of our hospital for further treatment. Patient α-fetoprotein (AFP) levels at the time of diagnosis were found to be elevated: 12125 >8.00 ng/mL. The patient received chemotherapy, with a preliminary diagnosis of hepatoblastoma. The patient was examined 4 months later because of a significant non-reduction in the tumor mass size (11.0x8.5 cm) despite chemotherapy and the persistence of AFP levels (17358 >8.00 ng/mL). A "left hepatectomy" was accordingly decided. During surgery, a mass originating in the pancreas, with no connection to the liver, was detected and then completely excised with enucleating. The pathology report declared an undifferentiated carcinoma. Although postoperative radiotherapy was provided, the patient died due to progressive metabolic disease after 18 months.

A 6-year-old boy (case #2) was admitted to our clinic for vague abdominal pain. A solid mass measuring 11 cm in diameter was detected at the head of the pancreas. A needle biopsy reported a pancreaticoblastoma. The patient received chemotherapy and subsequently underwent surgery to remove the residual mass measuring 1.5 cm by total tumor excision. This case was classified as an uneventful recovery.

Only 1 case of RMS was registered (case #3) that originated from the pancreas. The patient had distant metastasis in the bone marrow, skin, and prostate at the time of diagnosis, as assessed by needle biopsy. Although several treatment methods were performed by the pediatric oncology department, including chemotherapy, radiotherapy, and even autologous bone marrow transplantation, the patient died 18 months after the treatment initiation.

Of the 3 patients with solid SPTs, 1 (case #6) presented with abdominal pain, while 2 other SPTs (case #4 and case #5) were detected incidentally. Two of these 3 patients underwent needle biopsy for diagnosis. The SPT diagnosis in the other case was assessed, based on the appearance of the mass, using ultrasound (US) and computed tomography (CT), and completed with MRI for all cases. During US, hypoechoic, cystic, or cystic-solid masses with clear margins were noted. CT images revealed a cystic mass at the pancreatic neck, enhancing peripherally after contrast administration. MRI revealed hemorrhagic content in the cystic portion and diffusion restriction of the enhancing thick wall of the mass (Figure 1). None of the patients showed either suspicious regional nodes or distant metastases. In addition, cases #4, 5, and 6 underwent mid-pancreatectomy distal pancreaticojejunostomy, tumor excision, and distal pancreatectomy, respectively (Figure 2).

Table 1. Presentation, location, and treatment of pancreatic tumors

Case	Age	Sex	Presenting symptoms	Tumor location	Tumor nature/ number	Tumor size (cm)	Tumor type	Treatment/chronological order	Outcome
1	15	Male	Abdominal pain	Body	Solid-cystic/one	15	Undifferential carcinoma	Chemotherapy, surgery/tumor excision (enucleation), radiotherapy	Deceased
2	6	Male	Abdominal pain	Pancreas head	Solid/one	11	Pancreaticoblastoma	Chemotherapy, radiotherapy, surgery/ residual tumor excision (enucleation)	Uneventful recovery
3	17	Male	Lumbago	Pancreas head	Solid/one	4,5	Rhabdomyosarcoma	Chemotherapy, radiotherapy, otology bone marrow transfusion	Deceased
4	11	Female	Incidental/ cough	Body	Solid-cystic/one	4.5	Solid-pseudopapillary tumor	Surgery/central-pancreatectromy + distal pancreaticojejenostomy	Uneventful recovery
5	15	Female	Incidental/ urinary infection	Pancreas head	Solid/one	5.5	Solid-pseudopapillary tumor	Surgery/tumor excision (enucleation)	Uneventful recovery
6	13	Female	Abdominal pain	Pancreas tail	Solid-cystic/one	11	Solid-pseudopapillary tumor	Surgery/distal pancreatectomy	Uneventful recovery
7	11	Male	Incidental/ undescended testis	Pancreas head	Cystic/one	6.5	True congenital cysts	Surgery/csytogastrostomy	Uneventful recovery
8	1	Male	Incidental/ cough	Pancreas tail	Cystic/multiple	3	True congenital cysts	Surgery/tumor excision (enucleation)	Uneventful recovery
9	4	Female	Abdominal pain	Pancreas tail	Cystic/one	6.5	True congenital cysts	Surgery/tumor excision (enucleation)	Uneventful recovery

Congenital pancreatic cysts were detected in 3 patients (case #7, 8, and 9). Multiple cysts were detected in a 3-year-old girl (case #9), with all cysts completely removed. In case #7, the cysts were treated by a internally drainage method through cystogastrostomy, as the cyst was located at the head of the pancreas.

Discussion

Pediatric pancreatic tumors are much rarer than adult ones and are generally benign (albeit some have malignant potential) as well as have a different histopathological basis (2,3). In our study, benign (n=6) and malignant tumors (n=3) were encountered. The most common tumor of the pancreas is solid SPT, which accounts for 2%-3% of all pancreatic tumors (7). The male to female ratio is 1:9.5, and, in approximately 15% of the patients, it has a low-grade malignant potential with properties of invasion or metastasis (8). Most cases are located in the tail of the pancreas (9). However, in this study, 2 cases were reported in the body. This tumor frequently presents with nonspecific symptoms, including abdominal pain due to slow tumor growth, which is not unusual for these tumors to be detected incidentally by US (4). In our study, one patient was diagnosed while being investigated for abdominal pain and the remaining were diagnosed incidentally for unrelated reasons. In all patients, pancreatic and liver enzymes, as well as tumor markers were within normal limits, as reported previously in the literature (4). It has been reported that a mass with sharp margins, large, hypoechoic or echogenic, solid-cystic or pure solids, including internal septation or calcification is observed during US, whereas CT usually presents a well-encapsulated mass, with varying degrees of contrast (8). Percutaneous fine-needle aspiration was also reported in the diagnoses with 72% accuracy (8). Metastasis was not observed in any of our patients; however, in the literature, the liver, lymph node, and peritoneal metastasis have been reported. However, the presence of these metastasis does not affect survival (8). Despite complete tumor regression reported without requiring surgical intervention (10), surgical removal is the preferred treatment approach that is possible in most cases, even for large tumors (8). In 1 of our patients (case #4), a central pancreatectomy and

distal pancreaticojejunostomy was performed because the tumor was located at the neck of the pancreas. Although disseminated disease is not a negative indicator for survival, all patients required continued follow-up for surveillance for late metastasis or local recurrence (8).

True congenital pancreatic cysts are extremely rare in children and difficult to distinguish from other pancreatic cysts, such as retention, duplication, pseudocyst, neoplastic, and parasitic cysts. It is also difficult to distinguish them pathologically from retention and duplication cysts (11). Although these cysts are mostly reported as unilocular and located in the body/tail of the pancreas (12), we detected multiple cysts in 1 patient, and cysts located at the head of the pancreas in another patient. A past study has reported that cysts usually present with symptoms such as abdominal distension, vomiting, jaundice, or pancreatitis in patients aged <2 years of age (12). However, the diagnosis was made incidentally in a patient aged <2 years of age. When a cystic tumor of the pancreas is recognized, the laboratory data, clinical features, and modern imaging techniques are insufficient to distinguish them from other cystic lesions (11). Therefore, every effort should be made to exclude a history of acute pancreatitis, because pancreatic pseudocysts remain the single-most common cystic pancreatic mass (13). No trauma histories were noted in our patients. Pathologically, the cysts in all 3 patients (case #7, 8, and 9) were covered with cuboidal epithelium, and 1 patient (case #9) showed pancreatic tissues on the cyst wall. The literature reports that these cysts may also have had high amylase levels, as in the present patient (11). It has also been reported that surgical excision, cyst marsupialization with drainage, and aspiration were used in the treatment of these congenital cysts. However, despite aspiration having been used previously, it is not recommended presently (14). The cyst was treated through the internal drainage method in a patient through cystogastrostomy because the cyst was located at the head of the pancreas.

PBs comprises only 0.5% of pancreatic non-endocrine tumors and share similar histological and morphological features with hepatoblastomas that secrete AFP (6,15). Although reported with high prevalence in past studies (6), in the present study, only one case of this type of malignancy was recorded in a child presenting with a large abdominal mass (case #2). PBs affects a similar age group with hepatoblastoma. The tumor usually results in a satisfactory clinical response when using the same chemotherapeutic agents as for hepatoblastoma. PB is less aggressive in children when compared with that in adults; therefore, surgery is the optimal treatment and complete resection of the tumor provides the best prognosis (6). Moreover, adjuvant chemotherapy is not recommended when the tumor can be completely excised (15). However, we performed a true-cut biopsy in case #2 with a large mass located in the head of the pancreas and treated him with chemotherapy and radiotherapy. Approximately 24 months since the treatment initiation, the remaining 1.5-cm residual mass was totally removed with enucleation. The AFP levels may serve as a valuable tumor marker for preoperative diagnoses, and it can even indicate therapeutic effects and postoperative recurrences in PB patients (15). AFP

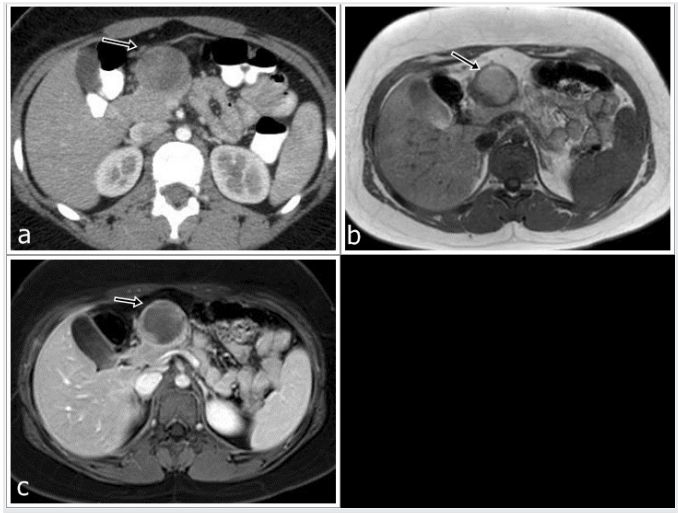

Figure 1. CT images detected a cystic mass at the pancreatic neck that enhanced peripherally after contrast administration. MRI showing the hemorrhagic content in the cystic part and the diffusion restriction of the enhancing thick wall of the mass. a) CT image showing the cystic mass at the pancreatic neck, with peripheral irregular enhancement after contrast administration. b) Axial T1-weighted MRI showing hyper-intense hemorrhagic content of the mass. c) Axial T2-weighted image showing the cystic portion and the peripheral enhancing thick wall of the mass

CT: Computed tomograpy, MRI: Magnetic resonance imaging

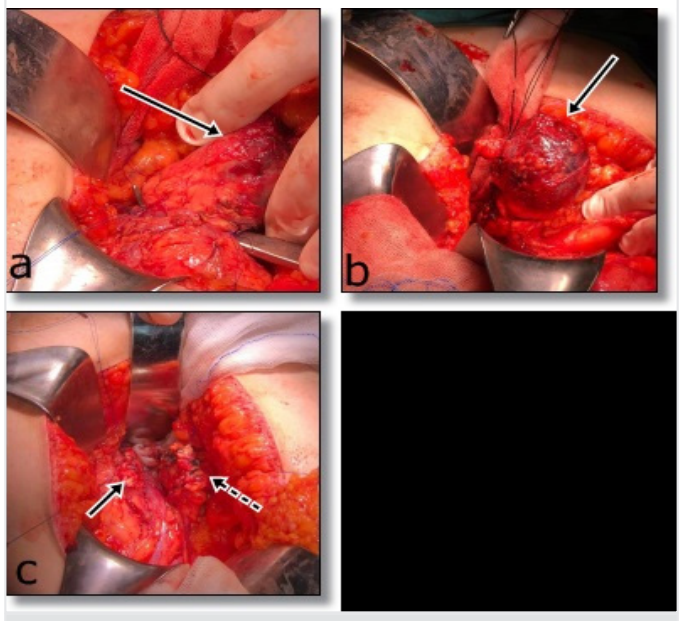

Figure 2. Surgery pictures: a) The presence of a mass located in the neck of the pancreas during the operation and the moment of suspension of the pancreas. The arrow indicates the tumor. b) The moment when the mass was to be separated from the head of the pancreas with limited pancreatic tissue remaining. The arrow indicates the tumor. c) Image of the proximal (normal arrow) and distal (dashed arrow) pancreas tissues after removal of the mass through central pancreatectomy

has been used as a marker in the follow-up period after residual mass excision and found to be normal.

RMS is a primary malignancy that arises from the embryonic mesenchyme, with the potential to differentiate into skeletal muscles (16). RMS constitutes approximately 50% of all soft tissue sarcomas in children. RMS of the biliary tree is extremely rare (approximately 0.5%) and encountered mostly in infants and children (17), as has been described in 4 patients in relation to the gallbladder (18). In our study, RMS in the pancreas was observed via true-cut biopsy in case #3 with disseminated disease (i.e., distant metastasis in the bone marrow, skin, and prostate regions). Despite providing intense treatments, including chemotherapy, radiotherapy, and a bone marrow transfusion, the patient died within 18 months of initiating the treatment.

Although endocrine tumors were not observed in this study, glucagon-, gastrin-, and somatostatin-secreting pancreatic tumors have all been reported in the pediatric age groups (19). Pancreatic endocrine tumors are mainly solitary and 90% benign, which often occurs in children aged >4 years (19). Specific hormones, over-secreted by the tumor, such as insulin, glucagon, gastrin, or somatostatin, determine the clinical features of these tumors. In addition, although the involvement of pancreatic Burkitt lymphomas (not observed in our study) is <1%, it should be distinguished from pancreatic adenocarcinoma because chemotherapy is typically more effective for pancreatic lymphoma than pancreatic adenocarcinoma (20).

In this study, we employed the use of abdominal US, followed by CT, as the initial imaging method. Enhanced CT is an extremely useful diagnostic technique. In CT images, the cystic portion of the tumors demonstrated no enhancement, but the solid portions showed a slight enhancement in the arterial phase and marked enhancement in the portal venous phase (21). When compared with MRI, CT has inherent limitations in detecting certain tissue characteristics, such as hemorrhage, cystic degeneration, or integrity of the tumor capsule, which are the factors that typically suggest pancreatic tumors (21). Because of its superior contrast resolution, MRI scans better display capsule and intratumoural hemorrhages when compared with CT scans. In cases of obstructive jaundice, endoscopic retrograde cholangiopancreatography with stent placement can be used to relieve biliary tract obstructions (21). In some special cases, an upper gastrointestinal contrast study may be used for the differentiation of duodenal duplication cysts from pancreatic head-located masses (22).

It has been reported that cystic pancreatic masses of <3 cm without any solid component, which can be followed-up safely through imaging (13). The majority of children with pancreatic tumors present with isolated lesions and are good surgical candidates. Primary surgical excision, without requiring a definitive preoperative tissue diagnosis, is also recommended (22). Masses located in the head of the pancreas must be treated by pancreaticoduodenectomy, with preservation of the pylorus or the Whipple procedure, to achieve macroscopic resection while avoiding complications and sparing the endocrine pancreas. Central tumors can be treated by central-pancreatic resection, although this surgery is complicated in terms of pancreatic and biliary fistulas. Tumors located in the tail of the pancreas can be easily removed through caudal pancreatectomy (7). A laparoscopic approach for pediatric pancreatic tumors has been reported previously (6), but it could not be performed in our study. For children who present with less typical lesions, tissue biopsy (percutaneous or laparoscopic) may be necessary to guide the treatment approach.

Conclusion

Pancreatic tumors are rare in children. Although these tumors may have malignant potential, they are usually benign. In the absence of a biologically active endocrine tumor, pancreatic tumors are typically diagnosed with nonspecific symptoms or diagnosed incidentally. In isolated pancreatic tumors with a trunk or tail tumor localization, primary resection appears to be the most appropriate treatment choice, which resulted in encouraging the prognoses for patients.

Ethics

Ethics Committee Approval: Our local ethics committee approved this study (project no: KA19/377).

Informed Consent: All patients and their families were fully informed about the study and they consented to their participation.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Ö.G., A.T., S.E., E.İ., N.Y., Ş.D., B.H., P.O., Concept: H.Ö.G., Design: H.Ö.G., E.İ., Data Collection or Processing: H.Ö.G., A.T., S.E., E.İ., N.Y., Ş.D., B.H., P.O., Analysis or Interpretation: H.Ö.G., A.T., S.E., Literature Search: H.Ö.G., A.T., S.E., E.İ., N.Y., Ş.D., B.H., P.O., Writing: H.Ö.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Scandavini C, Valente R, Rangelova E, Segersvärd R, Arnelo U, Permert J, et al. Pancreatectomies for pancreatic neoplasms in paediatric and adolescent age: A single institution experience. Pancreatology 2018;18:204-7.
2. Office for National Statistics (2011) Cancer Statistics Registrations, England (Series MB1), No. 42. http://www.ons.gov.uk/ons/rel/vsob1/cancer-statistics-registrations–england–series-mb1-/no–42–2011/sty-pancreatic-cancer.html. Accessed 20 Mar 2015.
3. Yu DC, Kozakewich HP, Perez-Atayde AR, Shamberger RC, Weldon CB. Childhood pancreatic tumours: A single institution experience. J Pediatr Surg 2009:44:2267-72.

4. Rebhandl W, Felberbauer FX, Puig S, Paya K, Hochschorner S, Barlan M, et al. Solid-pseudopapillary tumour of the pancreas (Frantz tumour) in children: report of four cases and review of the literature. J Surg Oncol 2001;76:289-96.
5. Hachiyaa M, Hachiyaa Y, Mitsuia K, Tsukimoto I, Watanabe K, Fujisawa T. Solid, cystic and vanishing tumours of the pancreas. J Clin Imag 2003;27:106-8.
6. Nasher O, Hall NJ, Sebire NJ, de Coppi P, Pierro A. Pancreatic tumours in children: diagnosis, treatment and outcome. Pediatr Surg Int 2015;31:831-5.
7. Muller CO, Guérin F, Goldzmidt D, Fouquet V, Franchi-Abella S, Fabre M, et al. Pancreatic resections for solid or cystic pancreatic masses in children. J Pediatr Gastroenterol Nutr 2012;54:369-73.
8. Seo HE, Lee MK, Lee YD, Jeon SW, Cho CM, Tak WY, et al. Solid-pseudopapillary tumour of the pancreas. J Clin Gastroenterol 2006;40:919-22.
9. Coleman KM, Doherty MC, Bigler SA. Solid-pseudopapillary tumour of the pancreas. Radiographics 2003;23:1644-8.
10. Hachiyaa M, Hachiyaa Y, Mitsuia K, Tsukimoto I, Watanabe K, Fujisawa T. Solid, cystic and vanishing tumours of the pancreas. J Clin Imag 2003;27:106-8.
11. Al-Salem AH, Matta H. Congenital pancreatic cyst: diagnosis and management. J Pediatr Gastroenterol Nutr 2014;59:38-40.
12. Onur MR, Bakal U, Kocakoc E, Tartar T, Kazez A. Cystic abdominal masses in children: a pictorial essay. Clin Imaging 2013;37:18-27.
13. Megibow AJ. Update in imaging of cystic pancreatic masses for gastroenterologists. Clin Gastroenterol Hepatol 2008;6:1194-7.
14. Kazez A, Akpolat N, Kocakoc¸ E, Parmaksiz ME, Köseoğullari AA. Congenital true pancreatic cyst: a rare case. Diagn Interv Radiol 2006;12:31-3.
15. Xu C, Zhong L, Wang Y, Wang W, Yang Z, Kang X, et al. Clinical analysis of childhood pancreatoblastoma arising from the tail of the pancreas. J Pediatr Hematol Oncol 2012;34:177-81.
16. Hayes-Jordan A, Andassy R. Rhabdomyosarcoma in children. Curr Opin Paediatrics 2009;21:373-8.
17. Nemade B, Talapatra K, Tunuja S, Shirpad B, Muckaden M, Laskar S. Embryonal rhabdomyosarcoma of the biliary tree mimicking a choledochal cyst. J Cancer Res Ther 2007;40-2.
18. Shirafkan Md A, Boroumand Md N, Komak Md S, Duchini Md A, Cicalese Md L. Pancreatic pleomorphic rhabdomyosarcoma. Int J Surg Case Rep 2015;13:33-6.
19. Teixeira RC, Nico MM, Ghideti AC. Necrolytic migratory erythema associated with glucagonoma: a report of two cases. Clinics 2008;63:267-70.
20. Sağlam M, Yılmaz MI, Mas MR, Taşçį I, Ors F, Sönmez A, et al. A case of pancreatic Burkitt lymphoma: radiological findings. Diagn Interv Radiol 2009;15:39-42.
21. Guo N, Zhou QB, Chen RF, Zou SQ, Li ZH, Lin Q, et al. Diagnosis and surgical treatment of solid pseudopapillary neoplasm of the pancreas: analysis of 24 cases. Can J Surg. 2011;54:368-74.
22. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. Am Fam Physician 2006;73:485-92.

Original Article

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Analysis of Personal, Environmental, and Occupational Factors Affecting the Activity Performance of Disabled Drivers

Engelli Sürücülerin Aktivite Performanslarını Etkileyen Kişisel, Çevresel ve Aktiviteye Ait Faktörlerinin İncelenmesi

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ABSTRACT

Objective: This study was planned to analyse environmental, personal and occupational factors on disabled drivers' performance who had been driving.

Methods: Twenty orthopedically (group II) and 20 neurologically disabled (group I) people were included in the study. Loewenstein Occupational Therapy Cognitive Assessment (LOTCA), trail making test, rapid pace walk test and alternate foot tap test, The Craig Hospital Inventory of Environmental Factors (CHIEF-SF) and semi-structured interview methods were used for assessments.

Results: Group I included 10 women and 10 men with mean age 33.9±12.05 years; group II included 19 men and 1 woman with mean age 36.5±12.45 years. Group I had not been able to comply with pre-driving test norms that needed for driving competency, controversially group II had proficient scores related to driving. Visio-motor organisation and thinking operations sub-scales of LOTCA were significantly lower than base scores ($p<0.05$) in group I. both groups defined barriers in CHIEF-SF.

Conclusion: Our study showed driving for our participant was an important activity. But lack of rehabilitation services and laws for driving might effect driving participation thus social participation. It is important to enabling driving rehabilitation services, community awareness of driving, law-maker awareness to enhance disabled people's activity performance and participation.

Keywords: Occupational therapy, disabled people, activities of daily living

ÖZ

Amaç: Bu çalışma, sürüş yapan engelli sürücülerin performansındaki çevresel, kişisel ve mesleki faktörleri analiz etmek için planlandı.

Yöntemler: Çalışmaya ortopedik 20 (grup 2) ve 20 nörolojik özürlü (grup 1) kişi alındı. Değerlendirmeler için Loewenstein Ergoterapi Kognitif Değerlendirme (LOTCA), iz sürme testi, kalk yürü testi ve sıralı ayak basma testi, Craig Hastanesi Çevresel Faktörler Envanteri (CHIEF-SF) ve yarı yapılandırılmış görüşme yöntemleri kullanılmıştır.

Bulgular: Grup 1'de 10 kadın ve 10 erkeğin yaş ortalaması 33,9±12,05 yıl, 2. grupta 19 erkek ve 1 kadında ortalama yaş 36,5±12,45 yıl olarak bulundu. Grup 1, sürüş yetkinliği için gerekli olan sürüş öncesi test normlarına uymayı başaramamış, diğer yandan olarak 2. grup sürüşe ilişkin yeterli puan almış. Visio-motor organizasyon ve düşünme operasyonları LOTCA'nın alt ölçekleri grup 1'de baz puanlardan anlamlı derecede düşüktü ($p<0,05$). Her iki grup da CHIEF-SF'de farklı bariyerler belirttiler.

Sonuç: Çalışmamız, katılımcımız için sürüşün önemli bir aktivite olduğunu göstermiştir. Ancak, rehabilitasyon hizmetlerinin eksikliği ve sürüş için yasalar sürüş katılımını ve dolayısıyla sosyal katılımı etkileyebilir. Engelli bireylerin etkinlik performansını ve katılımını artırmak için sürüş rehabilitasyon hizmetlerinin, toplum sürüş bilincini, kanun koyucu bilincini sağlamak önemlidir.

Anahtar Sözcükler: Ergoterapi, engelli kişiler, günlük yaşam aktiviteleri

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Introduction

Community mobility, an instrumental activity of daily living (IADL), is defined as "moving around in the community with the use of public or private transportation, such as driving, walking, bicycling, or accessing and riding in buses, taxi cabs, or other transportation systems" by the American Occupational Therapy Association (AOTA) (1). It is an important part of daily living which is related to social integration, participation to social roles, and role identification among others. Outside activities such as work, participating in social activity, shopping and grocery, prayer meetings, etc., for disabled persons are important, and can be accessible with community mobility. If participating in these activities is restricted by health issues, persons may feel depressed and incompetent, and limitations in the activity of daily living may occur (2). For most of the people, community mobility represents driving and independence (3). Independence, self-confidence, and community participation limitations may occur due to loss of driving ability (4).

Driving is a complex activity that depends on many factors such as attention, perception, cognitive ability, memory, experience, automatic motor performance, quick decision making, coping with different traffic situations, muscle strength of related muscles, lower extremity reaction speed, and visual range (5,6). Attention and cognitive ability is especially important for driver, passenger, and pedestrian safety (5). Besides personal factors, environmental and occupational (driving related) factors affect driving. Family/peer support, stigma, funding, traffic condition, high-way side-way driving, day and night driving, road condition, existence of other drivers, and their behaviour can be considered as environmental factors. In addition, adaptation limits, accessibility, and affordability of the car can be accepted as occupational factors of driving (4).

Disabled population of Turkey is 12% of its total population which is approximately 8 million citizen (7). According to the Turkish Republic National Police Traffic Services reports, 44,254 citizens have disabled driving licence which indicates that 0.7% are disabled people driving in Turkey (8) whereas 20% in United Kingdom (9) and 12% in United States of America (10), which shows that Turkey disabled driver rates are remarkably lower.

Current occupational therapy framework suggests that IADL's including driving may be affected by the person's body functions and performance skills which must be intervened by an occupational therapist (1,11). In addition, cognitive, perceptive ability, and executive functioning related to driving must be assessed, and problems should be addressed by occupational therapists (12,13). AOTA stated that the importance of occupational therapists in driver assessment includes client's sensory, cognitive, motor performance skills, safety concerns, environmental barriers, and ability to participate in daily living (11). With the presence of current literature that supports activity-based assessments of disabled/older drivers, the situation in Turkey consisting of physician-orientated and non-interdisciplinary manner may become a big limitation for disabled person's activity participation and performance. These reasons make the assessment and improvement of activity performance of disabled drivers in our country very important. Also, a need of interdisciplinary approaches enlightened with activity performance assessment results was noted. Pre-driving assessments of two different diagnostic groups (orthopaedic and neurological) were made to determine driving fitness for disabled people.

Method

This is methodological study embedded in two groups, clinical trials and comparisons were made with given standards. Current study was approved by Hacettepe University Ethic Committee with LUT 12/101 project number. Signed informed consent was obtained from all participants before study.

A total of 40 participants were included and divided equally into two groups: group I were participants with neurologic disorders and group II with orthopaedic disorders. Inclusion criterions were:

- age 18-65 years,
- with drivers licence,
- diagnosed with neurologic (group I) or orthopaedic disorder (group II),
- without visual and auditory problems
- with willingness to participate in the study.

Assessments

Personal Assessments

Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) and trail making test (TMT) A and B were used for cognition and alternate foot tap test (AFT) and rapid pace walk test (RPW) for physical function.

LOTCA is a tool that assesses cognitive skills and visual perceptions of participants. Test includes orientation, spatial perception, visio-motor perception, thinking organization, and attention. All domains were scored between 1-4 except for risk object classification I and II domains, which were scored between 1-5 (14).

The TMT assesses visual search, scanning, speed of processing, mental flexibility, and executive functions (15). Test consists of two parts: TMT-A, which requires a person to draw lines sequentially connecting 25 circled numbers on the test paper and TMT-B, which needs the same skills as TMT-A; however, the person must alternate between numbers and letters (e.g., 1, A, 2, B, 3, C, and so on). The score for the test was scored as the amount of time required to complete the task. The TMT is commonly used for driving prediction of disabled persons (5, 16,17).

Lower extremity mobility and reaction time were assessed with RPW and AFT, respectively. Both tests' completion durations were recorded (18).

Environmental Assessment

Craig Hospital Inventory of Environmental Factors-Short Form (CHIEF-SF) was used for environmental assessments. CHIEF-SF assesses physical, attitude-related, environmental, and political barriers and frequency of these barriers in the participant's perspective. In addition, driving importance and satisfaction were assessed using visual analogue scale (VAS) with a score ranging from 0-10 in which higher score indicates better satisfaction and importance. Family and peer support before and after driving, self-confidence about driving, and family and peer confidence about driving were assessed using a semi-structured interview. All questions apart from car and environment related problems were scored with a five-point likert scale (1: highly positive, 2: positive, 3: not sure, 4: negative, and 5: highly negative).

Tests used in our study were suggested to determine the driving ability in clinical settings (13,19). Required scores for accepting proficiency for driving are: ≤78 s for TMT-A; ≤180 s for TMT-B; ≤8 s in RPW; and 7.42 s for AFT.

SPSS 21.00 software was used to analyse data. Quantitative data were described with mean ± standard deviation and qualitative data were described with percent (%) values. Normality of data was evaluated with visual (histogram and stem-leaf plots) and analytic (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Significance was set an alpha level of 0.05 ($p<0.05$). Frequencies and descriptive statistical methods were used for semi-structured interviews and likert scales. Test results were compared with test norms with one way analysis of variance test. LOTCA results were compared to base scores of subtests due to the lack of Turkish mean scores.

Results

A total of 20 participants (10 women and 10 men) were recruited for group I and 20 participants (19 men and 1 woman) for group II. The mean age of group I was 33.9±12.05 years and group II was 36.5±12.45 years.

Both groups included participants with different diagnosis such as multiple sclerosis (MS) (n=4), myopathy (n=3), meningomyelocele (n=3), neuropathy (n=2), ataxia (n=2), hemiplegia (n=2), and spinal cord injury (n=2) in group I and poliomyelitis (n=6), lower extremity amputation (n=6), traumatic brachial plexus injury (n=1), crash injury (n=1), and shoulder arthrodesis (n=1) in group II.

A total of three participants diagnosed with myopathy and spinal cord injury from group I and six participants with polio, lower limb amputation, and crush injury from group II were unable to apply for RPW and AFT.

Table 1 presents standard values for driving competency and mean scores of TMT A and B, RPW, AFT, and p values and VAS scores for driving importance and satisfaction. Table 2 presents CHIEF-SF scores. Table 3 presents LOTCA scores for two groups.

Group II had better results than group I in LOTCA. A statistically significant difference between group I and LOTCA base scores ($p<0.05$) were noted. Group I had effected LOTCA visual-spatial perception and thinking operations scores which might be related to driving skills. Group I could not meet RPW and AFT required scores for driving which indicates increased lower extremity reaction time. In addition, other test scores for group I and all tests for group II were sufficient. Driving importance and driving satisfaction were high in both groups. Mean scores

Table 1. Clinical test results and comparison

	Group I	p	Group II	p	Test norms
Trail making test A	62.11±35.74	0.06	39.61±13.02	0.001	≤78 s
Trail making test B	154.17±85.26	0.19	105.62±37.05	0.001	≤180 s
Rapid pace walk test	19.74±10.17	0.001*	6.93±4.92	0.35	≤8 s
Alternate foot tap test	10.71±9.69	0.07	4.75±0.85	0.001	≤7.42 s
VAS importance	8.55±1.63		9.25±1.29		-
VAS satisfaction	7.05±3.26		8.90±1.71		-

*p<0.05, VAS: Visual analogue scale

Table 2. Environmental barrier scores (CHIEF-SF)

CHIEF-SF	Group I	Group II
Politics	4.0±4.2	3.4±4.6
Physical/structural	4.2±4.2	1.8±2.3
Work/school	3.3±4.2	1.8±2.7
Behaviour/support	4.8±4.8	1.5±2.5
Services/assistance	5.3±5.1	2.0±3.7
Total	21.7±14.3	10.6±11.0

CHIEF-SF: Craig Hospital Inventory of Environmental Factors-Short Form

Table 3. Loewenstein occupational therapy cognitive assessment results and comparison

LOTCA	Group I (n=20)	p	Group II (n=20)	p
Place	3.95±0.22	0.31	4.00	1.00
Time	4.00	1.00	4.00	1.00
Object identification	4.00	1.00	4.00	1.00
Shapes identification	4.00	1.00	4.00	1.00
Overlapping figures	4.00	1.00	4.00	1.00
Object constancy	3.80±0.5	0.07	3.94±0.22	1.00
Spatial perception	3.85±0.4	0.15	4.00	1.00
Praxis	4.0	1.00	4.00	1.00
Copying geometric forms	3.90±0.3	0.15	4.00	1.00
Reproduction of a two-dimensional model	3.75±0.5	0.03*	3.90±0.30	0.15
Pegboard construction	3.75±0.7	0.07	4.00	1.00
Colored block design	3.65±0.7	0.01*	3.80±0.41	0.03*
Plain block design	3.55±0.8	0.01*	3.75±0.44	0.018
Reproduction of a puzzle	3.5±0.8	0.009*	3.90±0.30	0.15
Drawing a clock	3.85±0.4	0.15	4.00	1.00
Categorization	3.9±0.8	0.001*	4.60±0.50	0.002*
ROC: unstructured	4.55±0.68	0.004*	4.90±0.30	0.15
ROC: structured	4.50±0.76	0.004*	4.90±0.30	0.07
Pictorial sequence A	3.70±0.9	0.15	4.00	1.00
pictorial sequence B	3.45±1.05	0.01*	3.75±0.44	0.01*
Geometrical sequence	3.70±0.7	0.07	3.95±0.22	0.31
Attention	3.85±0.36	0.07	4.00	1.00

*p<0.05, ROC: Risk object classification

of importance were 8.55±1.63 in group I and 9.25±1.29 in group II. Satisfaction mean scores were 7.05±3.26 in group I and 8.90±1.71 in group II.

Family support before and after driving, self-confidence about driving, family and peer confidence about driving, and car and environment related problems were assessed with semi-structured interviews which are shown in Table 4. Family and peer support increased after driving. Self-confidence was high in both groups; however, peer confidence was lower in group I than in group II. In addition, low self-confidence of two participants in group I was noteworthy that they continue driving with their low confidence.

Discussion

A total of 40 participants were included in this study, who had been driving with their disability. This study aimed to investigate participants driving competency according to literature values, environmental, and physical barriers effecting their driving. Our research found that drivers with neurological disorders had physical and cognitive barriers for their driving ability.

Various studies showed cognitive function affects driving ability (16,17,20-22). Our results show a low motor perception and thinking organizations scores of LOTCA in both groups, which means sensory-perceptual and perceptual-motor ability could affect driving. Therefore, specialized trainings for driving skill for disabled is a current issue in rehabilitation in Turkey, which is not included in the perspectives of rehabilitation services. We suggest that assessment and rehabilitation programs that build sensory, perceptual, and motor abilities are needed to improve driving abilities of disabled in our country.

TMT A and B, AFT, and RPW results of group II were better than test norms which show better driving ability. However, RPW and AFT of group I did not match test minimum standards. Based on these results, group I needs detailed assessment about their driving ability to ensure safe driving, although pre-driving assessments in our country must include literature-supported assessment methods to improve and prevent traffic safety for disabled and other drivers. Marshall et al. (5) mentioned that TMT A and B parts were predictors of driving in stroke survivors. The American Medical Association suggested the use of current test to predict driving ability in older adults (19).

CHIEF-SF was used to assess environmental barriers of participants, which include political, physical, social, services/support, and work/school related barriers. Both groups defined barriers in all parameters; however, the highest barriers defined by group I was services/support, whereas group II was politics and services/support. Salar's master thesis suggested that activity

Table 4. Semi-structured interview results

	Group I		Group II	
	N	%	N	%
Family support				
Highly positive	7	35	8	40
Positive	2	10	8	40
Uncertain	-	-	1	5
Negative	3	15	-	-
Highly negative	8	40	3	15
Peer support				
Highly positive	9	45	9	45
Positive	3	15	9	45
Uncertain	2	10	1	5
Negative	1	5	1	5
Highly negative	5	25	-	-
Family support after driving				
Highly positive	8	40	9	45
Positive	1	5	8	40
Uncertain	2	10	1	5
Negative	4	20	1	5
Highly negative	5	25	1	5
Peer support after driving				
Highly positive	8	40	9	45
Positive	3	15	9	45
Uncertain	4	20	1	5
Negative	2	10	1	5
Highly negative	3	15	-	-
Self confidence about driving				
Very high	12	60	8	40
High	1	5	12	60
Mild	4	20	-	-
Low	1	5	-	-
Very low	2	10	-	-
Peer confidence				
Very high	7	35	9	45
High	5	25	9	45
Mild	-	-	1	5
Low	4	20	1	5
Very low	4	20	-	-

barriers and participation of people with spinal cord injury include political, services/support, and behaviour, which supports our participants' defined barriers (23). Laws and regulations were defined as barriers in CHIEF-SF in our study. Traffic laws for disabled people in our country support physician-based assessments which might result to non-activity based assessments for driving ability and proficiency. Laws and regulations were thought to be a limitation for disabled people's driving because some of disabled driving candidates could not get driver's licence due to non-activity based assessments.

Driving interest and motivation to driving were reported as important in safe driving by Lundqvist and Rönnberg (24). Current study also showed interest to affect driving behavior, and capitalize driving problems related to behavior. In this study, participants indicated high driving importance and satisfaction that might be related to safe driving and activity willingness.

Family support before driving was negative in 55% of group I and 20% from group II. Social (peer support) before driving were negative in 40% of the group I and 10% from group II. After starting driving family and peer support changed to 45% negative in group I and 10% in group II. These negative attitudes before driving may be a result of stigma about disabled people and families and peers' protection instinct. Upon the start of driving, family and peer support increased in both groups. This change might had been affected with the observation of the participant's driving ability. When families and peers thought that disabled relatives are safe while driving, they were capable of supporting their relatives to drive. Although stigma for disabled driving was a problem, occupational therapists and driver rehabilitation services must inform the community about disabled driving to prevent stigma and enhance family/peer support for driving.

Study Limitations

This study included different disability groups, which might alter homogeneity of results and might be accepted as a limitation of the study. The other limitation is that we were unable to analyse the driving ability while disabled participants were driving. We concluded our findings based on clinical assessments; however, assessments made behind the wheel might reflect clearer results.

Conclusion

Rehabilitation for disabled people in our country includes basic physical trainings as isolated range of motion, walking exercises, etc. However, driving which includes many sensory, motor, and perceptual factors, must be rehabilitated in a perspective of specialized activity rehabilitation programs (24). To start and improve driver rehabilitation in our country, approaches to the rehabilitation must not be physician-focused but an interdisciplinary model.

Community-based rehabilitation studies should be prepared for community information about disabled driving in Turkey. With these applications stigmas, negative family/peer supports, activity limitations, and social isolation of the disabled may decrease. Further studies including these perspectives may improve the disabled driving skills and their perception on driver rehabilitation by related health practitioners. In addition, we suggest cross-cultural studies to improve perception of law-makers and governmental departments about driving rehabilitation and current situation in developed countries. Finally, future positive changes in laws and regulations, enabling of disabled drivers may result in an increase in participation as mentioned in the International Classification of Disability.

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Ethics

Ethics Committee Approval: Current study was approved by Hacettepe University Ethics Committee with LUT 12/101 project number.

Informed Consent: Signed informed consent was obtained from all participants before study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: O.T.A., H.K., Design: O.T.A., H.K., Data Collection or Processing: O.T.A., Analysis or Interpretation: O.T.A., H.K., Literature Search: O.T.A., Writing: O.T.A.

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References

1. The American Occupational Therapy Association. Occupational therapy practice framework: Domain and process, 2nd ed. American Journal of Occupational Therapy. 2008.p.625-83.
2. Beverly Foundation. Community Effectiveness in Safeguarding at-risk senior drivers. Pasadena, Calif: Beverly Foundation, 1998.
3. AA Foundation for Traffic Safety. Beverly Foundation: Transportation alternatives for seniors: high cost problems low cos solutions. In: Safety AFfT, 2004.
4. Bolding D, Adler C, Tripton-Burton M, Verran A. Occupational Performance and The Performance Areas: Evaluation and Intervention. In: Pendleton H. Mc , Schultz-Krohn W, editors. Pedretti's Occupational Therapy Practice Skills for Physical Dysfunction. USA: Elsevier; 2006.p.264-95.
5. Marshall SC, Molnar F, Man-Son-Hing M, Blair R, Brosseau L, Finestone HM, et al. Predictors of driving ability following stroke: a systematic review. Top Stroke Rehabil 2007;14:98-114.
6. Wheatley CJ, Pellerito JM Jr, Redepenning S. The Clinical Evaluation. In: Pellerito JM, Jr, editor. Driver Rehabilitation and Community Mobility: Principles and Practice. Missouri, USA: Elsevier, Mosby; 2006.p.103-65.
7. Turkish Republic State Institute of Statistics. Turkey Disability Survey. In: State Institute of Statistics TR, editor. Ankara: State Institute of Statistics Press, 2006.
8. Turkish Republic National Police Department Traffic Services. Turkish Republic National Police Department Car and Driver Licence Statistics,. In: Turkish Republic National Police Department Traffic Services, editor. Turkish Republic National Police Department Traffic Services, 2010.
9. Tong S, Brougton J, Tong R. Data gathering on disability and driving statistics, Stage 2:final report. United Nations: Department for Transport; 2007.
10. U.S. Department of Transportation, Bureau of transportation statistics. Freedom to Travel. Washington, DC 2003.
11. The American Occupational Therapy Association. Driving and Community Mobility. American Journal of Occupational Therapy 2010;64:112-25.
12. Korner-Bitensky N, Bitensky J, Sofer S, Man-Son-Hing M, Gelinas I. Driving evaluation practices of clinicians working in the United States and Canada. Am J Occup Ther 2006;60:428-34.
13. Stapleton T, Connelly D. Occupational therapy practice in predriving assessment post stroke in the Irish context: findings from a nominal group technique meeting. Top Stroke Rehabil 2010;17:58-68.
14. Katz N, Itzkovich M, Averbuch S, Elazar B. Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) battery for brain-injured patients: reliability and validity. Am J Occup Ther 1989;43:184-92.
15. Reitan RM. The relation of the trail making test to organic brain damage. J Consult Psychol 1955;19:393-4.
16. Akinwuntan AE, Feys H, De Weerdt W, Baten G, Arno P, Kiekens C. Prediction of driving after stroke: a prospective study. Neurorehabil Neural Repair 2006;20:417-23.
17. Mazer BL, Korner-Bitensky NA, Sofer S. Predicting ability to drive after stroke. Arch Phys Med Rehabil 1998;79:743-50.
18. Classen S; National Highway Traffic Safety Administration; American Occupational Therapy Association. Consensus statements on driving in people with Parkinson's disease. Occup Ther Health Care 2014;28:140-7.
19. American Medical Association. Physician's Guide to Assessing Older Driver. American Medical Association, 2010.
20. van Zomeren AH, Brouwer WH, Minderhoud JM. Acquired brain damage and driving: a review. Arch Phys Med Rehabil 1987;68:697-705.
21. Galski T, Bruno RL, Ehle HT. Prediction of behind-the-wheel driving performance in patients with cerebral brain damage: a discriminant function analysis. Am J Occup Ther 1993;47:391-6.
22. Cox DJ, Quillian WC, Thorndike FP, Kovatchev BP, Hanna G. Evaluating driving performance of outpatients with Alzheimer disease. J Am Board Fam Pract 1998;11:264-71.
23. Salar S. The Effects of Environmental Factors to Community Participation and Life Satisfaction in People with Spinal Cord Injury. Ankara: Hacettepe University; 2011.
24. Lundqvist A, Rönnberg J. Driving problems and adaptive driving behaviourafter brain injury: A qualitative assessment. Neuropsychol Rehabil 2001;11:171-85.

Original Article

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A Liquid Chromatographic Analysis of Gemifloxacin in Pharmaceutical Preparations Using 4-bromomethyl-7-methoxycoumarin Reagent

Gemifloksasinin 4-bromometil-7-metoksikumarin Belirteci Kullanılarak Farmasötik Preparatlarda HPLC ile Analizi

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ABSTRACT

Objective: In this study, analysis of gemifloxacin in pharmaceutical preparations was performed in the presence of 4-bromomethyl-7-methoxycoumarin reagent and dibenzo-18-crown-6 ether catalyst, by high-performance liquid chromatography.

Methods: The excitation wavelength of the compound formed as a result of the derivatization process was found as λext. =325 nm and the emission wavelength as λem. =390 nm. Optimum reaction conditions were carefully studied. Chromatographic separations were performed in a 150 cm x4.6 mm, 5 µm I.D C18 column, and the mobile phase consisting of acetonitrile: 0.05 M aqueous ammonium acetate (pH=5.0) (70:30, v/v) under flow rate of 1.0 mL/min.

Results: The calibration curve was found to be linear in the range of 10-200 ng.mL^{-1}. Average recovery was 100.32% and relative standard deviation values were below 2%.

Conclusion: The method developed has been successfully applied in the analysis of the drug substance in pharmaceutical preparations.

Keywords: Gemifloxacine, liquid chromatography, fluorometric detection, 4-bromomethyl-7-methoxycoumarin, pharmaceutical preparation, validation

ÖZ

Amaç: Bu çalışmada gemifloksasinin 4-bromometil-7-metoksikumarin belirteci ve dibenz-18-taç-6 eter katalizör varlığında farmasötik preparatlarda yüksek performanslı sıvı kromatografisi ile analizi gerçekleştirilmiştir.

Yöntemler: Türevlendirme işlemi sonucu oluşan bileşiğin eksitasyon dalga boyu λext. =325 nm ve emisyon dalga boyu λem. =390 nm olarak bulunmuştur. Optimum reaksiyon şartları dikkatlice çalışıldı. Kromatografik ayırmalar, 250x4,6 mm, 5 µm I.D C18 kolonda, asetonitril-0,05 M sulu amonyum asetat (pH=5,0) (70:30, v/v) mobil fazında, 1 mL/dak akış hızında gerçekleştirilmiştir.

Bulgular: Kalibrasyon eğrisi 10-200 ng.mL^{-1} aralığında doğrusal bulunmuştur. Ortalama geri kazanım %100,32 ve bağıl standart sapma değerleri %2'nin altında bulunmuştur.

Sonuç: Geliştirilen metod, ilaç maddesin farmasötik preparatlardaki analizine başarıyla uygulanmştır.

Anahtar Sözcükler: Gemifloksasin, sıvı kromatografisi, florimetrik dedeksiyon, 4-bromometil-7-metoksikumarin, farmasötik preparat

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Introduction

In addition to their gram-negative activity, quinolone antibiotics, which are formed by the addition of fluorine at the six position to the quinolone ring, are also effective in infections with gram-positive bacteria. The chemical formula of gemifloxacin (GMF) is [(R, S) -7- [3-aminomethyl-4-methoximino-1-pyrrolidinyl]-1-cyclopropyl-6-floro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (1-4) (Figure 1).

Various methods such as spectrophotometric method (5,6), high performance liquid chromatographic method (HPLC) (7-11), voltammetric method (12) and capillary electrophoretic method (13) have been encountered in the literature for determination of GMF. As a result of literature research, no analysis of GMF using 4-bromomethyl-7-methoxycoumarin (BrMmC) reagent was found. HPLC analysis based on fluorescence measurement gains importance in order to increase the selectivity and sensitivity of the method. The BrMmC reagent is often used for derivatization of molecules containing carboxylic acid functional groups (14-16). The aim of this study was to conduct an HPLC analysis based on fluorimetric detection of GMF in pharmaceutical preparations by using 4-bromomethyl-7-methoxycoumarin reagent. This method developed has also been successfully applied in the analysis of pharmaceutical preparations of the drug substance.

Method

Devices

Chromatographic separations were performed with the Shimadzu LC 20A (Kyoto, Japan) liquid chromatographic system. The system consists of LC 20 AT Pump, SIL-20AC autosampler, CTO-10A column oven and RF-10AXL fluorescence detector. The excitation wavelength of the compound formed as a result of the derivatization process was found as λext. = 325 nm and the emission wavelength as λem. =390 nm. Chromatographic separations were performed in a 150 cm x 4.6 mm, 5μm I.D C18 column, and the mobile phase consisting of acetonitrile: 0.05 M aqueous ammonium acetate (pH 5.0) (70:30, v/v) under flow rate of 1.0 mL/min.

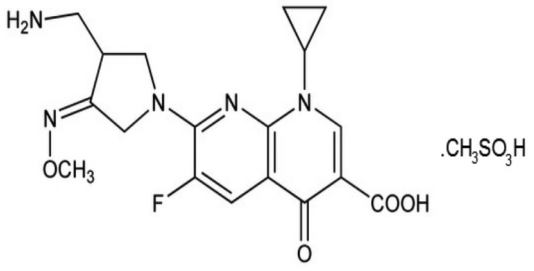

Figure 1. Chemical structure of gemifloxacin mesylate

Reagents and Solutions

The GMF and its pharmaceutical preparation (Factiva Film Tablet® 320 mg of GMF) were taken from Abdi Ibrahim Pharmaceuticals (Turkey), and BrMmC and dibenzyo-18-crown-6 ether catalyst were purchased from Sigma-Aldrich Chemie (Germany). All chemicals and reagents were used for analytical purity.

Stock Solutions

For the GMF stock solution, 133.33 mg of GMF mesylate was weighed exactly, dissolved in water in a 100 mL volumetric flask and made up to its volume (equivalent to 100 mg/mL GMF base). Standard solutions of GMF were taken from this solution and prepared with water. Stock and standard solutions are stable for about 1 week at +4 °C. The standard solution of BrMmC was freshly prepared daily in acetonitrile at a concentration of 100 μg.mL^{-1}. Dibenzo-18-crown-6 ether solution was prepared in acetonitrile to make up a volume of 1 μg.mL^{-1}.

General Analysis Method

Two hundred μL BrMmC, 50 μL dibenz-18-crown-6 ether solutions and 2 mg K_2CO_3 suspension were added to the substance solution (10-200 ng.mL^{-1}) containing different amounts of GMF in 100 μL volumes. The resulting mixture was stirred for 2 minutes and then reacted at 70 °C for 70 minutes. The blank trial was run with 100 μL of water as specified in this section. Volumes reached to 1000 μL with acetonitrile and then they were injected into the HPLC system.

Analysis Method for Tablets

The amount equivalent to 250 mg GMF was weighed and dissolved in 125 mL of water. Then, it was mixed in a mechanical stirrer for 20 minutes and in an ultrasonic bath for 20 minutes, and it was made up to 250 mL in volume and then filtered through filter paper. The filtrate was diluted with water and studied as specified in the "General Analysis Method". The amount of substance in the tablets was measured using the calibration chart and the corresponding regression equation.

Results

Determination of Chromatographic Conditions

Chromatographic conditions were studied in order to develop an HPLC method based on fluorimetric analysis of GMF with BrMmC reagent. For this purpose, columns such as C18, CN and C8 were tried to determine the most suitable column. Optimal conditions were provided with the following parameters: 250x4.6 mm, 5 μm ID C18 column, acetonitrile-0.05 M aqueous ammonium acetate (pH 5.0) (70:30, v/v) mobile phase, flow rate at 1 mL/min, λext. =325 nm wavelength and λem. =390 nm wavelength. The retention time of the GMF derivative was detected as approximately 3 min (Figure 2).

Optimization of Derivation Conditions

In this method developed, GMF was derivatized with 4-bromomethyl-7-methoxycoumarin reagent in the presence

of dibenz-18-crown-6 ether catalyst. In order to determine the optimum conditions, the effect of BrMmC concentration on derivative formation was examined first. It was observed that 200 µL of BrMmC solution (in the presence of 50 µL of Dibenzo-18-crown-6 ether and 2 mg of K_2CO_3 suspension) was sufficient for the derivatization reaction. When the effect of the presence of Dibenzo-18-crown-6 ether on the derivatization reaction was examined, it was observed that the efficiency of the derivative was increased. In order to determine the reaction temperature and reaction time, the reaction mixture was kept at 40, 50, 70 and 80 °C and for different periods. It was found that the most favorable results were obtained at 70 °C for 70 minutes (Figure 3). Conditions are given in Table 1.

Method Validation

The proposed analytical methods were validated according to the ICH guideline Q2 (R1) (17). A calibration curve was generated under the conditions stated above. According to the results obtained, it was observed that the calibration curve was linear in the range of 10-200 ng mL^{-1}. The equation of the measure curve was found as y=185.25 x +2146.2 (r2 = 0.9987), (x concentration is ng mL^{-1} and y is detector response).

The formula of LOD/LOQ = κSDa/b was used to calculate LOD or LOQ. Here the value of κ is 3 for LOD and 10 for LOQ. SDa indicates the standard deviation of the scale curve intersept and b is the slope. The LOD value was 0.0014 ng.mL^{-1} and the LOQ value was 0.0049 ng.mL^{-1}.

The precision values within day and between days were examined at 10, 100, and 200 ng.mL^{-1} for five consecutive days. The inter-day precision was 0.33-0.72% and the between-days precision was 0.48-0.93%. Results are given in Table 2.

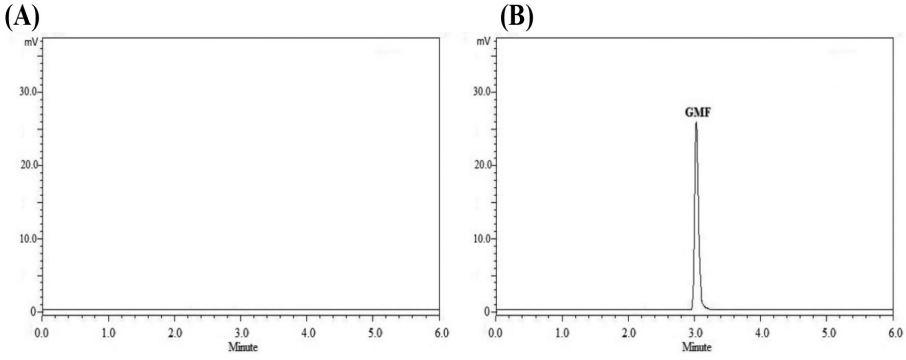

Figure 2. Chromatograms (A) Blank sample (B) GMF added sample (100 ng mL-1)

Table 1. Evaluation of derivatization parameters

Parameter	Range	Optimum value
Derivation time (minutes)	20-100	70
Temperature (°C)	40-80	70
µL of BrMmC	25-500	200
µL of Dibenzo-18-crown-6 ether	10-100	50
mg of K_2CO_3 compound	0.5-5	2

Table 2. Precision values of inter-day and between days

Concentration taken (ng.mL^{-1})	Concentration found (ng.mL^{-1}) ± SD	RSD %*
Intraday		
10.0	10.09±0.046	0.46
100.0	100.14±0.720	0.72
200.0	200.74±0.670	0.33
Between days		
10.0	10.11±0.046	0.67
100.0	100.49±0.930	0.93
200.0	200.98±0.970	0.48

*RSD: Relative standard deviation

The accuracy of the developed methods was examined using the standard addition technique. Standard solutions (10.0, 100.0, 150.0 ng.mL^{-1}) at 3 different concentration levels were added onto the pure analyte sample solution (10 ng.mL^{-1}), mixed and analyzed. The results obtained are presented in Table 2. The calculated average recovery percentage was found to be 100.32% on average. Results are shown in Table 3.

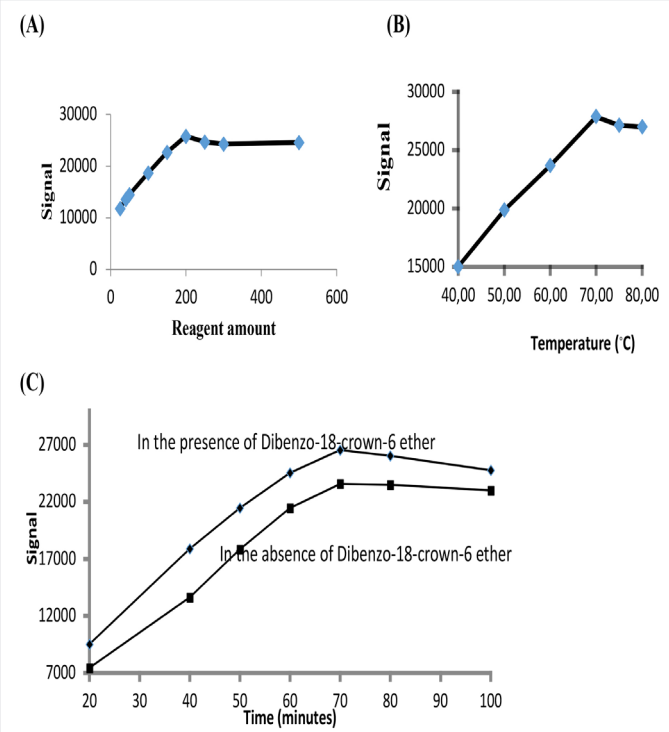

Figure 3. Effects of (A) reagent amount, (B) temperature, (C) reaction time and presence of Dibenzo-18-crown-6 ether on derivatization reaction

The developed method was also successfully applied in the analysis of the drug substance in pharmaceutical preparations and the results were compared with the spectrofluorimetric method recorded in the literature (5). The results were analyzed in terms of means and precision values using the t and f tests. According to these results, no interference was observed from additives and excipients. The results are given in Table 4.

Conclusion

In conclusion, in this study, the 4-bromomethyl-7-methoxycoumarin reagent used in the analysis of substances containing carboxyl groups was studied for the first time in GMF analysis and the developed HPLC analysis was successfully applied in pharmaceutical preparations of the drug substance. In the developed method, the analysis time was short (approximately 3 minutes) and the LOD and LOQ values were 0.0014 ng.mL^{-1} and 0.0049 ng.mL^{-1}, respectively. Since the developed method is more sensitive than other methods recorded in the literature, it is planned to be applied in the analysis of biological fluids in the later stages of the study.

Ethics

Peer-review: Externally peer reviewed.

Financial Disclosure: The authors declared that this study received no financial support.

Table 3. Recovery results

Concentration taken[a] (ng mL^{-1})	Added concentration (ng mL^{-1})	Concentration found[b] (ng.mL^{-1}) (mean ± SD[c])	Recovery (%)	RSD (%)
10.0	10.0	20.06±0.058	100.20	0.19
	100.0	110.16±0.61	99.33	0.80
	150.0	160.97±0.86	100.61	0.53

[a]Factive film tablets® (320 mg)
[b]n=5
[c]Standard deviation
RSD: Relative standard deviation, SD: Standard deviation

Table 4. Analysis of the tablet containing 320 mg GMF (n=5)

Amount stated on tablet[a] (mg/per tablet)	Reference method recovery (%) mean[b] ± SD[c]	RSD (%)	Recommended method recovery (%) mean[b] ± SD[c]	RSD (%)	t value	F value
320	100.15±0.14	0.45	100.18±021	0.67	1.942	1.075

[a]Factive film tablet® (320 mg)
[b]n=5
[c]Standard deviation
At the 95% confidence level, the t value is 2.78 and the F value is 6.39
RSD: Relative standard deviation, SD: Standard deviation

References

1. Budavari S. The Merck Index,Merck and Co. Whitehouse Station, NJ, USA: 13th ed, 2001.
2. Völgyi G, Vizserálek G, Takács-Novák K, Avdeef A, Tam KY. Predicting the exposure and antibacterial activity of fluoroquinolones based on physicochemical properties. Eu J Pharm Sci 2012;47:21-7.
3. Oh JI, Paek KS, Ahn MJ, Kim MY, Hong CY, Kim IC, et al. In vitro and in vivo evaluations of LB20304, a new fluoronaphthyridone. Antimicrob Agents Chemother 1996;40:1564-8.
4. Hohl AF, Frei R, Punter V, Graevenitz A, Knapp C, Washington J, et al. International multicenter investigation of LB20304, a new fluoronaphthyridone. Clin Microbiol Infect 1998;4:280-4.
5. Kepekci Tekkeli SE, Önal A. Spectrofluorimetric methods for the determination of gemifloxacin in tablets and spiked plasma samples. J Fluoresc 2011;21:1001-7.
6. Youssef NF, Bebawy LI. Spectrofluorimetric methods for the determination of gemifloxacin mesylate and cefamandole nafate in bulk powder and pharmaceutical preparations. Bulletin of the Faculty of Pharmacy 2006;44:215-27.
7. Rote AR, Pingle SP. Reverse phase-HPLC and HPTLC methods for determination of gemifloxacin mesylate in human plasma. J Chromatogr B 2009;877:3719-23.
8. Al-Hadiya BM, Khady AA, Mostafa GA. Validated liquid chromatographic-fluorescence method for the Quantitation of gemifloxacinin human plasma. Talanta 2010;83:110-6.
9. Kaiser M, Grünspan LD, Costa TD, Tasso L. Reversed phase liquid chromatography method with fluorescence detection of gemifloxacin in rat plasma and its application to the pharmacokinetic study. J Chromatogr B 2011;879:3639-44.
10. Nageswara RR, Naidu ChG, Guru PK, Padiya R, Agwane SB. Determination of gemifloxacin on dried blood spots by hydrophilic interaction liquid chromatography with fluorescence detector: application to pharmacokinetics in rats. Biomed Chromatogr 2012;26:1534-42.
11. Doyle E, Fowles SE, McDonnell DF, White SA Rapid determination of gemifloxacin in human plasma by high performance liquid chromatography-tandem mass spectrometry. J Chromatogr B 2000:746:191-8.
12. Radi AE, Khafagy A, El-Shobaky A, El-Mezayen H. Anodic Voltammetric determination of gemifloxacin using screenprinted carbon electrode J Pharm Anal 2013;3:132-6.
13. Elbashir, AA. Saad, B.. Ali, ASM, Al-Azzam, KMM, Aboul-Enein HY, Validated stability indicating assay of gemifloxacin and lomefloxacin in tablet formulations by capillary electrophoresis J Liq Chromatogr Relat Technol 2008;31:1465-77.
14. Zacharis CK, Raikos N, Giouvalakis N, Tsoukali-Papadopoulou H, Theodoridis GA. A new method for the HPLC determination of gamma-hydroxybutyric acid (GHB) following derivatization with a coumarin analogue and fluorescence detection: application in the analysis of biological fluids. Talanta 2008;75:356-61.
15. Hulshoff A, Förch AD. Alkylation with alkylhalides as a derivatization method for the gas chromatographic determination of acidic pharmaceuticals. J Chromatogr 1981;220:275-311.
16. Wang K, Nano M, Mulligan T, Bush ED, Edom RW. Derivatization of 5-fluorouracil with 4-bromomethyl-7-methoxycoumarin for determination by liquid chromatography-mass spectrometry. J Am Soc Mass Spectrom 1998;9:970-6.
17. ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Validation of Analytical Procedures: Text and Methodology Q2 (R1), 2005.

Original Article

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Effect of Birth Ball Exercising for the Management of Childbirth Pain in Turkish Women

Türk Kadınlarında Doğum Ağrısı Yönetiminde Doğum Topu Egzersizinin Etkisi

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ABSTRACT

Objective: To investigate the effect of the birth ball exercise on management of childbirth pain during the first stage of labor in primipara pregnant women.

Methods: This was a semi-experimental randomized controlled study conducted on pregnant women between February and May 2016. The women were randomly categorized into 2 groups, with 30 women in each group (intervention vs. control groups). The pain visual analog scale (VAS) was used to determine the pain level of the women. Women in the intervention group were provided with a birth ball exercise program during labor. The control group performed no birth ball exercises. The VAS pain scores of the both the groups were registered when the cervical dilatation was 2-8 cm. The data were analyzed using means, t-test, and ANOVA.

Results: Our results indicate that the pain scores of the women in the intervention group who implemented birth ball exercises were significantly lower than those of women in the control group when the cervical dilatation was 4-8 cm.

Conclusion: The pain severity was "moderate" in the intervention group, but "severe" in the control group. Birth ball exercises were therefore found to be effective in decreasing childbirth pain in this study.

Keywords: Birth ball exercises, childbirth, childbirth pain, management of pain, methods of non-pharmacologic

ÖZ

Amaç: Bu çalışmanın amacı, doğum eyleminin birinci evresindeki primipar gebelerde doğum ağrısının yönetiminde doğum topu egzersizinin etkisini belirlemektir.

Yöntemler: Bu çalışma Şubat-Mayıs 2016 tarihleri arasında gebe kadınlarla yürütülen yarı deneysel randomize kontrollü bir çalışmadır. Çalışmada kadınlar rastgele iki gruba ayrıldı ve her gruptan 30 kadınla tamamlandı (müdahale-kontrolü). Kadınların ağrı düzeyini belirlemek için ağrıda görsel analog skala (VAS) kullanıldı. Müdahale grubundaki kadınlara doğum sırasında doğum topu egzersizi uygulandı. Kontrol grubuna ise doğum top egzersizi uygulanmadı. Her iki grubun VAS ağrı skorları servikal dilatasyon 2 cm'den 8 cm'ye kadar kaydedildi. Veriler ortalama, t-testi, ANOVA kullanılarak analiz edildi.

Bulgular: Çalışma bulgularımız, müdahale grubundaki doğum topu egzersizi uygulanan kadınların servikal dilatasyonu 4 cm'den 8 cm'ye kadar olduğunda ağrı skorlarının kontrol grubundaki kadınlardan anlamlı derecede düşük olduğunu göstermektedir.

Sonuç: Müdahale grubunda ağrı şiddeti "orta" iken kontrol grubunda "şiddetlidir". Dolayısıyla bu çalışmada doğum topu egzersizinin doğum ağrılarını azaltmada etkili olduğu bulunmuştur.

Anahtar Sözcükler: Doğum topu egzersizi, doğum, doğum ağrısı, ağrının yönetimi, farmakolojik olmayan yöntemler

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Introduction

Birth is a natural process that can be managed without any medical intervention (1) and is a happy life event for most women (2). However, some physiological factors (such as uterine contractions), psychosocial factors (such as fear and anxiety) experienced by woman during labor, as well as the cultural practices and acquired knowledge on this subject possibly aggravates the discomfort associated with childbirth pain (3-5). Managing childbirth pain effectively and keeping it under control are therefore important. Childbirth pain is not a natural and inevitable experience for every woman.

Childbirth pain can be managed effectively by various approaches, such as through pharmacological or non-pharmacological methods. Narcotics, sedatives, epidural, and general anesthesia can be used as the pharmacological intervention agents (6). In addition, these methods provide effective analgesia and can sometimes cause medical side-effects such as fetal distress and the loss of the sense of pushing (6,7). Therefore, several women prefer non-pharmacologic interventions (such as birth ball, massage, Lamaze, yoga, massage, aromatherapy, and the use of hot and cold packs) for the management of childbirth pain (2,8,9). Because these non-pharmacologic methods can provide an adequate decrease in the pain experienced during childbirth and offer several benefits, they have no side-effect on the mothers or fetuses. Moreover, they do not prevent the progress of labor and there is no possibility of developing any allergic reaction. However, these interventions can decrease the excitement and anxiety of the mother. They increase the blood flow to the uterus and decrease the muscle tension as well as increase the birth-related motivation of the pregnant woman with effective care offered during the prenatal period (9,10). Considering these points, the goal of all non-pharmacologic intervention was to build a mother's confidence in her ability to give birth through the presentation of classes that help pregnant women understand how to cope with pain in ways that both facilitates labor and promotes comfort. At this point, it is therefore important for nurses to teach a few effective non-pharmacological approaches to pregnant women during the prenatal period. The best time for teaching them is the second trimester of pregnancy to a few weeks prior to the term (6,11).

Recently, one of the effective non-pharmacological methods useful in the control of childbirth pain is reported to be birth ball exercising. This exercise improves the blood flow to the uterus in pregnant women by ensuring relaxation in the pelvic region muscles, which reduces the pain. In addition, the birth ball exercising improves the associated comfort and decreases pain by relaxing the back muscles in these pregnant women. Focusing on the movements and positions during exercise decreases a pregnant woman's attention and perception of pain (3,12). The birth ball exercise has been found to decrease the pain in the pelvic region and back (8,13,14) during labor, facilitates fetal progression through the birth channel, shortens the latent phase, decreases the need for epidural analgesia and the cesarean birth rate (2,11), and increases childbirth motivation and comfort by reducing or controlling the anxiety of the pregnant women (9).

The aim of the present study was to identify the effect of birth ball exercise on the childbirth pain during the first stage of labor in primipara pregnant women.

Method

Study Design

The present study was a semi-experimental randomized controlled study conducted with participants who were about to give birth at a labor ward between February and May 2016 in Turkey. The annual number of births at this maternity hospital in 2015 was 988. The women were randomly categorized into the intervention and control groups with an equal number of subjects in accordance with a computer-generated randomization list prepared by an independent statistician. The names of the distributed participants were given to the two certified nurses in sealed envelopes.

Participants

The inclusion criteria of the participants were as follows: pregnant women of age 18-35 years, who attended regular follow-up and pregnancy check-ups, in their 35th week of gestation, without multiple pregnancy, with normal birth weight and vertex position, with planned normal spontaneous birth (the birth decision was determined by the certified nurses/doctors and women), with a maximum cervical dilatation of 2 cm, and who could possibly give term birth. Pregnant women unwilling to participate in the study were not included. Women who developed gestational hypertension and diabetes mellitus, underwent emergency cesarean section, had fetal anomalies, were using antipsychotic drugs, had hearing and communication problems, were physically disabled, or underwent epidural anesthesia were excluded from the study. Power analysis was used to determine the sample size. The sample size was determined as suggested by a previous study conducted by Gau et al. (8). The alpha level was taken as 0.05 (α=0.05) and reliability was accepted as 95% during the power analysis calculation. The sample size in our study was identified to be 26 participants for each group. However, taking the estimated attrition rate from the previous studies (40%-60%) taken into account, 42 participants were included in each study group. Finally, the study was completed with 30 participants in each of the groups.

Data Collection Tools

We used the data collection form that questioned the socio-demographic and obstetric characteristics of pregnant women for collection of the data in the study. The data collection form was created by investigators after reviewing relevant studies in the literature (1,8,10,11). The form included 11 questions on socio-demographic characteristics (such as age and marriage duration) and 8 questions were related to obstetric characteristics (the number of prenatal follow-ups and prenatal education class attendance). A 10 centimeter (cm) horizontal pain visual analog scale (VAS) was used to determine the pain level of the patients. The VAS included values of 0-10 and is an extremely simple, effective, and repeatable pain severity measurement method. It is

often used clinically to rapidly measure the pain severity. A VAS score of 1-3.9 is evaluated as "mild pain," 4-7.9 as "moderate pain," and 8-10 as "severe pain". Regarding the VAS validity, the ease of application is a significant advantage. The answers given after repetition of the test at short intervals were similar (15).

The Intervention Program Used in This Study

The birth ball exercise program involved provision of a tutorial booklet (of 26 pages) and an educational videocassette (19-min-long) (16,17). The birth ball exercise program was created by obtaining the opinions of the relevant specialists (i.e., certified prenatal childbirth specialists, certified nurses, and physical therapist) and evaluation of the relevant literature by the investigators. The final state of the intervention program was developed based on the specialist opinions. The birth ball exercise program included 8 exercises in 4 different positions (i.e., sitting, standing, knelling, and squatting) (8,11). However, before starting the exercise program with the pregnant women, the researchers determined the size of the birth balls that would be used for the exercise. The height and the leg length of each pregnant woman were measured. The size of the birth ball was determined according to the leg length of the pregnant woman. Two different ball sizes were used in this study (55-cm- and 65-cm-diameter). Large balls (65-cm-diameter) were used for long-legged pregnant women and small balls (55-cm-diameter) were used for short-legged women. In order to ensure the safety of the women in the intervention group, the balls were fully inflated and no objects that could cause injury were left in the exercise area.

The investigators informed each intervention group participants face-to-face about the exercises program, birth ball exercise education, and implementation of the exercise with the required positions from the 35th week onward. Exercises and positions were performed once a week under the supervision of the investigators at the hospital (approximately 20-25 min for each session) to ensure the compliance of the women in the intervention group and their partners with the exercise program at the beginning. The women in the intervention group and their partners were also asked to implement the exercises and the positions for 20 min at least 3 times in a week at home for approximately 6-8 weeks. The questions of the women in the intervention group about the birth ball exercise program were answered during the weekly hospital training sessions and the prenatal follow-ups conducted every 2 weeks. Moreover, the women in the intervention group were also informed that they could leave the study if they could not implement the birth ball exercise program.

The control group received no birth ball training and performed no birth ball exercises. Women in both the groups received prenatal care (7-9-times on an average) and the routine hospital care during the regular interventions. The progression of the fetus through the birth channel, which is characteristics of uterine contractions, and the health of the fetuses were followed-up at frequent intervals during labor in both the groups. Vaginal examinations were performed every 2-4 h during the birth to determine cervical dilatation by certified nurses and doctors. All women and infants received care from the obstetricians and nurses in the prenatal and postnatal periods. In addition, each nurse routinely followed-up a maximum of 3 pregnant women.

Data Collection

The women meeting the study inclusion criteria were randomly divided into 2 groups. The passage of the participants through each trial stage is presented in Figure 1. The investigators required that the women of both groups visit the hospital when they develop uterine contractions at every 15-20 min. The cervical dilatation was 2 cm at this point of time, and the women who came to the hospital were included in the study groups. In addition, routine nursing care was provided by the hospital staff to both the groups. The investigators only collected the data about the women.

Intervention Group

The investigators were informed by the nurses at the hospital delivery room when the women reached the hospital to give birth. The cervical dilatation of the women in the intervention group was identified after the initial examination. The pregnant women were administered the data collection form and the VAS by the investigator when the cervical dilatation was 2 cm. The cervical dilatation was determined with a vaginal examination every 2-4 h, and the fetal condition, duration, frequency, and severity of the uterine contractions were routinely followed-up. Later, the women in the intervention group were provided with a birth ball of an appropriate relevant size to implement the exercise program during childbirth. The women were encouraged to use the most comfortable positions, movements, and exercises every hour during childbirth by the nurses. The birth ball exercises, movements, and positions were implemented under the supervision of certified nurses. Rest intervals were allowed when the women were tired. The partners of the women acted as passive coaches during the childbirth process. The VAS scores of the women in the intervention group were inquired and registered in the latent period when the uterine contractions developed every 4-5 min and the cervical dilatation was 4 cm. The cervical dilatation was expected to reach 6 cm when the uterine contractions developed every 2-3 min and to 8 cm when they developed every 1-2 min. The VAS scores were registered again when the cervical dilatation was 6 cm and 8 cm, respectively.

Control Group

The investigators were informed by the nurses at the delivery room of the hospital when the women in the control group arrived at the hospital to give birth. The initial examination of the women in the control group was performed and cervical dilatation was determined, followed by a close follow-up. The investigator administered the data collection form and VAS while the cervical dilatation was 2 cm. The VAS values were registered again when the cervical dilatation was 4, 6, and 8 cm, respectively.

The data collection form was completed, and the VAS score was registered in both the groups in approximately 10-12 min while the cervical dilatation of the participants was 2 cm. The VAS

scores were registered at 1-2 min while the cervical dilatation was 4 cm, 6 cm, and 8 cm, respectively. All questionnaires were administered between these uterine contractions. All the questions in the questionnaire and the VAS were read by the investigators and answered by the participants.

Ethical Considerations

The data were collected after receiving approval from the hospital, and the clinical research ethics committee of a university (study no: 99950669/54 on 2016). All women included in the study were explained about the purpose of the study. The protocol and the procedures to be used (and their advantages/disadvantages) were explained to all participants, and their written consent to participate in the study were voluntarily obtained. All participants were told that they could leave the study at any time and that their health care would not be compromised in any case. In addition, the nurses and obstetricians in the delivery room of the hospital where the study was being conducted were informed about the purpose and the method of the study.

Data Analysis

The Statistical Package for Social Sciences (SPSS) version 16.0 was used for the data management (SPSS Inc., Chicago, IL, USA). The means and standard deviations of continual variables (VAS level) along with the frequencies and percentages of binary variables (sociodemographic and obstetrical variables) were computed using the SPSS version 16. The chi-square test (X^2) and independent t-test were used to analyze the group difference. Repeated measurements analysis of variance were used to detect whether there were any differences between the pain measurements in the intervention and control groups as well as to determine the differences among the in group measurements.

Results

A total of 84 women were included in the study at first, 42 each in the intervention and control groups. However, some women were later excluded from the study due to various reasons such as emergency cesarean section (n=9), epidural anesthesia (n=9), preterm labor (n=3), post-term labor (n=1), and unwillingness to continue the study (n=2) (Figure 1). Twelve women from the intervention group and 12 from the control group were excluded because their attrition rate was 28.6%. Finally, 30 women from the intervention group and 30 from the control group were included in the study. No statistically significant difference was observed when some of the socio-demographic data [such as age, education level, prenatal class attendance, performing Pilates, body mass index (BMI), duration of marriage] were compared between the women excluded from the study (n=24) and those who completed the study (n=60) (p>0.05).

Among the 60 women who completed the study, the mean age was 28.4 [standard deviation (SD): 2.8] years. The mean BMI was 24.6 (SD: 2.4), and the mean marriage duration was 4.0 (SD: 0.9) years. All pregnant women were primiparous. It was determined that 45% of the women were university graduates, 50% were housewives, and 55% had a "medium" income. Moreover, it was found that 48.3% of the women attended the prenatal education classes and 85% did not perform Pilates. Some sociodemographic data (such as age, education level, prenatal education class attendance, performing Pilates, BMI, the duration of marriage) of the women in the intervention and control group were compared, with no statistically significant difference between the groups (Table 1, p>0.05).

The mean gestational age of the women was 39.6 (SD: 0.8) weeks. We found that 61.6% of the women were satisfied with the passive coaching of their partner during the childbirth process, and 65.0% of the women received induction. Some obstetric data (such as gestational age, satisfaction with the passive coaching of the partner, and induction) were compared between the intervention and control groups; the difference was not considered to be statistically significant (Table 2, p>0.05).

VAS score comparisons of the women from the intervention and control groups are shown in Table 3 and Figure 2, respectively. We detected that birth ball exercise reduced the birth pain. The VAS score difference (0.60) between the intervention and control groups when the cervical dilation was 2 cm was not statistically significant (F=6.141, p=0.016). The VAS score difference (0.80) between the intervention group and the control group when

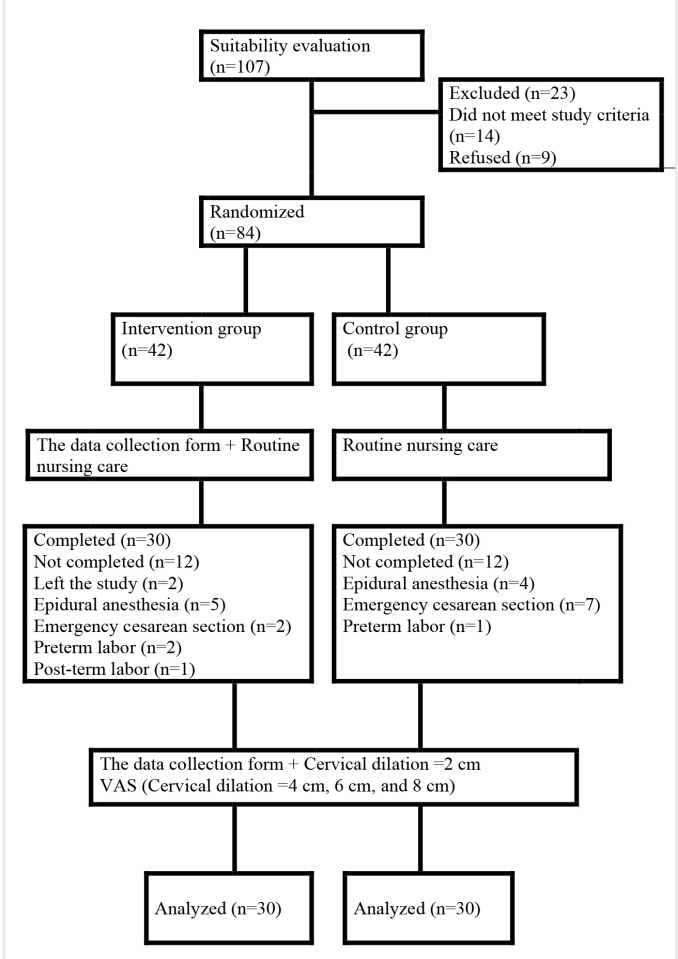

Figure 1. Passage of participants through each trial stage

the cervical dilatation was 4 cm was found to be statistically significant (F=6.146, p=0.010). The VAS score difference (1.50) between the intervention group and the control group when the cervical dilatation was 6 cm was also statistically significant (F=8.660, p=0.001). In addition, the VAS score difference (2.60) between the intervention and control groups when the cervical dilatation was 8 cm was found to be statistically significant (F=25.870, p=0.001). These results indicate that the pain scores of the women in the intervention group who implemented birth ball exercises were significantly lower those of the women in the control group when the e cervical dilation was 4-8 cm. The pain severity was "moderate" in the intervention group, but "severe"

Table 1. Distribution of some socio-demographic characteristics of the participating women

Some socio-demographic characteristics	Groups Intervention group (n=30) **n (%)**	 Control group (n=30) **n (%)**	Statistic **Statistic**	**p value**
Education level				
Junior high school	3 (10.1)	5 (16.8)		
Senior high school	11 (36.6)	14 (46.6)	0.171[x]	0.131
University	16 (53.3)	11 (36.6)		
Occupation				
House wife	12 (40.0)	18 (60.0)	2.400[x]	0.121
Working	18 (60.0)	12 (40.0)		
Income level				
Medium	15 (50.0)	18 (60.0)	0.606[x]	0.436
Higher	15 (50.0)	12 (40.0)		
Prenatal education class attendance				
Yes	16 (53.4)	13 (43.3)	1.286[x]	0.238
No	14 (46.6)	17 (56.7)		
Performing pilates				
Yes	4 (13.0)	5 (17.0)	0.131[x]	0.718
No	26 (87.0)	25 (83.0)		
Age (years), mean (SD)	28.1 (2.7)	28.8 (2.9)	0.747*	0.458
Body mass index (BMI), mean (SD)	24.2 (2.3)	25.3 (2.5)	3.606*	0.158
Duration of marriage/(years), mean (SD)	3.9 (0.9)	4.1 (0.9)	0.120*	1.867

SD: Standard deviation, *: Independent t-test; [x]: X^2

Table 2. Distribution of some obstetric characteristics of the participating women

Some obstetric characteristics	Groups Intervention group (n=30) **n (%)**	 Control group (n=30) **n (%)**	Overall (n=60) **n (%)**	**Statistic**	**p value**
Gestational age (weeks), mean (SD)	39.5 (0.7)	39.7 (0.8)	39.6 (0.8)	2.144*	0.558
Satisfaction with the passive coaching of the partner					
Yes	21 (70.0)	16 (53.3)	37 (61.6)	4.286[x]	0.179
No	9 (30.0)	14 (46.7)	23 (38.3)		
Induction					
Yes	22 (73.3)	17 (56.6)	39 (65.0)	3.354[x]	0.067
No	8 (26.7)	13 (43.4)	21 (35.0)		

*: Independent t-test; [x]: X^2, SD: Standard deviation

in the control group. Birth ball exercises were therefore found to be effective in decreasing childbirth pain in this study (Table 3, Figure 2).

Variables such as age, educational level, occupational status, income level, prenatal class attendance, performing Pilates, BMI, duration of marriage, gestational age, satisfaction from the extent of passive coaching provided by the partner, and induction were found to have no effect on the pain scores during the childbirth process of the women in both the groups.

Discussion

Birth ball exercises are one of the non-pharmacological intervention approaches useful in decreasing birth-related pain. These methods have been commonly used to control childbirth pain, especially in some countries of the Far East and Europe in the recent years, with much research as well (13,18,19). However, there was no study yet on birth ball exercises in Turkey. Therefore, we believe that our study will contribute to the literature significantly. Movements in different positions such as sitting and squatting relaxes the muscles in the pelvic region and decreases the uterine contraction severity in pregnant women who are assigned with the birth ball exercise program. This exercise program increases the blood flow to the uterus and decreases the associated pain (11,19). In addition, pregnant women who control their bodies well during an exercise can also effectively manage their pain levels (18,20). The soft surfaces of the balls used by the pregnant women in the birth ball exercise program decreases pain by reducing the pressure in the lower region of the back and providing support to the perineal region during the movements (8). The pain scores of the women in the intervention group were found to be significantly lower than those of the women in the control group when the cervical dilation was 4-8 cm in our study. The pain severity was "moderate" in the intervention group and "severe" in the control group. The birth ball exercise was therefore found to be effective in decreasing the childbirth-related pain in this study. The results of a randomized controlled study by Gau et al. (8) on 87 women also supported our results. Gau et al. (8) reported that the use of birth ball exercise can shorten the birth duration and decrease the need for epidural anesthesia and the related cesarean birth rate. Childbirth pain and the need for analgesia were found to decrease significantly after incorporating birth ball exercises in another study conducted by Leung et al. (11). Birth ball exercises has been found to be effective in the management of childbirth pain in several other studies as well (3,12,14,19). Our study results are similar to those reported in the literature.

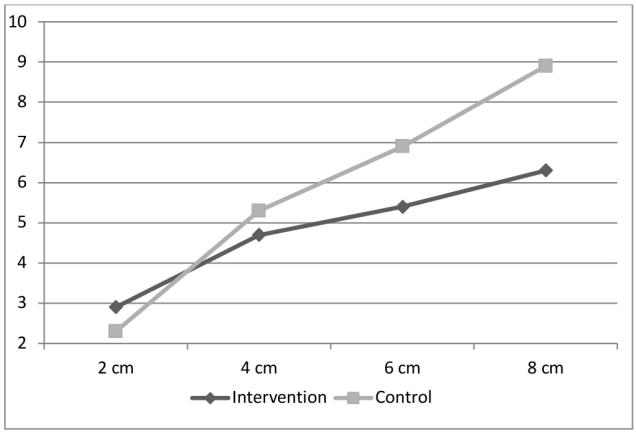

Figure 2. VAS score of the intervention and control groups
VAS: Visual analog scale

Conclusion

The VAS scores of the women in the intervention group who were assigned with birth ball exercises were found to be lower than those of the women in the control group with a statistically significant difference ($p<0.05$). The exercises were therefore found to be effective in decreasing the associated childbirth pain. Birth ball exercises can therefore be an alternative non-pharmacological intervention method in decreasing the childbirth pain. We therefore recommend the use of this exercise program by certified health professionals for the control or management of childbirth pain in the delivery room.

Ethics

Ethics Committee Approval: The data were collected after receiving approval from the hospital, and the clinical research ethics committee of a university (study no: 99950669/54 on 2016).

Table 3. VAS score comparisons of the women between the intervention and control groups

VAS score	Groups		Overall		
	Intervention group	Control group			
	Mean SD	**Mean SD**	**Mean SD**	**F**	**p†**
VAS (2 cm)	2.9 0.8	2.3 1.0	2.6 0.9	6.141	0.016
VAS (4 cm)	4.7 0.9	5.5 0.9	5.1 0.9	6.146	0.010
VAS (6 cm)	5.4 1.2	6.9 0.9	6.1 1.1	8.660	0.001
VAS (8 cm)	6.3 0.8	8.9 1.2	7.6 1.0	25.870	0.001

VAS: Visual analog scale, SD: Standard deviation, †: Variance analysis

Informed Consent: In addition, the nurses and obstetricians in the delivery room of the hospital where the study was being conducted were informed about the purpose and the method of the study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: D.A., S.K., M.E., E.G.B., F.R.G., Design: D.A., S.K., M.E., E.G.B., F.R.G., Data Collection or Processing: D.A., S.K., M.E., E.G.B., F.R.G., Analysis or Interpretation: D.A., S.K., M.E., E.G.B., F.R.G., Literature Search: D.A., S.K., M.E., E.G.B., F.R.G., Writing: D.A., S.K., M.E., E.G.B., F.R.G.

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References

1. Mirzakhani K, Hejazinia Z, Golmakani N, Sardar MA, Shakeri MT. The effect of birth ball exercises during pregnancy on mode of delivery in primiparous women. JMRH2015;3:269-5.
2. Avcıbay B, Alan S. Nonpharmacological methods for management of labor pain. Mersin University Journal of Health Sciences 2011;4:18-24.
3. Hau WL, Tsang SL, Kwan W, Siu-King Man L, Lam KY, Ho LF. The use of birth ball as a method of pain management in labour. Hong Kong J Gynaecol Obstet Midwifery 2012;12:63-8.
4. Makvandi S, Roudsari RL, Sadeghi R, Karimi L. Effect of birth ball on labor pain relief: a systematic review and meta-analysis. J Obstet Gynaecol Re 2015;41:1679-86.
5. Sani RM. Cultural approach to birth pain. Hacettepe University Faculty of Health Sciences Journal 2015;1:1-7.
6. Yıldırım G, Şahin NH. Nursing approach in controlling labor pain. Cumhuriyet Universitesi Journal of Nursing School 2003;7:14-20.
7. Basgöl S, Beji NK. Common practices and evidence based approach in first stage of labor. Journal of Duzce University Health Sciences Institute 2015;5:32-9.
8. Gau ML, Chang CY, Tian SH, Lin KC. Effects of birth ball exercise on pain and self-efficacy during childbirth: a randomised controlled trial in taiwan. Midwifery 2011;27:293-300.
9. Kwan Winny SC, Chan S, Wan-Hon LI. The birth ball experience: outcome evaluation of the intrapartum use of birth ball. Hong Kong J Gynaecol Obstet Midwifery 2011;11:59-64.
10. Shu-Hui T, Chien-Huei K, Kuan-Chia L, Ching-Yi C, Meei-Ling C. Effects of birth ball exercises on labor pain and childbirth satisfaction. JNHR 2013;9:13-22.
11. Leung Regina WC, Jess Li FP, Leung Mary KM, Fung Brigitte KY, Fung Lawrence CW, Tai SM. Efficacy of birth ball exercises on labour pain management. HKMJ 2013;19:393-9.
12. Shallow H. My rolling programme: the birth ball ten years experience of using the physiotherapy ball for labouring women. MIDIRS Midwifery Digest 2003;13:28-30.
13. Delgado-García BE, Orts-Cortés MI, Poveda-Bernabeu A, Caballero-Pérez P. Randomised controlled clinical trial to determine the effects of the use of birth balls during labour. Enfermería Clínica 2012;22:35-40.
14. Taavoni S, Abdolahian S, Haghani H, Neysani L. Effect of birth ball usage on pain in the active phase of labor: a randomized controlled trial. JMWH 2011;56:137-40.
15. Eti Aslan F. The assesment methods of pain. Cumhuriyet Universitesi Journal of Nursing School 2002;6:9-16.
16. Chang CY, Yu MH, Chen JJ, Gau ML. Designed a VCD teaching birth ball exercises to assist parturient women during labour. J Health Sci Edu 2008;10:99-110.
17. Watkins SS. Get on the ball the "birth ball" that is! Inter J Childbirth Edu 2001;16:17-9.
18. Mathew A, Nayak S, Vandana K. A Comparative study on effect of ambulation and birthing ball on maternal and newborn outcome among primigravida mothers in Selecte Hospitals in Mangalor. Nitte University Journal of Health Science 2012;2:2-5.
19. Zaky HH. Effect of pelvic rocking exercise using sitting position on birth ball during the first stage of labor on its progress. Journal of Nursing and Health Science 2016;5:19-27.
20. Taşçı E, Sevil Ü. Nonpharmacological approach intended for labor pain. Electron J Gen Med 2007;17:181-6.

Original Article

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Comparison of Mother-Infant Relationship in Turkish Primiparous Women in Accordance with Vajinal Birth and Cesarean Section

Türk Primipar Kadınlarda Anne-Bebek İlişkisinin Vajinal Doğum ve Sezaryene Göre Karşılaştırılması

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ABSTRACT

Objective: The relationship between the mother and the infant begin on the first day of birth and that affects the future life of the infant. Thus, the aim of the present study was to compare the mother-infant relationship between women who had vaginal birth and those who had cesarean section.

Methods: This prospective descriptive study was conducted on 300 primiparous women after obtaining the necessary permission. The study sample was categorized into 3 groups: vaginal delivery (VD; n=100), emergency cesarean section (EmCS; n=100), and elective cesarean section (ElCS; n=100). The Descriptive Characteristics Form, Maternal Attachment Scale (MAS), Neonatal Perception Inventory (NPI), and Postpartum Parenting Behavior Scale (PPBS) were used as the data collection tools.

Results: The mean MAS score of the mothers was 96.6±5.58; 83.7% of the mothers perceived their babies as positive and 16.3% as negative (according to the NPI). No statistically significant relationship was noted among the MAS, NPI, and the mode of delivery (p>0.05). The mean PPBS score of the mothers was 3.24±1.59 (mean PPBS score by groups; VD =3.62±1.57, EmCS =2.84±1.52, ElCS =3.28±1.60). Mothers who had VD showed higher mean PPBS scores than those who had EmCS (p=0.001).

Conclusion: Our results suggest that the mode of delivery affects the parenting behavior during the early postpartum period.

Keywords: Attachment, mode of delivery, mother-infant relationship, parenting, perception

ÖZ

Amaç: Doğumdan sonraki ilk günlerde başlayan anne bebek ilişkisi bebeğin gelecekteki yaşamını etkilemektedir. Bundan dolayı bu çalışmada anne-bebek ilişkisinin vajinal doğum ve sezaryene göre karşılaştırılması amaçlanmıştır.

Yöntemler: Prospektif tanımlayıcı tipte yapılan çalışma, gerekli izinler alındıktan sonra 300 primipar kadın ile gerçekleştirilmiştir. Örneklem, vajinal doğum (n=100), acil sezaryen (n=100) ve elektif sezaryen (n=100) olmak üzere üç gruba ayrılmıştır. Veri toplama aracı olarak Tanıtıcı Özellikler Formu, Maternal Bağlanma Ölçeği (MBÖ), Yenidoğanı Algılama Ölçeği (YAÖ) ve Doğum Sonrası Ebeveynlik Davranışı Ölçeği (DSEDÖ) kullanılmıştır.

Bulgular: Annelerin ortalama MBÖ skoru 96,6±5,58'dir. Annelerin %83,7'si bebeklerini pozitif olarak algılarken, %16,3'ü (YAÖ'ye göre) bebeklerini olumsuz olarak algılamıştır. MBÖ, YAÖ ve doğum şekli arasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır (p>0,05). Annelerin ortalama DSEDÖ skoru 3,24±1,59'dir. (DSEDÖ gruplara göre; vajinal doğum (VD) =3,62±1,57, acil sezaryen =2,84±1,52, elektif sezaryen =3,28±1,60). VD yapan annelerde, ortalama DSEDÖ skoru, acil sezaryen olan annelere göre daha yüksek bulunmuştur (p=0,001).

Sonuç: Doğum şeklinin doğum sonrası dönemde ebeveynlik davranışını etkilediği sonucuna varılmıştır.

Anahtar Sözcükler: Bağlanma, doğum şekli, anne-bebek ilişkisi, ebeveynlik, algılama

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Introduction

Postpartum period is a significant milestone in the protection and development of family and community health which involves physical, social, and emotional changes (1). During this period, the mother develops a deep psychological and biological relationship with the infant. This relationship, which begins in the first days of life for the baby, forms the basis of the mother-infant relationship to be formed in the future. In addition, the mother-infant relationship affects the emotional and social development of a baby throughout the life, starting from the infancy. In addition, it makes has significant contributions to boasting the self-confidence and problem-solving abilities of the child by affecting his or her relationship with people and their psychological state (2). The mother-infant interaction is closely related to attachment, parenting behavior, and maternal neonatal perception.

Attachment is a life experience that begins with the first contact between the mother and baby, and it continues throughout the postpartum period, with predominating emotional aspects (3). Reflexes of the newborn observed immediately after birth in the form of capture, sucking, searching, finger sucking, and orienting toward mother are defined as attachment behavior (4). Generally, the mother and the infant stay together during the first few minutes of birth, during which time, the mother sees the infant, touches him/her, and initiates the interaction; this interaction positively affects her perception of the baby (5). The parents' behaviors, such as talking to the infant, making eye contact, touching infant's hands and feet, caressing, and examining the baby are considered as parenting behaviors, which provides important clues about the attachment process between mother and the infant (6). Since infancy is the fastest period of development, the relationship that the infant establishes with the caregiver during this period is of great importance for his/her development in the entire life.

The following factors affect the formation and development of maternal attachment: separation from the infant for any reason (such as prematurity and routine procedures) (7,8), unplanned pregnancy, and unwanted pregnancy (9,10), any disorder following the mode of delivery, fatigue (11,12), mode of delivery (13,14), maternal complications (15,16), and support systems, among others (17,18). Weak interactions affect an infant's cognitive, social, and emotional development as well as the physical health and interpersonal relationships, which can cause long-term issues (2). Therefore, it is believed that early intervention in the mother-infant relationship is an appropriate approach to prevent problems that may occur in establishing the mother-infant attachment later (19). Implementations such as breastfeeding as quickly as possible, mother and the infant sharing the same room, kangaroo care, getting social support, and giving infant massage, among others play an important role in the development of mother-infant attachment (20).

On the other hand, mothers face some difficulties while trying to interact with the newborn in the postpartum period. When considering the mode of delivery, it has been noted that women with cesarean section experience more physical and psychological issues in the postpartum period than women who had vaginal delivery (VD) (21,22). Women with VD need less help in meeting their personal care and needs. She can start breastfeeding shortly after birth, which facilitates the initiation of the mother-infant relationship. However, women who have cesarean section face difficulties in taking care of the baby and breastfeeding, in taking care of their own in attaching to the infant, they also face the discomfort due to seeing their baby late, along with the guilt of not fulfilling their roles and responsibilities (23-26). In the study by Cooklin et al. (27), the mothers in the postpartum period (n=229) were evaluated in terms of their physical health symptoms during the first, second, third, fourth, and eighth weeks of birth. The pain was persistent in one-fifth of all women who had a cesarean section and in one-third of those who had VD; the latter stated that the pain was relieved within 2 months. Moreover, one-fifth of all women reported having no pain in the third week. In addition, the postpartum fatigue levels of women with cesarean section were greater than those of women who delivered vaginally and faced difficulties in infant care activities. In addition, it has been reported that maternal attachment level decreases as the postpartum fatigue level increases (11,12). In the study conducted by Erbas (25), in order to determine the health problems experienced by women during the postpartum period based on the mode of delivery, breastfeeding, nutrition, domestic relations, and pain problems were noted more frequently in patients with cesarean section than in those with VD, and the difference was found to be significant.

Healthy social relationships begin with a positive emotional attachment between the mothers and their infants. The foundations of this emotional attachment are based on the early postpartum period (2). In the recent years, the increased rates of cesarean section suggest that the mode of delivery possibly has an effect on the maternal-infant attachment. Therefore, mother-infant attachment has become a major issue in the postpartum care, essentially for primiparous women. Understanding neonatal perception, maternal attachment, and parenting behavior related to the mode of delivery would help nurses and midwives to counsel women during the postnatal support care so as to improve the quality of maternal and infant care. However, there are only a limited number of studies on postpartum maternal-infant interaction in Turkey. Thus, the aim of the present study was to compare the mother-infant relationship in accordance with to the mode of delivery.

Method

Type of Study

We employed a prospective descriptive study design to determine the relationship among neonatal perception, maternal attachment, parenting behavior, and the mode of delivery in primiparous women who were referred to a private hospital.

Population and Sample

A total of 300 primiparous women aged 18-49 years who did not have any medical problems that could affect the maternal

and infant health during the postpartum period were included in the study. The study subjects was admitted to the obstetrics clinic of the largest hospital on the European side of Istanbul and a private hospital with approximately 5,000 annual birth rate. The number of population was calculated as 2,436, and the minimum sample size was 224 with a simple random sample size estimation formula. The G *Power 3.1.9.2 program was used for post-hoc power analysis. The influence size was 0.21 according to the PPBS scores between the groups. The power obtained for the alpha 0.05 based on the sample numbers of vaginal delivery group (n=100), emergency cesarean group (n=100), and elective cesarean group (n=100) was found to be 91%. The percent of power calculated in the study provides the desired statistical power excessively. A total of 21 women were excluded from the study because of missing data (postpartum women did not return within 30 days for the NPI II) and because of their unwillingness to continue the research.

Sample Selection Criteria: Age of least 18 years, first-time pregnant women, who gave birth at term (37-42 gestational weeks), singleton pregnancy, without any health issues, volunteering to participate in the study, not having any communication disorder, and comprehension disorder individuals.

Exclusion Criteria: Preterm delivery, multiple pregnancy, infant health problem, communication disorder, and individual with impaired understanding.

Data Collection Tools

Collection of research data was achieved by means of the Descriptive Characteristics Form, Maternal Attachment Scale (MAS), Neonatal Perception Inventory (NPI), and Postpartum Parenting Behavior Scale (PPBS).

Descriptive Characteristics Form: This form consisted of 15 questions, 4 on sociodemographic characteristics and 11 on obstetrics characteristics.

Maternal Attachment Scale (MAS): This scale was developed by Muller (28) to measure loving maternal attachment. The validity and reliability of the scale were tested by Kavlak and Şirin (8). The scale consisted of 26 items. Each item is scored on a Likert-type scale from 1 to 4, where 1 indicates = seldom, 2= sometimes, 3= very often, and 4= always, and the item total score was evaluated. A high mean score indicates a high level of maternal attachment, while a low mean score indicates a low level of maternal attachment. Cronbach alpha values were reported to be 0.77 in a previous study (8), while it was 0.83 in the present study.

Neonatal Perception Inventory (NPI) (I and II): It was developed in 1971 by Broussard and Cassidy to measure mothers' perception of their infants. As a result of the measurement, the existing problems in the expectation and relationship with the infant of the mother are determined and risky infants that may develop emotional disorders in the future were identified. The validity and reliability study of the Turkish version of the NPI was conducted by Balci (29) in 1997 in our country. The data to be obtained from the NPI was calculated by a researcher in accordance with the scale's directive and the "mother's perception of the infant score" was obtained. Although the mother's perception of her infant score was obtained, the total score of "your infant forms" was deducted from the total score obtained from "any infant forms." A total score of ≤0 was deemed as a negative perception, while that above 0 was accepted as a positive perception. The NPI-I form was used in a face-to-face interview of the mother in the first days of birth. II. form was filled by getting in touch with the mothers through phone when the infant was aged 30 days. The Cronbach alpha values obtained in the present study were 0.827.

Postpartum Parenting Behavior Scale (PPBS): It was developed in 2001 by Britton et al. (30) to evaluate the parenting behavior toward infant during the first encounter with the infant after birth. The validity and reliability of the Turkish version of the scale was performed by Calisir et al. (31) in 2009 in Turkey. In the application of the scale, during the first 10 min of the encounter of the mother with the infant after birth, the observer observed that the behaviors of the mother toward the infant was in accordance with the articles specified in the "PPBS," and the existing behavior was marked with (+) and missing behavior with (-) and these marks were recorded. For each article of the 6-item scale, the observed behavior was evaluated as one (1) point and the unobserved behavior as zero (0) points. The total score of the scale is 0-6 points. The higher total score obtained from the scale indicated more positive parenting behavior toward the infant. The Cronbach alpha values obtained in the present study were 0.702.

Data Collection

Primiparous women who were admitted to the obstetrics clinic and who were deemed suitable as per the sample selection criteria were provided with information regarding the research, and their written and verbal consent were obtained. Data collection was started in January 2017 and continued until the required number of samples were reached and, finally, discontinued in June 2017. First, PPBS was implemented after an observation by the researcher during the first encounter of the mother and infant after the birth. Next, NPI I was implemented on the postpartum days 1-2. On day 30, MAS and NPI II were implemented. Each interview took 15-20 min.

Ethical Considerations

Researchers obtained a written approval from the ethics committee of the İstanbul Medipol University and the participants before beginning the data collection process. Written informed consent form was obtained from the participants (protocol number 2016/497).

Data Analysis

While evaluating the findings, IBM SPSS Statistics 22 for statistical analysis (SPSS IBM, Turkey) program was employed. Descriptive statistical methods when evaluating the study data; Student's t-test and Mann-Whitney U test were used for the comparison between the two groups. Kruskall-Wallis and One-

Way analysis of variance tests were performed to compare the data between more than 2 groups, while Turkey HSD tests were used to determine the group causing the difference. Chi-square test was used to evaluate the qualitative data. Pearson's correlation was performed to determine the relationship of dependent variables on each other.

Results

Findings on the Descriptive Characteristics of the Participating Mothers

The ages of the mothers ranged 21-38 years (mean age: 27.46±35.2 years). In addition, 65.7% (n=197) of the mothers who participated in the study had bachelor-master's degree, and 51.7% (n=155) of them were employed. In terms of income, 77% (n=231) had low-moderate income. According to the obstetric history, 85% (n=255) were primigravida, 86.0% (n=258) had a planned pregnancy, and 11.7% (n=35) had a miscarriage/curettage history.

There was a significant difference between the age groups and the delivery mode ($p<0.05$). Vaginal birth rates of mothers aged <25 years and elective cesarean rates of mothers >30 years were found to be high. A significant relationship was noted between the income status and the mode of delivery, with women with higher income opting for elective cesarean section (ElCS). No significant relationship among the education level, working status, the number of pregnancies, miscarriage/curettage, and planned pregnancy with the delivery mode ($p>0.05$) (Table 1).

Findings on Neonatal Perception Inventory

In terms of the perception status, 16.3% of all mothers perceived their infant as negative, while 83.7% perceived them as positive. No significant relationship was noted between the mode of delivery and the perception status ($p>0.05$) (Table 2). In addition, no significant relationship was noted between the mothers' perception status and the descriptive characteristics of the mothers according to the results of the scores received from NPI ($p>0.05$).

Table 1. Descriptive characteristics

		Vaginal delivery	Emergency C-section	Elective C-section	Total	Statistical test and significance	
		n (%)	**n (%)**	**n (%)**	**n (%)**	**x^2**	**p**
Age	18-24 years	29 (44.6)	24 (36.9)	12 (18.5)	65 (21.7)	16.298	0.003
	25-29 years	48 (31.6)	56 (36.8)	48 (31.6)	152 (50.7)		
	30-39 years	23 (27.7)	20 (24.1)	40 (48.2)	83 (27.7)		
Education	Primary school	8 (34.8)	7 (30.4)	8 (34.8)	23 (7.7)	1.824	0.768
	High school	22 (27.5)	30 (37.5)	28 (35.0)	80 (26.7)		
	Bachelor-mMaster degree	70 (35.5)	63 (32.0)	64 (37.5)	197 (65.7)		
Working status	Yes	53 (34.2)	51 (32.9)	51 (32.9)	155 (51.7)	0.107	0.948
	No	47 (32.4)	49 (33.8)	49 (33.8)	145 (48.3)		
Income status	Low-moderate	83 (35.9)	81 (35.1)	67 (29.0)	231 (77.0)	8.583	0.014
	High	17 (24.6)	19 (27.5)	33 (47.8)	69 (23.0)		
Number of pregnancies	Primigravida	89 (34.9)	83 (32.5)	83 (32.5)	255 (85.0)	1.882	0.390
	Multigravida	11 (24.4)	17 (37.8)	17 (37.8)	45 (15.0)		
Miscarriage/curettage	Yes	8 (22.9)	12 (34.3)	15 (42.9)	35 (11.7)	2.394	0.302
	No	92 (34.7)	8 (33.2)	85 (32.1)	265 (88.3)		
Planned of pregnancy	Planned	83 (33.7)	88 (34.1)	83 (32.2)	258 (86.0)	1.163	0.559
	Unplanned	17 (31.0)	12 (28.6)	17 (40.5)	42 (14.0)		

Chi-square test, Fisher's exact test

Table 2. Comparison of the mothers' perception status toward infants in reference to the mode of delivery

Status of perception	Vaginal delivery (n=100)		Emergency C-section (n=100)		Elective C-section (n=100)		Statistical test and significance	
	Number	**%**	**Number**	**%**	**Number**	**%**	**x^2**	**p**
Negative perception (Negative or 0 score)	14	14.0	15	15.0	20	20.0	1.512	0.469
Positive perception (Positive score)	86	86.0	85	85.0	80	80.0		

chi-square test

Findings on Maternal Attachment Scale

The mean MAS score of the mothers was 96.6±5.58. The mean MAS score was 96.17±5.99 in mothers who delivered vaginally, 96.95±5.62 in those who delivered via emergency cesarean section (EmCS) and 96.68±5.12 in mothers with ElCS, respectively. There was no significant difference between delivery mode and mean MAS score (p>0.05) (Table 3). However, the mean MAS score of primary school mothers was found to be significantly lower than the mothers with high school and higher education level (p<0.05). The mean score of MAS: primary school graduates =93.82±6.04, high school-associate degree =96.97±5.60, undergraduate-graduate =96.77±5.45, p=0.044). There was no significant difference between age, working status, income status, number of pregnancies, history of miscarriage/curettage, pregnancy planning with the mean MAS score (p>0.05).

Findings Findings on Postpartum Parenting Behavior Scale

The mean score of PPBS of the mothers was 3.24±1.59. The mean score of PPBS of the mothers was 3.62±1.57 in VD, 2.84±1.52 in EmCS, and 3.28±1.60 in ElCS. There was a statistically significant difference between the mode of delivery and the mean PPBS of the mothers score of the mothers (p=0.002). Mothers who had VD had higher mean scores of PPBS than mothers who had EmCS. (p<0.01) (Table 4).

Correlation

Correlation analysis between the mean PPBS score and the mean MAS score was found to be positively weak (r=0.289, p=0.0001) (Table 5).

No correlation was noted between the mean score of the NPI and the mean score of the MAS (r=0.109, p=0.060) (Table 6).

Table 3. Comparison of score average of MAS of mothers by mode of delivery

Score average of Maternal Attachment Scale	Vaginal delivery (n=100)	Emergency C-section (n=100)	Elective C-section (n=100)	Statistical test and significance	
Score average of Maternal Attachment Scale =96.6±5.58	$\overline{X}$ ± SD (min-max) 96.17±5.99 (81-104)	$\overline{X}$ ± SD (min-max) 96.95±5.62 (84-104)	$\overline{X}$ ± SD (min-max) 96.68±5.12 (82-104)	F 0.502	p 0.606

min: Minimum, max: Maximum, SD: Standard deviation

Table 4. Comparison of score average of PPBS averages of mothers by mode of delivery

Score average of Postpartum Parenting Behavior Scale	Vaginal delivery (n=100)	Emergency C-section (n=100)	Elective C-section (n=100)	Statistical test and significance	
Postpartum Parenting Behavior Scale	$\overline{X}$ ± SD (median) 3.62±1.57 (3.0)	$\overline{X}$ ± SD (median) 2.84±1.52 (3.0)	$\overline{X}$ ± SD (median) 3.28±1.60 (3.0)	KW 12.039	p 0.002

Kruskall-Wallis, SD: Standard deviation, PPBS: Postpartum Parenting Behavior Scale

Table 5. The relationship between MAS and PPBS

	Maternal Attachment Scale Average	
	r	p
Postpartum Parenting Behavior Scale	0.289	0.0001

Pearson's correlation, MAS: Maternal Attachment Scale, PPBS: Postpartum Parenting Behavior Scale

Table 6. The relationship between MAS and NPI

	Maternal Attachment Scale Average	
	r	p
Neonatal Perception İnventory average	0.109	0.060

Pearson's correlation, MAS: Maternal Attachment Scale, NPI: Neonatal Perception İnventory

Discussion

Attention was paid to ensure that the study groups were homogeneous. Nevertheless, some differences were detected between the groups of different delivery methods. Women who had cesarean section were older, and women with higher family income had more number of cesarean sections (32). Similarly, elderly women with high financial income (33) reported that they prefer to undergo cesarean section more rather than VD. In addition, in the Turkey Demographic and Health Survey (TDHS) 2018, it was stated that the cesarean rates were highest among mothers with the highest educational level (63%) and of those mothers who live in the highest welfare households (68%) (34). Although the highest rate of cesarean section is recommended by the World Health Organization (WHO) as 15%, the cesarean rates continue to increase dramatically across the world and the country. Turkey is a country with a high rate of cesarean section. According to the WHO 2015 report: Cesarean section is performed more in countries such as primarily Brazil, South America countries, Cyprus, Egypt, Iran, Chile, and Turkey. This ratio is 37% in Turkey (35). When the TDHS 2018 was examined, 37% of cesarean section rate in 2008 increased to 52% in 2018 in Turkey. In addition, 54% of the first deliveries were performed by cesarean section (34).

The positive perception of mothers toward her infant constitutes the beginning of a quality mother-infant relationship and contributes to the growth and development of the infant. If the mother's perceptions about her infant do not develop positively, the mother will not benefit from prenatal care adequately and will hence risk both her and the infant's health (29). The positive perception of the infant with the mother is the positive connection between the mother and the infant whereby effective communication is established. In our study, it was observed that there was no significant relationship between the mode of delivery and the mothers' perception of their infants ($p>0.05$). In the study performed by Cakir and Alparslan (36), 230 mothers and newborns were included in the study in order to determine the effect of delivery mode on mother-infant interaction, and a mother's perception of her newborn. Similar to our findings, no significant difference was noted between the delivery mode and the perception attitude of mothers on the newborn (36). However, a few studies in the literature indicated that negative perception of the infant causes the development of insecure attachment during infancy and adulthood (19,37). Therefore, it is believed that the positive perception of the mother toward her infant may be a factor affecting the mother-infant relationship and that the factors affecting the perception should be examined. However, examination of the literature yielded that studies investigating the factors affecting the perception of newborn perception of mothers is limited, warranting more studies.

In the study, when the mean score of MAS of the mothers was examined according to the mode of delivery, the mean MAS score was 96.6±5.58. These averages were 96.17±5.99 in VD, 96.95±5.62 in EmCS, and 96.68±5.12 in ElCS (Table 3). In the study of Kavlak and Şirin (8), which performed the Turkish adaptation of the MAS, the mean MAS score reported for 165 mothers, was 94.74±6.23 for mothers with a 1-month-old infant. In the study conducted by Alan and Ege (17) to determine the effect of social support on maternal attachment, the mean maternal attachment score was found to be 96.53±9.25. Our findings are similar to those performed by other researches. No significant difference was noted between the delivery mode and the mean MAS score ($p>0.05$). Cinar et al. (18) conducted a study in order to determine the relationship among maternal attachment, perceived social support, and breastfeeding adequacy, indicating no significant difference between the mode of delivery and maternal attachment. The literature findings support the present research findings (5,11,14). Unlike our findings, Reenen and Rensburg (38) and Zanardo et al. (39) reported that unplanned cesarean section negatively affects the attachment status. It is believed that the difference between the findings is attributable to the social structure we live in.

It is believed that women who undergo cesarean section experience frustration, stress, and dissatisfaction and that cesarean section adversely affects the mother-infant interaction and therefore poses a risk for infants (40). In the present study, when the mean scores of PPBS of the mothers were examined in accordance with the mode of delivery, the mean score of women who had VD was statistically significant and higher than that of women who had EmCS ($p=0.002$). The fact that mothers who give vaginal birth start to breastfeed shortly after the delivery, enabling skin to skin contact, whereby the infant reinforces the interaction with the mother. However, problems such as pain, effect of anesthesia, and physical limitations caused by cesarean section, which is a surgical intervention, complicate the mother-infant interaction (11,20,24). This is an expected consequence considering the negative effects of cesarean section. Unlike our findings, Koc et al. (41) stated that the mean PPBS scores of mothers who underwent cesarean section were significantly higher than those of women who had VD. The reason for the difference is believed to be due to the type of anesthesia applied in the cesarean section. However, the type of anesthesia was not considered in the study performed by Koc et al. (41)

In a correlational analysis, a weak positive relationship was noted between the mean score of MAS and the mean score of PPBS ($r=0.289$, $p=0.0001$). Britton et al. (30) reported that mothers with a high mean PPBS score exhibited safe attachment behavior. No significant correlation was noted between the mean score of the NPI and the mean score of the MAS.

Study Limitations

The results of the present study are limited by the sample size and the institutions in the scope of the research. In addition, it is believed that the factor of pain may have an effect on the parenting behavior of mothers during the postpartum period. Therefore, it is recommended to work with the addition of pain assessment to the variables.

Conclusion

It is believed that the results of the present study will provide important information to facilitate researchers and guide future

researches. We noted that the mode of delivery did not affect the maternal attachment and a mother's perception of her newborn, although it affected the parenting behavior in the early postpartum period. Positive parenting behavior positively affects the formation of maternal attachment. In line with the results obtained from the present research, we recommend the following:

- In the prenatal period, the mother and father candidates should be informed about the attachment between the mother and the infant, and the points that will support the formation and development of the attachment should be clearly indicated.
- As long as there is no health problem, nurses should encourage women to give vaginal birth.
- Trainings should be provided to help mothers to get used to this period by providing trainings on problems that may be encountered in the postpartum period, such as infant care and breastfeeding.
- In the early postpartum period, nurses should carefully monitor the mother's behavior toward her infant in order to evaluate the mother-infant interaction.
- The nurse should consider the family as a whole, define the social support systems of the mother, and ensure that the mother and the newborn are supported in their needs, along with eliminating the elements that can prevent the interaction between the mother and the infant.

Ethics

Ethics Committee Approval: İstanbul Medipol University 19.10.2016 received on (Decision number: 497).

Informed Consent: Written informed consent form was obtained from the participants

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: E.Z.Ç., F.O., Design: E.Z.Ç., F.O., Data Collection or Processing: E.Z.Ç., Analysis or Interpretation: E.Z.Ç., F.O., Literature Search: E.Z.Ç., F.O., Writing: E.Z.Ç., F.O.

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References

1. Fahey JO, Shenassa E. Understanding and meeting the needs of women in the postpartum period: the perinatal maternal health promotion model. J Midwifery Womens Health 2013;58:613-21.
2. Johnson K. Maternal-infant bonding: A review of literature. International Journal of Childbirth Education 2013;28:17-22.
3. Young R. The importance of bonding. International Journal of Childbirth Education 2013;28:11-6.
4. Guneri S. Evidence based practices in early postpartum period. Gümüşhane University Journal of Health Sciences 2015;4:482-96.
5. Taffzoli M, Asadi MM, Aminyazdi SA, Shakeri MT. The relationship between maternal-fetal attachment and mother-infant attachment behaviors in primiparous women referring to mashhad health care centers. J Midwifery Reprod Health 2015;3:318-27.
6. Ozkan H, Kanbur A, Apay S, Kilic M, Agapinar S, Ozorhan EY. The evaluation of parenthood attitudes of the mothers in postpartum period. The Medical Bulletin of Şişli Etfal Hospital 2013;47:117-21.
7. Bystrova K, Ivanova V, Edhborg M, Mathiesen AS, Ransjö-Arvidson AB, Mukhamedrakhimov R et al. Early contact versus separation: Effects on mother–infant interaction one year later. BIRTH 2009;36:97-109.
8. Kavlak O, Şirin A. The Turkish version of Maternal Attachment Inventory. International Journal of Human Sciences 2009;6:188-202.
9. Karacam Z, Emine S, Amanak K. Effects of unplanned pregnancy on neonatal health in Turkey: A case-control study. International Journal of Nursing Practice 2010;16:555-63.
10. Brockington IF, Aucamp HM, Fraser C. Severe disorders of the mother-infant relationship: Definitions and frequency. Arch Womens Ment Health 2006;9:243-51.
11. Lai YL, Hung CH, Stocker J, Chan TF, Liu Y. Postpartum fatigue, baby-care activities, and maternal–infant attachment of vaginal and cesarean births following rooming-in. Applied Nursing Research 2015;28:116-20.
12. Yesilcinar I, Yavan T, Karasahin KE, Yenen MC. The identification of the relationship between the perceived social support, fatigue levels and maternal attachment during the postpartum period. J Matern Fetal Neonatal Med 2016;30:1-8.
13. Orun E, Yalcin SS, Mutlu B. Relations of maternal psychopathologies, social-obstetrical factors and mother-infant bonding at 2-month postpartum: A sample of Turkish mothers. World J Pediatr 2013;9:350-5.
14. Figueiredo B, Costa R, Paecho A, Paris A. Mother-to-infant emotional involvement at birth. Matern Child Health J 2009;13:539-49.
15. Cankaya S, Yilmaz SD, Can R, Kodaz ND. Effect of postpartum depression on maternal attachment. Acibadem University Health Sciences Journal 2017;4:232-40.
16. Ozturk R, Saruhan A. Invastigation of correlation between depression and maternal attachment of mothers with 1- to 4-month-old premature babies treated at the hospital. Turkish Journal of Research & Development in Nursing 2013;15:32-47.
17. Alan H, Ege H. The influence of social support on maternal-infant attachment in Turkish society. Journal of Anatolia Nursing and Health Sciences 2013;16:234-240.
18. Cinar N, Kose D, Altinkaynak S. The relationship between maternal attachment, perceived social support and breast-feeding sufficiency. J Coll Physicians Surg Pak 2015;25:271-5.
19. Povedano M, Noto IS, Pinhero MS, Guinsburg R. Mother's perceptions and expectations regarding their newborn infants: The use of Broussard's Neonatal Perception Inventory. Rev Paul Pediatr 2011;29:239-44.

20. Redshaw M, Hennegan J, Kruske S. Holding the baby: Early mother–infant contact after childbirth and outcomes. Midwifery 2014;30:e177-e87.
21. Kartal YA, Ozsoy A, Uner K. Determination of postnatal comfort levels of puerperants in a public hospital and affecting factors. International Journal of Health Sciences Research 2018;8:206-12.
22. Karakaplan S. The effects of birth methods on postnatal comfort of mothers and on newborn. (Master's thesis). İstanbul: Marmara University. 2007.
23. Gungor I, Gokyildiz S, Nahcivan NO. Opinions of a group of women who had caesarean sections about their births and her problems in the early postpartum period. Florence Nightingale Journal of Nursing 2004;13:185-97.
24. Cakmak H, Kuguoglu S. Comparison of the breastfeeding patterns of mothers who delivered their babies per vagina and via cesarean section: An observational study using the LATCH breastfeeding charting system. Int J Nurs Stud 2007;44:1128-37.
25. Erbas N. Determination of the health problems among women in postpartum period depending on the way of giving birth: An example from Sivas for the year 2012. Journal of Continuing Medical Education 2017;26:133-8.
26. Cetisli NE, Arikan G, Top ED. Maternal attachment and breastfeeding behaviors according to type of delivery in the immediate postpartum period. Rev Assoc Med Bras (1992) 2018;64:164-9.
27. Cooklin AR, Amir LH, Cullinane M, Fisher JR, Donath SM. Physical health, breastfeeding problems and maternal mood in the early postpartum: A prospective cohort study. Arch Womens Ment Health 2018;21:365-74.
28. Muller ME. A questionnaire to measure mother-to-infant attachment. Journal of Nursing Measurement 1994;2:129-141.
29. Balci S. The Mothers' perception of their babies who had their first babies. (Master's thesis) İstanbul: Istanbul University. 1997.
30. Britton HL, Gronwaldt V, Britton JR. Maternal postpartum behaviors and mother-infant relationship during the first year of life. J Pediatr 2001;138:905-9.
31. Calisir H, Karacam Z, Akgul FA, Kurnaz DA. Validity and Reliability of The Turkish Version of The Postpartum Parenting Behavior Scale. Journal of Atatürk University School of Nursing 2009;12:1-8.
32. Buyukbayrak EE, Kaymaz O, Kars B, Karsidag AY, Bektas E, Unal O, Turan C. Caesarean delivery or vaginal birth: Preference of Turkish pregnant women and influencing factors. J Obstet Gynaecol 2010;30:155-8.
33. Dereli Yilmaz S, Demirgoz Bal M, Kizilkaya Beji N, Uludag S. Women's preferences of method of delivery and influencing factors. Iran Red Crescent Med J 2013;15:683-9.
34. Hacettepe University Institute of Population Studies. 2018 Turkey Demographic and Health Survey (TDHS). Hacettepe University Institute of Population Studies, T.C. Presidency of Strategy and Budget and TUBITAK: Ankara, Turkey, 2019.
35. World Health Organization (WHO). World Health Statistic. Geneva: WHO Library Cataloguing-in-Publication Data, 2015.
36. Cakir D, Alparslan O. The investigation of the effects of the birth type variable on the mother-infant interaction and mother's perception of her the infant. Journal of Contemporary Medicine 2018;8:139-47.
37. Broussard ER, Cassidy J. Maternal perception of newborns predicts attachment organization in middle adulthood. Attach Hum Dev 2010;12:159-72.
38. Reenen SL, Reensburg E. The influence of an unplanned caesarean section on initial mother-infant bonding: Mothers' subjective experiences. J Psychol Afr 2013;23:269-74.
39. Zanardo V, Soldera G, Volpe F, Giliberti L, Parotto M, Giustardi A, et al. Influence of elective and emergency cesarean delivery on mother emotions and bonding. Early Human Development 2016;99:17-20.
40. Lobel M, Deluca RS. Psychosocial sequelae of cesarean delivery: Review and analysis of their causes and implications. Soc Sci Med 2007;64:2272-84.
41. Koc O, Ozkan H, Bekmezci H. Evaluating the correlation between maternal role and parenting behavior. The Journal of Dr. Behcet Uz Children's Hospital 2016;6:143-50.

Original Article

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Turkish Version of the Multidimensional Index of Life Quality in Patients with Acute Coronary Syndrome

Akut Koroner Sendromlu Hastalarda Çok Boyutlu Yaşam Kalitesi İndeksinin Türkçe Versiyonu

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ABSTRACT

Objective: Decreased quality of life is an important state in which patients with acute coronary syndrome (ACS) frequently experienced. Thus, measuring the quality of life of these patients is necessary. This study aimed to translate, cross-culturally adapt, and psychometrically test the Turkish version of the Multidimensional Index of Life Quality in patients with ACS.

Methods: The study sample consisted of 370 patients with ACS who were admitted to a university hospital between October 2010 and June 2011. In this cross-sectional study, backward and forward translation methods were used between the Turkish and English version of the scale. The following psychometric properties were evaluated: content validity, exploratory and confirmatory factor analyses, Cronbach's alpha coefficient, test–retest analysis, and equivalent forms method.

Results: Goodness-of-fit index (GFI) results of the confirmatory factor analysis indicated that the a priori hypothesized nine-factor model had a non-acceptable fit in the sample based on the following: $\chi 2$=1854.58, df=523, $\chi 2$/df=3.54; p<0.001; root mean-square error of approximation = 0.09, standardized root mean residual =0.09, normed fit index (NFI) =0.81, non-NFI =0.84, GFI =0.71; adjusted GFI =0.65. The exploratory factor analysis showed six components with an eigenvalue of >1.0, explaining 69.7% of the cumulative variance. Cronbach's alpha coefficient was 0.94 for the total scale.

ÖZ

Amaç: Akut koroner sendromlu (AKS) hastalarda azalmış yaşam kalitesi önemli bir durumdur. Bu nedenle, hastalar için yaşam kalitesi ölçümlerinin yapılması yararlıdır. Bu çalışmada, AKS'li hastalarda çok boyutlu yaşam kalitesi indeksinin Türkçe'ye çeviri ve kültürlerarası uyarlama yapılması ve psikometrik olarak test edilmesi amaçlanmıştır.

Yöntemler: Araştırmanın örneklemini bir üniversite hastanesine Ekim 2010 ve Haziran 2011 tarihleri arasında başvuran 370 AKS'li hasta oluşturmuştur. Kesitsel tipteki çalışmada ölçeğin Türkçe ve İngilizce fomları arasında ileri-geri çeviri yöntemleri kullanılmıştır. Psikometrik özellikler kapsam geçerliği, açımlayıcı ve doğrulayıcı faktör analizi, Cronbach's alfa katsayısı, test-tekrar test analizi ve eşdeğer formlar yöntemi kullanılarak değerlendirildi.

Bulgular: Doğrulayıcı faktör analizinin uyum indeksi sonuçları, ölçeğin önceden belirlenmiş dokuz faktörlü model yapısını doğrulamadı: $\chi 2$ =1854.58, df =523, $\chi 2$/df =3,54; p<0,001; RMSEA =0,09, SRMR =0,09, NFI =0,81, NNFI =0,84, GFI =0,71; AGFI =0,65. Açımlayıcı faktör analizi, özdeğeri 1,0'ın üzerinde olan ve toplam varyansın %69,7'sini açıklayan altı bileşen ortaya çıkarmıştır. Cronbach's alfa katsayısı toplam ölçek puanı için 0,94 olarak bulunmuştur. Test-tekrar test analizi, ölçeğe uygulanan birinci ve ikinci test arasında anlamlı bir ilişki göstermiştir (r=0,88, p<0,001).

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The test-retest analysis found significant correlation between the first and second tests of the scale (r=0.88, p<0.001).

Conclusion: The findings showed that the scale can be used to determine the level of the quality of life of Turkish patients with acute coronary syndrome.

Keywords: Multidimensional index of life quality, quality of life, reliability, validity

Sonuç: Bulgular, bu ölçeğin akut koroner sendromlu Türk hastaların yaşam kalitesini belirlemek için kullanılabileceğini göstermiştir.

Anahtar Sözcükler: Çok boyutlu yaşam kalitesi indeksi, yaşam kalitesi, güvenirlik, geçerlik

Introduction

Cardiovascular diseases (CVDs) are the primary cause of mortality worldwide. Acute coronary syndrome (ACS) among CVDs is responsible for 17.7 million deaths in 2015 (1) and is the most common cause of chest pain and emergency room admissions (2). ACS occurs due to inadequate blood circulation or atherosclerotic plaque rupture in the coronary arteries (3). ACS has three clinical manifestations based on the differences in diagnosis and treatment process: unstable angina, non-ST segment elevation myocardial infarction, and STEMI (4,5). It is also a major health problem in Turkey. Among CVDs, ischemic heart diseases ranked first with approximately 64,000 deaths, which accounted for 38.4% of all deaths in 2018 (6). The increasing incidence of ACS and the high number of deaths reveal the social importance of this disease.

ACS is a debilitating health problem that causes various biopsychosocial complications (7). Despite being physically, mentally, and emotionally healthy in the first few months after an acute cardiac event (8,9), patients can have poor health-related quality of life (HRQoL) in the succeeding years (10). In addition, patients' feelings and attitudes about life may change and decreased QoL can be observed, which is a part of the subjective well-being of the HRQoL (11). Decreased QoL is usually related to individual judgments about factors such as consequences of coronary invasive and surgical interventions for ACS, changes in the vascular structure and body organs with age, physical discomfort associated with chest pain, management of risk factors, effects of cardiac medication, uncertainty, difficulties in returning to work, perceived social support, and coping (7,8,10). Therefore, it is useful that QoL is measurable.

HRQoL measurements that are frequently examined in Turkish studies are an important issue. Several general (EuroQol-5 Dimension, Nottingham Health Profile, 36-Item Short Form Survey, World Health Organization Quality of Life Instruments) and disease-specific instruments [Quality of Life Index-Cardiac Version, MacNew, Myocardial Infarction Dimensional Assessment Scale-Turkey (MIDAS-TR)] have been used to assess different domains of HRQoL in patients with CVDs (12). However, they are less focused on the life satisfaction aspect. The multidimensional index of life quality (MILQ) is a general QoL instrument (13), and only its Dutch translation has been made from the original language (14). Studies have shown its use in patients with ACS (9,15) as well as in various clinical situations or different populations (16-19). Through nine subdimensions, a multidimensional measurement of HRQoL is feasible with MILQ.

Therefore, MILQ can be administered to patients with ACS in Turkey. Through MILQ, the functional status and the emotional, cognitive, psychological, socioeconomic, and behavioral responses of individuals with ACS can be evaluated multidimensionally. Unlike other measurement tools, MILQ measures life satisfaction including relationship with health professionals. The use of the scale in these patients may contribute to determining the effects of the disease and its treatment on the daily lives of the individuals. The obtained results may contribute to the nursing care process and may direct nursing interventions. Therefore, MILQ, whose original study has been carried out in the USA and its original language is English, was translated into Turkish by using standard translation methods. This study aimed to translate, cross-culturally adapt, and psychometrically test the Turkish version of the MILQ in patients with ACS.

Methods

Settings and Participants

The Turkish version of the MILQ was administered in 370 patients. Adult patients with ACS from three cardiology clinics of the university hospital in South Turkey were invited to participate. For inclusion, patients should be 18-65 years old and do not have a chronic disease such as diabetes and chronic respiratory disease. Data were collected by the researcher between October 2010 and June 2011 through face-to-face interview with patients with ACS who met the sample criteria and agreed to participate in the study.

Instruments

The MILQ was developed by Avis et al. (13), which includes 35 items in the following nine subdimensions: mental health, physical health, physical functioning, cognitive functioning, social functioning, intimacy, productivity, financial status, and relationship with health professionals. Each sub-dimension has four items, but one item is included in two domains. MILQ has a seven-point Likert scale that ranges from 1 (very dissatisfied) to 7 (very satisfied). Its scores range from 4 to 28 for each sub-dimension, with higher scores showing better functioning or status. Cronbach's alpha coefficient is 0.89 for the total scale, and the sub-dimension coefficients range from 0.62 to 0.93.

The MIDAS-TR was used to test equivalent forms method. MIDAS was developed by Thompson et al. (20). Its Turkish validity and reliability study was performed by Uysal et al. (21). MIDAS-TR includes 35 items and six subdimensions: physical activity, insecurity, emotional reaction, social activity, dependency, and concern over medication (21). Its five-point Likert type scale was calculated by scoring between "0" (never) and "4" (always) (20). The score for each sub-dimension ranges from "0" (best possible health) through to "100" (worst health). Low scores indicate better QoL. Cronbach's alpha coefficients of the subdimensions range from 0.65 to 0.87 for MIDAS-TR, and the alpha for the total scale is 0.88 (21).

Methodology of Translation and Procedures

After the English version of the MILQ was provided by the website, authors obtained permission to adapt the Turkish version of the MILQ from Nancy Avis. The cross-sectional study was carried out with forward and backward translations. Then, the following language translation procedures were performed:

1. The MILQ was translated from English into Turkish (forward translation) by four experts (two instructors and two lecturers).

2. These translations were combined by the researchers, and the scale form was rearranged.

3. Thereafter, backward translation into English was performed by an independent translator and a lecturer who understood and spoke both languages (Turkish-English).

4. Language translations were compared, and appropriate expressions for the scale items were identified.

Then, five expert nurses gave their opinions of the content validity of the MILQ. The experts assessed the suitability of each item in the scale of over 10 points (item is suitable). Kendall's concordance (Wa) coefficient was calculated to determine whether the scale items were applicable or not. If the p value was greater than 0.05, the scale items were considered valid.

Ethical Considerations

Ethical approval was obtained from the ethics committee (09.21.2010/117). The study was conducted in accordance with the Declaration of Helsinki and based on the voluntary principle. The participants were informed about the aim of the study and confidentiality of their personal information, and their consent was obtained.

Data Analysis

Data were analyzed using the Statistical Package for Social Sciences and Sensory Activation Solutions. Descriptive statistics were calculated with percentage, mean, and standard deviation. Construct validity was analyzed by performing confirmatory factor analysis (CFA) and explanatory factor analysis (EFA). Before, the Kaiser-Meyer-Olkin (KMO) and Bartlett's tests were peformed to examine the adequacy of the sample size for the factor analysis. In the CFA, several fit indices were used to identify the fitness of the model, including chi-square (χ^2) statistics, degrees of freedom (df), ratio of χ^2 to df (χ^2/df), root-mean-square error of approximation (RMSEA), standardized root mean-square residual (SRMR), normed fit index (NFI), non-NFI (NNFI), goodness-of-fit index (GFI), adjusted GFI (AGFI). The factor extraction method was performed using the principal component analysis and varimax rotation for the EFA. Reliability was performed with Cronbach's alpha coefficient, test-retest, and equivalent forms method. Cronbach's alpha coefficient was used to determine internal consistency. For the test-retest analysis, 2 weeks after the administration of the first questionnaire, 50 participants responded to determine if there was no change over time. The test–retest reliability was calculated by Pearson correlation coefficient. A paired sample t-test was used to determine whether a statistical difference exists between the two tests. The p value was accepted as >0.05 for the t-test. The equivalent forms method was also calculated by identifying the correlation between MILQ and MIDAS-TR using the Pearson correlation coefficient. The p value was accepted as <0.05 for the correlation coefficient.

Results

The majority of the patients, with a mean age of 58.63±7.76 years, were male (75.4%). Most of the patients were married (93.8%) and have a social security (99.2%). Moreover, 51.9% of the participants were followed up for MI, and 32.7% of them have less than 1 year of disease diagnosis. In this study, 65.7% of the patients were hospitalized once due to heart diseases. While 63.2% of the patients stated that they were on a diet therapy, 65.1% did not exercise. The most common symptoms were chest pain (9.0%) and fatigue (22.4%).

Validity

Kendall's Wa value was statistically compatible with the applicability of the scale elements for the content validity (p=0.063). The KMO value was 0.93, and Bartlett's test of sphericity was at the significance level (χ2=9931.43, df=595, p<0.001). In the CFA, the goodness-of-fit indices were as follows: χ2=1854.58, df=523, χ2/df=3.54, p<0.001, RMSEA=0.09, SRMR=0.09, NFI=0.81, NNFI=0.84, GFI=0.71, and AGFI=0.65. In the EFA, the principal component analysis and varimax rotation indicated that the factor loading of item 9 was 0.19. Item 9 was then deleted from the scale, and EFA was performed again with 34 items. Six factors with eigenvalues of >1.00 were identified. Factor 1 (15 items-items 5, 6, 8, 10, 11, 12, 14, 15, 20, 21, 22, 24, 33, 34, and 35), factor 2 (4 items-items 1, 2, 3, and 4), factor-3 (5 items-items 28, 29, 30, 31, and 32), factor 4 (4 items-items 7, 13, 18, 19, and 23), factor 5 (3 items-items 25, 26, and 27) and factor 6 (two items-items 16 and 17). All of the six factors explained 69.7% of the cumulative variance (Table 1).

Reliability

Cronbach's alpha coefficient for the 34-item MILQ-TR was 0.94, and the coefficients for the subscales ranged from 0.72 to 0.94. Factor 1 (α=0.93) and factor 2 (α=0.93) subscales had the highest internal consistency coefficients, while factor 6 had the lowest (α=0.72) (Table 1). In the test–retest reliability

Table 1. Factor Structure of the 34-Item MILQ-TR

Item number	Subscales/items	Factor loadings	Cumulative variance (%)	Cronbach's alpha
Physical health (factor 1)			23.48	0.94
5	How satisfied are you with how you feel physically?	0.69		
6	How satisfied are you with your energy to do what you want?	0.68		
8	How satisfied are you with the physical exercise you get?	0.79		
10	How satisfied are you with your ability to lift and carry things around the house?	0.56		
11	How satisfied are you with being physically able to take vacations or trips?	0.79		
12	How satisfied are you with physically being able to work?	0.74		
14	How satisfied are you with being able to help family members by babysitting, caring for relatives, etc.?	0.55		
15	How satisfied are you with the amount of time you spend with friends?	0.49		
20	How satisfied are you with your sex life?	0.67		
21	How satisfied are you with feeling alert?	0.57		
22	How satisfied are you with your ability to concentrate?	0.63		
24	How satisfied are you with being able to remember things that happened awhile ago?	0.60		
33	How satisfied are you with the amount of time your health permits you to work?	0.79		
34	How satisfied are you with being able to do the type of work you want?	0.80		
35	How satisfied are you with feeling productive?	0.69		
Mental health (factor 2)			35.67	0.93
1	How satisfied are you with your overall mood?	0.84		
2	How satisfied are you with how hopeful you feel about the future?	0.80		
3	How satisfied are you with how happy you are?	0.86		
4	How satisfied are you with feeling calm?	0.82		
Relationship with health professionals (factor 3)			46.06	0.85
28	How satisfied are you with your social security?	0.45		
29	How satisfied are you with the information you get from health personnels?	0.90		
30	How satisfied are you with being able to ask health personnels questions?	0.80		
31	How satisfied are you with the quality of medical care you are getting?	0.85		
32	How satisfied are you with the support you get from health personnels?	0.83		
Interpersonal relations (factor 4)			56.06	0.82
7	How satisfied are you with being free of pain?	0.53		

Table 1 contiuned

13	How satisfied are you with your family letting you do the things you want?	0.60		
18	How satisfied are you with the amount of affection your spouse/partner expresses toward you?	0.80		
19	How satisfied are you with being able to confide in your spouse/ partnerthe amount of wantg do th?	0.79		
23	How satisfied are you with your ability to make decisions by yourself?	0.61		
Financial status (factor 5)			63.56	0.84
25	How satisfied are you with your financial income?	0.84		
26	How satisfied are you with your ability to pay monthly expenses?	0.86		
27	How satisfied are you with the amount of money you have in savings?	0.73		
Social functioning (factor 6)			69.77	0.72
16	How satisfied are you with participating in community activities?	0.68		
17	How satisfied are you with the activities you do with your spouse/ partner?	0.68		
Cumulative variance =69.7% (MILQ-TR) **Cronbach's alpha =**0.94 (MILQ-TR)				
MILQ-TR: Turkish version of the multidimensional index of life quality				

analysis, positive, high-level, and significant correlation was found between the first and second tests of the MILQ (r=0.88, p<0.001). In the paired sample t test, the p value was 0.69 (Table 2). The correlation between MILQ-TR and MIDAS-TR was negative, moderate, and statistically significant (r=-0.42, p<0.001). The correlation coefficients between the MIDAS-TR and MILQ-TR subdimensions were -0.39, -0.42, -0.08, --0.28, -0.27, and -0.13, respectively.

Discussion

In this study, the psychometric properties of the 35-item MILQ were investigated. Significant findings were obtained, but since only the English version of the MILQ could be obtained, the comparison was made through a single study.

Factor analysis plays a key role in the validation of assessment scale data. In a previous study, KMO and Bartlett's test were used to examine the adequacy of the sample size for the factor analysis (22). If the KMO index is at least 0.05 and Bartlett's test is significant (p<0.05), it is considered suitable for the factor analysis (23). CFA is used when the goal is to test the validity of a hypothesized model of factors and the relationships of those factors to a set of observed variables. Numerous inferential and descriptive fit indices assist the evaluation of the goodness-of-fit of a CFA model as a whole (24). For a good model, the χ^2/df ratio should be low (≤3) and have a statistically insignificant p value for χ^2. The χ^2/df ratio of the current model was 3.54, and the p value was < 0.001. The acceptable compliance for the RMSEA should be 0.05-0.08 and that for SRMR should be ≤0.05 (25). For good model compliance, both conditions were not met in this study (RMSEA=0.09, SRMR=0.09). The NFI, NNFI, GFI, and AGFI should be >0.90 for model compliance. These fit indices were not also met in this study: NFI=0.81, NNFI=0.84, GFI=0.71, and AGFI=0.65. The NFI, GFI, and AGFI are sensitive to the sample size and can reject a good-compliance model (26). In this study, fit indices showed that the 9-factor MILQ is not suitable for the Turkish population. In the implementation of a scale to two different cultures, participants can be influenced by culture-driven trends.

Table 2. Comparisons of test-retest reliability coefficient and mean scores for the MILQ-TR

	Time 1 mean ± SD	Time 2 mean ± SD	r/p[b]	t/p[c]
MILQ	182.20±33.60	183.10±29.80	0.88/<0.001	0.397/0.69

[a]Values are expressed as mean ± SD.
[b]p<0.001.
[c]p>0.05.
MILQ-TR: Turkish version of the Multidimensional Index of Life Quality; SD: Standard deviation

In this study, EFA was performed twice. In the first analysis, item 9 was removed from the scale because the factor loading was <0.40 (23). In the second analysis, the 34-item MILQ-TR showed a six-factor structure. A difference was found according to the factor structure of the original scale. While the original MILQ has nine subdimensions, the Turkish scale has six subdimensions. These subdimensions include physical health, mental health, and relationship with health professionals. However, the scale was found to show significant consistency in reflecting cultural values when the items under each factor are examined.

Reliability means that the same conceptual structure is measured consistently between independent measurements (23). Cronbach's alpha coefficient was used to measure internal consistency. The alpha value obtained for all items indicates the total reliability of the questionnaire. The generally acceptable alpha value is ≥0.70, but it should be >0.90 for excellent consistency (27). The alpha coefficient was 0.94 for the total MILQ-TR. The alpha coefficients of the six factors were also above the desired value. In the English MILQ, the alpha coefficient of all subscales, except of social functioning, was ≥0.76 (13). The high alpha value of the MILQ-TR indicates that the characteristics to be measured with the original scale can be measured consistently for the Turkish population. This finding suggests that the scale items are consistent with each other even when applied to a Turkish population.

Test-retest reliability refers to the degree to which the measure is able to differentiate between participants under repeated administrations of the measure under the same or similar conditions (28). In this study, high-level and significant correlations were found in the measurements performed with 2-week intervals ($r=0.88$, $p<0.001$). However, the statistically insignificant p value for the t test showed that the two tests remained constant over time (23). The characteristics to be measured by the scale items did not change with time in the Turkish population. Equivalent forms reliability examines the correlations between scores obtained by applying two or more forms of a test to the same individuals. The acceptable correlation coefficient for the equivalent forms reliability is considered ≥0.80 (29). Poor-moderate level, negative, and significant correlations were determined between the MILQ-TR and MIDAS-TR. This finding can be interpreted as a less appropriate equivalent form of MIDAS-TR for the MILQ-TR. In further studies with MILQ-TR, high correlations can be obtained by testing a different version of the scale.

Study Limitations

Although sufficient and significant findings were obtained in this study, certain limitations were encountered. First, testing of the MILQ adapted to different cultures and languages was not performed. Thus, cross-cultural comparisons were carried out only based on the original work that developed MILQ. Second, in the scale validation and development studies, the sample group should be divided into two groups: the first group should be tested for the CFA and the second group for EFA, synchronously. In this study, the sample size was insufficient for this analysis. Hence, CFA and EFA were tested in the same sample. Further studies should be conducted with a larger sample, and we can recommend re-testing of the CFA.

Conclusion

The findings support that the MILQ-TR generally has adequate validity and reliability to measure the HRQoL of Turkish patients with ACS. Importantly, this study will set as an example for cross-cultural adaptation conducted over the same scale in the future. The use of the scale will help determine the effects of disease and treatment on the daily lives of the individuals.

QoL measurement studies related to ACS have gained the interest of researchers. Indeed, QoL measurements are a key determinant of the health outcomes of these patients. However, in previous studies, all aspects of the QoL that may affect the health of individuals have not been examined. This study presents the aspects of QoL that have not been previously examined for these patients. The current scale can provide a multidimensional measurement of the QoL of individuals with CVDs.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the ethics committee (09.21.2010/117).

Informed Consent: The participants were informed about the aim of the study and confidentiality of their personal information, and their consent was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: Ş.D., Z.Ö., Design: Ş.D., Z.Ö., Data Collection or Processing: Ş.D., Analysis or Interpretation: Ş.D., Z.Ö., Literature Search: Ş.D., Z.Ö., Writing: Ş.D., Z.Ö.

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References

1. World Health Organization. World health statistics 2018: monitoring health for the SDGs, sustainable development goals (cited 2019 March 11). Available from: https://www.who.int/gho/publications/world_health_statistics/2018/en/.
2. Lashari NA, Lakho NI, Memon SA, Ahmed A, Waseem MF. Acute coronary syndrome. Professional Med J 2017;24:409-13.
3. Oriolo V, Albarran JW. Assessment of acute chest pain. British Journal of Cardiac Nursing 2010;5:587-93.
4. Dias CM, Macedo LB, Gomes LT, de Oliveira PL, Albuquerque IV, Lemos AQ, et al. Quality of life of patients after an acute coronary event: hospital discharge. J Clin Med Res 2014;6:362-8.
5. Humphreys M. Nursing the Cardiac Patient. West Sussex: John Wiley & Sons; 2011.

6. Türkiye İstatistik Kurumu. Ölüm Nedeni İstatistikleri, 2018. (cited 2019 March 11). Available from: http://www.turkstat.gov.tr/HbPrint.do?id=27620.
7. Taghadosi M, Ghanbari-Afra L, Ghanbari-Afra M, Gilasi HR. Quality of life and its influencing factors in patients with acute coronary syndrome. Nursing Practice Today 2016;3:63-9.
8. Kristofferzon ML, Löfmark R, Carlsson M. Perceived coping, social support, and quality of life 1 month after myocardial infarction: a comparison between Swedish women and men. Heart Lung 2005;34:39-50.
9. Staniūtė M, Brožaitienė J. Changes in health-related quality of life among patients with coronary artery disease: a 2-year follow-up. Medicina 2010;46:843-50.
10. Rančić N, Petrović B, Apostolović S, Kocić B, Ilić M. Health-related quality of life in patients after the acute myocardial infarction. Open Medicine 2013;8:266-72.
11. Tate DG, Forchheimer M. Quality of life, life satisfaction, and spirituality: Comparing outcomes between rehabilitation and cancer patients. Am J Phys Med Rehabil 2002;81:400-10.
12. Demir Ş, Özer Z. Kardiyovasküler Hastalıklarda Yaşam Kalitesinin Değerlendirilmesi. Medical Network Cardiol 2014;21:182-91.
13. Avis NE, Smith KW, Hambleton RK, Feldman HA, Selwyn A, Jacobs A. Development of the Multidimensional Index of Life Quality: a quality of life measure for cardiovascular disease. Medical Care 1996;34:1102-20.
14. van Mastrigt GA, Joore MA, Nieman FH, Severens JL, Maessen JG. Health-related quality of life after fast-track treatment results from a randomized controlled clinical equivalence trial. Quality of Life Research 2010;19:631-42.
15. Sleeper LA, Ramanathan K, Picard MH, Lejemtel TH, White HD, Dzavik V, et al; SHOCK Investigators. Functional status and quality of life after emergency revascularization for cardiogenic shock complicating acute myocardial infarction. J Am Coll Cardiol 2005;46:266-73.
16. Avis NE, Smith KW. Quality of life in older adults with HIV disease. Res Aging 1998;20:822-45.
17. Blinderman CD, Homel P, Billings JA, Tennstedt S, Portenoy RK. Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. J Pain Symptom Manage 2009;38:115-23.
18. Smith KW, Larson MJ. Quality of life assessments by adult substance abusers receiving publicly funded treatment in Massachusetts. Am J Drug Alcohol Abuse 2003;29:323-35.
19. Strada EA, Homel P, Tennstedt S, Billings JA, Portenoy RK. Spiritual well-being in patients with advanced heart and lung disease. Palliat Support Care 2013;11:205-13.
20. Thompson DR, Jenkinson C, Roebuck A, Lewin RJ, Boyle RM, Chandola T. Development and validation of a short measure of health status for individuals with acute myocardial infarction: the myocardial infarction dimensional assessment scale (MIDAS). Qual Life Res 2002;11:535-43.
21. Uysal H, Özcan Ş, Enç N. Adaptation of Myocardial Infarction Dimensional Assessment Scale to Turkish: a validity and reliability study. Turk Kardiyol Dern Ars 2009;37:543-50.
22. Watson JC. Establishing evidence for internal structure using exploratory factor analysis. Measurement and Evaluation in Counseling and Development 2017;50:232-8.
23. LoBiondo-Wood G, Haber J. Nursing research, methods, appraisal and utilization. St Louis: Mosby Elsevier; 2002.
24. Dimitrov DM. Statistical methods for validation of assessment scale data in counseling and related fields. USA: John Wiley & Sons; 2014.
25. Çelik HE, Yılmaz V. LISREL 9.1 ile yapısal eşitlik modellemesi: Temel kavramlar-uygulamalar-programlama. Ankara: Anı Yayıncılık; 2016.
26. Byrne B. Structural equation modelling with AMOS: Basic concepts, application, and programming. 3rd ed. New York: Taylor & Francis Group; 2016.
27. George D, Mallery P. SPSS for windows step by step: A simple guide and reference, 11.0 update. 4th ed. Boston: Allyn & Bacon; 2003.
28. Barton B, Peat J. Medical statistics: A guide to SPSS, data analysis and critical appraisal. 2nd ed. West Sussex: John Wiley & Sons; 2014.
29. Fawcett AJL. Principles of assessment and outcome measurement for occupational therapists and physiotherapists: theory, skills and application. West Sussex: John Wiley & Sons; 2007.

Original Article

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Effect of Mouthrinses on Water Sorption and Solubility of Flouride-Releasing Restorative Materials

Fluorid Salabilen Restoratif Materyallerin Su Emilimi Ve Çözünürlüğü Üzerine Gargaraların Etkisi

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ABSTRACT

Objective: This study aimed to investigate water sorption/solubility behavior of glass ionomer cement-based-containing restorative materials.

Methods: A total of 21 specimens for each material (Riva Self Cure, Riva Light Cure, GCP Glass Fill) were prepared using a teflon ring (10x2 mm). These specimens were stored in a desiccator for 24 hours at 37±1 ºC and the weight of each sample was measured using a sensitive balance. Afterwards, the specimens were stored in an incubator containing distilled water, mouthrinse with alcohol, and mouthrinse without alcohol at 37±1 ºC for one day. The specimens were later dried to a constant mass in a desiccator, and each specimen was measured using a digital electronic caliper. Data were statistically analyzed ($p<0.05$).

Results: Data were evaluated using one-way ANOVA and post-hoc Tukey tests. Water sorption values were found to be significantly higher for the resin-modified glass ionomer cement group than for the high-viscosity glass ionomer cement (HVGIC) group in all the three different media ($p<0.05$). HVGIC material showed similar water sorption values for all three media.

Conclusion: Compositions of restorative materials play key roles in their water sorption/solubility in different areas.

Keywords: Glass ionomer, glass carbomer, solubility, sorption, mouthrinse

ÖZ

Amaç: Bu çalışmanın amacı, cam iyonomer siman bazlı restoratif materyallerin su emilimi ve çözünürlüğü özelliklerini araştırmaktır.

Yöntemler: Teflon halkalar (10x2 mm) kullanılarak her bir materyal (Riva Self Cure, Riva Light Cure, GCP Glass Fill) için toplam 21 örnek hazırlandı. Örnekler desikatör içerisine yerleştirilerek 24 saat 37±1 ºC'de bekletildi ve bu süre sonunda her örneğin ağırlığı hassas terazi ile ölçüldü. Aynı örnekler daha sonra üç gruba ayrılarak bir gün boyunca distile su, alkollü gargara ve alkolsüz gargara içeren solüsyonlarda 37±1 ºC'de saklandı. Örnekler sabit bir kütleye gelinceye kadar tekrar desikatörde kurutuldu. Her örneğin çap ve kalınlıkları dijital elektronik kumpas kullanılarak ölçüldü. Veriler one-way ANOVA and post-hoc Tukey testleri kullanılarak değerlendirildi ve alfa hata düzeyi 0,05 olarak seçildi.

Bulgular: Su emilim değerleri, resin modifiye cam iyonomer siman grubu için yüksek viskoziteli cam iyonomer siman (HVGIC) grubundan üç farklı ortamın hepsinde anlamlı olarak yüksek bulunmuştur ($p<0,05$). HVGIC materyali üç ortamın tümü için benzer su emilim değerleri göstermiştir.

Sonuç: Restoratif materyallerin içerikleri, farklı alanlarda su emilim/çözünürlüklerinde kilit rol oynar.

Anahtar Sözcükler: Cam iyonomer, cam carbomer, emilim, çözünürlük, gargara

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Introduction

Despite advanced preventive measures, dental caries still maintains its frequency and importance among oral diseases. Dentists should choose the most appropriate restorative material based on characteristics associated with patient and caries. In addition, physical properties, biocompatibility, esthetic features, and application information of restorative materials help in making the most appropriate choice (1,2).

Conventional glass ionomer cements (GIC) were developed by combining advantages of silicate and polycarboxylate cements. They have advantages such as chemical bonding to dental tissues, releasing and recharging fluoride, compatibility of thermal expansion coefficient with tooth enamel and dentin, and low cytotoxicity. Besides, GICs have disadvantages of a low wear resistance, short working time, long curing time, sensitivity to moisture contamination, and a high rate of microleakage, which limit their usage in restoration of permanent teeth and in areas that will be exposed to an occlusal force in primary teeth (3).

While the first GICs were described as being of a lower viscosity nature, later "high-viscosity" GICs (HVGIC) have been developed to improve insufficient mechanical properties and wear resistance to high occlusal forces of conventional GICs. In addition, they were produced as restorative materials to expand the areas of use restricted to Class I and Class V cavities (3,4).

In order to overcome problems observed in GICs, resin-modified GIC (RMGIC) have been developed (5). Due to resin monomer polymerization, higher resistance to compressive and tensile forces, improved fracture strength, modulus of elasticity, and retention rates are reported with these materials (6,7). Working time of RMCIS is longer than that of conventional GICs. Compared to conventional GICs, RMGICs have disadvantages of weaker adhesions to dental tissues and a lower fluoride release. Increased microleakage due to polymerization shrinkage constitutes further disadvantages of the material (8).

Carbomer-based restoratives contain carbomer fillers and fluoroapatite/hydroxyapatite nanoparticles (9). Glass carbomer (GC) cements are free of monomers like resin, solvent, metal etc. and are easy to diagnose postoperatively due to their radiopacity. Moisture tolerant nature of this material makes it handy in pediatric dentistry. It is stated that pulp capping should not be performed directly with glass carbomer cements (10).

Resistance of a restorative material to intraoral conditions is very important for longevity of restorations. Water sorption and solubility features of restorative materials have a significant impact on clinical success and can not be completely controlled. Water sorption causes dimensional changes in materials, leading to discoloration and a fracture in marginal contours. Water solubility is a phenomenon that adversely affects compatibility of restorations with biological structures and increases rate of deterioration. Studies have shown that sorption and solubility of restorative materials depend on features of solutions (1,11,12).

In order to prevent plaque formation in children aged ≥6 years, supervised use of fluoride-based mouthrinses as well as toothpastes prevents demineralization of tooth structure and provides remineralization of early caries lesions (13).

Few studies have been conducted to evaluate effects of oral mouthrinses on the water sorption and solubility properties of restorative materials. Mouthrinses contain different concentrations of water, antimicrobial agent, salt, preservatives, and alcohol. In particular, alcohol has been reported to cause increased wear of the material (14,15).

In this study, our purpose was to compare water sorption and solubility values of GC (GCP Glass Carbomer Cement), HVGIC (Riva Self Cure HV), and RMGIC (Riva Light Cure HV) restorative materials in mouthrinse with alcohol (Listerine Cool Mint), mouthrinse without alcohol (Listerine Total Care Zero), and artificial saliva. The null hypothesis stated that water sorption and solubility values do not differ according to the restorative material or solvent type tested.

Method

Sample Preparation

Restorative materials used in the present study and polymerization types recommended by the manufacturer are shown in Table 1 and the solutions used in the study are shown in Table 2. Samples were prepared for each material using circular teflon molds with a diameter of 10 mm and a thickness of 2 mm. The mold was isolated with petroleum jelly to prevent the materials from sticking to the mold. The materials were mixed in amalgamators at room temperature according to the manufacturer's instructions and were placed into the molds. Transparent matrix strips (Universal Strips, Extreme Dental, İstanbul, Turkey) were placed on the upper surface of the molds to overflow the surplus. The samples were polymerized according to the manufacturer's instructions. After the hardening of the material, the molds were carefully removed and the debris around them was cleaned. Twenty-one samples were prepared for each material group, which were divided into three sub-groups of seven to be placed in different solution media.

Table 1. Materials used in the study

Brand	Type	Manufacturer
Riva self cure HV	High-viscosity glass ionomer	SDI Dental, Australia
Riva light cure HV	Resin-modified glass ionomer	SDI Dental, Australia
Riva coat	Surface coat	SDI Dental, Australia
GCP glass carbomer fill	Glass carbomer	GCP Dental, Holland
GCP gloss	Surface coat	GCP Dental, Holland

Table 2. Solutions used in the study

Solutions	Ingredients	Alcohol percentage	pH
Listerine Cool Mint (Johnson & Johnson, İstanbul, Turkey)	Thymol 0.064%, eucalyptol 0.092%, methyl salicylate 0.060% and menthol 0.042%. water, alcohol 21.6%, sorbitol solution, flavoring, poloxamer 407, benzoic acid, sodium saccharin, sodium benzoate, and FD & C green.	21.6%	3.92
Listerine Total Care Zero (Johnson & Johnson, İstanbul, Turkey)	Eucalyptol 0.091%, menthol 0.042%, thymol 0.063%, sodium fluoride 0.022%, zinc chloride 0.09%, aroma (flavor), benzoic acid, blue 1, methyl salicylate, poloxamer 407, propylene gly-col, Red 1, sodium benzoate, sodium lauryl sulfate, sodium saccharin, sorbitol, su-cralose, water	-	6.02
Artificial Saliva	4.8 mM NaCl, 137 mM KCl, 1.5 mM $CaCl_2$, 8.2 mM $NaHCO_3$, 4.0 mM KH_2PO_4	-	7.4

Table 3. Sorption values of materials in different environments and statistical evaluation of the groups

Water sorption (μg/mm³)	Artifical Saliva	Mouthrinse with alcohol	Mouthrinse without alcohol	p"
HVGIC	70.1±5.9 (A, 1)	63.6±3.4 (A, 1)	68.7±4.8 (A, 1)	p=0.123
RMGIC	131.5±7.4 (B, 1)	89.4±4.7 (B, 2)	119.1±3.5 (B, 3)	<0.001, =0.001, <0.001
GC	148.9	92.3±18.6	101.9±7.3	
p*	p<0.001	p<0.001	p<0.001	

Letters and numbers are used to indicate differences in the columns and rows, respectively.
*p values represent comparison results between HVGIC and RMGIC materials
The three p values represent comparison results between the artificial saliva and mouthrinse with alcohol, artificial saliva and mouthrinse without alcohol, mouthrinse with alcohol and mouthrinse without alcohol environments, respectively.
HVGIC: High-viscosity glass ionomer cement, RMGIC: Resin-modified glass ionomer cement, GC: Glass carbomer

Table 4. Solubility of materials in different environments and statistical evaluation of the groups

Solubility (μg/mm³)	Artifical Saliva	Mouthrinse with alcohol	Mouthrinse without alcohol	p"
HVGIC	4.1±3.8 (A,1)	23.3±2.8 (A, 2)	16.2±3.8 (A, 2)	p<0.001, p=0.006, p=0.206
RMGIC	30.0±6.6 (B, 1)	31.4±4.3 (A, 1)	34.5±6.1 (B, 1)	p=0.480
GC	-11.9	42.3±42.7	-14.0±3.0	
p*	p<0.001	p=0.114	p<0.001	

Letters and numbers are used to indicate differences in the columns and rows, respectively.
*p values represent comparison results between HVGIC and RMGIC materials
The three p values represent comparison results between the artificial saliva and mouthrinse with alcohol, artificial saliva and mouthrinse without alcohol, mouthrinse with alcohol and mouthrinse without alcohol environments, respectively.
HVGIC: High-viscosity glass ionomer cement, RMGIC: Resin-modified glass ionomer cement, GC: Glass carbomer

Sorption and Solubility Measurements

All samples were stored in a desiccator with an anhydrous self-indicating silica gel at 37±1 ºC for 24 hours. Then, the initial weights of the samples were measured on an electronic analytical balance (brand) as micrograms (μg) and recorded as *m*L. The samples were suspended in different solutions according to their groups for 24 hours at 37 °C. Subsequently, the samples were removed from the solutions and their weights were measured one minute after removal and recorded as *m*2. After the measurement process, the samples were placed again in the desiccator for 24 hours to evaporate the water content and, subsequently, their weights were measured and recorded as *m*3. The volumes of the samples were found in mm3 according to the formula $V=\pi x r^2 x h$, where *r* is the radius of the average diameter/2 and h is the average thickness. Then, the water sorption and solubility of the samples were found in μg/mm³ with the formulas $m2 - m3/V$ and $m1 - m3/V$, respectively.

Statistical Analysis

The IBM SPSS Statistics 20 program was used to perform statistical tests with a significance level set at 5%. Besides, descriptive statistics, one-way ANOVA, and post-hoc Tukey tests were used to compare means of sorption and solubility between the groups.

Results

The mean water sorption and solubility values for each material and medias used in the study are shown in Tables 3 and 4, respectively. Also, in Figure 1, both the mean water sorption and solubility values were presented for each material at different media.

The glass carbomer materials used in the study were mostly found to be fragmented. Only 1, 3, and 2 sound samples were left to be measured for the artificial saliva, mouthrinse with alcohol and mouthrinse without alcohol groups, respectively. Although the results of this group are shown in the tables, they were not included in the statistical analysis due to the small number of samples.

Water sorption values were found to be significantly higher for the RMGIC group compared to the HVGIC group in all the three different media ($p<0.001$). HVGIC material showed similar water sorption values for all the three media ($p=0.123$). However, RMGIC material showed the highest sorption in artificial saliva, which was followed by the mouthrinse without alcohol and mouthrinse with alcohol, respectively ($p_{\text{saliva-with alcohol}}<0.001$, $p_{\text{saliva-without alcohol}}=0.001$, $p_{\text{with alcohol-without alcohol}}<0.001$).

Solubility values were significantly lower in the HVGIC group compared to the RMGIC group in artificial saliva ($p<0.001$) and mouthrinse without alcohol environments ($p<0.001$), but no significant difference was found in the mouthrinse with alcohol environment ($p=0.114$). While RMGIC showed similar solubility in all three environments ($p=0.480$), the HVGIC material showed significantly lower solubility in artificial saliva compared to other media ($p_{\text{saliva-with alcohol}}<0.001$, $p_{\text{saliva-without alcohol}}=0.006$, $p_{\text{with alcohol-without alcohol}}=0.206$).

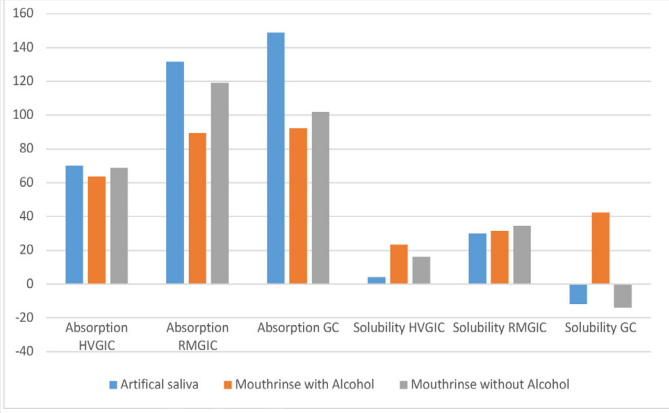

Figure 1. Average sorption and solubility values for materials in different media
HVGIC: High-viscosity glass ionomer cement, RMGIC: Resin-modified glass ionomer cement, GC: Glass carbomer

Discussion

Due to esthetic properties, polymer-based materials are used in dental restorations, but hydrophilic properties of these materials result in some degree of water sorption or dissolution in these materials (16). Water sorption and dissolution have been reported to adversely affect the clinical success of these restorations (17,18).

Conventional GICs are restorative materials that can easily draw water into their structures. It is very necesaary to investigate water sorption and solubility levels of restorative materials in order to increase clinical success rate of restorations and determine their application areas (19). In conventional GIC, water sorption occurs primarily within the matrix. Due to the water sorption, hydrolysis of the cement matrix occurs. Cement mass deteriorates over time and loss of surface properties, marginal integrity, esthetic appearance, and consequent deterioration in restorations occur (5). To overcome well-known disadvantages of GICs, RMGICs and high-viscosity GICs have been developed. While there are many studies evaluating the physical properties of high-viscosity GICs in the literature, the studies evaluating water sorption and solubility are limited (11,20-22). In previous studies, the sample dimensions were chosen to be 10-15 mm in diameter and 1-4 mm in thickness. Sample sizes are effective in diffusion of water to the polymer matrix. Smaller sample size shortens stabilization time in the material (23,24). The diameter of the specimens used in our study was prepared as 10 mm according to diameter of the tip of the light curing device, and the thickness was selected as 2 mm according to the layering method. There are studies with just one-hour storage solutions as well as one-year storage solutions to assess water sorption and solubility (25,26). Residence time is known to affect water sorption and solubility levels of the materials. Since it is known that pH changes may affect diffusion and solubility, the residence time used in our study was chosen as 24 hours to prevent variations in pH. In order to determine water sorption and solubility of the materials, different formulas are used in different studies (27-34). We used the formulas prepared under the guidance of the ISO standard in our study. All these methodological differences (sample size, solution storage time, formulation of the water sorption, and solubility) may have a role in the result inconsistencies in the literature.

RMGIC materials have been reported to exhibit higher water sorption and solubility than composites (35). It has also been reported that RMGIC materials have a higher and faster water sorption than conventional GIC materials (28). In another study, RMGIC materials showed similar or higher sorption values than HVGIC materials (33).

It has been claimed that high water sorption of RMGIC is caused by the initial desiccation procedure, which disrupts acid-base reactions (30). Another suggestion is that polycarboxylic acid, inorganic glass particles, and HEMA contained in RMGIC

structure retain large amounts of water (28). In our study, based on existing literature, the water sorption values were significantly lower in all the three solution environments for the HVGIC group compared to the RMGIC group. In solubility values, it was observed that the HVGIC group showed less dissolution than the RMGIC, except in the alcohol-free mouthrinse group. With increasing concerns about more effective oral hygiene habits, particularly with regard to the pediatric population, the use of chemical control agents (e.g., mouthwashes) has been adopted to complement toothbrushing and dental flossing (36). Their composition is based on water, antimicrobial agents, salts, preservatives, alcohol, and hydrogen peroxide (37). It has been reported that mouthrinses, containing alcohol or not, can increase the sorption and solubility for restorative materials compared to distilled water, but this effect may vary according to the material tested (29,31,32). In our study, the HVGIC material showed a significantly lower solubility in the artificial saliva environment than in other environments as expected, because mouthwashes trigger a decrease in the oral pH, which has been associated with an increase in the solubility of dental materials (38,39). However, RMGIC showed similar solubility in all the three environments, which may be explained by its already high solubility in artifical saliva due to its hydrophilicity. The sorption values of the RMGIC material were higher in the mouthrinse without alcohol environment than in the mouthrinse with alcohol environment. Also in artificial saliva environment RMGIC showed highest sorption values. These results may be due to the rapid water sorption of HEMA, a significant resin component found in the RMGIC material. In the HVGIC group, there was no difference between the two mouthrinses and artificial saliva environments in terms of sorption. Contrary to previous studies (37,40), mouthrinses did not increase the sorption of the HVGIC materials used in the present study, which may be explained by the more resistant structure of these materials to the chemical ingredients of the mouthrinses (41,42).

Savas et al. (33) and Subramaniam et al. (34) evaluated water solubility of GC in their study and reported that it is lower than conventional GICs. They did not mention fragmentation as in our study (33,34). In the present study, after the fragmentation of GC samples, new specimens were prepared by applying a surface covering on the GC materials, but sample loss due to serious fragmentation was experienced again.

Subramaniam et al. (34) modified the section 7.12 of ISO 4049 by placing specimens in a solution of artificial saliva immediately after preparation. They claimed that desiccation might affect the glass ionomer specimens' water sorption and solubility results due to damage (30). The reason for the disintegration of our GC samples may be bacause they were placed in a desiccator immediately after curing and removal from the mold as described in section 7.12 of ISO 4049.

Study Limitations

The main limitations of this study are *in vitro* design and the use of arguably shorter time periods to test water sorption and solubility. Clinical studies must be conducted to confirm the results.

Conclusion

High-viscosity GIC and RMGIC materials show significant water sorption and solubility; especially, RMGIC materials perform poorly in terms of sensitivity to water and this may cause degradation in the oral environment. Whether it contains alcohol or not, mouthwashes may have an adverse effect on the material structure by increasing sorption of RMGICs and solubility of GICs.

Further long-term studies are needed to investigate the sorption and solubility characteristics of these fluoride-releasing restorative materials.

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References

1. Bhatia HP, Singh S, Sood S, Sharma N. A Comparative Evaluation of Sorption, Solubility, and Compressive Strength of Three Different Glass Ionomer Cements in Artificial Saliva: An in vitro Study. Int J Clin Pediatr Dent 2017;10:49-54.
2. Terry DA, Leinfelder KF, Maragos C. Developing form, function, and natural aesthetics with laboratory-processed composite resin--Part I. Pract Proced Aesthet Dent 2005;17:313-8; quiz 320.
3. Naasan M, Watson T. Conventional glass ionomers as posterior restorations. A status report for the American Journal of Dentistry. Am J Dent 1998;11:36-45.
4. Gao W, Peng D, Smales RJ, Yip KH-K. Comparison of atraumatic restorative treatment and conventional restorative procedures in a hospital clinic: evaluation after 30 months. Quintessence Int 2003;34:31-7.
5. Rosenstiel SF, Land MF, Crispin BJ. Dental luting agents: A review of the current literature. J Prosthet Dent 1998;80:280-301.
6. Mitra SB, Kedrowski BL. Long-term mechanical properties of glass ionomers. Dent Mater 1994;10:78-82.
7. Uno S, Finger WJ, Fritz U. Long-term mechanical characteristics of resin-modified glass ionomer restorative materials. Dent Mater 1996;12:64-9.
8. Çapan BŞ, Akyüz S. Current fluoride-releasing restorative materials used in pediatric dentistry. Clin Exp Health Sci 2016;6:129-34.

9. Koenraads H, Van der Kroon G, Frencken J. Compressive strength of two newly developed glass-ionomer materials for use with the Atraumatic Restorative Treatment (ART) approach in class II cavities. Dent Mater 2009;25:551-6.
10. Algera TJ, Kleverlaan CJ, Prahl-Andersen B, Feilzer AJ. The influence of environmental conditions on the material properties of setting glass-ionomer cements. Dent Mater 2006;22:852-6.
11. Hinoura K, Onose H, Masutani S, Matsuzaki T, Moore B. Volumetric change of light cured glass ionomer in water. J Dent Res 1993;72:222.
12. Soderholm KJ, Zigan M, Ragan M, Fischlschweiger W, Bergman M. Hydrolytic degradation of dental composites. J Dent Res 1984;63:1248-54.
13. Burt BA. Prevention policies in the light of the changed distribution of dental caries. Acta Odontol Scand 1998;56:179-86.
14. Aguiar FHB, Lima DANL, Paulillo LAMS, Lovadino JR. Effect of light curing modes and ethanol immersion media on the susceptibility of a microhybrid composite resin to staining. J Appl Oral Sci 2007;15:105-9.
15. Cavalcanti AN, Mitsui F, Ambrosano G, Mathias P, Marchi GM. Effect of different mouthrinses on Knoop hardness of a restorative composite. Am J Dent 2005;18:338-40.
16. Ito S, Hashimoto M, Wadgaonkar B, Svizero N, Carvalho RM, Yiu C, et al. Effects of resin hydrophilicity on water sorption and changes in modulus of elasticity. Biomaterials 2005;26:6449-59.
17. Lopes LG, Cefaly DF, Franco EB, Mondelli RF, Lauris JR, Navarro MF. Clinical evaluation of two" packable" posterior composite resins: two-year results. Clin Oral Investig 2003;7:123-8.
18. Witzel MF, Calheiros FC, Gonçalves F, Kawano Y, Braga RR. Influence of photoactivation method on conversion, mechanical properties, degradation in ethanol and contraction stress of resin-based materials. J Dent 2005;33:773-9.
19. Küçükeşmen HC, Küçükeşmen Ç, Öztaş D, Kaplan R. Farklı Tiplerdeli Geleneksel ve Rezin-Modifiye Cam İyonomer Simanların Su Emilimi ve Suda Çözünürlüğü. A.Ü. Diş Hek. Fak. Derg 2005;32:25-34.
20. Salinovic I, Stunja M, Schauperl Z, Verzak Z, Ivanisevic Malcic A, Brzovic Rajic V. Mechanical Properties of High Viscosity Glass Ionomer and Glass Hybrid Restorative Materials. Acta Stomatol Croat 2019;53:125-31.
21. Bonifacio CC, Kleverlaan CJ, Raggio DP, Werner A, de Carvalho RC, van Amerongen WE. Physical-mechanical properties of glass ionomer cements indicated for atraumatic restorative treatment. Aust Dent J 2009;54:233-7.
22. Yamakami SA, Ubaldini ALM, Sato F, Medina Neto A, Pascotto RC, Baesso ML. Study of the chemical interaction between a high-viscosity glass ionomer cement and dentin. J Appl Oral Sci 2018;26:e20170384.
23. Al Sunbul H, Silikas N, Watts DC. Resin-based composites show similar kinetic profiles for dimensional change and recovery with solvent storage. Dent Mater 2015;31:e201-e17.
24. Archegas L, Caldas D, Rached RN, Vieira S, Souza EM. Sorption and solubility of composites cured with quartz-tungsten halogen and light emitting diode light-curing units. J Contemp Dent Pract 2008;9:73-80.
25. Alshali RZ, Salim NA, Satterthwaite JD, Silikas N. Long-term sorption and solubility of bulk-fill and conventional resin-composites in water and artificial saliva. J Dent 2015;43:1511-8.
26. Palin W, Fleming G, Burke F, Marquis P, Randall R. The influence of short and medium-term water immersion on the hydrolytic stability of novel low-shrink dental composites. Dent Mater 2005;21:852-63.
27. Rahim TNAT, Mohamad D, Akil HM, Ab Rahman I. Water sorption characteristics of restorative dental composites immersed in acidic drinks. Dent Mater 2012;28:e63-e70.
28. Cattani-Lorente M-A, Dupuis V, Payan J, Moya F, Meyer J-M. Effect of water on the physical properties of resin-modified glass ionomer cements. Dent Mater 1999;15:71-8.
29. Değer C, Kari P, Müjdeci A. Kompozir Rezinlerin Su Emilimi ve Çözünürlüğü Üzerine Gargaraların Etkisi. A.Ü. Diş Hek. Fak. Derg 2017;44:129-39.
30. Gerdolle DA, Mortier E, Jacquot B, Panighi MM. Water sorption and water solubility of current luting cements: An in vitro study. Quintessence Int 2008;39:e107-14.
31. Leal JP, da Silva JD, Leal RFM, Oliveira-Júnior CdC, Prado VLG, Vale GC. Effect of Mouthwashes on Solubility and Sorption of Restorative Composites. Int J Dent 2017;2017:5865691.
32. Ozer S, Sen Tunc E, Tuloglu N, Bayrak S. Solubility of two resin composites in different mouthrinses. Biomed Res Int 2014;2014:580675.
33. Savas S, Colgecen O, Yasa B, Kucukyilmaz E. Color stability, roughness, and water sorption/solubility of glass ionomer–Based restorative materials. Niger J Clin Pract 2019;22:824-32.
34. Subramaniam P, Girish Babu K, Jayasurya S. Evaluation of solubility and microleakage of glass carbomer sealant. J Clin Pediatr Dent 2015;39:429-34.
35. Akman H, Tosun G, Kahvecioğlu F. Kütlesel olarak yerleştirilebilen restoratif materyallerin su emilimi ve suda çözünürlük özelliklerinin değerlendirilmesi. Selcuk Dent J 2018;5:13-21
36. Perala SR, Bhupathiraju P. Efficacy of Four Fluoride Mouth Rinses on Streptococcus mutans in High Caries Risk Children - A Randomized Controlled Trial. J Clin Diagn Res 2016;10:ZC56-ZC60.
37. Armas-Vega A, Casanova-Obando P, Taboada-Alvear MF, Aldas-Ramirez JE, Montero-Oleas N, Viteri-Garcia A. Effect of mouthwashes on the integrity of composite resin and resin modified glass ionomer: In vitro study. J Clin Exp Dent 2019;11:e179-e84.
38. Trauth KG, Godoi AP, Colucci V, Corona SA, Catirse AB. The influence of mouthrinses and simulated toothbrushing on the surface roughness of a nanofilled composite resin. Braz Oral Res 2012;26:209-14.
39. Jyothi K, Crasta S, Venugopal P. Effect of five commercial mouth rinses on the microhardness of a nanofilled resin composite restorative material: An in vitro study. J Conserv Dent 2012;15:214-7.
40. da Silva AB, Raposo NM, Gomes IA, Goncalves LM, Paschoal MA. In vitro quantitative comparison of erosive potential of

infant mouthwashes on glass ionomer cement. J Clin Exp Dent 2018;10:e206-e11.

41. Toledano M, Osorio R, Osorio E, Aguilera FS, Romeo A, de la Higuera B, et al. Sorption and solubility testing of orthodontic bonding cements in different solutions. J Biomed Mater Res B Appl Biomater 2006;76:251-6.

42. Kielbassa AM, Glockner G, Wolgin M, Glockner K. Systematic review on highly viscous glass-ionomer cement/resin coating restorations (Part I): Do they merge Minamata Convention and minimum intervention dentistry? Quintessence Int 2016;47:813-23.

Original Article

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Prevalence of Pressure Injuries and Risk Factors in Long-Term Surgical Procedures

Uzun Süren Cerrahi Girişimlerde Basınç Yaralanması Prevalansı ve Risk Faktörleri

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ABSTRACT

Objective: To determine the risk factors and prevalence associated with intraoperative pressure injury (IPI) in surgical procedures lasting more than two hours, and to draw attention of surgical nurses to the prevention of IPI.

Methods: This cross-descriptive study included 170 patients in whom major surgical procedures were planned in a private foundation university hospital's orthopedics and general surgery departments between February 2017 and May 2018. The study was approved by the ethics committee and informed written permission was obtained from the institutions and volunteers. Data were collected by using Braden Risk Assessment Tool (BRAT) and literature based patient diagnosis form.

Results: The mean age of the participants was 47.72±22.20 years, 55.9% were female and 44.1% were male. Of the participants, 81.8% underwent surgery in the supine position, with a mean surgery duration of 246.707±145.3 minutes. Of the patients 24.1% developed stage I IPI. Forty-one (24.2%) patients with pressure injury had a lower BRAT score (18.434±6.621) than 129 (75.8%) patients without pressure injury (20.243±3.954), (p=0.035). According to multivariate analysis, both preoperative additional nutritional requirement and low albumin level increased the risk of IPI by 2.4 fold (p=0.038; 0.043, respectively). Each one hour of prolongation in duration of surgery increased the risk of IPI by 1.007 times (p=0.002).

ÖZ

Amaç: İki saatten uzun süren cerrahi girişimlerde ameliyat sırasındaki basınç yaralanması (ASBY) ile ilişkili risk faktörlerini ve ASBY prevalansını belirlemek, ASBY'nin önlenmesine cerrahi hemşirelerin dikkatini çekmektir.

Yöntemler: Kesitsel-tanımlayıcı bir araştırma olarak özel bir vakıf üniversitesi hastanesinin ortopedi, genel cerrahi servislerinde, Şubat 2017-Mayıs 2018 tarihlerinde, 170 büyük cerrahi girişim planlanan gönüllü bireyin katılımı ile yapıldı. Etik kurul onayı ile kurum ve gönüllülerden bilgilendirilmiş yazılı izin alındı. Veriler Braden basınç yarası ölçeği ve literatüre dayalı hasta tanımlama formuyla toplandı.

Bulgular: Katılımcıların yaş ortalaması 47,72±22,20 yıl idi, %55,9'u kadındı ve %44,1'i erkekti. Katılımcıların %81,8'i supine pozisyonunda ameliyat oldu, ameliyatın ortalama süresi 246,707±145,3 dakikaydı. Hastaların %24.1'inde evre 1 ASBY gelişmişti. Basınç yaralanması gelişen 41 (%24,2) hastanın Braden risk puanı (18,434±6,621) basınç yaralanması olmayan 129 hastadan (%75,8) (20,243±3,954) daha düşüktü (p=0,035). Multivaryans analizine göre, ameliyat öncesi hem ek beslenme gereksinimi olmak, hem albümin düşüklüğü ASBY riskini 2,4 kat artırdı (sırasıyla p=0,038; 0,043). Ameliyat süresinin her bir saatlik uzaması ASBY riskini 1.007 kat yükseltti (p=0,002).

The research was presented as an oral presentation in English at the 3rd International & 11th National Congress of Turkish Surgical and Operating Room Nurses (3rd International 11th National Congress of Turkish Surgical and Operating Room Nurses) held in İzmir-Çeşme on 3-6 October 2019.

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Conclusion: The risk of development of IPI is high in major surgical procedures. In determining the risk of IPI, the patient's nutritional deficiency, low albumin level, length of duration of surgery and BRAT score are important.

Keywords: Intraoperative period, pressure injury, risk factor, prevalence of pressure injury

Sonuç: Büyük cerrahi girişimlerde ASBY gelişme riski yüksektir. ASBY riskinin belirlenmesinde hastanın beslenme yetersizliği, albümin düşüklüğü, ameliyat süresi uzunluğu ve Braden risk puanı önemlidir.

Anahtar Sözcükler: Ameliyat sırası dönem, basınç yarası, risk faktörü, basınç yarası prevalansı

Introduction

Intraoperative pressure injury (IPI) is one of the perioperative care problems that negatively affect the expected postoperative outcomes. This injury, which is seen within the first 48-72 hours after surgery, is a costly complication that may result in morbidity (1-3). Particular attention is paid to the "intraoperative process" in which the pressure injury emerges. In this process, many risk factors such as patient characteristics, surgery time and position affect the formation of pressure wounds (4-7).

It has been reported in the literature that the incidence of IPI varies between 2.8-12% depending on the type and duration of the surgery (8-10), and that the frequency is 8.5-39.5% in long-term surgical interventions (11-14). Studies conducted in Turkey report the prevalence of pressure injury in surgical patients between 8.9-36.4 % (15-17).

Many studies draw attention to the length of surgery in the development of IPI (13,18,19). Patient characteristics such as nutritional status, albumin level, body mass index (BMI) are also highlighted, especially in surgeries longer than two hours, and the importance of research is emphasized. In addition, the importance of patient preparation and skin care in long surgical interventions is emphasized (4,20).

Although anesthesiologists are shown as the first responsible for positioning the patient on the operating table, anesthesiologists may not consider the risk of IPI or may be insufficient in this (21). However, the operating room nurse is expected to determine the internal and external risks of the patient according to the patient's position and reduce the risk of IPI with position support devices (22,23). However, there is no ideal method to determine patients at risk of developing IPI (21). In this direction, the aim of the study was to determine the risk factors and prevalence of IPI in surgical interventions lasting more than two hours, and to draw the attention of surgical nurses to prevent IPI.

Research Questions

In surgical procedures lasting more than two hours;

• Are sociodemographic and some clinical features a risk factor for the development of IPI?

• Does the surgery time constitute a risk factor for IPI?

• Do preoperative vital signs (blood pressure, pulse, respiratory rate) constitute a risk factor for IPI?

• What is the risk of IPI in the assessment with the Braden Risk Assessment Tool (BRAT)?

• Are albumin value and nutritional problems a risk factor for IPI?

• Do the support materials used for the position and position given for surgery affect the formation of IPI?

Method

The research was a descriptive-cross-sectional study.

Place and Time

The study was carried out between June 2017 and May 2018 in a private foundation university hospital's orthopedics (bed capacity 41) and general surgery clinics (bed capacity 35).

Universe and Sampling

Power analysis was done for the sample. For this, the number of surgeries (10,23-25) of the orthopedics and general surgery clinics in the last year was obtained from the hospital's database. Of this number, 19-20% consisted of major surgeries. In this case, the sample size was calculated as 170 according to the confidence level (95%) and the acceptable error (5%). Individuals were included in the study with a "purposeful sampling" according to the selection criteria.

Inclusion criteria:

- Being 18 years or older
- Surgery planned to last for at least two hours
- No pressure injury and no activity limitation before surgery
- Planning surgery under general anesthesia
- Volunteering to participate in research
- Being able to communicate

Exclusion criteria:

- In case of emergency surgery
- Planning small surgical intervention
- The dependent variable is IPI.

Independent variables are age, gender, chronic disease, habits, BMI, whether requiring special nutritional support, dehydration,

low hemoglobin (Hb) and low albumin level, hypotension, body temperature, heart rate, surgery time, position in the surgery, and the quality of position support tools.

Data Collection Tools

The data were collected using the Participant information form developed based on the literature (3,4,23,26,27) and the BRAT.

Participant information form contains questions about age, gender, chronic illness, habits, BMI, whether requiring special nutritional support, dehydration, low Hb and/or albumin level, hypotension, body temperature, pulse, surgery time, position in the surgery, and quality of position support tools.

The BRAT was developed by a team including Bergestrom and Braden in 1987 to prevent pressure injury. It was reported that its specificity and sensitivity were between 64% and 90% (28). It was emphasized that the scale had satisfactory reliability when used by specialist nurses. Pressure injury risk factors of patients were taken into consideration in the scale (28). Its validity and reliability study in Turkish was made in 1998 by Pınar and Oğuz (29).

The BRAT consists of 6 sub-dimensions. These dimensions are; sensory perception (1-4 points), humidity (1-4 points), activity (1-4 points), mobility (1-4 points), nutrition (1-4 points), friction and tearing (1-3 points). The total score of the scale ranging from 6-23 is obtained by summing the sub-dimension scores. According to the total score, 6-10 points are considered to be very high-risk, 11-15 points as high-risk, 16-19 points as moderate risk, and 20-23 points as low risk (28).

Although the BRAT has been suggested to have low sensitivity and moderate specificity for surgical patients, it is one of the most widely used scales (21,30,31). The reason for preference in the presented study was that it was used as a common scale in all clinics of the institution where the study was conducted. It was thought that this situation would facilitate the initiation of applications in the data source hospital where the results would be shared.

Collection of Data

In the presented study, 80% of the data were collected by researchers and about 20% by clinical nurses who were informed about the research. Communication was made easy because the nurses also used the clinical forms in the clinic where they worked. Short interviews were conducted with the nurses to ensure mutual consensus on pressure injury staging information by the researchers. All evaluation of the forms was done by the researchers. Written consent was obtained from the patients who met the inclusion criteria after the purpose of the study was explained. Patient characteristics were determined with the "introductory (individual and clinical) information form" on the morning of the surgery. The BRAT skin diagnosis was made and the patient was sent to surgery. After the surgery, the operating room nurse was interviewed for the position during the surgery, the duration of the surgery, position support materials, and the presence of any injurious condition, and the operating room epicrisis was examined. The patient, who was sent from the operating room to the ward to determine IPI, was evaluated with the BRAT within the first 2-4 hours. The pressure injury conditions seen in the patient were shared with the team.

Statistical Analysis

The data were analyzed by using SPSS 15.0 package program. Statistical significance tests were chosen according to the distribution of the data. In this study, frequency, mean (mean) and standard deviation were used for descriptive statistics, chi-square (χ^2) test, Mann-Whitney U test, Kruskal-Wallis test, independent t-test, and multivariate and univariate analyzes were performed. The significance value was accepted as p=0.05.

Ethical Aspects

The permission was obtained from the Clinical Research Ethics Committee of the relevant University Hospital for the research (Ethics committee permission no: 05.07.2017-11968-11/160), and institutional permission (could not be disclosed because it was stated that the name would not be specified at the time of publication) was obtained. Written informed consent was obtained from the participants.

Results

Table 1 shows the socio-demographic and some clinical characteristics of the participants. According to the characteristics of the patients in the preoperative period; the mean age of the participants was 47.72±22.20 years, 52.9% of them were 51 years old or older, and 55.9% were women. Only 35.3% of the patients were smoking, 67.7% of the BMI was 18.5-24.9 kg/m^2 (within normal limits), 63.3% were patients of general surgery clinic, 51.8% had chronic diseases. Of the participants, 97.1% were conscious patients. Of the patients, 25.3% had to take additional nutrition outside of the nutrition program. In addition, 12.4% of them had a Hb level of 13.5 g/dL (the lowest Hb level of the patients was 13.5 g/dL and the highest Hb level was 17.7 g/dL), 24.7% of them had an albumin level 3.4 g/dL or lower. However, blood pressure, respiratory status and body temperatures of the vast majority of the patients were within normal limits.

According to the operative period characteristics of the participants; 81.8% of the participants had surgery in the supine position. All of the patients were laid on a mattress on the operating table, pressure areas and body cavities were supported only with sheets and handmade pads.

IPI of stage I was detected in 24.2% of the patients in the coccyx and sacral region.

Table 2 includes the IPI status of the participants according to some sociodemographic characteristics. As the age of the patients increased, it was determined that the incidence of IPI increased, but this increase was not statistically significant (p>0.05). In this study presented, more IPI occurred in male patients than in female patients, but the difference was not statistically significant (p>0.05). The mean surgery duration

Table 1. Sociodemographic and some clinical characteristics of the participants (n=170)

Characteristics	n	%
Age¥		
18-28	19	11.2
29-39	28	16.5
40-50	33	19.4
>51	90	52.9
Gender		
Female	95	55.9
Male	75	44.1
Smoking history		
Smoker€	60	35.3
Not a smoker	110	64.7
BMI		
<18.5 kg/m²	13	7.6
18.5-24.9 kg/m²	115	67.7
25.0-29.9 kg/m²	42	24.7
Department		
Orthopedics	62	36.5
General surgery	108	63.5
Chronic disease		
Yes	88	51.8
No	82	48.2
Pre-operative consciousness		
Conscious	165	97.1
Unconscious	5	2.9
Nutritional status		
Normal diet	127	74.7
Need nutritional support	43	25.3
Hemoglobin*		
13.5 g/dL	21	12.4
13.6-17.7 g/dL	149	87.6
Albumin		
≤3.4 g/dL	42	24.7
3.5-5.5 g/dL	128	75.3
Blood pressure		
100-140/60-80 mmHg	130	76.5
>140-90 mmHg	40	23.5
Pulse		
60-100 min	159	93.5
>100 min	11	6.5
Preoperative temperature		
36-36.8 °C	169	99.4
Preoperative respiratory rate Ω		
12-20 dk.	161	94.7
Surgical position		
Supine	139	81.8
Prone or lateral	31	18.2
Surgical position support materials		
Mattresses/sheets and pads Ø	170	100.0
Postoperative pressure injury		
Yes **	41	24.2
No	129	75.8

¥: Mean age 47.72±22.20, €: only 7 (4.1%) participants smoke more than one pocket of cigarette a day, *Range: 13.5 g/dL-17.7g/dL.
Ω: Nine patients (5.3%) had a respiratory rate ≥21/min.
Ø: Position support material made by the operating room nurse with cotton and gauze
**Stage I pressure injury is a diffuse rash around the sacral and coccygeal regions that does not fade with pressure
BMI: Body mass index

(211.00±132.83/165.32±83.27) of male patients was longer than that of females, and the difference was statistically significant (p=0.01) (Table 4).

Table 3 includes IPI according to the clinical characteristics of the participants. There was no statistically significant relationship between the patients' IPI and BMI, smoking history, and chronic disease history (p>0.05) (Table 3). However, the surgery durations of the patients with high and low BMI were shorter than those with normal BMI (140.76±121.13; 156.42±67.67; 201.13±118.15, respectively) (p=0.034) (Table 4).

It was observed that patients of general surgery clinic developed more IPI than orthopedic patients, and this difference was statistically significant (p=0.047) (Table 3). The surgery duration in orthopedic patients was shorter than in patients of general surgery clinic, but the difference was not significant (p=0.207) (Table 4). In the preoperative period, patients who received regular nutrition developed less IPI than patients who required additional nutritional support (Table 3) (p=0.007), and the duration of the surgery was also shorter in patients who received regular nutrition (p=0.001) (Table 4)

In patients with pre-operative albumin levels below 3.5 g/dL, IPI developed more than those with albumin levels within the normal range (3.5-5.5 g/dL), and the difference was significant (p=0.015). In addition, no relationship was found between low albumin level and the duration of the surgery (p=0.861). Those with Hb level <13.5 g/dL had more IPI than those with Hb level 13.6-17.7 g/dL, but the difference was not statistically significant (p=0.213), (Tables 3 and 4). There was no statistically significant difference between blood pressure and IPI (p=0.054). When the relationship between the positions assigned to the patients during surgery and IPI was examined, the patients with the supine position had higher IPI. However, this difference was not statistically significant (p=0.656) (Tables 3 and 4).

Table 4 contains the mean duration of surgery and multivariate analysis results according to some characteristics of the patients. The duration of the surgery was longer in patients with IPI (246.70±145.58) than those without IPI (166.00±88.14) and the difference was statistically significant (p=0.002). Multivariate analysis showed that each one hour extension of the duration of surgery increased the risk of IPI by 1.007 times.

It was observed that the mean BRAT score of the patients in the study was not high. According to the BRAT mean score, it was determined that 24.2% of the patients had a medium (18.434±6.621 points) risk of IPI, and 75.8% had a very low risk of IPI (20.243±3.954 points). The difference between the mean scores was statistically significant (p=0.035). The difference between the mean scores was statistically significant (p=0.035). Each category point change in the BRAT score indicated a 0.8-fold risk for IPI.

According to the multivariate analysis, the risk of IPI was 2.4 times higher in patients who needed to take additional nutrition and had low albumin levels (p=0.038; 0.043, respectively).

Table 2. Intraoperative pressure injury (IPI) by some sociodemographic characteristics (n=170)

Characteristics	IPI (+) n (%)	IPI (-) n (%)	Total n (%)	Test	p value
Age					
18-28	4 (21.1)	15 (78.9)	19 (100)	0.558	0.906
29-39	8 (28.6)	20 (71.4)	28 (100)		
40-50	7 (21.2)	26 (78.8)	33 (100)		
>51	22 (24.4)	68 (75.6)	90 (100)		
Gender					
Female	21 (22.1)	74 (77.9)	95 (100)	0.476	0.304
Male	20 (26.7)	55 (73.3)	75 (100)		
Total	41 (24.2)	129 (75.8)	170 (100)		

IPI: Intraoperative pressure injury

Table 3. Intraoperative pressure injury (IPI) by some clinical characteristics (n=170)

Characteristics	IPI (+) n (%)	IPI (-) n (%)	Total n (%)	Test	p value
BMI					
<18.5 kg/m^2	3 (23.1)	10 (76.9)	13 (100)	0.132^{Ø}	0.936
18.5-24.9 kg/m^2	27 (23.5)	88 (76.5)	115 (100)		
25.0- 29.9 kg/m^2	11 (26.2)	31 (73.8)	42 (100)		
Smoking history					
Not a smoker	29 (26.4)	81 (73.6)	110 (100)	0.859$^{¥}$	0.354
Smoker	12 (20.0)	48 (80.0)	60 (100)		
Chronic disease					
No	22 (26.8)	66 (73.2)	88 (100)	6.775$^{¥}$	0.148
Yes	19 (23.2)	63 (76.8)	82 (100)		
Department					
General surgery*	31 (28.7)	77 (71.3)	108 (100)	3.403;$^{¥}$	0.047
Orthopedics*	10 (16.1)	52 (83.9)	62 (100)		
Nutritional status					
Normal diet	24 (18.9)	103 (81.1)	127 (100)	7.476$^{¥}$	0.007
Need nutritional support	17 (39.5)	26 (60.5)	43 (100)		
Hemoglobin (g/dL)					
13.6-17.7 g/dL	34 (22.8)	115 (77.2)	34 (22.8)	1.112$^{¥}$	0.213
13.5 g/dL	7 (33.3)	14 (66.7)	21 (100)		
Albumin (g/dL)					
3.5-5.5 g/dL	25 (19.5)	103 (80.5)	128 (100)	5.955$^{¥}$	0.015
≤3.4 g/dL	16 (38.1)	26 (61.9)	42 (100)		
Blood pressure (systolic/diastolic)					
100-140/60-80 mmHg	27 (20.8)	103 (79.2)	130 (100)	3.385	0.054
>140/90 mmHg	14 (35.0)	26 (65.0)	40 (100)		
Surgical position					
Supine	34 (20.0)	105 (61.8)	139 (81.8)	0.198	0.656
Lateral or other	7 (4.1)	24 (14.1)	31 (18.2)		
Total	41 (24.2)	129 (75.8)	170 (100.0)		

Ø: Kruskal-Wallis chi-square test, ¥: Pearson chi-square test, BMI: Body mass index, IPI: Intraoperative pressure injury

Table 4. Mean surgery duration by some important characteristics of the patients, multivariate analysis results

Characteristics	Duration of surgery mean ± SD	Median (percentile)	Test	p value	Multivariantanalysis Exp (β); p
Gender					
Female	165.32±83.27	165	-2.602¥	0.010	
Male	211.00±132.83	180			
Department					
General surgery	194.49±90.21	180	-1.270¥	0.207	
Orthopedics	169.76±137.29	120			
Pressure injury					
Yes	246.70±145.58	210	3.359¥	0.002	**1.007; 0.002**
No	166.00± 88.14	150			
Nutritional status					
Need nutritional support	203.26±118.87	180	41.506*	0.001	**2.419; 0.038**
Normal diet (regimen III)	179.45±106.65	160			
Albumin					
3.5-5.5g/dL	188.69±143.34	180	0.175¥	0.861	**2.400; 0.043**
≤3.4 g/dL	184.94±94.83	165			
Braden pressure injury score	18.434± 6.62		2.131	0.035	**0.869;0.035**
Surgery duration by BMI					
<18.5 kg/m²	140.76±121.13	120			
18.5-24.9 kg/m²	201.13±118.15	180	6.783**	0.034	
25.0- 29.9 kg/m²	156.42±67.67	150			

¥Independent t-test, *chi-square test , **Kruskal-Wallis test
According to the Braden score, 6 or less points are considered to be very high-risk, 10-12 points as high risk, 13-14 points as moderato risk, and 15-23 as mild to no risk in terms of development of pressure injury, SD: Standard deviation, BMI: Body mass index

Discussion

Surgical patients may have some sociodemographic and clinical factors preoperatively that may contribute to pressure-related tissue injury. Among the sociodemographic characteristics, it has been suggested that as age increases, it may pose a risk for IPI (32-34). Age was not a risk factor for IPI in the presented study. This might be due to the fact that the mean age of the patient group represented a younger group.

The relationship of gender with pressure injury is controversial in researches. However, there are studies showing women at higher risk (15). In the present study, longer surgery duration in men compared to women might have a role in the higher incidence of IPI in male patients.

It is argued that longer surgery duration and increased BMI may be related. It is suggested that the adipose tissue increases the extent of surgical intervention and with the presence of chronic diseases in which tissue nutrition is impaired, they may prolong the surgery duration (34-36). Conversely, low BMI has been shown to leave soft tissue vulnerable to pressure (8). In the study presented, there was no relationship between IPI and BMI and presence of chronic disease. The reason for this might be that the majority of the patients had a normal BMI. The number of those with low or high BMI was very small and their surgery duration was shorter. It could be concluded that the size of the surgery of the patients was decisive here.

In the literature, direct effect of the clinics where patients are hospitalized on IPI has not been shown. It has been argued that the characteristics of patients hospitalized in clinics may play a role in IPI (24,32,37). Some studies suggest that patients of general surgery clinic carry the risk of IPI because they are patients with nutritional problems (24,38,39). In the presented study, IPI was higher in the patients of general surgery clinic. In this result, longer surgery duration in the patients of general surgery clinic than in orthopedic patients might have a role. However, as it is known, the duration of prosthetic surgeries is long and it should be considered that this situation may reverse for the orthopedic patients in case of sufficient sample size. Studies report that there is a direct proportion between IPI and the duration of surgery (9,10,22).

Hb deficiency and nutritional deficiency can play an important role in the development of pressure sores (40,41). In the present study, the Hb level was normal or close to normal, as planned surgical intervention was applied in all patients. Therefore, Hb level was not among the factors affecting the development of IPI. However, even if surgical intervention was planned, the

need for additional nutrients was an important variable for the development of IPI. In addition, the need for additional nutrients was thought to be effective in longer duration of surgery in those patients. It is also reported in the literature that the diet and nutritional needs of surgical patients may be important in the development of IPI. Therefore, pre- and postoperative care protocols that shorten the fasting period have been developed (5,22).

As it is known, edema occurs in tissues with a decrease in albumin level (<3.5 g/dL) and tissue resistance to pressure decreases. Thus, the incidence of pressure injury increases (10,32,42). In the present study, a strong relationship between low albumin levels and IPI, regardless of the duration of the surgery, supported this literature finding.

Studies have suggested that hypotension, tachycardia, and hypothermia may cause pressure injury by increasing peripheral resistance. The decrease in tissue oxygenation with the decrease in blood pressure and body temperature in patients under general anesthesia can also increase this risk (3,14,20,41). In the presented study, the blood pressure, heart rate, respiration and body temperature values of the patients were within normal limits before surgery. No risk associated with IPI was determined.

The role of position given during surgery and position support materials used in the prevention of IPI has been shown in many studies (18,43-45). In the presented study, the majority of patients were operated in the supine position, so a comparison between positions could not be made. However, the fact that IPI occured in the sacral area and the coccyx in the study and that effective position support material could not be used showed that these injuries were related to the position. It has been reported that the position given during surgery and position support materials used during the surgery (such as gel pad, smart pad, foam support) may be determinants for the location of the pressure injury (6,18,19,22,43). It is pointed out that this risk will increase exponentially for every 30 minutes after the duration of surgery exceeds two hours, and the importance of position support materials is emphasized (10,19,22,46).

In the presented study, there was no patient with a low BRAT score. Because all patients were patients with planned surgery and all of them could be mobilized. However, the frequency of stage I IPI, which did not fade with pressing, was higher than the expected prevalence limit for a planned long surgical procedure. This result may be related to either the lack of preoperative pressure injury risk preparations or low specificity and sensitivity of the BRAT. Although BRAT scores in patients with IPI varied within the normal score range, they showed two conditions: First, skin diagnosis with a preoperative scale suggested that a careful nurse could detect the risky patient early. Second, as the duration of the operation increased, even if a patient's pressure injury score was low, he/she might develop a pressure injury. The literature on this subject suggests that skin evaluation should be continued for at least 48-72 hours including periods before, during and after surgery to prevent IPI in long surgical procedures (43,41,46).

Study Limitations

In this study, as in many institutions, a scale specific to the evaluation of ASBI was not used. It was thought that it would be more useful to show the results of scales actively used in clinics rather than scales preferred by researchers. This scale might not be able to precisely define the effect of variables belonging to surgical stage on the results, since it could not make a clear evaluation of the surgery. Since the study included only patients of general surgery clinic and orthopedic patients, the effects of different surgical positions could not be evaluated. These two situations were the most important limitations of the study.

Conclusion

According to the data of this study, it could be concluded that IPI was a perioperative care problem that nurses should monitor carefully in planned major surgical procedures. Inadequate nutritional level, low albumin level, length of duration of surgery, change in BRAT score (even if it varied within normal limits) should be evaluated as important for IPI. Preoperative risk diagnosis and skin diagnosis of surgery nurses and operating room nurses were important for long surgical procedures. Nevertheless, BRTA should be used with caution in assessing the risk of IPI.

According to the limitations and findings of this study, a more comprehensive study with the "3S Operating Room Pressure Injury Risk Assessment Scale" was planned and presented to the institution.

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Ethics

Ethics Committee Approval: The permission was obtained from the Clinical Research Ethics Committee of the relevant University Hospital for the research (Ethics committee permission no: 05.07.2017-11968-11/160).

Informed Consent: The study was approved by the ethics committee and informed written permission was obtained from the institutions and volunteers.

Peer-review: Externally peer reviewed.

Authorship Contributions

Design: Y.Y.S., C.A., Data Collection or Processing: C.A., Analysis or Interpretation: Y.Y.S., C.A., Literature Search: Y.Y.S., C.A., Writing: Y.Y.S.

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References

1. Kandilov AM, Coomer NM, Dalton K. The impact of hospital-acquired conditions on Medicare program payments. Medicare Medicaid Res Rev 2014;4:1-22.
2. Shafipour V, Ramezanpour E, Gorji MA, Moosazadeh M. Prevalence of postoperative pressure ulcer: A systematic review and meta-analysis. Electronic Physician 2016;8:3170-6.
3. Walton-Geer PS. Prevention of pressure ulcers in the surgical patient. AORN J 2009;89:538-48.
4. Karayurt Ö, Çelik B. Ameliyata bağlı basınç yarası ve hemşirelik bakımı. Türkiye Klinikleri Cerrahi Hastalıkları Hemşireliği-Yara ve Hemşirelik Bakımı Özel Sayısı 2017;3:176-82.
5. O'Brien DD, Shanks AM, Talsma A, Brenner PS, Ramachandran SK. Intraoperative risk factors associated with postoperative pressure ulcers in critically ill patients: a retrospective observational study. Crit Care Med 2014;42:40-7.
6. Kim JM, Lee H, Ha T, Na S.Perioperative factors associated with pressure ulcer development after major surgery. Korean J Anesthesiol 2018;71:48-56.
7. Gül Ş. Cerrahi girişim uygulanan hastalarda basınç ülseri gelişiminin önlenmesi. Hacettepe Üniversitesi Hemşirelik Fakültesi Dergisi 2014;54-61.
8. Tschannen D, Bates O, Talsma A, Guo Y. Patient-specific and surgical characteristics in the development of pressure ulcers. Am J Crit Care 2012;21:116-25.
9. Hayes RM, Spear ME, Lee SI, Krauser Lupear BE, Benoit RA, Valerio R, et al. Relationship between time in the operating room and incident pressure ulcers: a matched case-control study. Am J Med Qual 2015;30:591-7.
10. Primiano M, Friend M, McClure C, Nardi S, Fix L, Schafer M, et al. Pressure ulcer prevalence and risk factors during prolonged surgical procedures. AORN J 2011;94:555-66.
11. Katran HB. Bir cerrahi yoğun bakım ünitesinde bası yarası görülme sıklığı ve bası yarası gelişimini etkileyen risk faktörlerinin irdelenmesi. JAREN 2015;1:8-14.
12. Chen HL, Chen XY, Wu J. Theincidenceofpressure ulcers in surgical patients of the last 5 years: a systematic review. Wounds 2012;24:234-41.
13. Spruce L, Van Wicklin SA. Back to basics: positioning the patient. AORN J 2014;100:298-305.
14. Fu Shaw L, Chang, PC, Lee JF, Kung HY, Tung TH. Incidence and predicted risk factors of pressure ulcers in surgical patients: experience at a medical center in Taipei, Taiwan. BioMed Research International 2014;1-10.
15. Tan A. Cerrahi Yoğun bakım hastalarında basınç yarası gelişme riski. İnönü Üniversitesi Sağlık Bilimleri Enstitüsü, Yüksek Lisans tezi (yayınlanmamış) 2015. http://abakus.inonu.edu.tr/xmlui/bitstream/handle/11616/5085/Tez%20Dosyası.pdf?sequence=1&isAllowed=y
16. Mutlu S. Açık kalp ameliyatı uygulanan hastalarda basınç yaralanması oluşumunu etkileyen faktörlerin incelenmesi. DEÜ Sağlık Bilimleri Enstitüsü, Yüksek lisans tezi (yayınlanmamış) 2012.
17. Uzun O, Tan M. A. A prospective, descriptive pressure ulcer risk factor and prevalence study at a university hospital in Turkey. Ostomy Wound Manage 2007;53:44-56.
18. Beckett AE. Are we doing enough to prevent patient injury caused by positioning for surgery?. J Perioper Pract 2010;20:26-9.
19. Shen WQ, Chen HL, Xu YH, Zhang Q, Wu J. The relationship between length of surgery and the incidence of pressure ulcers in cardiovascular surgical patients: A retrospective study. Adv Skin Wound Care 2015;28:444-50.
20. Cherry C, Moss J. Best practices for preventing hospital-acquiredpressureinjuriesinsurgicalpatients. Can Oper Room Nurs J 2011;29:22-6.
21. He W, Liu P, Chen HL. The Braden Scale cannot be used alone for assessing pressure ulcer risk in surgical patients: a meta-analysis. Ostomy Wound Manage. 2012;58:34-40.
22. Nilsson UG. Intraoperative positioning of patients under general anesthesia and the risk of postoperative pain and pressure ulcers. J Perianesth Nurs 2013;28:137-43.
23. Günes ÜY, Efteli E. Predictivevalidityandreliabilityof the Turkish version of the risk assessment pressure sore scale in intensive care patients: results of a prospective study. Ostomy Wound Manage 2015;61:58-62.
24. RaoAD, PrestonAM, StraussR, StammR, ZalmanDC. Risk factors associated with pressure ulcer formation in critically Ill cardiac surgery patients: A systematic review. J Wound Ostomy Continence Nurs 2016;43:242-7.
25. Spruce L. Back to basics: preventing perioperative pressure injuries. AORN J 2017;105:92-9.
26. ChenHL, ShenWQ, LiuP, LiuK. Lengthofsurgery and pressure ulcers risk in cardiovascular surgical patients: a dose– responsemeta-analysis. Int Wound J 2017;14:864-9.
27. Tanrıverdi F, Dikmen Y. Yoğun bakım hastalarında basınç yaraları: Risk faktörleri ve önlemler. J Hum Rhythm 2017;3:177-82.
28. Bergstrom N, Braden BJ, Laguzza A, Holman V. The Braden scale for predicting pressure sore risk. Nurs Res 1987;36:205-10.
29. Pınar R, Oğuz S. Norton ve braden bası yarası değerlendirme ölçeklerinin yatağa bağımlı aynı hasta grubunda güvenirlik ve geçerliğinin sınanması: Uluslararası Katılımlı VI. Ulusal Hemşirelik Kongresi, Kongre Kitabı, Ankara, 1998;172-5.
30. Chan WS, Pang SM, Kwong EW. Assessing predictive validity of the modified Braden scale for prediction of pressure ulcer risk of orthopaedic patients in an acute care setting. J Clin Nurs 2009;18:1565-73.
31. Gao XL, Hu JJ, Ma Q, Wu HY, Wang ZY, Li TT, et al. Design and research on reliability-validity for 3S intraoperative risk assessment scale of pressure sore. J Huazhong Univ Sci Technolog Med Sci 2015;35:291-4.
32. Lindgren M, Unosson M, Krantz AM, Ek AC. Pressure ulcer risk factors in patients undergoing surgery. J Adv Nurs 2005;50:605-12.
33. Efteli EÜ, Güneş Ü. Basınç yaralanması gelişiminde perfüzyon değerlerinin etkisi. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi 2014;17:3.
34. Chen HL, Chen XY, Wu J. Theincidenceofpressure ulcers in surgical patients of the last 5 years: a systematic review. Wounds 2012;24:234-41.

35. Lowe JR. Skinintegrityincriticallyillobesepatients. Critical Care Nursing Clinics 2009;21:311-22.

36. Chaboyer W, Gillespie BM. Understanding nurses' views on a pressure ulcer prevention care bundle: a first step towards successful implementation. J Clin Nurs 2014;23:3415-23.

37. Agrawal K, Chauhan N. Pressure ulcers: Back to the basics. Indian J Plast Surg 2012;45:244-54.

38. Dolgun E, Yavuz M. Aşırı şişmanlık cerrahisinde hemşirelik bakımı. Maltepe Üniversitesi Hemşirelik Bilim ve Sanatı Dergisi 2009;3:85-92.

39. Karadağ M, Gümüşkaya N. The incidence of pressure ulcer in surgical patients: a sample in Turkey. J Clin Nurs 2006;15:413-21.

40. Dumlu EG, Bozkurt B, Tokaç M, Kıyak G, Özkardeş AB, Yalçın S, et al. Cerrahi hastalarda malnütrisyon ve beslenme desteği. Ankara Medical Journal 2013;13:33-7.

41. Inan DG, Otunç G. Pressure ulcer prevalence in Turkey: a sample from a university hospital. J Wound Ostomy Continence Nurs 2012;39:409-13.

42. Webster J, Lister C, Corry J, Holland M, Coleman K, Marquart L. Incidenceand risk factors for surgically acquired pressure ulcers. J Wound Ostomy Continence Nurs 2015;42:138-44.

43. Lumbley JL, Ali SA, TchokouaniL S. Retrospective review of predisposing factors for intraoperative pressure ulcer development. J Clin Anesth 2014;26:368-74.

44. Adedeji R, Oragui E, Khan W, Maruthainar N. The importanceofcorrectpatientpositioningintheatresandimplicationsof mal-positioning. J Perioper Pract 2010;20:143-7.

45. Black J, Fawcett D, Scott S. Ten top tips: preventing pressure ulcers in the surgical patient. Wounds Int J 2014;5:14-8.

46. Aloweni F, Ang SY, Fook-Chong S, Agus N, Yong P, Goh MM, et al. A prediction tool for hospital-acquired pressure ulcers among surgical patients: Surgical pressure ulcer risk score. Int Wound J 2019;16:164-75.

Original Article

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Comparison of Small-diameter-hole and Traditional Microfracture in Cartilage Repair and the Effect of Adding a Hyaluronic Acid-based Acellular Matrix Scaffold: An Animal Study

Kıkırdak Doku Onarımında Küçük Çaplı Delik Yönteminin Geleneksel Mikro Kırık Yöntemi ile Karşılaştırılması ve Hyalüronik Asit Temelli Hücresiz Matriks Skafold Eklemenin Etkisi: Bir Hayvan Çalışması

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ABSTRACT

Objective: Since, there is no standardized technique for the treatment of focal cartilage defects that can recreate original cartilage tissue; researchers continue to explore and evaluate various treatment modalities. This study compared post-operative healing of cartilage defects after treatment with small-diameter-hole microfracture (SDHM) technique with that of traditional microfracture technique. The effects of the hole density and augmentation with hyaluronic acid-based acellular matrix (HA-based AM) on cartilage healing were also investigated.

Methods: Articular cartilage defects measuring 5 mm in diameter and 3 mm in depth were created in each femoral trochlear groove of 21 New Zealand rabbits. Rabbits were assigned to seven groups comprising six knees each. The rabbits were sacrificed 12 weeks later, and the regenerated cartilage was harvested for histological evaluation using the Wakitani scoring system.

Results: All defects were filled with regenerated tissue macroscopically. Group I (14; range 10-14 points) had significantly higher Wakitani score than in groups VI (6; range 1-11 points) and

ÖZ

Amaç: Fokal kıkırdak defektlerinin tedavisinde hala orijinal kıkırdak dokusu sağlayan mükemmel bir yöntem yoktur, bu nedenle en iyi tedavi seçeneklerini bulmak için araştırmalar devam etmektedir. Bu çalışmada amaç, kıkırdak defektlerinde küçük çaplı delik (SDHM) ve geleneksel mikro kırık tedavilerinin iyileştirme kalitesini karşılaşmaktır. Bununla beraber delik yoğunluğunun ve defekti hyalüronik asit bazlı aselüler matriks (HA bazlı AM) ile desteklemenin kıkırdak iyileşmesi üzerindeki etkileri de incelenmiştir.

Yöntemler: Yirmi bir Yeni Zelanda tavşanının her iki femur trochlear oluğunda 5 mm çapında ve 3 mm derinliğinde artiküler kıkırdak defekti oluşturuldu. Her biri 6 dizden oluşan yedi grup oluşturuldu. Tavşanlar 12 hafta sonra sakrifiye edildi ve rejenere kıkırdak Wakitani skorlama sistemi kullanılarak histolojik değerlendirme için toplandı.

Bulgular: Tüm defektler rejenere doku ile makroskopik olarak dolduruldu. 1. Grup [14 (10-14) puan], VI [6 (1-11) puan] ve VII. [5 (3-10) puan] gruplara göre anlamlı derecede yüksek Wakitani

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VII (5; range 3-10 points) (p=0.043 and p=0.016, respectively). No significant differences were observed among the other groups. Augmentation with HA-based AM did not contribute to cartilage healing.

Conclusion: Improved cartilage healing was observed with increasing SDHM density than with traditional microfracture technique. SDHM combined with HA-based AM implantation did not improve the quality of the regenerated cartilage.

Keywords: Microfracture, cartilage repair, small-diameter-hole microfracture, hyaluronic-acid-based acellular matrix, cartilage healing

skoruna sahipti (p=0.043 ve p=0.016). Diğer gruplar arasında anlamlı bir fark gözlenmedi. Hyaluronik asit bazlı aselüler matriks ile destekleme, kıkırdak iyileşmesine katkıda bulunmadı.

Sonuç: SDHM yoğunluğunun artırılması, geleneksel mikro kırık ile karşılaştırıldığında kıkırdak iyileşmesini artırır. Hyalüronik asit bazlı aselüler matriks implantasyonu ile desteklenen SDHM'nin artırılması ise rejenere kıkırdak kalitesini artırmadı.

Anahtar Sözcükler: Mikrokırık, kıkırdak onarımı, küçük çap delikli mikrokırık, hyalüronik asit bazlı aselüler matriks, kıkırdak iyileşmesi

Introduction

Microfracture, a bone-marrow-stimulating technique introduced by, Steadman et al. (7) for the treatment of focal full-thickness, symptomatic cartilage defects, consists of multiple holes in the subchondral bone to enable pluripotent stem cells to migrate from the bone marrow into the defect and to promote formation of fibrocartilage repair tissue (1-7).

The amount of hyaline-like cartilage in the repair tissue depends on alterations in the subchondral bony architecture during microfracture, as compression of the cancellous bone around the holes prevents connection with the bone marrow, thus reducing the number of mesenchymal stem cells (MSCs) that can reach the defect (8,9). This disadvantage of microfracture led to the recent development of a technique called 'small-diameter-hole microfracture' (SDHM) (9-11). Some experimental studies showed that deep, small-diameter drill holes are more effective in promoting cartilage repair than large-diameter, shallow drill holes (10,11). The repair tissue after deep subchondral perforations contains less type I and more type II collagen, and the defect is better filled with hyaline-like cartilage (9-11). Despite promising results of SDHM in comparison with conventional microfracture, the role of hole density (how many SDHMs should be performed for a cartilage defect of a given size) has not been adequately investigated.

Another limitation of the marrow-stimulating techniques is related to the amount of defect filling. A thickness of 5 mm is necessary to fill a full-thickness articular cartilage defect in the knee and it is difficult to create sufficient thickness to fill in the defect without a scaffold. For this reason, several studies investigated the efficacy of MSCs transferred to a scaffold at the time of implantation to treat focal cartilage defect (12-15). The rationale of this treatment is that the scaffold triggers the proliferation and chondrogenic differentiation of MSCs. Moreover, the scaffold contributes to fill the defect.

An alternative to the engineered scaffold implantation is the autologous matrix-induced chondrogenesis (AMIC), which consists of implanting a cell-free scaffold over microfracture (16). Satisfactory results have been reported with this technique (17), albeit no evidence exists on the combination of matrix aided chondrogenesis and SDHMs (18).

The aim of the present study was twofold: to assess the efficacy of SDHMs with and without matrix augmentation in comparison with conventional microfracture for the treatment of focal full-thickness chondral defects of the knee, and to investigate the role of hole density on cartilage repair in SDHM technique. The hypotheses of the study were that SDHMs enhance cartilage repair with and without matrix augmentation, and that hole density positively correlates with cartilage repair.

Method

Twenty-one, mature, male New Zealand white rabbits with a mean weight of 3.4 kg (range: 3-4.2 kg) were used for the present study. All experiments were conducted in accordance with the guidelines of the local ethic committee for animal experimentation (approval number: 2014/140).

Surgical Technique

All of the surgical procedures were performed under general anaesthesia and by use of sterile conditions. A 2-cm longitudinal anterior skin incision was made over the right knee, and the joint was approached via a medial parapatellar arthrotomy. A cylindrical cartilage defect measuring 5 mm in diameter was created on the femoral trochlea (Figure 1A and 1B). Non-calcified and calcified layers of cartilage were removed from the defect area and care was taken to avoid damage to the subchondral bone.

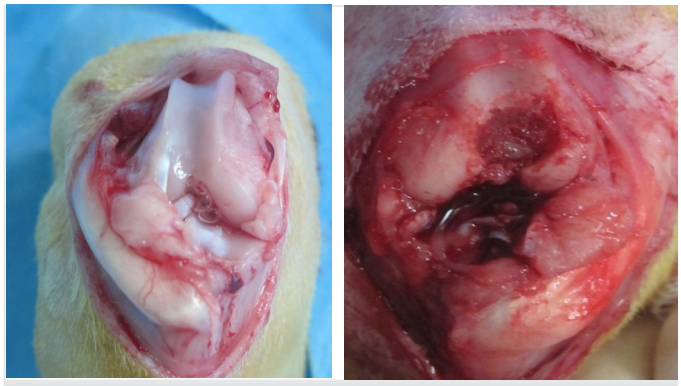

Figure 1. (A) Articular cartilage of the femoral condyles and trochlear groove of the rabbit. (B) A cylindrical cartilage defect measuring 5 mm in diameter and 3 mm in depth was created in the trochlear groove

Animals were divided into seven groups of six rabbits each, according to the treatment protocol. In group 1 (conventional microfracture or control group), three holes with 5 mm depth were created in the subchondral bone using a standard 1.2-mm arthroscopic awl. In groups 2 to 7, a custom-made device was used to create SDHMs into the defect, which measured 0.8 mm in diameter and 5 mm in depth. Four, five and six holes were created in groups 2, 4 and 6, respectively (Figure 2). Figure 3 illustrates the 6 holes of SDHM in the cartilage defect. In the remaining groups (3, 5 and 7 respectively), SDHMs were combined with a hyaluronic acid-based acellular matrix (HAAM) (Hyalofast; Anika Therapeutics, Bedford, MA, USA), which was placed over the defect after creating four, five and six holes in groups 3, 5, and 7, respectively (Figure 4). The joint was irrigated, haemostasis was controlled, the capsule was sutured with 2-0 Vicryl, and the skin was closed with 3-0 silk sutures.

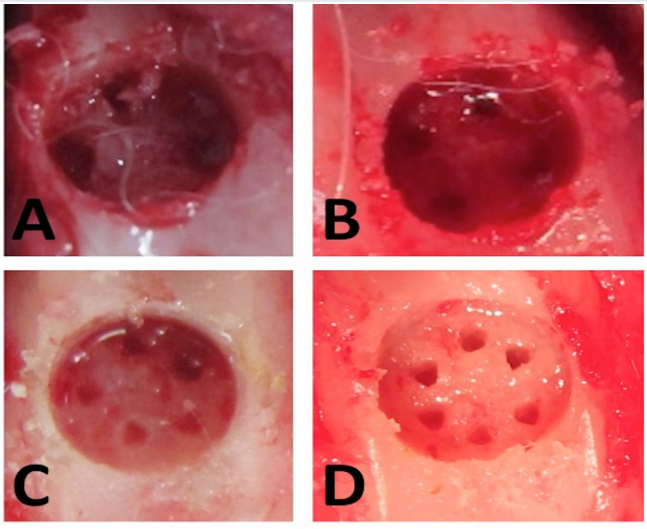

Figure 2. The defects were treated using (A) microfracture with three holes in group I, SDHM with (B) four holes in groups II and III, (C) five holes in groups IV and V, and (D) six holes in groups VI and VII

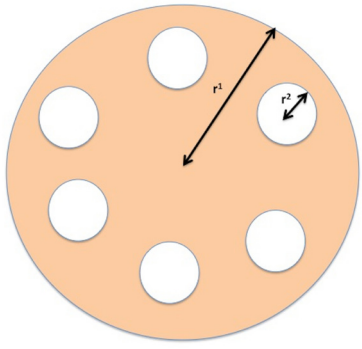

Figure 3. Six holes of SDHM are illustrated. r1 is the radius of the cartilage defect (2.5 mm) and r2 is the radius of the SDHM hole (0.4 mm)

SDHM: Small-diameter-hole microfracture

Postoperatively, the rabbits were returned to their cages without any immobilization of the operated limb and full weight-bearing was allowed as tolerated. General health monitored during recovery.

Outcome Measurements

The rabbits were sacrificed under general anaesthesia 12 weeks postoperatively. The distal femur was dissected and harvested for both macroscopic and histological evaluations.

Macroscopic appearance of the repair site was evaluated by three different investigators and rated according to the International Cartilage Repair Society (ICRS) evaluation score (19). This scoring system consists of a 12-point scale based on three categories (degree of defect repair, integration to border zone, and macroscopic appearance). The tissue samples were then fixed in 10% neutral buffered formalin for 72 hours, rinsed with water, and decalcified in decalcifying solution (OSTEOMOLL; Merck Millipore, Billerica, MA, USA). After decalcification, the samples were dehydrated gradually using increasing concentrations of alcohol (70%, 90%, 96%, and 100%) and cleared in xylene. Then, the samples were submerged in paraffin overnight at 60°C and embedded in paraffin blocks the next day. After the blocking process, 5-µm-thick sections perpendicular to the lesion surface were obtained from the samples and placed on slides, stained with haematoxylin and eosin (H&E) and toluidine blue for histological evaluation, and examined under a light microscope (Nikon Eclipse i5; Nikon, Tokyo, Japan).

Histological findings were scored using the scale described by Wakitani et al. (20) according to the intensity of basophilic staining caused by hematoxylin (20-22). Sections were graded according to cell morphology (maximum 4 points), matrix staining (maximum 3 points), surface regularity (maximum 3 points), cartilage thickness (maximum 2 points), and donor material integration into adjacent host cartilage (maximum 2

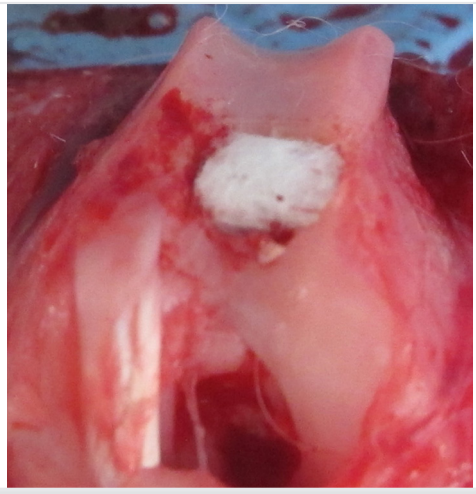

Figure 4. HA-based AM (Hyalofast, Anika Therapeutics, Bedford, MA, USA) was placed over the defect area after performing SDHM in groups III, V, and VII

SDHM: Small-diameter-hole microfracture

points). The maximum score was 14 points. A higher Wakitani score represents lower-quality repair tissue.

Three trained observers blinded to group allocation performed all macroscopic and histological evaluations.

Statistical Analysis

All the outcome measurements were expressed as mean values ± standard deviations. The data were analysed using statistical software SPSS 10.0 for Windows (IBM, Chicago, IL, USA). Groups were compared for histologic scores using the Kruskal–Wallis test. Post hoc Dunn test was used for multiple pairwise comparisons. Significance was considered for p values less than 0.05.

Results

There were no wound complications, infections, or deaths.

Gross evaluation showed that the defects were filled with the cartilage completely in group 6 and group 7, and partially in the other groups. The mean ICRS evaluation score of each group was showed in the table 1.

Histologic evaluation shows that matrix of hyaline cartilage is seen metachromasia and one of the best dyes for it is the toluidine blue. In addition, hematoxylin stains matrix of hyaline cartilage as basophilic. In our study, we scored the matrix staining in the Wakitani score (Table 2). The defect area was incompletely filled with fibrous tissue in group 1 and group 2, and completely filled with fibrocartilage tissue in group 3 and group 4. The defects were filled with repair tissue that contained hyaline cartilage in groups 5 to 7 (Figure 5). Although cartilaginous tissue was formed these groups, the basophilic matrix appeared in group 6 and group 7. The surface of the repaired tissue was more irregular in groups 1 to 5, and smoother in groups 6 and 7.

Overall histologic scoring assessment showed a significant difference between groups. Post hoc analysis showed that groups 6 and 7 had significantly better results than group 1 (p=0.043 and p=0.016, respectively). All other pairwise comparisons showed no significant differences.

Analysis of cell morphology subscore showed a significant difference between groups. Post hoc analysis showed that groups 6 and 7 had significantly better results than group 1 (p=0.041 and p=0.001, respectively).

Matrix staining subscore did not significantly differ among the groups.

Surface regularity subscore was significantly lower in groups 6 and 7 than in group 1 (p=0.029 and p=0.029, respectively).

Cartilage thickness and integration subscores did not significantly differ among the experimental groups.

Osteoarthritic changes were not observed in healthy cartilaginous tissue adjacent to the treatment area in all groups. The outer surface of the articular cartilage has normal appearance and has not wear or ridge and osteophyte. Vertical cracks, vascularization and inflammation have not been observed in the hyaline cartilage tissue. Chondrocytes, territorial and interterritorial matrix were normal in morphology. Histopathological findings were not found. Additionally, degeneration was not observed in the subchondral bone. Hyaline cartilage matrix was mostly made up of type II collagen. The metachromatic staining observed in our HE-stained sections showed that the amount of collagen was high and packed tightly. Metachromatic staining in the newly formed tissue matrix indicates that healing and cartilaginous tissue formation.

Table 1. Macroscopic evaluation of the samples according to the ICRS scoring system (point)

	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII
Min.	3	4	4	6	7	10	10
Max.	3	5	5	8	8	11	11
Mean	3	4.3	4.3	7	7.3	10.5	10.6

ICRS: International Cartilage Repair Society, Min.: Minimum, Max.: Maximum

Table 2. Histologic comparisons of the groups using Wakitani's score

	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII	p
Morphology	4	3	3	2	2	2	1	0.001; VII vs I 0.041; VI vs I
Matrix	3	3	2	2	1	1	1	n.s
Surface	3	3	2	2	1.5	1	1	0.029; VII vs I 0.029; VI vs I
Thickness	2	1.5	1.5	1	1	1	1	n.s
Integration	2	1	1.5	1.5	1	1	1	n.s
Total	14	11.5	9.5	8	6.5	6	5	0.016; VII vs I 0.043; VI vs I

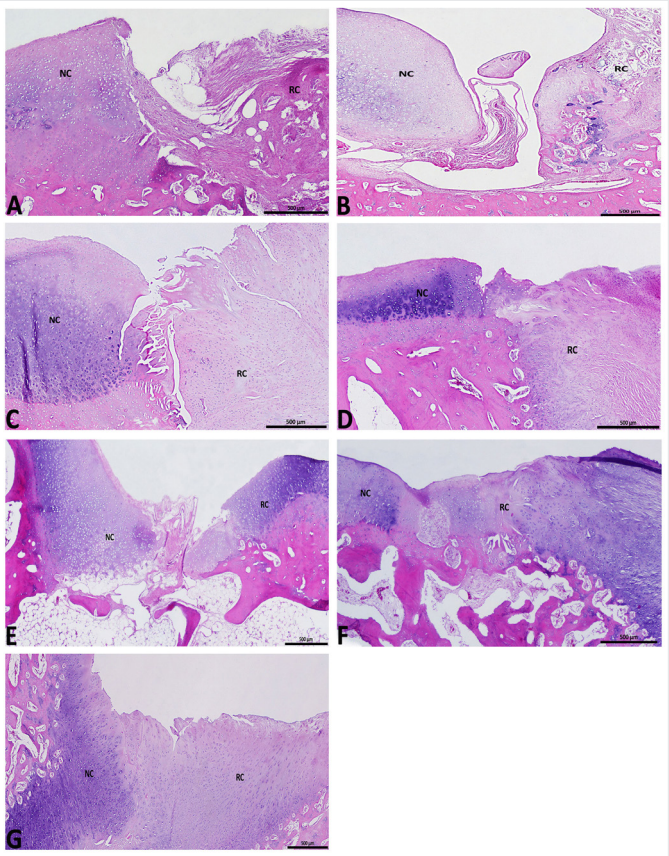

Figure 5. (A) Irregular surface, mostly non-cartilaginous tissue and non-metachromatic matrix staining in repaired cartilage (RC) tissue in Group 1. (B) Irregular surface, mostly non-cartilaginous tissue and significantly decreased matrix staining in Group 2. (C) Irregular surface, mostly fibro-cartilaginous tissue, significantly decreased matrix staining and integrated one edge between normal and repaired cartilage tissue in Group 3. (D) Moderate surface regularity, mostly fibro-cartilaginous tissue, significantly decreased matrix staining and integrated one edge between normal and repaired cartilage tissue in Group 4. (E) Regular surface, mostly hyaline cartilage, slightly decreased matrix staining and integrated one edge between normal and repaired cartilage tissue in Group 5. (F) Regular surface, mostly hyaline cartilage, metachromatic matrix staining and integrated both edges between normal and repaired cartilage tissue in Group 6. (G) Regular surface, hyaline cartilage, metachromatic matrix staining and integrated both edges between normal and repaired cartilage tissue in Group 7

NC: Normal cartilage tissue, RC: Repaired cartilage tissue, Staining: H&E, scale bar =500 μm

Discussion

The unique features of our method are as follows: 1) a SDHM with sufficient thickness for cartilage repair can be performed without a HA-based AM scaffold; and 2) increasing the number of SDHM applied to the defect area increases cartilage regeneration.

In recent years, several methods have been developed for repairing full-thickness cartilage defects. The MF technique performed arthroscopically as described by Steadman et al. (7) is a popular treatment method because it is easy applicable and cost-effective (23,24). Microfracture repairs the defective cartilage area by enabling the arrival of stromal cells. However, it results in shallow channels, wall compression, and increased trabecular thickness and density, as demonstrated by micro-computed tomography (microCT) and histology in several clinical and animal studies (25,26). Thus, it does not allow the regeneration of normal hyaline cartilage, perhaps because of the lack of sufficient MSCs or poor cellular differentiation (27-29). Compared with traditional microfracture, SDHM creates more holes with smaller diameters, which damage trabecular structures less. Therefore, more MSCs fill the defect (10,11,30,31).

Min et al. (30) compared the numbers of MSCs in 5-mm^2 cartilage defects in the femoral trochlear grooves of rabbits treated by microfracture with 3 (1.5 mm diameter) or 10 (0.8-mm diameter) holes, and found more MSCs in the latter group. They concluded that bone marrow stimulation technique affect the number of MSCs drained from the bone marrow, which may lead to increased cartilage healing. Eldracher et al. (10) performed microfracture using 1.8- or 1-mm awls and observed better osteochondral healing with the smaller awl. Orth et al. (11) created 4 × 8-mm cartilage defects on the femoral condyles and performed microfracture using 1- or 1.2-mm awls and found better histological cartilage healing in the small-awl group. Contrasting these studies, Marchand et al. (32) created 3.5x4.5-mm cartilage defects in rabbits and treated them using microfracture with two (0.9-mm in diameter) or three (0.5-mm in diameter) holes; they found no difference in cartilage healing.

In our study, the cartilage healing revealed by histological analyses of the 20-mm^2 defects did not differ significantly among groups with three (group I; the holes included 16.8% of the defect area), four (group II; 10% of the defect), or five (group IV; 12.5% of the defect) hole, whereas SDHM with six holes (groups VI and VII; 15% of the defect area) resulted in significantly higher scores compared with group I ($p=0.043$ and $p=0.016$, respectively). This suggests that SDHM involving a minimum of 15% of the defect area improves cartilage healing. Although microfracture involved a similar percentage of the defect (16.8%), we did not observe the same results with microfracture. We think that this difference depends on damage to the cancellous bone caused by the traditional awl. These results parallel the literature (10). Moreover, the cell morphology and cartilage surfaces scores were superior in groups VI and VII compared with group I.

Lim et al. (33) performed microfracture for the focal cartilage defects between 1 to 4 cm^2 and found good and excellent results and complete cartilage regeneration in 80% of the patients in second-look arthroscopy at the end of first year. To our knowledge, there is no a study investigating cartilage healing after SDHM, with ICRS evaluation system, using second-look arthroscopy. In the current study, we observed about normal cartilage regeneration in every sample in which six-holes SDHM was performed. In this group, the defects were completely filled

with hyaline-like cartilage and regular surfaces were seen. In conventional microfracture group, about 50% of the defects were filled with the bone and small cartilage islands.

Several studies have examined the effectiveness of HA-based scaffolds in cartilage healing (34-37). In our study, there was no difference between the HA-based acellular matrix groups and the SDHM-only groups (p=1.0 for group II vs. group III, group IV vs group V, and group VI vs group VII). Contrary to common belief and the literature, our study revealed that in the treatment of focal cartilage defects with SDHM, HA-based acellular matrix does not contribute to cartilage healing, although we still need more evidence regarding this issue. According to a hypothesis, the scaffold might block cells and factors derived from the synovium or cause high pressure in the chondral defect, resulting in prevention of cells and growth factors gushing out from the bone marrow, which leads to disadvantages for cartilage repair.

This study has some limitations. First, it would have been better if we had investigated the subchondral bone after SDHM and MF using microCT. Second, in addition to the histological analyses, the surface strengths of the repaired cartilages should be tested biomechanically. Third, the rabbits were 5 months old, and they reach skeletal maturity at their 7-8 months. It could be better if we used older rabbits in order to decrease the risk of spontaneous cartilage repair. Lack of immune-histo-chemical analysis for collagen type 1 or type 2, which was better to explore the hyaline cartilage nature of the regenerated cartilage, was another limitation. The last limitation is that weight bearing can not be restricted. Although microfracture has been applied to the trochlea, it may have affected as a result of increased pressure on the cartilage due to weight bearing.

Conclusion

SDMH with the optimum numbers of holes covering a minimum of 15% of the defect size can increase the quality of cartilage repair compared with the traditional microfracture (16.8% of the defect size) technique for defects of the same size in rabbits. HA-based AM implantation after microfracture does not improve the quality of the regenerated cartilage.

Ethics

Ethics Committee Approval: All experiments were conducted in accordance with the guidelines of the local ethics committee for animal experimentation (approval number: 2014/140).

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: G.U., F.Y. V.G., Concept: F.Y., V.U., V.G., Design: N.M.E., F.Y., M.E., Data Collection or Processing: V.U., O.E.T, G.U., Analysis or Interpretation: Y.G., G.U., F.Y., Literature Search: V.U., G.U., Writing: G.U., F.Y.

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References

1. Shapiro F, Koide S, Glimcher MJ. Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. J Bone Joint Surg Am 1993;75:532-53.
2. Karthikeyan S, Roberts S, Griffin D. Microfracture for acetabular chondral defects in patients with femoroacetabular impingement: results at second-look arthroscopic surgery. Am J Sports Med 2012;40:2725-30.
3. Knutsen G, Drogset JO, Engebretsen L, Grontvedt T, Isaksen V, Ludvigsen TC, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. J Bone Joint Surg Am 2007;89:2105-12.
4. Saris D, Price A, Widuchowski W, Bertrand-Marchand M, Caron J, Drogset JO, et al. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Two-Year Follow-up of a Prospective Randomized Trial. Am J Sports Med 2014;42:1384-94.
5. Kreuz PC, Steinwachs MR, Erggelet C, Krause SJ, Konrad G, Uhl M, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. Osteoarthritis Cartilage 2006;14:1119-25.
6. Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br 2003;85:223-30.
7. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. Arthroscopy 2003;19:477-84.
8. Mithoefer K, Williams RJ, 3rd, Warren RF, Potter HG, Spock CR, Jones EC, et al. Chondral resurfacing of articular cartilage defects in the knee with the microfracture technique. Surgical technique. J Bone Joint Surg Am 2006;88 Suppl 1 Pt 2:294-304.
9. Chen H, Hoemann CD, Sun J, Chevrier A, McKee MD, Shive MS, et al. Depth of subchondral perforation influences the outcome of bone marrow stimulation cartilage repair. J Orthop Res 2011;29:1178-84.
10. Eldracher M, Orth P, Cucchiarini M, Pape D, Madry H. Small subchondral drill holes improve marrow stimulation of articular cartilage defects. Am J Sports Med 2014;42:2741-50.
11. Orth P, Duffner J, Zurakowski D, Cucchiarini M, Madry H. Small-Diameter Awls Improve Articular Cartilage Repair After Microfracture Treatment in a Translational Animal Model. Am J Sports Med 2016;44:209-19.
12. Kaneshiro N, Sato M, Ishihara M, Mitani G, Sakai H, Mochida J. Bioengineered chondrocyte sheets may be potentially useful for the treatment of partial thickness defects of articular cartilage. Biochem Biophys Res Commun 2006;349:723-31.
13. Ando W, Tateishi K, Hart DA, Katakai D, Tanaka Y, Nakata K, et al. Cartilage repair using an in vitro generated scaffold-free tissue-engineered construct derived from porcine synovial mesenchymal stem cells. Biomaterials 2007;28:5462-70.

14. Cheuk YC, Wong MW, Lee KM, Fu SC. Use of allogeneic scaffold-free chondrocyte pellet in repair of osteochondral defect in a rabbit model. J Orthop Res 2011;29:1343-50.
15. Nakamura T, Sekiya I, Muneta T, Hatsushika D, Horie M, Tsuji K, et al. Arthroscopic, histological and MRI analyses of cartilage repair after a minimally invasive method of transplantation of allogeneic synovial mesenchymal stromal cells into cartilage defects in pigs. Cytotherapy 2012;14:327-38.
16. Kramer J, Bohrnsen F, Lindner U, Behrens P, Schlenke P, Rohwedel J. In vivo matrix-guided human mesenchymal stem cells. Cell Mol Life Sci 2006;63:616-26.
17. Volz M, Schaumburger J, Frick H, Grifka J, Anders S. A randomized controlled trial demonstrating sustained benefit of Autologous Matrix-Induced Chondrogenesis over microfracture at five years. Int Orthop 2017;41:797-804.
18. Benthien JP, Behrens P. Nanofractured autologous matrix induced chondrogenesis [NAMIC(c)]--Further development of collagen membrane aided chondrogenesis combined with subchondral needling: A technical note. Knee 2015;22:411-5.
19. van den Borne MP, Raijmakers NJ, Vanlauwe J, Victor J, de Jong SN, Bellemans J; International Cartilage Repair S. International Cartilage Repair Society (ICRS) and Oswestry macroscopic cartilage evaluation scores validated for use in Autologous Chondrocyte Implantation (ACI) and microfracture. Osteoarthritis Cartilage 2007;15:1397-402.
20. Wakitani S, Goto T, Pineda SJ, Young RG, Mansour JM, Caplan AI, et al. Mesenchymal cell-based repair of large, full-thickness defects of articular cartilage. J Bone Joint Surg Am 1994;76:579-92.
21. Xia X, Li J, Xia B, Yang H, Zhang D, Zhou B, et al. Matrigel scaffold combined with Ad-hBMP7-transfected chondrocytes improves the repair of rabbit cartilage defect. Exp Ther Med 2017;13:542-50.
22. Dai Y, Gao Z, Ma L, Wang D, Gao C. Cell-Free HA-MA/PLGA Scaffolds with Radially Oriented Pores for In Situ Inductive Regeneration of Full Thickness Cartilage Defects. Macromol Biosci 2016;16:1632-42.
23. Bekkers JE, Inklaar M, Saris DB. Treatment selection in articular cartilage lesions of the knee: a systematic review. Am J Sports Med 2009;37 Suppl 1:148S-55S.
24. Schindler OS. Current concepts of articular cartilage repair. Acta Orthop Belg 2011;77:709-26.
25. Chen H, Sun J, Hoemann CD, Lascau-Coman V, Ouyang W, McKee MD, et al. Drilling and microfracture lead to different bone structure and necrosis during bone-marrow stimulation for cartilage repair. J Orthop Res 2009;27:1432-8.
26. Fortier LA, Cole BJ, McIlwraith CW. Science and animal models of marrow stimulation for cartilage repair. J Knee Surg 2012;25:3-8.
27. Dorotka R, Bindreiter U, Macfelda K, Windberger U, Nehrer S. Marrow stimulation and chondrocyte transplantation using a collagen matrix for cartilage repair. Osteoarthritis Cartilage 2005;13:655-64.
28. Henderson I, Lavigne P, Valenzuela H, Oakes B. Autologous chondrocyte implantation: superior biologic properties of hyaline cartilage repairs. Clin Orthop Relat Res 2007;455:253-61.
29. Otsuka Y, Mizuta H, Takagi K, Iyama K, Yoshitake Y, Nishikawa K, et al. Requirement of fibroblast growth factor signaling for regeneration of epiphyseal morphology in rabbit full-thickness defects of articular cartilage. Dev Growth Differ 1997;39:143-56.
30. Min BH, Choi WH, Lee YS, Park SR, Choi BH, Kim YJ, et al. Effect of different bone marrow stimulation techniques (BSTs) on MSCs mobilization. J Orthop Res 2013;31:1814-9.
31. Burr DB, Radin EL. Microfractures and microcracks in subchondral bone: are they relevant to osteoarthrosis? Rheum Dis Clin North Am 2003;29:675-85.
32. Marchand C, Chen G, Tran-Khanh N, Sun J, Chen H, Buschmann MD, et al. Microdrilled cartilage defects treated with thrombin-solidified chitosan/blood implant regenerate a more hyaline, stable, and structurally integrated osteochondral unit compared to drilled controls. Tissue Eng Part A 2012;18:508-19.
33. Lim HC, Bae JH, Song SH, Park YE, Kim SJ. Current treatments of isolated articular cartilage lesions of the knee achieve similar outcomes. Clin Orthop Relat Res 2012;470:2261-7.
34. Loken S, Jakobsen RB, Aroen A, Heir S, Shahdadfar A, Brinchmann JE, et al. Bone marrow mesenchymal stem cells in a hyaluronan scaffold for treatment of an osteochondral defect in a rabbit model. Knee Surg Sports Traumatol Arthrosc 2008;16:896-903.
35. Unterman SA, Gibson M, Lee JH, Crist J, Chansakul T, Yang EC, et al. Hyaluronic acid-binding scaffold for articular cartilage repair. Tissue Eng Part A 2012;18:2497-506.
36. Gobbi A, Scotti C, Karnatzikos G, Mudhigere A, Castro M, Peretti GM. One-step surgery with multipotent stem cells and Hyaluronan-based scaffold for the treatment of full-thickness chondral defects of the knee in patients older than 45 years. Knee Surg Sports Traumatol Arthrosc 2017;25:2494-501.
37. Liu Y, Shu XZ, Prestwich GD. Osteochondral defect repair with autologous bone marrow-derived mesenchymal stem cells in an injectable, in situ, cross-linked synthetic.

Original Article

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The Effects of Thermo-mechanical Aging on Microleakage in Composite Restorations Polymerized Using One New Generation and Two Conventional Led Light Curing Units

Termomekanik Yaşlandırma Sonrası Sınıf V Kompozit Restorasyonların Mikrosızıntısı Üzerine Biri Yeni Nesil İkisi Geleneksel LED Işık Cihazlarının Etkisi

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ABSTRACT

Objective: This study aimed to evaluate the effects of thermo-mechanical aging (TMA) on the microleakage scores of Class V composite restorations polymerized using one new generational and two conventional light emitting diodes (LED) light curing units (LCU).

Methods: Class V cavities were prepared and restored on the buccal and lingual surfaces of 60 extracted human premolar teeth using a dental phantom head to simulate clinical conditions. After application of the adhesive system (Optibond Solo Plus, Kerr, USA) using total etch procedures, the cavities were restored with composite resin (Herculite XRV, Kerr, USA) using one new generational (Demi Ultracapacitor, Kerr, USA) and two conventional (Valo Cordless, USA and BA Optima International, UK) LED light devices. The restored teeth were then subdivided into the test (underwent TMA) and control (did not undergo TMA) groups, and the specimens were stained with 0.5% basic fuchsin dye and sectioned. Dye penetration was scored using a stereomicroscope at 40x magnification. Differences between groups were compared using the Kruskal-Wallis, Mann-Whitney U, and Wilcoxon Signed Ranks tests ($p<0.05$).

ÖZ

Amaç: Bu çalışmanın amacı termomekanik yaşlandırma (TMY) sonrası Sınıf V kompozit restorasyonların mikrosızıntısı üzerine, biri yeni nesil, ikisi geleneksel olmak üzere ışık yayan diyot (LED) ışık cihazlarının etkisini değerlendirmektir.

Yöntemler: Altmış adet çekilmiş insan premolar dişi kullanıldı. Sınıf V kaviteler dişlerin bukkal ve lingual yüzeylerine açıldı. Kompozit restorasyonların yapımı LED ışık cihazlarının uzaklığını ağız ortamındaki gibi taklit edebilmek amacıyla bir fantom kafa içerisinde gerçekleştirildi. Adeziv sistem (Optibond Solo Plus, Kerr, ABD) total etch prosedürü ile uygulandıktan sonra kaviteler kompozit rezin (Herculite XRV, Kerr, ABD) ile restore edildi. Polimerizasyon, biri yeni nesil (Demi Ultracapacitor, Kerr, ABD) diğerleri geleneksel olan iki LED ışık cihazı (Valo Cordless, Ultradent, ABD ve BA Optima 10 LED LCU (B.A. International, İngiltere) ile gerçekleştirildi. Daha sonra TMY prosedürüne (yapılan ve yapılmayan) göre dişler 2 alt gruba ayrıldıktan sonra bir gruba TMY uygulandı. Örnekler %0,5 bazik fuksin ile boyandıktan sonra kesildi. Boya sızıntı skorları x40 büyütmede stereomikroskop altında incelendi. İstatistiksel analizler Kruskal-Wallis, Mann-Whitney U ve Wilcoxon Signed Ranks testleri kullanılarak yapıldı ($p<0,05$).

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Results: Comparison of the test and control groups by the LCUs used for polymerization showed a statistically significant difference in microleakage scores between the two ($p<0.05$). However, no differences in scores were observed between the new generational and two conventional LED LCUs ($p>0.05$).

Conclusion: Thermal and mechanical aging procedures increased microleakage in Class V composite restorations, regardless of the light curing unit used.

Keywords: Oral simulation, thermo-mechanical aging, LED light curing units, microleakage, class V cavity

Bulgular: Farklı ışık cihazları ile polimerize edilen deney grupları yaşlandırma prosedürü açısından karşılaştırıldığında, gruplar arasında istatistiksel olarak anlamlı bir fark görüldü ($p<0,05$). Mikrosızıntı skorlarına göre yeni nesil ile iki geleneksel LED ışık cihazları arasında arasında fark gözlenmedi ($p>0,05$).

Sonuç: Termal ve mekanik yaşlandırma prosedürleri, ışık cihazlarının jenerasyonlarına bakılmaksızın, Sınıf V kompozit restorasyonlarda mikro sızıntıyı artırdı.

Anahtar Sözcükler: Oral simülasyon, termo-mekanik yaşlandırma, LED ışık cihazları, mikro sızıntı, sınıf V kavite

Introduction

Composite resins are becoming increasingly popular in restorative dentistry due to their aesthetic acceptability. These materials typically do not contain mercury and restorations can be completed with minimal invasive cavity preparation and the use of adhesive bonding systems (1). This increasing demand for composite resins has led to considerable improvements in their physical properties while ensuring adequate polymerization so as to avoid poor bonding to the dental tissues and subsequent microleakage, postoperative sensitivity, discoloration, secondary caries, and irritation of the pulp (2).

The thickness of resin placed in the cavity may influence the degree of polymerization by dispersing the applied light and significantly decreasing its intensity, brightness, and curing action as it descends into the deeper layers (3).

Photo-polymerization of composite resins using blue light was first carried out in the 1970s (4). Since then, almost all commercially available dental composites utilize light curing units (LCUs) based on various physical principles such as quartz-tungsten-halogen (QTH) bulbs, lasers, plasma arc lights, and light emitting diodes (LEDs), with the standard device of choice in modern dental practices being LED LCUs (5). Upon commencement of polymerization, photo-initiator molecules present in the composite resin are activated by a light source in a similar spectrum (1), with conventional LCU and those belonging to newer generations being effective at <1,000 mW/cm^2 and ≥1,000 mW/cm^2 wavelengths, respectively. One of the major advantages of new generation LED LCUs over conventional ones include narrow emission range, effective and rapid photo-polymerization (5), overall energy efficiency per cure cycle (5), and prolonged lifetime (6). Nowadays, all commercially available high-powered LED curing devices emit light within the spectrum and power density necessary to ensure sufficient curing of the resin composite (7,8), and some manufacturers have also chosen to increase the power output of these devices in order to achieve an equal degree of curing within a shorter exposure time (7).

Due to unfavorable features, LED LCUs are the most commonly preferred sources. The advantages of LED LCUs include prolonged lamp life, no heat production during usage, no need for filters, a lack of wires, and no changes in light intensity over time (9). However, unlike tungsten lamps which have a wide emission spectrum, these light sources are limited by their monochromatic emission spectrum similar to lasers (10).

The majority of LED light sources have a wavelength of 450-470 nm and are considered to be powerful despite having a narrow light spectrum as they allow adequate polymerization within shorter irradiation periods (5) and contain photo initiators that can be activated by this wavelength (9).

C.U.R.E (Curing Uniformity and Reduced Energy) Technology is a new generation, wireless, battery-free, LED light curing unit with a patented ultracapacitor light source (11) that generates adequate power to provide uniform cure depth with low heat over a short period of time. While ultra-capacitors resemble conventional batteries with regard to their shape and size, they operate differently by producing re-usable energy within a couple of seconds and maintaining their energy capacity for years. In clinical practice, ultra-capacitors can achieve curing in 25 to 40 seconds (11).

Composite restorations performed in the clinical setting differ considerably from *in vitro* restorations carried out in a phantom jaw with regard to factors that affect treatment success including level of clinician comfort, risk of saliva contamination, unstable patient head position, pain caused by rotary instruments, and insufficient light and visibility when treating posterior teeth. Moreover, in the oral environment, teeth are continuously subjected to stress and fatigue caused by mastication, swallowing, parafunctional habits and thermal applications (12), and reproduction of these conditions in *in vitro* settings is necessary for accurate results (13).

The aim of the current study was to investigate the effects of thermo-mechanical aging (TMA) on microleakage in Class V composite resin restorations polymerized using one new generational and two conventional LED LCUs. The restorations were created on a phantom head using human extracted premolar teeth, and the null hypotheses were that microleakage in Class V composite resin restorations would a) be affected by TMA and b) would decrease upon use of LED LCUs.

Method

This study utilized 60 freshly extracted human mandibular premolar teeth which were cleaned and polished with scalers to

remove organic debris. The teeth were examined under a light microscope to allow exclusion of those with cracks, and were then stored in 0.2% Cloramin T solution at 4 °C for one week to prevent bacterial growth.

Cavity Preparation

The same operator prepared Class V cavities on the buccal and lingual aspects of all teeth, ensuring that the occlusal and gingival margins were located on the enamel and dentin, respectively. No bevels were applied to the teeth, and the cavity dimensions (width x height x depth: 3 x 2 x 2 mm) were controlled using a periodontal probe (Figure 1).

Simulation Model: A mandibular prototype model was created using dental stone, and the right mandibular premolar region was excavated to allow placement of the extracted premolar human teeth using silicon impression material. Thereafter, restorations were performed on the dental phantom head (KDF-01 Phantom Unit System for Students-Kemal Dis, Turkey) with the mouth opening (measured between the incisal edges) fixed at 58 mm in order to simulate application of LED LCUs in the oral environment (Figure 2).

Restoration of the Teeth: The teeth were randomly divided into three groups (n=20) as per the LCU used. Thereafter, 37% phosphoric acid (Kerr, USA) was used to etch the enamel margins and dentin structure for 30 and 15 seconds, respectively, and the teeth were then rinsed with water for 40 seconds. The adhesive system (Opti Bond Solo plus, Kerr, USA) was applied in 2 coats as per the manufacturers' instructions using a micro-brush, and then polymerized for 5 seconds with the Demi Ultracapacitor (Kerr, USA) or for 10 seconds with the Valo Cordless (Ultradent, USA) and BA Optima 10 LED LCUs (BA International, UK). The composite resin restorations (Herculite XRV Ultra, Kerr, USA) were polymerized with the same LCUs for 20 seconds as per the manufacturers' instructions, and then finished and polished using a multi-step polishing system (Super-Snap Rainbow Technique Kit, Shofu, Japan) implemented by the same operator. The tested materials and LCUs included in this study have been shown in Table 1 and 2, respectively.

After completion of the restorations, the 3 groups were subdivided according to aging conditions and all samples were stored in distilled water in dark colored glass bottles at room temperature for 24 hours.

Thermal Cycling and Mechanical Loading Procedures

The test groups subjected to aging procedures underwent thermal cycling (1000 times) between 5 and 55 °C, with a dwell time of 30 seconds at each temperature and a transfer interval of 10 seconds (SD Mechatronic, Germany). Upon completion of these procedures, the samples were subjected to mechanical loading (Dentarge Chewing Simulator, Gaziantep/Turkey) using 50,000 load cycles at a frequency of 1.7 Hz to replicate an intermittent vertical load of 98N on the restorations (14). All samples were submersed in distilled water during the mechanical loading test.

Microleakage Evaluation

Thereafter, all tooth surfaces (excluding 1 mm around the restoration margins) were sealed using two layers of nail polish to prevent dye penetration, and the apices were sealed with composite resin. The teeth were then immersed in 0.5% basic fuchsin dye solution for 24 hours, after which any surface adherent dye was rinsed off under tap water. The teeth were then sectioned longitudinally along the bucco-lingual plane through the center of the restoration using a water cooled, slow speed diamond blade (Esetron Smart Robotechnologies, Ankara/Turkey) to form two sections. The marginal sealing ability, as indicated by the depth of dye penetration around the enamel and dentinal margins, was evaluated under a stereomicroscope (SMZ1000, NIKON, JAPAN) at 40x magnification. The scoring scale used to assess extent of dye penetration at the tooth-

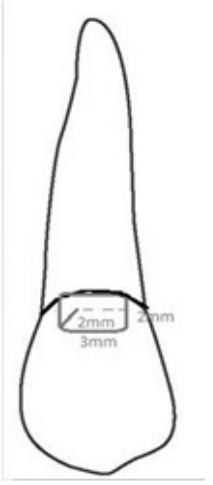

Figure 1. Schematic representation of the cavity configuration

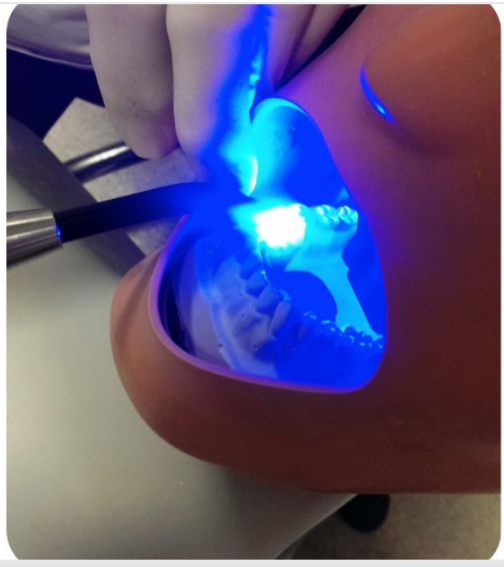

Figure 2. Restorations were performed on a dental phantom head to mimic the oral environment

restoration interface has been shown below (15), and all visual analyses were performed by two previously calibrated examiners (ND, YSU).

0: No penetration

1: Infiltration up to the enamel-dentin junction in the occlusal wall or penetration up to ¼ of the length of the gingival wall.

2: Penetration of the dye up to ½ the length of the cavity wall.

3: Penetration of the dye extending to the total depth of the cavity wall.

Microleakage was evaluated in the tested groups after completion of the TMA procedures and in the control groups (which did not undergo TMA procedures) after 24 hours.

Statistical Analyses

All statistical analyses were performed using SPSS Software for Windows 20.0. As the microleakage values did not exhibit normal distribution, non-parametric tests (Kruskal-Wallis, Mann-Whitney U, and Wilcoxon Signed Ranks tests) were used to carry out pair-wise comparisons among groups. A p value <0.05 was considered to be statistically significant.

Results

Table 3 shows the distribution of the microleakage scores and the results of the statistical analyses. Comparison of the groups showed no significant differences in microleakage scores between the new generation and two conventional LED LCUs used (Table 3).

Upon comparison of the test and control groups polymerized using the new generation LED LCU, a statistically significant difference in microleakage scores was observed along the gingival margins ($p<0.05$) but not along the occlusal margins ($p>0.05$).

Comparison of the test and controls groups polymerized using two conventional LED LCUs showed that the former exhibited a higher microleakage score and this difference was statistically significant along the occlusal and gingival margins ($p<0.001$) (Figure 3).

Table 1. Materials used in this study

Product manufacturer	Classification	Composition	Procedures
Herculite XRV Ultra, Kerr, Orange, CA, USA	Nanohybrid composite	Uncured methacrylate ester monomers; TiO2 and pigments; MHQ, BPO, TMPTA and initiators	Applied in 2 increments, light cured for 20 seconds
Optibond Solo Plus Kerr, Orange CA, USA	Single component Total-etch adhesive	Ethanol, 2-HEMA glass, oxide, chemicals silica, amorphous, fumed, cryst-free 2-hydroxy-1,3-propanediyl bismethacrylate Silanamine 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica alkali fluorosilicates (Na)	1. Etch enamel and dentin for 15 seconds; rinse for 15 seconds, and gently air dry. Do not desiccate. 2. Apply optibond solo plus for 15 seconds 3. Air thin for 3 seconds. 4. Light cure for 20 seconds
Super-Snap Rainbow Technique Kit, Shofu	Multi-step disk-based polishing system		Apply as per color
Kerr Etchant (Kerr Corporation, California, USA)		Etchant gel 37.5% phosphoric acid	Apply for 15 seconds; rinse with water for 15 seconds; then dry with clean, oilfree air without desiccating the dentin

Table 2. Curing units used in this study and their outputs

Curing unit	Manufacturer	Serial no	Setting	Light intensity mW/cm^2
High power intensity (LED)	Demi Ultra, Ultracapacitor KERR	35664	Standard	1100
High power intensity (LED)	Optima BA International (UK)	L1340755H	Full power Ramp (soft), Pulse	1200
High intensity (LED)	Valo Cordless, ULTRADENT	C46176	Standard, high, Xtra	1000

LED: Light emitting diodes

Table 3. Distribution of microleakage scores and median values of groups for microleakage

Aging Condition	Light Curing Units	Occlusal score				Gingival score				Occlusal	Gingival
		0	1	2	3	0	1	2	3	Median (min-max)	Median (min-max)
With TMC	Demi Ultra	3	7	3	7	2	7	-	11	1.5 (0-3)	3 (0-3)
	Optima	-	10	7	3	-	7	1	12	1.5 (1-3)	3 (1-3)
	Valo	-	6	6	8	-	6	1	13	2 1-3)	3 (1-3)
Without TMC	Demi Ultra	11	9	-	-	6	14	-	-	0 (0-1)	1 (0-1)
	Optima	9	11	-	-	5	13	2	-	1 (0-1)	1 (0-2)
	Valo	14	6	-	-	12	8	-	-	0 (0-1)	0 (0-1)

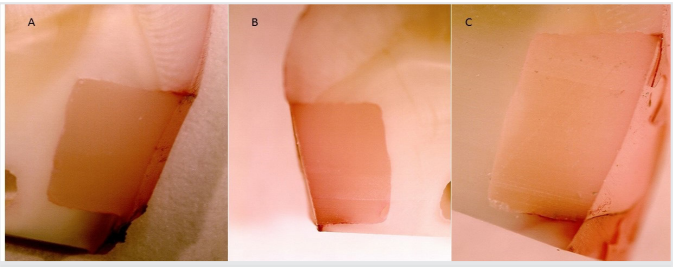

Figure 3 (A, B, C). Dye penetration on the gingival margin by thermos-mechanical aging groups. A (DEMI): score 2; B (VALO): score 2; C (OPTIMA): score 3

Discussion

The current study examined and compared the effects of TMA on the microleakage scores of Class V composite restorations polymerized using one new generational and two conventional LED LCUs on a phantom simulation device. The findings showed that TMA increased microleakage in Class V composite restorations, irrespective of the type (new generational or conventional) of LED LCU used. Therefore, the first null hypothesis was accepted and the second was rejected.

Composite resins should be completely polymerized in order to achieve the maximum degree of conversion and highest endurance against occlusal and lateral loads and thermal variations. Previous studies have suggested that LCUs should be held as close as possible to the tooth surface to achieve adequate polymerization (12), with light intensity, composite resin microhardness, and degree of polymerization decreasing as the distance between the light tip and the cavity increases (16,17). Delivery of a sufficient amount of light at the correct wavelength is essential in order to achieve adequate resin polymerization (18), and failure to accomplish this can lead to increased wear, fracture, lesser degree of conversion, and microleakage and subsequent secondary caries (19). Consequently, treatment success is influenced by many factors such as the skill of the operator, type of resin material, application technique, adequate isolation of the cavity, and sufficient light curing (20). The current *in vitro* study used a dental phantom head to mimic oral conditions, and all prepared human premolar teeth were fixed on a mandibular prototype model made from dental stone.

The distance between the tip of the light curing unit and the tooth is affected by the position of the latter in the dental arch and in relation to the tongue and cheek. Holding the tip of the light curing unit as close to the tooth as possible is a crucial factor affecting polymerization, degree of conversion, microleakage, and the longevity of the restoration (12). According to the ADA (2014) (21) report, increasing the distance between the LCU and the tooth from 2 mm to 9 mm decreases the curing depth. Therefore, in the current study, the distance between the light curing unit and the tooth was determined using a standard protocol and all restorations were cured using LCUs held at the same distance.

Other factors that affect resin composite polymerization include the mode, exposure time, type, wavelength, and irradiance (22). In 1999, Chiche (23) reported a lack of an optimal light curing protocol despite the commercial availability of several LCUs with standard, high, ramped or pulsed exposure modes operating over a wide range of spectral radiant power. Harlow et al. (24) used six different LED light sources in their study and found that the radiant energy produced during exposure with ramp mode was not the same as the energy produced when using the standard mode. Additionally, the radiant energy produced with higher power modes over shorter exposure times was also lower than that produced with the standard mode. Devices with high light intensity have several advantages including shorter application time and deeper curing. However, they are also associated with several limitations. Firstly, very rapid polymerization often limits the ability of the composite to flow to the surface of the tooth, thereby transferring polymerization contraction stress from the tooth structure to the bonding surface (25). Secondly, rapid polymerization may also result in the formation of shorter chains with fewer cross-links and lower molecular weight which, in turn, affect the physical properties of the composite resin (13). Therefore, the standard mode of LED LCUs was preferred over the high intensity mode due to the limitations associated with the latter.

As per the manufacturer's instructions, the exposure time for the adhesive system was 10 and 5 seconds with the conventional and new generational LED LCUs, respectively. In contrast, the exposure time for the composite resin was the same for both LED LCUs. Currently, there is a wide range of commercially available

LUCs that claim to exhibit superior properties; therefore the aim of this study was to evaluate whether there were any differences in microleakage when using three different LED LCU systems. However, as all the light devices used similar wavelengths and irradiance, no differences in microleakage between the new generational and two conventional LED LCUs were observed, suggesting that the former did not exhibit superior properties as suggested.

Previous studies have suggested that higher energy intensity did not augment the hardness of the composite resin, but rather affected its physical properties (26). Despite controlling the effects of polymerization contraction, marginal microleakage may occur at the adhesive interface of dental restorations, which are subjected to fluctuations in the temperature and pH of the oral environment, leading to chemical, thermal, and mechanical stresses (27). Thermal stresses may lead to the formation of gaps which, in turn, result in microleakages at the interface caused by a mismatch between the coefficients of thermal expansion between the restorative material and natural tooth structure (28). Since microleakage tests usually assess the sealing ability of restorative materials, previous studies have recommended the use of both thermal and mechanical aging tests to evaluate stress at the adhesive interface in order to mimic *in vivo* conditions (29). Therefore, the present study utilized thermos-mechanical aging of the restorations to mimic the oral environment and evaluate microleakage scores. Microleakage is often caused by thermal cycles or mechanical loading that cause stress and disruptions at the tooth-composite restoration interface due to differences between the restorative material and dental structure (30,31). The current study found that although TMA increased microleakage in all groups, there were no significant differences between the test and control groups when examined by the different types of LCUs used (Figure 3). These findings were consistent with those reported by Soares et al. (13) who examined the effects of thermo-mechanical load cycling (TMC), polymerization time, and mode on microleakage scores in Class II composite restorations and reported that TMC increased microleakage. Similarly, Erdilek et al. (32) found that microleakage from the gingival margins of two composite resins (Spectrum TPH and Admira Ormocer) significantly increased following cyclic loading (50,000 cycles of 50 Newton force).

Upon comparison of the test and controls groups polymerized using new generation LED LCUs, a statistically significant difference in microleakage score was observed at the gingival margin (score 3:11; $p<0.001$) but not at the occlusal margins (score 3:7;$p>0.001$) (Table 3). However, 7 samples in the current study exhibited a highest score of 3 at the occlusal margin. Conversely, a statistically significant difference ($p<0.001$) in microleakage scores was observed at the gingival and occlusal margins when comparing test and control groups polymerized using two conventional LED LCUs (Table 3). The highest microleakage scores were observed in the test groups, with the scores in the gingival margins being higher than that of the occlusal margins. This could be attributed to the effects of TMA. The other reason for the higher microleakage on the gingival margin in the aged group may be due to the ending of the gingival margin on the dentin tissue where the adhesive bonding is more difficult to seal that part of the cavity.

Rapid polymerization of composite resins using high-intensity (Valo cordless) LCUs often leads to polymerization contraction, as suggested by Yoshikawa et al. (33) who compared low and high-intensity LCUs and found that the latter yielded inadequate polymerization of the resin composite and poor adaptation to the cavity wall, causing marginal gap formation.

Nalçacı et al. (34) reported that the performance of resin composite restorations was affected by the polymerization light sources and modes used. Similarly, Yilmaz et al. (35) compared microleakage in resin composites polymerized with QTH and two types of LED LCUs and found that microleakage could be minimized by polymerizing with high-density output LEDs. They also stated that microleakage was affected by the type of light curing unit used.

Study Limitations

The limitation of this study can be the thermomechanical aging that was applied to the specimens corresponding to 1 month. It may be better to apply thermomechanical aging procedure which equals to 1 year.

Conclusion

Within the limitations of the study, it may be concluded that thermal and mechanical aging procedures increase the microleakage in Class V composite restorations regardless of the type of light curing unit used.

Ethics

Ethics Committee Approval: This study was approved by Bezmialem Vakif University Ethics Committee (No: 04.04.2017-7/54).

Informed Consent: *In vitro* study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Design: Y.Ş.U., Data Collection or Processing: A.U., Analysis or Interpretation: Ş.H.S., Writing: N.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Gladwin M, Bagby M. "Clinical aspects of dental materials. Theory, practice, and cases". 3rd ed. China: Lippincott Williams &Wilkins, 2009.p.55-73. http://thuvienso.vanlanguni.edu.vn/handle/Vanlang_TV/13592
2. de Camargo EJ, Moreschi E, Baseggio W, Cury JA, Pascotto RC. Composite depth of cure using four polymerization techniques. J Appl Oral Sci 2009;17:446-50.

3. Ceballos L, Fuentes MV, Tafalla H, Martinez A, Flores J, Rodriguez J. Curing effectiveness of resin composites at different exposure times using LED and halogen units. Med Oral Patol Oral Cir Bucal 2009;14:E51-6.
4. Rueggeberg FA, Giannini M, Arrais CAG, Price RBT. Light curing in dentistry and clinical implications: a literature review. Braz Oral Res 2017;31(suppl 1):e61.
5. Jandt KD, Mills RW. A brief history of LED photopolymerization. Dent Mater 2013;29:605-17.
6. Cayless MA, Marsden AM. "Tungsten halogen lamps. In: Lamps and lighting". 3rd ed. London: Edward Arnold Ltd, 1983.p.169-82.
7. Ernst CP, Schattenberg A, Stender E, Willershausen B. Relative Oberfl¨achenh¨ arte verschiedener Komposite nach LED-Polymerisation aus 7mm Abstand. [Relative surface hardness of various composites after LED polymerization from 7mm distance.] Dtsch Zahn¨ arztl Z 2005;60:154-60.
8. Vandewalle KS, Roberts HW, Andrus JL, Dunn WJ. Effect of light dispersion of LED curing lights on resin composite polymerization. J Esthet Restor Dent 2005;17:244-54; discussion 254-5.
9. Soh MS, Yap AU, Siow KS. The effectiveness of cure of LED and halogen curing lights at varying cavity depths. Oper Dent 2003;28:707-15.
10. Rawls HR, Esquivel-Upshaw JF. "Restorative resins". In: Anusavice KJ, editor. Phillip's Science of dental materials. 11th ed. St.Louis MO:Mosby; 2003.p.399-442.
11. Demi ultra LED ultracapacitor-curing-light-system [Internet]. Available from: URL: https://www.kerrdental.com/kerr-restoratives/demi-ultra-led-ultracapacitor-curing-light-system. https://www.kerrdental.com/kerr-restoratives/demi-ultra-led-ultracapacitor-curing-light-system
12. Price RB, Labrie D, Whalen JM, Felix CM. Effect of distance on irradiance and beam homogeneity from 4 light-emitting diode curing units. J Can Dent Assoc 2011;77:b9.
13. Soares GP, Ambrosano GM, Lima DA, Marchi GM, Correr-Sobrinho L, Lovadino JR, et al. Effect of light polymerization time, mode, and thermal and mechanical load cycling on microleakage in resin composite restorations. Lasers Med Sci 2014;29:545-50.
14. Jung SH, Min KS, Chang HS, Park SD, Kwon SN, Bae JM. Microleakage and fracture patterns of teeth restored with different posts under dynamic loading. J Prosthet Dent 2007:98:270-6.
15. Shahabi S, Ebrahimpour, Walsh LJ. Microleakage of composite resin restorations in cervical cavities prepared by Er,Cr:YSGG laser radiation. Aust Dent J 2008;53:172-5.
16. Lindberg A, Peutzfeldt A, van Dijken JW. Effect of power density of curing unit, exposure duration, and light guide distance on composite depth of cure. Clin Oral Investig 2005;9:71-6.
17. Schattenberg A, Lichtenberg D, Stender E, Willershausen B, Ernst CP. Minimal exposure time of different LED-curing devices. Dent Mater 2008;24:1043-9.
18. Roberts HW, Vandewalle KS, Berzins DW, Charlton DG. Accuracy of LED and halogen radiometers using different light sources. J Esthet Restor Dent 2006;18:214-24.
19. Vandewalle KS, Ferracane JL, Hilton TJ, Erickson RL, Sakaguchi RL. Effect of energy density on properties and marginal integrity of posterior resin composite restorations. Dent Mater 2004;20:96-106.
20. Price RB. Light energy matters. J Can Dent Assoc 2010;76:a63.
21. ADA Professional Product Review. A publication of the council on scientific affairs. In: David C, editor, Sarret JADA 2014;145:1164-6.
22. Caughman WF, Rueggeberg FA, Curtis JW Jr. Clinical guidelines for photocuring restorative resins. J Am Dent Assoc 1995;126:1280-2, 1284, 1286.
23. Chiche GJ. The search for a standard light-curing protocol. Pract Periodontics Aesthet Dent 1999;11:260.
24. Harlow JE, Sullivan B, Shortall AC, Labrie D, Price RB. Characterizing the output settings of dental curing lights. J Dent 2016;44:20-6.
25. Asmussen E, Peutzfeldt A. Polymerization contraction of resin composite vs. energy and power density of light-cure. Eur J Oral Sci 2005;113:417-21.
26. Pires JA, Cvitko E, Denehy GE, Swift EJ Jr. Effects of curing tip distance on light intensity and composite resin microhardness. Quintessence Int 1993;24:517-21.
27. Geis-Gerstorfer J. In-vitro corrosion measurements of dental alloys. J Dent 1994;22:247-51.
28. Versluis A, Douglas WH, Sakaguchi RL. Thermal expansion coefficient of dental composites measured with strain gauges. Dent Mater 1996;12:290-4.
29. Leibrock A, Degenhart M, Behr M, Rosentritt M, Handel G. In vitro study of the effect of thermo and load-cycling on the bond strength of porcelain repair systems. J Oral Rehabil 1999;26:130-7.
30. Mitsui FH, Peris AR, Cavalcanti AN, Marchi GM, Pimenta LA. Influence of thermal and mechanical load cycling on microtensile bond strengths of total and self-etching adhesive systems. Oper Dent 2006;31:240-7.
31. Cavalcanti AN, Mitsui FH, Silva F, Peris AR, Bedran-Russo A, Marchi GM. Effect of cyclic loading on the bond strength of class II restorations with different composite materials. Op Dent 2008;33:163-8.
32. Erdilek D, Dörter C, Koray F, Kunzelmann KH, Efes BG, Gomec Y. Effect of Thermo-mechanical load cycling on microleakage in class II ormocer restorations. Eur J Dent 2009;3:200-5.
33. Yoshikawa T, Burrow MF, Tagami JA. Light curing method for improving marginal sealing and cavity wall adaptation of resin composite restorations. Dent Mater 2001;17:359-66.
34. Nalçacı A, Salbafl M, Ulusoy N. The effects of soft start vs continuous – light polymerization on microleakage in class II resin composite restorations. J Adhes Dent 2005;7:309-14.
35. Yilmaz F, Gonulol N, Guler E, Ersoz E, Aytac F. Effects of different light sources on microleakage of composite resins with different monomer structures. J Dent Sci 2014;9:364-70.

Original Article

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The Efficacy of Eltrombopag Treatment in Patients who developed Platelet Engraftment Failure after Allogeneic Stem Cell Transplantation: A Single Center Experience

Allojenik Kök Hücre Nakli Sonrası Trombosit Engrafman Yetersizliği Gelişen Hastalarda Eltrombopag Tedavisinin Etkinliği: Tek Merkez Deneyimi

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ABSTRACT

Objective: Persistent thrombocytopenia is a common complication of allogeneic stem cell transplantation (ASCT). Treatment of platelet engraftment failure after ASCT remains controversial. Drugs, such as eltrombopag, are used for this purpose. Eltrombopag is an Food and Drug Administration -approved oral thrombopoietin receptor agonist. We aim to present the results of 12 patients treated with eltrombopag in our center for severe thrombocytopenia after ASCT.

Methods: From January 2018 to February 2020, a total of 56 patients underwent ASCT. Twelve patients had persistent thrombocytopenia following ASCT. All patients received eltrombopag.

Results: Primary platelet engraftment failure developed in six of 12 patients who developed persistent thrombocytopenia after ASCT. Secondary platelet engraftment failure developed in six of them. After eltrombopag treatment, eight (66.7%) patients achieved transfusion independence, whereas four patients (33.3%) could not. The maximum platelet count after the eltrombopag treatment was median 118.000 (range: 24,000-253,000)/μL. The median time from the start of eltrombopag until the platelet count was >50,000/μL was 18 (range: 14-112) days. The median duration of treatment with eltrombopag was 70 (range: 26-180) days. Eltrombopag was discontinued in all patients who survived and had full platelet recovery.

ÖZ

Amaç: Kalıcı trombositopeni, allojenik kök hücre transplantasyonunun (AKHN) yaygın komplikasyonlarından biridir. AKHN sonrası trombosit engrafman yetersizliğinin tedavisi hala tartışmalıdır. Eltrombopag bu amaçla kullanılan ilaçlardan biridir. Eltrombopag, FDA onaylı oral trombopoietin reseptör agonistidir. AKHN sonrası şiddetli trombositopeni nedeniyle merkezimizde eltrombopag ile tedavi edilen 12 hastanın sonuçlarını ortaya koymayı amaçladık.

Yöntemler: Kök hücre nakil merkezimizde ocak 2018'den şubat 2020'ye kadar 56 hastaya AKHN yapıldı. Oniki hastada AKHN sonrası kalıcı trombositopeni gelişti. Tüm hastalar eltrombopag aldı.

Bulgular: AKHN sonrası inatçı trombositopeni gelişen 12 hastanın altısında birincil trombosit engrafman yetersizliği, altısında ise ikincil trombosit engrafman yetersizliği gelişti. Eltrombopag tedavisi sonrası sekiz hasta (%66,7) transfüzyon bağımsızlığına ulaşılırken dört hastada (%33,3) ulaşılamadı. Eltrombopag tedavisinden sonra maksimum trombosit sayısı medyan 118.000 (aralık: 24.000-253,000)/μL oldu. Eltrombopag başlangıcından trombosit sayısı >50.000/μL olana kadar geçen süre medyan 18 (aralık:14-112) gün idi. Eltrombopag ile medyan tedavi süresi 70 (aralık: 26-180) gün oldu. Yaşayan ve tam trombosit iyileşmesi olan tüm hastalarda eltrombopag kesildi.

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Conclusion: Thrombocytopenia after ASCT is a condition that should be treated as it can lead to life-threatening bleeding.

Keywords: Hematopoietic stem cell transplantation, platelet engraftment failure, eltrombopag

Sonuç: AKHN sonrası kalıcı trombositopeni, yaşamı tehdit eden kanamalara yol açabileceği için tedavi edilmesi gereken bir durumdur.

Anahtar Sözcükler: Allojenik kök hücre nakli, trombosit engrafman yetersizliği, eltrombopag

Introduction

Persistent thrombocytopenia is a common complication of allogeneic stem cell transplantation (ASCT) (1). Its causes are not well understood. Poor graft function, viral infections such as cytomegalovirus (CMV), impaired platelet production due to side effects of immunosuppressive or antiviral drugs, increased destruction associated with infection and immune-mediated processes, or a combination of these mechanisms may play a role (2). A platelet count >20,000/μL for three days after transplantation is considered platelet engraftment. There are two forms of thrombocytopenia after ASCT. Primary platelet engraftment failure is characterized by the absence of initial donor cell engraftment (donor cells less than 95%); peripheral blood platelet count < $20x10^9$/L by day +28 after allo-HSCT from peripheral blood or bone marrow progenitors in the absence of relapse (3). It is seen in 5%-20% of transplantations. If the posttransplant platelet count reaches 50,000/μL and then persistently decreases to <20,000/μL, it is called secondary platelet engraftment failure (SPEF). Its prevalence is around 20% (4).

There is evidence which is proving that eltrombopag can induce hematopoiesis with a non-competitive activation of c-MPL. In immune thrombocytopenia, TPO levels are at the upper or near the upper limit of the mean, while they increase significantly in aplastic anemia (5).

Romiplostim and eltrombopag, which are FDA-approved thrombopoietin receptor agonists, stimulate platelet production, especially in immune thrombocytopenia (6,7). The efficacy and safety of eltrombopag have been demonstrated in a study by Wong et al. (8) in immune thrombocytopenic purpura (ITP) and a study by Townsley et al. (9) severe aplastic anemia. Given the similarity between severe aplastic anemia and graft failure, it was suggested that eltrombopag therapy could also be successful in graft failure (10). Recently, several articles with small numbers of cases showing the efficacy of eltrombopag in persistent thrombocytopenia developed after HSCT have been published (11-13).

Herein we reported the results of 12 patients treated with eltrombopag in our center with severe thrombocytopenia after HSCT retrospectively.

Method

From January 2018 to February 2020, 119 patients had hematopoietic stem cell transplantation in our center's bone marrow transplantation unit. Fifty-six patients underwent ASCT, and 12 of them developed persistent thrombocytopenia. Our study was approved by the Bezmialem Vakıf University ethics committee.

Endpoint: The endpoints were determined as platelet levels >50,000/μL after initiating treatment with eltrombopag either permanently after cessation of drug or need to continue therapy and no response after four months therapy at a dose of 150 mg/day.

Eltrombopag Treatment

Eltrombopag was initiated at a dose of 50 mg/day in seven patients. The eltrombopag dose was increased by 50 mg weekly to attain a final dose of 150 mg/day. Due to the lack of platelet response in patients who received a daily dose below 150 mg, three patients were started with 100 mg, and two patients were directly started at 150 mg/day. Eltrombopag was given to all patients with a maximum dose of 150 mg. After the platelet count exceeded 150,000/μL, it was planned to taper first by decreasing 50 mg and 25 mg. When a decrease in platelet count was also detected during the cessation period, the dose was increased to the previous dose again. Platelet transfusions were performed when the platelet count was <15,000/μL in clinically stable patients and had no fever and bleeding symptoms and in patients with signs of bleeding, even if the platelet count was between 20,000/μL and 50,000/μL.

Statistical Analysis

Average values, standard deviation, median lowest, highest values, frequency, and ratio values were used in the descriptive statistics. The distribution of the variables was checked by the Kolmogorov-Smirnov test. The Wilcoxon test was used to analyze quantitative dependent data. The SPSS 22.0 program was used for the analyses. The Kaplan-Meier method was used for survival analysis.

Results

In a total of 12 patients who developed persistent thrombocytopenia after ASCT, 10 were men, and two were women. The median age was 40.5 (range: 19-67) years. Platelet engraftment failure was observed in 12 out of 56 patients (21.4%). The diagnoses of these patients were acute lymphoblastic leukemia (n=3; 25%), acute myeloid leukemia (n=6; 50%), Hodgkin lymphoma (HL, n=1; 8.3%), myelodysplastic syndrome (MDS, n=1; 8.3%) and non-HL (NHL, n=1; 8.3%). Nine patients had ASCT from a sibling donor (one of which was haploidentical), and three patients from an unrelated donor. Nine of the donors were a full match, two donors had one mismatch, and one donor had two mismatches

peripheral stem cell source, and myeloablative regimens were used in all patients. The median given stem cell number was 6.65 (4.7-9.3) x10^6/kg. Neutrophil engraftment could be achieved in all patients. The median time to neutrophil engraftment was 20 (9-27) days). Six patients developed PPEF, and the SPEF occurred in the other six patients. Cyclophosphamide was used in four patients after transplantation. Transfusion independence was achieved in three of these patients. Patient-donor blood groups were the same in seven patients and different in five patients. Before eltrombopag, the frequency for transfusion was once a week in two patients, 1-2 times a week in seven patients, and more than two times a week in three patients. A decreased number of megakaryocytes in the bone marrow were seen in six patients, whereas it was normal in the other six patients. The median time from transplant to eltrombopag initiation was 69 (range: 48-128) days. After eltrombopag treatment, eight patients achieved transfusion independence. The median platelet count four months after the start of eltrombopag treatment was 118.000 (range: 24,000-253,000)/μL. The median time for the platelet count to reach 50,000/μL was 18 (range: 14-112) days. The median duration of treatment with eltrombopag was 70 (range: 26-180) days. Currently, five of these patients are alive, and seven died due to septicemia. Eltrombopag treatment was discontinued in all patients who survived and had full platelet recovery. Patient characteristics are summarized in Table 1.

The patients' response rates were evaluated according to their status before eltrombopag are summarized in Table 2.

The duration of achieving transfusion independence in responders was 61.9 days (36.4-87.3)(Figure 1).

The duration of achieving transfusion independence in patients who had one or fewer transfusions per week before eltrombopag was significantly shorter than those with two or more platelet needs before eltrombopag [46.5 and 83.4 days (HR: 0.255, 95% CI: 0.050-1.29, p=0.045] (Figure 2).

In the group whose patient-donor blood group was compatible [34.1 and 86.1 days HR: 5.071, 95% CI, p=0.040], the time to achieve transfusion independence was significantly shorter than the group without blood group compatibility (Figure 3).

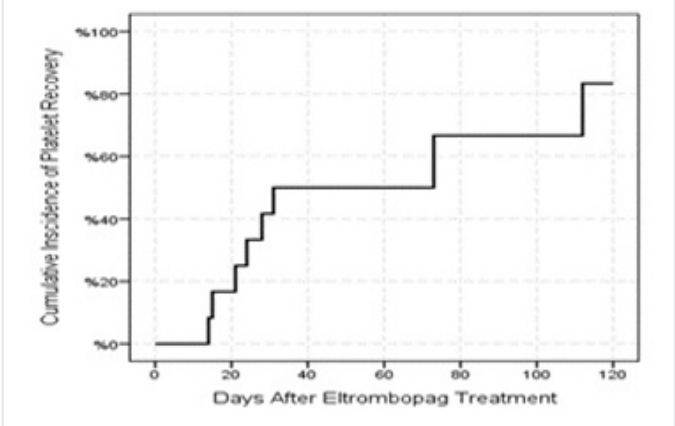

Figure 1. Cumulative transfusion independence

There was no significant difference regarding the time to achieve transfusion independence in primary and secondary failure. The time to achieve transfusion independence in patients who had a normal megakaryocyte count in their bone marrow was significantly shorter than those who had a low megakaryocyte count [85.0-38.8 days, HR: 3.667, 95% CI 0.698-19.25, p=0.045] (Figure 4).

The duration of achieving transfusion independence in the group using posttransplant cyclophosphamide (47.7 and 68.7 days, p>0.05) did not differ from the group that did not use cyclophosphamide (Figure 5).

The transfusion frequency decreased in three of four patients who did not respond to eltrombopag therapy. According to our study, a dose of eltrombopag <150 mg/day was not effective.

In the last outpatient visit, the median number of platelets was 80.500 (range: 19,000-210,000)/μL and was statistically significant (Table 3) (Figure 6).

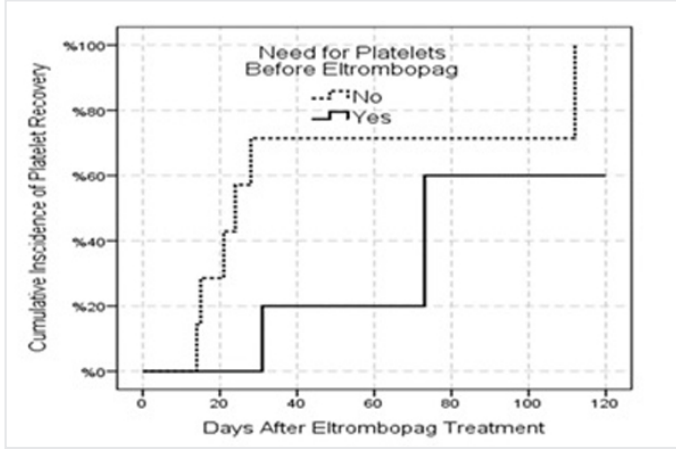

Figure 2. Need for platelets before eltrombopag

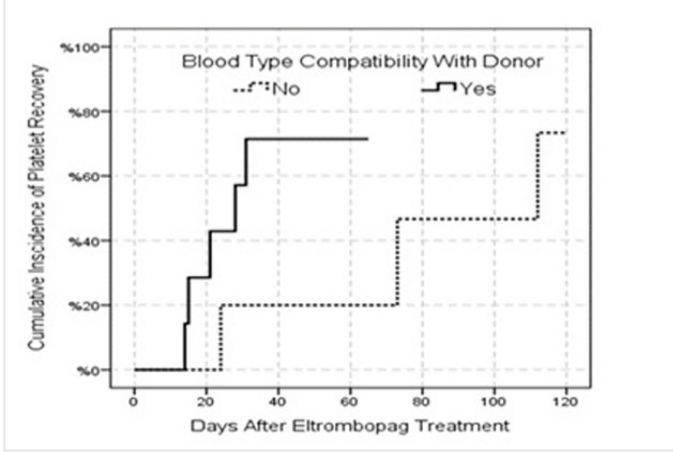

Figure 3. Patient-donor blood group compatibility

Table 1. Patient characteristics

		Min - Max			Median	Mean ± SD/n-%		
Patient age at transplantation		19.0	-	67.0	40.5	42.1	±	12.9
Gender	Female					2		16.7%
	Male					10		83.3%
Disease	ALL					3		25.0%
	AML					6		50.0%
	Hodgkin's lymphoma					1		8.3%
	MDS					1		8.3%
	NHL					1		8.3%
Donor	Sibling					8		66.7%
	Unrelated					3		25.0%
	Sibling haploidentical					1		8.3%
HLA	1 mismatch					2		16.7%
	2 mismatch					1		8.3%
	Match					9		75.0%
Stem cell source	Peripheral blood					12		100.0%
CD34+ cell dose x 10^6		4.7	-	9.3	6.7	6.5	±	4.6
Neutrophil engraftment time (days)		9.0	-	31.0	20.0	19.3	±	5.4
Patient-donor blood Group compatibility	Compatible					7		58.3%
	Not compatible					5		41.7%
Thrombocytopenia Status	PPEF					6		50.0%
	SPEF					6		50.0%
Platelet transfusion Before starting Eltrombopag	Once per week					2		16.7%
	2 times per week					7		58.3%
	>2 per week					3		25.0%
Megakaryocyte count Before starting eltrombopag	Decreased					6		50.0%
	Normal					6		50.0%
Starting dose of eltrombopag	100 mg					3		25.0%
	150 mg					2		16.7%
	50 mg					7		58.3%
Max dose of eltrombopag	150 mg					12		100.0%
The time until the start of the eltrombopag after ASCT (days)		48.0	-	128.0	69.0	75.7	±	25.3
Achievement of transfusion independence	Yes					8		66.7%
	No					4		33,3%
Final status	Alive					5		41.7%
	Dead					7		58.3%
Treatment time (days)		26.0	-	180.0	70.0	78.0	±	48.1

ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, MDS: Myelodysplasticsydrome, NHL: non-Hodgkin lymphoma, HLA: Human leucocyte antigen, PPEF: Primary platelet engraftment failure, SPEF: Secondary platelet engraftment failure, ASCT: Allogeneic stem cell transplantation, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. Response rates to treatment

		Transfusion independence (-)				Transfusion independence (+)			
		Mean ± SD/n-%			Median	Mean ± SD/n-%			Median
Age		47.3	±	11.0	51.5	39.5	±	13.7	39.5
Gender	Female	0		0.0%		2		25.0%	
	Male	4		100.0%		6		75.0%	
Patient-donor blood group compatibility	Compatible	2		50.0%		3		37.5%	
	Not compatible	2		50.0%		5		62.5%	
Thrombocytopenia status	PPEF	2		50.0%		4		50.0%	
	SPEF	2		50.0%		4		50.0%	
Platelet transfusion before starting eltrombopag	(-)	1		25.0%		6		75.0%	
	(+)	3		75.0%		2		25.0%	
Platelet count before starting eltrombopag		14,000	±	4,243	15,000	20,000	±	6,866	21,500
Max platelet count after eltrombopag		39,000	±	11,165	42,000	16,5125	±	54,186	166,000
Days from starting eltrombopag to platelet 50.000/µL						26.5	±	33.9	18.0

PPEF: Primary platelet engraftment failure, SPEF: Secondary platelet engraftment failure, SD: Standard deviation

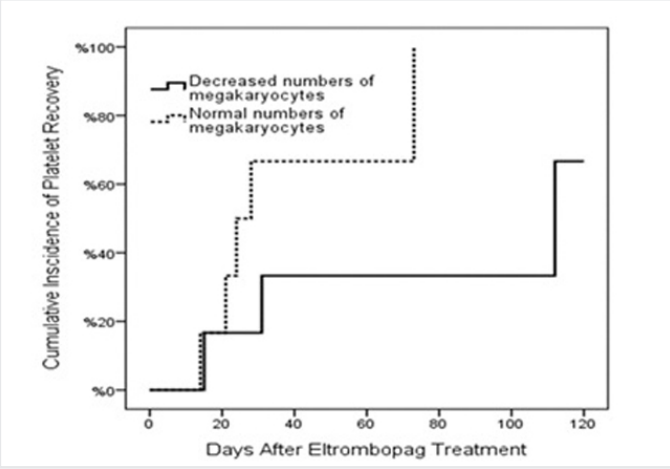

Figure 4. Megakaryocyte counts before starting eltrombopag

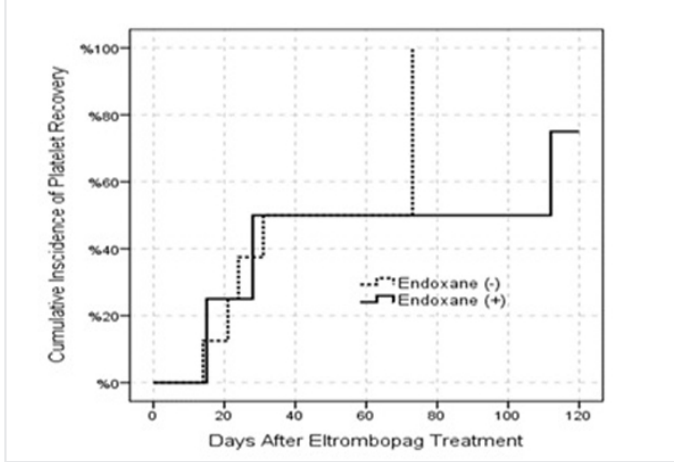

Figure 5. Using cyclophosphamide after ASCT

ASCT: Allogeneic stem cell transplantation

Discussion

Engraftment failure after ASCT has been a life-threatening complication with a rate of 5%-27% (14-16). After hematopoietic stem cell transplantation, two types of engraftment failure can be observed: PPEF and SPEF (3,4). Various methods have been tried to activate engraftment. These are growth factors, CD34+ stem cell enhancement, mesenchymal stem cells, and a second ASCT (16-19). However, none of these methods was completely effective. Eltrombopag, a thrombopoietin receptor agonist, has recently been started to be used.

In this article, we wanted to share our experience with eltrombopag in a patient who developed thrombocytopenia after ASCT. In our ASCT patients, platelet engraftment failure was found to be 21.4%. Eltrombopag treatment provided transfusion independence in 66.7% of patients and it was discontinued in all living patients. The dose was increased to 150 mg/day in all patients.

Bielski et al. reported that the post-ASCT PPEF prevalence was 3% (3). In three separate reports, two of four patients reported as PPEF were treated with romiplostim and the other two were treated with eltrombopag. Transfusion independence was

Table 3. Platelet counts before and after eltrombopag

	Min - Max			Median	Mean ± SD			p	
Platelet count (x10³)/µL									
Before eltrombopag	5.0	-	27.0	18.5	18.0	±	6.6	0.002	w
After eltrombopag	19.0	-	210.0	80.5	89.5	±	62.4		

Min: Minimum, Max: Maximum, SD: Standard deviation

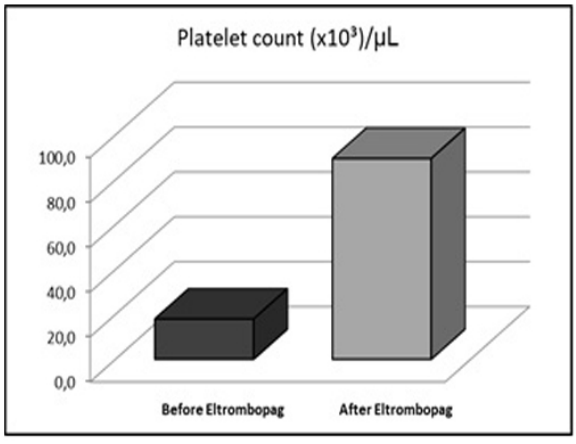

Figure 6. Platelet count before and after eltrombopag

achieved in all four patients (20-22). Tanaka et al. (12) treated five PPEF patients with eltrombopag and reported that they achieved transfusion independence in 60% of the patients. Transfusion dependence continued in two patients, but the frequency of transfusions decreased (12). We treated six patients diagnosed as PPEF with eltrombopag. Transfusion independence was achieved in four (66.7%) patients, and transfusion frequency decreased in the other two patients.

Bruno et al. (4) reported the prevalence of SPEF as 20%. Twenty-two patients identified as SPEF in seven different reports treated with romiplostim and transfusion independence was achieved in 91% of patients (20,23-28). Tanaka et al. (12) described a transfusion independence rate of 86% with six patients in a total of seven SPEF patients treated with eltrombopag. Six patients were diagnosed with SPEF and treated with eltrombopag in our patient group (max dose of 150 mg/day). Transfusion independence was achieved in four (66.7%) of these patients. Transfusion frequency decreased in one of the two nonresponder patients.

Tang et al. (11) treated 12 patients with poor graft function after ASCT with eltrombopag. In this study, eltrombopag was started at 25 mg/day and a maximum dose of 75 mg/day. A complete response (CR) was achieved in 66.7% of these patients. In our study, transfusion independence (CR) was achieved in 66.7% of patients.

Two of four patients for whom transfusion independence could not be achieved had grade ≥2 gastrointestinal tract GvHD. This was observed in three of four patients in the study by Tanaka et al. (12). Gastrointestinal absorption disorders might be effective in this condition.

In our study, the response to eltrombopag therapy was significantly better in patients who need a lower frequency of transfusions and had donor-patient blood group compatible transplantations. In addition, transfusion independence was achieved in five (83%) patients with normal bone marrow megakaryocyte counts. However, transfusion independence was achieved in only three (50%) of six patients with reduced bone marrow megakaryocyte counts (Figure 5). A study conducted by Tanaka et al. (12) supports this result. In the same study, the response to eltrombopag treatment was significantly higher in patients with secondary platelet failure than those with primary failure (12). However, in our study, there was no difference between the two groups.

Eltrombopag was well tolerated in all 12 patients. Side effects, such as cataracts, thrombosis, or 3/4 degree of toxicity and treatment-related mortality identified in the "EXTEND" (8) and "RAISE" phase III studies (29). These studies demonstrated the efficacy and safety of eltrombopag in patients with ITP. In various studies, it has been reported that eltrombopag does not induce leukemia or MDS cell growth (30). None of our patients had a transformation of leukemic or myelodysplastic syndrome. The efficacy and safety of eltrombopag have been demonstrated in ITP and aplastic anemia in various studies (8,9).

Study Limitations

The small number of cases is a limitation of this study.

Conclusion

Thrombocytopenia that develops after ASCT is a condition that should be treated as it can lead to life-threatening bleeding. Recently, the administration of eltrombopag USA after ASCT has become widespread and is effective and safe. It can be considered an effective option in the treatment of this difficult condition. Despite a small patient population, eltrombopag was an effective and safe treatment option for persistent thrombocytopenia that developed after allogeneic stem cell transplantation. Patient-donor blood group compatibility, pre-eltrombopag transfusion frequency, and pre-eltrombopag bone marrow megakaryocyte count may help predict the response to eltrombopag. Further studies with more patients are necessary to assess its full potential.

Ethics

Ethics Committee Approval: Our study was approved by the Bezmialem Vakıf University ethics committee.

Informed Consent: Patient consent was not obtained because the study was retrospective.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.E., A.T.A., Concept: A.E., Design: A.E., Data Collection or Processing: A.E., Analysis or Interpretation: A.T.A., Literature Search: A.E., Writing: A.E

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Kuzmina Z, Eder S, Bohm A, Pernicka E, Vormittag L, Kalhs P. et al. Significantly worse survival of patients with NIH-defined chronic graft-versus-host disease and thrombocytope- nia or progressive onset type: results of a prospective study. Leukemia 2012;26:746-56.
2. Yamazaki R, Kuwana M, Mori T, Okazaki Y, Kawakami Y, Ikeda Y, et al. Prolonged thrombocytopenia after allogeneic hematopoietic stem cell transplantation: associations with impaired platelet production and increased platelet turnover. Bone Marrow Transplant 2006;38:377-84.
3. Bielski M, Yomtovian R, Lazarus HM, Rosenthal N. Prolonged isolated thrombocytopenia after hematopoietic stem cell transplantation: mor- phologic correlation. Bone Marrow Transplant 1998;22:1071-6.
4. Bruno B, Gooley T, Sullivan KM, Davis C, Bensinger WI, Storb R, et al. Secondary failure of platelet recovery after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2001;7:154-62.
5. Emmons RV, Reid DM, Cohen RL, Meng G,_Young NS, Dunbar CE, et al. Human thrombopoietin levels are high when thrombocytopenia is due to megakaryocyte deficiency and low when due to increased platelet destruction. Blood 1996;87:406871.
6. Bussel JB, Kuter DJ, Pullarkat V, Lyons RM, Guo M, Nichol JL. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood 2009;113:2161-71.
7. Bussel JB, Cheng G, Saleh MN, Psaila B, Kovaleva L, Meddeb B, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med 2007;357:2237-47.
8. Wong RSM, Saleh MN, Khelif A, Salama A, Portella MSO, Burgess P, et al. Safety and efficacy of long-term treatment of chronic/persistent ITP with eltrombopag: final results of the EXTEND study. Blood 2017;130:2527-36.
9. Townsley DM, Scheinberg P, Winkler T, Desmond R, Dumitriu B, Rios O, et al. Eltrombopag added to standard immunosuppression for aplastic anemia. N Engl J Med 2017;376:1540-50.
10. Yuan C, Boyd AM, Nelson J, Patel RD, Varela JC, Goldstein SC, et al. Eltrombopag for Treating Thrombocytopenia after Allogeneic Stem Cell Transplantation. Biol Blood Marrow Transplant 2019;25:1320-4.
11. Tang C, Chen F, Kong D, Ma Q, Dai H, Yin J, et al. Successful treatment of secondary poor graft function post allogeneic hematopoietic stem cell transplantation with eltrombopag. J Hematol Oncol 2018;11:103.
12. Tanaka T, Inamoto Y, Yamashita T, Shigeo F, Okinaka K, Kurosawa S, et al. Eltrombopag for Treatment of Thorombocytopenia after Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant 2016;22:919-24.
13. Bento L, Bastida JM, Garcia I, Garcia E, Rivera D, Bosch A, et al. Thrombopoietin Receptor Agonist for Severe Thrombocytopenia after Allogeneic Stem Cell Transplantation: Experience of the Spanish Group of Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant 2019;25:1825-31.
14. Lee KH, Lee JH, Choi SJ, Lee JH, Kim S, Seol M, et al. Failure of trilineage blood cell reconstitution after initial neutrophil engraftment in patients undergoing allogeneic hematopoietic cell transplantation - frequency and outcomes. Bone Marrow Transplant 2004;33:729-34.
15. Woolfrey A, Anasetti C. Allogeneic hematopoietic stem-cell engraftment and graft failure. Pediatr Transplant 1999;3(Suppl 1):35-40.
16. Bittencourt H, Rocha V, Filion A, Ionescu I, Herr AL, Garnier F, et al. Granulocyte colony-stimulating factor for poor graft function after allogeneic stem cell transplantation: 3 days of G-CSF identifies long-term responders. Bone Marrow Transplant 2005;36:431-5.
17. Ghobadi A, Fiala MA, Ramsingh G, Gao F, Abboud CN, Stockerl-Goldstein K, et al. Fresh or cryopreserved CD34(+)-selected mobilized peripheral blood stem and progenitor cells for the treatment of poor graft function after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2017;23:1072-7.
18. Liu X, Wu M, Peng Y, Chen X, Sun J, Huang F, et al. Improvement in poor graft function after allogeneic hematopoietic stem cell transplantation upon administration of mesenchymal stem cells from third-party donors: a pilot prospective study. Cell Transplant 2014;23:1087-98.
19. Guardiola P, Kuentz M, Garban F, Blaise D, Reiffers J, Attal M, et al. Second early allogeneic stem cell transplantations for graft failure in acute leukaemia, chronic myeloid leukaemia and aplastic anaemia. French Society of Bone Marrow Transplantation. Br J Haematol 2000;111:292-302.
20. Poon LM, Di Stasi A, Popat U, Champlin RE, Ciurea SO. Romiplostim for delayed platelet recovery and secondary thrombocytopenia following allogeneic stem cell transplantation. Am J Blood Res 2013;3:260-4.
21. Reid R, Bennett JM, Becker M, Chen Y, Milner L, Phillips GL, et al. Use of eltrombopag, a thrombopoietin receptor agonist, in post-transplantation thrombocytopenia.Am J Hematol 2012;87:743-5.
22. Fujimi A, Kamihara Y, Hashimoto A, Kanisava Y, Nakajima C, Hayasaka N et al. Identification of anti-thrombopoietin receptor antibody in prolonged thrombocytopenia after allogeneic hematopoietic stem cell transplantation treated successfull with eltrombopag. Int J Hematol 2015;102:471-6.
23. Beck JC, Burke MJ, Tolar J. Response of refractory immune thrombocytopenia after bone marrow transplantation to romiplostim. Pediatr Blood Cancer 2010;54:490-1.

24. Calmettes C, Vigouroux S, Tabrizi R, Milpied N. Romiplostim (AMG531, Nplate) for secondary failure of platelet recovery after allo-SCT. Bone Marrow Transplant 2011;46:1587-9.

25. Bollag RJ, Sterett M, Reding MT, Key NS, Cohn CS, Ustun C. Response of complex immune-mediated thrombocytopenia to romiplostim in the setting of allogeneic stem cell transplantation for chronic myelogenous leukemia. Eur J Haematol 2012;89:361-4.

26. DeRemer DL, Katsanevas K, Bradley A, Awan FT. Romiplostim resistance in secondary failure of platelet recovery. J Oncol Pharm Pract 2013;19:369-72.

27. Maximova N, Zanon D, Rovere F, Maestro A, Schillani G, Paparazzo R. Romiplostim for secondary thrombocytopenia following allogeneic stem cell transplantation in children. Int J Hematol 2015;102:626-32.

28. Battipaglia G, Ruggeri A, Brissot E, Mamez AC, Malard F, Belhocine R, et al. Safety and feasibility of romiplostim treatment for patients with persistent thrombocytopenia after allogeneic stem cell transplantation. Bone Marrow Transplant 2015;50:1574-7.

29. Cheng G, Saleh MN, Marcher C, Vasey S, Mayer B, Aivado M, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 2011;377:393-402.

30. Will B, Kawahara M, Luciano JP, Bruns I, Parekh S, Erickson-Miller CL, et al. Effect of the nonpeptide thrombopoietin receptor agonist Eltrombopag on bone marrow cells from patients with acute myeloid leukemia and myelodysplastic syndrome. Blood 2009;114:3899-908.

Original Article

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Comparison of Dosage Loss Between Medications Crushed with Two Different Methods by Two Nurses: An *In Vitro* Study

İki Farklı Yöntemle ve İki Farklı Hemşire Tarafından Ezilen İlaçlar Arasındaki Doz Kaybının Karşılaştırılması: *İn Vitro* Çalışma

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ABSTRACT

Objective: Administration of crushed medications can lead to various problems associated with use of inappropriate crushing method, such as administration of an incorrect dosage, alterations in drug bioavailability, and reduction in the effectiveness of the treatment. This experimental study aimed to compare the dosage loss of crushed metoclopramide hydrochloride (MT-HCI) 10-mg tablet using two crushing methods.

Methods: MT-HCI 10 mg tablets (n=80) were crushed by two nurses, and each nurse used a pill crusher and a pestle and plastic bag to crush the tablet. Dosage loss was calculated by a specialist pharmacist in a laboratory environment.

Results: The dosage loss was 0.515±0.299 mg (5.16%) with the pestle and self-sealing plastic bag and 0.415±0.359 mg (4.16%) with the pill crusher. No statistically significant difference was found between the two methods (p>0.05). The mean dosage loss was 0.482±0.367 mg for the first nurse and 0.449±0.298 mg for the second nurse. No statistically significant difference was noted in the mean dose between the two nurses (p>0.05).

Conclusion: This study found no significant difference between the nurses and the crushing methods, but the mean dosage loss with both methods was not within the limits recommended by the United States Food and Drug Administration.

Keywords: Medications, dosage loss, tablet crushing, tablets crushing device, nursing skills

ÖZ

Amaç: İlaçların ezilerek verilmesi, ilaçların uygun olmayan yöntemlerle ezilmesi, yanlış dozda verilmesi, biyoyararlanımının değişmesi, tedavinin etkinliğinin azaltılması gibi birçok soruna yol açabilir. Bu deneysel çalışma, farklı iki hemşire tarafından, iki farklı yöntemle metoklopramid hidroklorür (MT-HCI) 10 mg tabletlerin ezildikten sonra, rezervuarda kalan doz kaybını karşılaştırmak amacıyla yapıldı.

Yöntemler: MT-HCI 10 mg tabletler (n=80) iki araştırmacı hemşire tarafından iki farklı yöntemle ezildi. Her hemşire ezmek için her iki yöntemi de (tablet ezici veya kilitli plastik torba içinde havaneli ile ezilerek) kullandı. Tablet ezici ve plastic torba içinden ilaç alındıktan sonra kalan doz kaybı laboratuvar ortamında uzman bir eczacı tarafından hesaplandı.

Bulgular: Kalan doz kaybı, kilitli plastik torbada havaneli yöntemiyle ezme yöntemiyle ortalama 0,515±0,299 mg, (%5,16) ve tablet ezici ile 0,415±0,359 mg (%4,16) olarak hesaplandı. İki yöntem arasında istatistiksel olarak anlamlı bir fark yoktu (p>0,05). Ortalama doz kaybı birinci hemşire için ortalama 0,482±0,367 mg ve ikinci hemşire için ortalama 0,449±0,298 mg idi. İki hemşire arasında kalan doz ortlamaları açısından istatistiksel olarak anlamlı bir fark yoktu (p>0,05).

Sonuç: Bu çalışma, ezme yöntemleri ile hemşireler arasında anlamlı bir fark olmadığını gösterdi. Ancak her iki yöntemde de ortalama doz kaybı Amerika Birleşik Devletleri Gıda ve İlaç İdaresi tarafından önerilen sınırlar içinde değildi.

Anahtar Sözcükler: İlaç hazırlama, doz kaybı, tablet ezme, tablet ezici, hemşirelik uygulamaları

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Introduction

Solid medications are administered in cut or crushed form to patients with dysphagia, patients fed through a gastric tube in critical care environments, or pediatric patients who cannot swallow such medications (1-4). Solid medications have to be cut and/or crushed under proper conditions, diluted with liquids, and administered by disposable syringes via a feeding tube or orally (3,5,6). However, when drugs are in solid form, nurses administer enteric-coated and extended release tablets to patients through a feeding tube after crushing them with inappropriate methods (7,8).

While nurses generally follow written and standardized protocols for administration of parenteral medications, they do not use standardized protocols when they crush or change the original administration form, making administration errors possible (8-10). Thus, medication preparation and administration should include cutting the medication in correct dosage under proper conditions, crushing and mixing it with liquid (drinking water, distilled water, etc.), collecting the mixture with a disposable syringe, and finally administering it orally or through a feeding tube (3,5,6).

Administration of medications after crushing or changing the original medication form can result in various problems associated with the use of inappropriate crushing methods, such as administration of incorrect dosage, alterations in drug bioavailability, and reduction of the effectiveness of the treatment (11-13). The most common problems associated with crushing medications are as follows: 1) no separate crushing apparatus for each patient; 2) hardness of the medication; 3) dosage loss or contamination due to improper crushing methods such as using an inappropriate sheet of paper as lining, crushing the medication while inside the packing of a medical equipment, or crushing by hitting the medication with a piece of wood or side of a glass intravenous fluid bottle or scissors; 4) insufficient dilution with a proper liquid; 5) reduction of the effectiveness of medication due to insufficient flushing of the enteral feeding tube and adhesion of the medication to the inner surface of the tube; 6) and drug interaction due to insufficient cleaning of the medication-crushing apparatus (3,14-17). Moreover, dosage loss may occur if a wrong solution is chosen and therefore cannot properly dissolve the medication. In this case, the feeding tube may be obstructed and lead to dosage loss, decreased effectiveness of the medication or toxicity, and consecutively decreased benefit from the treatment (11-13).

Many studies have evaluated dosage loss when tablets are crushed and transferred with syringes. In a study where a mortar and pestle was used for crushing, the dosage loss during the transfer with a syringe was 4%-38% (18). Similarly, in another study using a mortar and pill crusher, the dosage loss was 0%-4.8% (3). However, flushing the mortar, which contains the crushed medication, has been reported to decrease the dosage loss (19).

Nurses are not only licensed for medication administration but are also responsible for the administration of the prescribed medication at the prescribed dosage and route (10,11). Nurses have a key role in avoiding medication administration errors, maintaining patient safety, and ensuring an effective treatment process, as they are the patient-facing part of the treatment team, in which physicians and pharmacists are also involved (20,21). However, most nurses who encounter problems with administration of medications that need crushing or modification of the original administration form do not tend to consult a pharmacist or clinical guidelines (8,22).

The correct administration of oral medications in crushed form is a challenge for nurses (23). To our knowledge, only one descriptive study from Turkey has focused on the administration of crushed medications or medications in modified forms (24), and only a few global studies have reported on the crushing method ensuring the smallest dosage loss, but these studies have different methodological designs and do not generate evidence-based data (3,18,25).

Thus, this experimental study aimed to compare the dosage loss of crushed metoclopramide hydrochloride (MTC HCl) 10-mg tablets using two crushing methods.

Method

This experimental study was conducted during the period from August 2018 to December 2018 in a laboratory environment. To easily detect any related difficulties in practice, MTC HCl 10-mg tablets were chosen as the active ingredient and distilled water as the dissolving solution. The dosage loss due to the undissolved MTC HCl 10-mg tablet residues in distilled water was then evaluated. A specialist pharmacist calculated the dosage loss of the medications in solid form after the tablet was crushed with a pill crusher or the pestle method before administration; the tablets were crushed by two nurse researchers in the laboratory environment. The MTC HCl 10-mg tablet was chosen as the crushable and transformable medication. A total of 80 tablets were crushed either with a pill crusher or with the pestle method by two nurse researchers, and each nurse used both crushing methods. The nurse researchers crushed the tablets at the same time, and the process took 3 h. The experiment was done in 1 day. The process involved crushing the drug, diluting and vacuuming the drug by an injector from the reservoir, diluting and vacuuming the remaining dose by an injector from the reservoir again, coding the injectors for the pharmacist with an adhesive tape, and cleaning the pill crusher to crush a new drug or preparing a new self-sealing plastic bag. One of the nurse researchers had 9 and the other had 17 years of intensive care unit and clinical care experience, and both had a PhD in the Fundamentals of Nursing.

Medication Crushing Methods

Pill Crusher

A pill crusher identical to the ones used in clinical care was used by the nurse researchers. The medication in solid form was placed in the pill crusher, and the upper part was closed. To achieve complete crushing, the upper part was rotated by 360°,

the pill crusher shaken, and then rotated until the tablet was properly crushed. Twenty of the 40 MTC HCl 10-mg tablets were crushed by one of the nurse researchers, and the rest by the other nurse on different occasions (Figure 1). The crushed components were diluted with 5 mL of distilled water in the pill crusher and aspirated with a syringe. To calculate the dosage of the residues in the pill crusher, the device was rinsed with 2 ml of ethanol and the material was aspirated with a separate syringe. The pill crusher was washed under clear water, dried with a paper towel, and left open for 5 min between uses. All phases of the procedure were observed by a physician who was not otherwise associated with the study.

Pestle Method

Self-locking 8x10 cm^2 plastic bags for routine medication administration in the clinics were used in this method (Figure 1). The tablets were placed inside the plastic bag one by one and crushed by hitting them with a pestle from the outside. Twenty of the 40 MTC HCl 10-mg tablets were crushed by one of the nurse researchers, and the rest by the other nurse researcher on different occasions and a new plastic bag was used each time. The crushed medication was diluted with 5 mL of distilled water in the plastic bag and aspirated with a syringe. To calculate the quantity of the residues, the plastic bag was rinsed with 2 mL of ethanol and the mixture was aspirated with a separate syringe.

During the crushing with the pestle, some of the plastic bags were damaged or punctured. The procedure was stopped in that case, and the process was repeated with a new medication in a new plastic bag. All phases of the procedure were observed by a physician who was otherwise not associated with the study.

The syringes in which medication residues were transferred to analyze the dosage loss were labeled under the supervision of the physician, acting as the external observer, so as to identify the research nurse and the method. The research pharmacist analyzed the dosage loss under the supervision of a pharmacist acting as an external observer.

Determination of Dosage Loss

Medications crushed with both methods were diluted with distilled water and collected with a disposable syringe. The reservoir was then rinsed with 2 mL of ethanol, and the remaining medication solution was collected with another disposable syringe to determine dosage loss. The high-pressure liquid chromatography (HPLC) method was used with the Agilent Model 1100 series. According to developed HPLC method, the non-crushed 10-mg MTC tablet was 10.08 mg, and the detection limit of the developed HPLC method was within the acceptable limits given by the pharmacopeia. Chromatographic separations were performed using an ACE 5 Phenyl (4.6x150 mm^2) column as the stationary phase. The injection volume was 20 µL, and flow rate was 1 mL/min. An ultraviolet diode array detector was adjusted to 308 nm. MTC HCl was dissolved by the mobile phase, and all stock solutions were stored at +4 °C. The calibration equation was obtained by serial dilution of five points from a concentration of 100 µg/mL to 5 µg/mL with the mobile phase.

Sample Size of the Study

The sample size of the study was calculated using the Power Analysis and Sample Size Software, Version 11.0 (PASS V. 11.0), based on similar published studies (3,18,25). Using a confidence interval (CI) of 95%, power of 80%, and interclass correlation coefficient (ICC) of 0.75-0.90 between the amounts to be prepared by the two nurses, it would be enough to crush 40 tablets. Each nurse researcher therefore crushed 20 tablets with each method for a total of 40 tablets, and a grand total of 80 tablets were crushed (Figure 2).

Ethical Statements

This study did not collect or use physiological specimens. This study was not conducted on humans or any living subjects, but in a laboratory environment. Thus, a board approval in accordance with the journal policy is not necessary. The institution provided approval for the use of the laboratory for the application and evaluation phase of the research.

Statistical and Analytical Methods

The Statistical Package for Social Sciences for Windows Version 22.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the

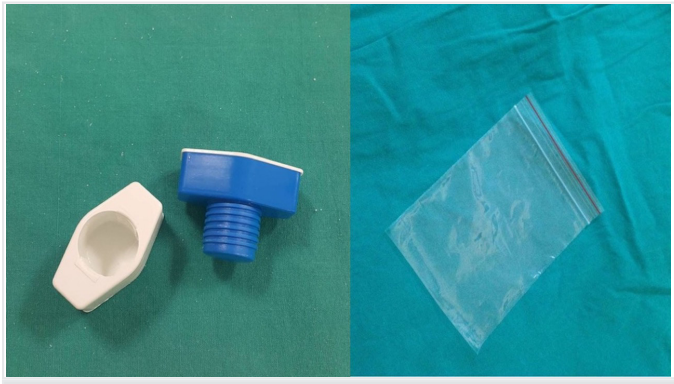

Figure 1. Pill crusher and plastic bag

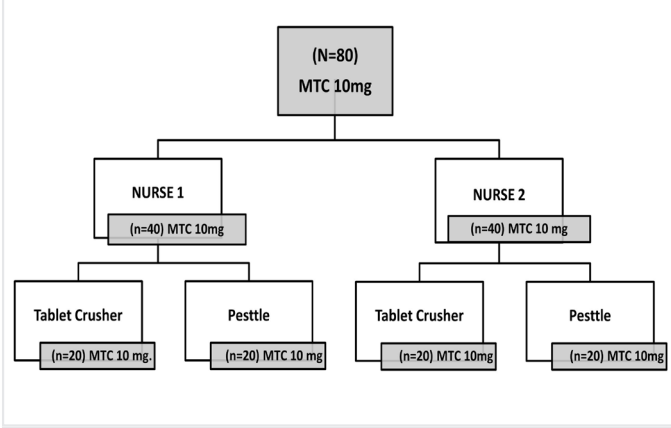

Figure 2. Study flow chart

collected data. Normality tests of the variables were conducted by the Shapiro-Wilk test and graphical methods. For descriptive statistics, mean ± standard deviation was used to present continuous variables, while number and percentage were used for categorical variables. Student's t-test and two-way analysis of variance were used when comparing the dosage loss between the two nurse researchers and the two crushing methods; $p<0.05$ was accepted as statistically significant.

Results

Both nurse researchers stated that crushing the tablets was easier with the pill crusher than with the pestle method and preferred the pill crusher. In the pestle method, seven self-locking plastic bags were damaged and lost, so new tablets were crushed again using new self-sealing plastic bags (nurse 1 damaged 3 plastic bags; nurse 2 damaged 4 plastic bags). The procedure was stopped in these cases, and the procedure was repeated with a new medication in a new plastic bag. The dosage loss was 0.415±0.359 mg [minimum-maximum (min-max): 0.07-1.58 mg] with the pill crusher and 0.515±0.299 mg (min-max: 0.15-1.39 mg) with the pestle method in a self-sealing plastic bag. The dosage loss rates were 4.16% and 5.16% with the pill crusher and pestle method, respectively. The ICC between nurses was 0.78 (0.58-0.88 with 95% CI). When the remaining doses of the crushed tablets in the reservoir were measured, the dosage loss was more than 3% in 57.8% (n=47) of the tablets.

No statistically significant difference was found between the mean dosage loss rates between the two methods (mean (pill crusher) =0.415±0.359 mg, mean (pestle) =0.515±0.299 mg, t=1.350, p=0.181). The mean dosage loss was 0.482±0.367 mg for nurse 1 (40 tablets crushed with both methods) and 0.449±0.298 mg for nurse 2 (40 tablets crushed with both methods) with no statistically significant difference (t=0.443, p=0.659). Two-way variance analysis of the mean dosage loss by two nurse researchers with the two methods (2 nurses x 2 methods) and the post hoc Sidak's multiple comparisons test revealed no statistically significant difference between the groups (*F* (nurse) =0.201, p=0.665; *F* (method) =1.815, p=0.182; *F*(nurse*method) =0.739, p=0.392) (Figure 3). However, in some calculations, the dosage loss was not compatible with the limitations of the United States Pharmacopeia that states "the dosage delivered to the patient should not be less than 90% or more than 110% of the prescribed dosage".

Discussion

This study compared the dosage loss when crushing solid medications with two different methods by two nurse researchers and the efficiency of the two methods. No statistically significant difference was found between the nurse researchers and the crushing methods, but the mean dosage loss rates with the pill crusher and pestle method were 4% and 5%, respectively.

The manuals published by the United States Food and Drug Administration (FDA) (26) and Green et al. (27) recommend that the dosage loss for enteral medications should be less than 3%.

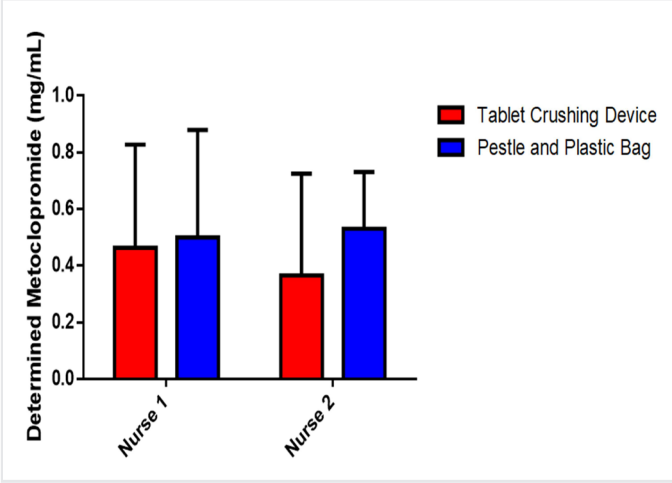

Figure 3. Comparison of the dosage loss between the two research nurses and two crushing methods

Methods to minimize the dosage loss and the use of pill crushers are evaluated in several studies (27). Ruzsíková et al. (18) have studied 18 different combinations of methods and tablets and found a dosage loss range of 4%-38%. Thong et al. (25) found a dosage loss of 4.2%-24.2% with various pill crushers and crushing methods and indicated that the dosage loss was higher with the use of disposable plastic bags and pill crushers with a reservoir. According to them, many pill crushers in the market were not suitable in the context of dosage loss. Several studies have recommended to rinse the reservoir of the pill crusher, not once but several times, to help minimize dosage loss (9,19,25). Many studies have reported dosage loss higher than the suggested limits, regardless of the crushing method, similar to our results (9,18,25). In this study, the mean dosage loss was higher with the pestle method using a plastic bag, similar to the findings of Thong et al. (25). We believe that medication residues collected by the second rinsing should be administered to the patients to minimize dosage loss, as suggested in various studies (9,19,25).

This study was conducted in a laboratory environment without any time restrictions, with minimal external stimulants, an easily crushable medication, under the supervision of an external observer, and the nurse researchers had sufficient experience in crushing medications in solid form. Given these conditions, it is possible that we found no statistically significant difference between the two nurse researchers and the two different methods due. However, the results in clinical practice may be quite different considering the workload of the nurses, medication type, ease of crushing the medication, time limitations, and inadequate or improper equipment or devices (3-5,12,16,17,24,28).

Although the MTC HCl 10-mg tablets had no reported health-threatening major adverse effects in healthy adults, a major concern is the transfer of medication dust through the skin or respiratory system of individuals who have crushed them. Aerosolization during crushing and preparation of the solution via the enteral route is therefore a risk for healthcare professionals, particularly for nurses. Secondary intake of the medication through the respiratory system is possible when the crushing is unintentional,

especially with chemotherapeutics and antibiotic agents, leading to allergic reactions and even toxicity (25,29). Thong et al. (25) reported that the dosage loss by aerosolization is 1.1% during the crushing process while tapping the remnant dust of the crushed tablet and 0.2% when it is collected by rinsing the reservoir with water. It is therefore recommended to crush the medication in a sealed plastic bag or a closed pill crushers and to dilute it in the reservoir where it was crushed, as we performed in this study; dosage loss by aerosolization is important.

Study Limitations

This study had some limitations. First, a medication that can be easily crushed was selected. Medications that are hard to crush or break may lead to different results. Second, this study was conducted under controlled conditions in a laboratory environment with experienced nurse researchers. However, dosage loss is affected not only by the crushing method or device but also by many factors including, but not limited, to stressors in clinical care, experience of the nurse, workload of the nurse, time limitation, availability and convenience of the pill crusher, and the cost effectiveness of the method.

Treatment and administration of medication is a complex process, which involves physicians, pharmacist, and nurses. In this process, the nurse is responsible for the proper preparation and administration of medication and the post-administration observation of possible intended or adverse effects of the medication (2,24,28). Risk of dosage loss at every phase of the treatment should be taken into account by the physician who prescribes and decides on the administration method of the medication, by the pharmacist who supplies it in the prescribed form, and by the nurse who modifies it into the administration form or who trains the patients and their relatives on how to alter the medication in solid form into solutions to be administered through an enteral feeding tube (1,4,25). In this scientifically and technologically advanced new era, it is recommended to prefer medications in liquid form instead of changing medications in solid form into solutions by crushing.

However, if crushing solid medications is inevitable, using a closed reservoir such as a pill crusher or a self-sealing plastic bag, ensuring minimal residues in the reservoir, and avoiding dosage loss in other phases of medication administration are recommended.

Further clinical studies and publishing evidence-based guidelines on safe and secure medication administration through an enteral feeding tube without dosage loss may contribute to better clinical practice and improve patient outcomes.

Conclusion

In this study, no significant difference was found between the research nurses and the crushing methods, but the mean dosage loss with both methods were not within the limits recommended by the United States FDA, 2013 (30) on the dosage loss for enteral medications. As a standard protocol in the literature, during the transfer of the drug from the pill crusher or from the single-use medication-crushing bag, the whole reservoir must be washed twice and kept. Moreover, to the best of our knowledge, no guideline has been established on the use of pill crusher in any country. However, more research is needed to determine whether device performance varies between tablet types and users and to what extent laboratory research reflects the drug loss during clinical use. Indeed, more clinical studies are needed to obtain new evidence, and guidelines should be published in the light of this evidence.

Ethics

Ethics Committee Approval: The institution provided approval for the use of the laboratory for the application and evaluation phase of the research.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: B.T., N.Ü., N.Ö., Concept: B.T., N.Ü., N.Ö., Design: B.T., N.Ü., N.Ö., Data Collection or Processing: B.T., N.Ü., N.Ö., F.A., Analysis or Interpretation: B.T., N.Ü., N.Ö., F.A., Literature Search: B.T., N.Ü., N.Ö., F.A., Writing: B.T.

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References

1. Fodil M, Nghiem D, Colas M, Bourry S, Poisson-Salomon AS, Rezigue H, et al. Assessment of clinical practices for crushing medication in geriatric units. J Nutr Health Aging 2017;21:904-8.
2. Paparella S, Horsham PA. Identified safety risks with splitting and crushing oral medications. J Emerg Nurs 2010;36:156-8.
3. Palese A, Bello A, Magee J. Triturating drugs for administration in patients with difficulties in swallowing: evaluation of the drug lost. J Clin Nurs 2011;20:587-90.
4. Richey RH, Hughes C, Craig JV, Shah UU, Ford JL, Barker CE, et al. A systematic review of the use of dosage form manipulation to obtain required doses to inform use of manipulation in paediatric practice. Int J Pharm 2017;25:155-66.
5. Clauson H, Rull F, Thibault M, Ordekyan A, Tavernier J. Crushing oral solid drugs: Assessment of nursing practices in health-care facilities in Auvergne, France. Int J Nurs Pract 2016;22:384-90.
6. Clarke S. Drug administration via nasogastric tube. Paediatr Nurs 2008;20:32-3.
7. Beckwith MC, Feddema SS, Barton RG, Graves C. A guide to drug therapy in patients with enteral feeding tubes: dosage form selection and administration methods. Hosp Pharm 2004;39:225-37.
8. Boullata JI. Drug administration through an enteral feeding tube. Am J Nurs 2009;109:34-42.
9. Bourdenet G, Saussereau E, Goullé JP, Guerbet M, Doucet J. Crushing drugs in geriatric units: are cleaning methods and devices appropriate? Eur J Clin Pharmacol 2019;75:127-9.

10. Kelly J, Wright D, Wood J. Medicine administration errors in patients with dysphagia in secondary care: a multi-centre observational study. J Adv Nurs 2011;67:2615–27.
11. Best C, Wilson N. Advice on safe administration of medications via enteral feeding tubes. Br J Community Nurs 2011;6:6-10.
12. Kirkevold Ø, Engedal K. What is the matter with crushing pills and opening capsules? Int J Nurs Pract 2010;16:81-5.
13. Podilsky G, Berger-Gryllaki M, Testa B, Buclin T, Roulet M, Pannatier A. The bioavailability of bromazepam, omeprazole and paracetamol given by nasogastric feeding tube. Eur J Clin Pharmacol 2009;65:435-42.
14. Demirkan K, Ekincioğlu AB. The Importance of Pharmaceutical Dosage Forms in Administration via Enteral Feeding Tubes. J Turkish Soc Intens Care 2016;14:1-8.
15. Decloedt E, Maartens G. Pitfalls of administering drugs via nasogastric tubes. SAMJ Forum 2009;99:148-9.
16. Kelly J, Wright D. Administering medication to adult patients with dysphagia: part two. Nurs Stand 2010;24:61-8.
17. Saimbi S, Madden V, Stirling H, Yahyouche A, Batchelor H. Comparison of hydrocortisone 10 mg tablets: tablet hardness optimised for adult use has negative consequences for paediatric use. Arch Dis Child 2016;101:e2.
18. Ruzsíková A, Součková L, Suk P, Opatřilová R, Kejdušová M, Šrámek V. Quantitative analysis of drug losses administered via nasogastric tube-in vitro study. Int J Pharm 2015;478:368-71.
19. Crean B, Finnie C, Crosby A. Evaluation of crushed ticagrelor tablet doses: recovery following crushing and naso-gastric tube passage ex vivo. Drugs R D 2013;13:153-7.
20. Taylor C, Lillis C, Lemone P, et al. Fundamentals of Nursing: The Art and Science of Nursing Care. 7th ed. Philadelphia, 2011.p.51-9.
21. Elliott M, Liu Y. The nine rights of medication administration: an overview. BJN 2010;19:300-5.
22. Barnes L, Cheek J, Nation RL, Gilbert A, Paradiso L, Ballantyne A. Making sure the residents get their tablets: medication administration in care homes for older people. J Adv Nurs 2006;56:190-9.
23. van den Bemt PM, Cusell MB, Overbeeke PW, Trommelen M, van Dooren D, Ophorst WR, et al. Quality improvement of oral medication administration in patients with enteral feeding tubes. Qual Saf Health Care 2006;15:44-7.
24. Çelik S, Demiray Y, Acar T, Köymen H, Coşkun Y, Doğru Ö, et al. Evaluation of drug administrations via enteral tube of intensive care nurses. J Contemp Med 2014;4:18-25.
25. Thong MY, Manrique YJ, Steadman KJ. Drug loss while crushing tablets: Comparison of 24 tablet crushing devices. PLoS ONE 2018;13:e0193683.
26. Food and Drug Administration FDA. Center for Drug Evaluation and Research (CDER), Food and Drug Administration. Guidance for Industry, Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation, 2013.
27. Green G, Berg C, Polli JE, Barends DM. Pharmacopeial standards for the subdivision characteristics of scored tablets. Pharma Times 2010;42:15-24.
28. Van Welie S, Wijma L, Beerden T, van Doormaal J, Taxis K. Effect of warning symbols in combination with education on the frequency of erroneously crushing medication in nursing homes: an uncontrolled before and after study. BMJ 2016;6:e012286.
29. Salmon D, Pont E, Chevallard H, Diouf E, Tall M-L, Pivot C, Pirot F. Pharmaceutical and safety considerations of tablet crushing in patients undergoing enteral intubation. Int J Pharm 2013;443:146-53.
30. United States Pharmacopeia (USP), United States Pharmacopeia 2018. http://www.usp.org. (accessed 30 November 2018).

Review

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A Current View of Care of High Risk Pregnancy

Yüksek Riskli Gebeliklerin Bakımına Güncel Bir Bakış

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ABSTRACT

Although the pregnancy is planned to go smoothly, it brings with it a number of risks. Pregnancy risks are grouped as low risk, moderate risk and high risk. Every pregnant woman is at risk after pregnancy, even if it is low. Pregnancies which have the conditions that may endanger the life of the mother/baby, t occurring prior to pregnancy orduring pregnancy are defined as high risk pregnancy. Individualized care is very important in the care of high-risk pregnancies. Early diagnosis of high-risk pregnancies is useful in preventing further serious complications that may occur in the future. Pregnant women may also need to be hospitalized for the care and treatment processes of high-risk pregnancies. However, this situation brings with it many disadvantages for the pregnant woman. Problems related to patient safety also arise during hospitalizations. Falls in high-risk pregnancies have an important role in patient safety. The widespread use of mobile applications available at home has contributed to the participation of high-risk pregnant women in the care process, reducing hospitalizations, length of hospital stay and health care needs. These include the treatment of high-risk pregnant women in hospital, coordination of the health care team, providing patient safety, providing health education, providing psychosocial support to the pregnant and her family, and using mobile applications that can be used in the care of pregnant women at home. It is a unique opportunity for nurses to protect, promote and improve the health of pregnant women and their infants. The aim of this review is to provide an up-to-date overview of the care of high-risk pregnancies.

Keywords: Risk, pregnancy, care

ÖZ

Gebelik süreci, sorunsuz geçmesi planlanmasına rağmen beraberinde bir takım riskleri getirir. Gebelik riskleri düşük riskli, riskli ve yüksek riskli olarak gruplandırılır. Her gebe, gebeliği kesinleştikten sonra düşük de olsa risk altındadır. Sıkı takip ve izlemle riskli gebeliklerde, sağlıklı bir şekilde gebeliğin sürdürülmesi hedeflenir. Gebelik öncesinde oluşan veya gebelikle birlikte ortaya çıkan annenin/bebeğin yaşamını tehlikeye sokabilecek durumlara sahip olan gebelikler yüksek riskli gebelik olarak ifade edilir. Yüksek riskli gebeliklerin bakımında bireyselleştirilmiş bakım oldukça önemlidir. Yüksek riskli gebeliklerin erken dönemde tanılanması, ilerideki süreçte oluşabilecek daha ciddi komplikasyonların önlenmesinde yararlıdır. Yüksek riskli gebeliklerin bakım ve tedavisinde gebenin hastaneye yatması da gerekebilir. Fakat bu durum gebe için birçok olumsuzluğu beraberinde getirir. Hastaneye yatışlarda hasta güvenliği ile ilgili sorunlar da ortaya çıkmaktadır. Yüksek riskli gebeliklerin hastaneye yatışında düşmeler hasta güvenliği konusunda önemli bir yere sahiptir. Son dönemlerde evde yararlanılabilen mobil uygulamaların kullanımının yaygınlaşması, yüksek riskli gebelerin bakım sürecine katılmasına, hastaneye yatışların, hastanede kalma sürelerinin ve sağlık bakım gereksinimlerinin azalmasına katkı sağlamıştır. Hastanede yatan yüksek riskli gebenin tedavisi, sağlık ekibinin koordinasyonu, hasta güvenliğinin sağlanması, sağlık eğitimi verilmesi, gebe ve ailesine psikososyal destek sağlanması ve evde bakımı sağlanacak gebelerin bakımında yararlanılabilecek mobil uygulamaların kullanılması bu roller arasındadır. Hemşirelere, gebe ve bebeğinin sağlığının korunması, geliştirilmesi ve iyileştirmesi konusunda eşsiz bir fırsat sağlar. Bu literatür incelemesinin amacı yüksek riskli gebeliklerin bakımına güncel bir bakış sunmaktır.

Anahtar Sözcükler: Riskli, gebelik, bakım

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Introduction

Although it is aimed to have a non-problematic pregnancy, delivery and postpartum period, all pregnant women are in danger for a risky pregnancy. An actual or potential danger to the health/well-being of the mother and fetus and an unexpected medical or obstetric condition related to pregnancy is considered a high risk pregnancy (1). Worldwide, 20 million women have high-risk pregnancies, and more than 800 women die daily from perinatal causes. Of these losses, 6-33% are in the high risk pregnancy group. Worldwide, 5-10% of all pregnancies are complicated by preeclampsia. Malaria, tuberculosis and chronic iron deficiency anemia are among the other most common pregnancy complications (2). Majella et al. (3) determined that 18.3% of 569 pregnant women who were admitted to primary health care services in South India were high-risk pregnants and emphasized the importance of early diagnosis in the care and management of high-risk pregnancies. There are many risk factors in high risk pregnancies. Conditions that may pose a potential risk for high-risk pregnancy have been classified by The National Institutes of Health (Table 1) (4).

Risk perception during pregnancy affects the status of high-risk pregnant women seeking care and medical support. Risk perception is defined as "the person's expectation about the probability of an event happening". In a study conducted with nulliparous women, it was determined that pregnancy-related anxiety, medical risk conditions (reproductive history, medical condition, pregnancy complications), gestational age, the effect of the healthcare provider, previous experiences and one's life philosophy can affect the risk perception during pregnancy (5). Attention should be given to individuality in care, as the way the pregnant woman defines pregnancy-related risks may affect her ability to seek obstetric care and her willingness to maintain/comply with the planned care plan. Risky situations perceived by the pregnant woman should be determined and the pregnant woman should be informed about the risks that she is not aware of (5).

This literature review was prepared in line with the literature in order to provide an up-to-date overview of the care of high-risk pregnancies. In the scope of the review, perinatal optimality was discussed in high-risk pregnancies in order to provide perinatal care without unnecessary interventions. The roles of the nurse and the models/theories that could be used in providing perinatal optimality were included. Patient safety, which was an important component of perinatal care, home care of high risk pregnant women and mobile applications that could be used in care were mentioned. In addition, consultancy and health education for improving maternal and fetal health in high risk pregnancies were discussed.

Perinatal Optimality

It is necessary to provide optimal care in order to continue the process in a healthy way both during high-risk pregnancy and healthy pregnancies. Optimal care in high-risk pregnancies focuses on obtaining and developing optimal results for the pregnancy and postpartum process for the pregnant, fetus, and the family. Optimality approach aims to provide individual care services in the complex pregnancy process, unlike routine obstetric interventions. One of the main conditions for ensuring optimality in this care process is to benefit from evidence-based approaches. Evidence-based individual-centered care provides safe and effective practices, improving the quality of perinatal care given to high-risk pregnant women and fetuses, and standardizing the care provided (3).

High-risk pregnancies may require lifestyle changes, medical support, technical support, and even hospitalization. Depending on the seriousness of the pregnant woman's health condition, a hospital stay may be necessary, starting weeks or months before the birth of the baby in high-risk pregnancies. Long-term hospitalization causes physical changes in the pregnant woman such as muscle atrophy, cardiovascular problems and bone loss (6). Pregnant women hospitalized in the antepartum period may experience psychological problems such as shock, depression, anxiety, sleep disorders, boredom, fear for the fetus and their own health, guilt, feeling trapped, loss of control, weakness, loneliness, anger and anxiety. The hospitalized pregnant can often experience anxiety for weeks or months with fear of the unknown. In the literature, it has been stated that pregnant women have more anxiety in high risk situations such as preterm birth risk, gestational diabetes and hypertension compared to normal pregnancy period. In addition, headache, constipation, hemorrhoids, gastrointestinal disorders, edema, back and lower abdominal pain that can be seen during pregnancy can be aggravated by hospitalization (3). High-risk pregnancy can also cause sleep problems, which are common during pregnancy, to emerge more prominently. One of the biggest problems experienced by high-risk pregnant women hospitalized is poor sleep quality. Poor sleep and short sleep time increase the risk of preterm birth and cesarean delivery. When the high-risk pregnant woman is hospitalized, her sleep becomes even more problematic as she experiences anxiety and stress for the fetus or her own health. Due to an uncomfortable bed, excessive light and sound exposure at night, and the foreign hospital environment, the sleep of the pregnant woman is frequently interrupted (6). In the study conducted by Lee and Gay (7) to improve the sleep quality of high-risk pregnant women in antepartum period in line with the BETTER model, it was determined that the sleep time and sleep quality scores of pregnant women increased in line with

Table 1. Classification of potential risk factors for high risk pregnancy

Current health conditions	Hypertensive disorders, polycystic ovary syndrome, diabetes, kidney disease, autoimmune diseases, thyroid disease, infertility, obesity, HIV/AIDS
Age	Adolescent pregnancies, first pregnancy after the age of 35
Lifestyle factors	Use of alcohol, tobacco and illegal drugs
Pregnancy conditions	Multiple pregnancy, gestational diabetes, preeclampsia and eclampsia

the program implemented. The content of the sleep program developed in the study is given in Table 2. No other study utilizing the BETTER model in the care of high-risk pregnancies has been found in the literature. Accordingly, it may be suggested to perform new studies using the BETTER model to increase evidence-based studies in the care of high-risk pregnancies.

The Roles of the Nurse in Providing Optimal Care

Although the care of high-risk pregnant women requires a multidisciplinary approach, the responsibility of nurses in care is quite high. For this reason, nurses play a leading role in defining the problems and offering necessary solutions from the moment the high-risk pregnant woman encounters the healthcare team (8). Nurses in the multidisciplinary team have practiced on determining the real and possible risks in high risk pregnancies, making the necessary planning for care, supporting the implementation of care and treatment, and requesting consultation when necessary. Nurses have an important role in ensuring effective communication between the patient and the healthcare team and providing optimal care, since they are professionals within the health care team that the patient can easily reach. In addition, nurses should know the physiological care needs of high-risk pregnancy and aim to provide optimal care, and be sensitive about providing psychosocial support to the pregnant woman and her family. They should follow the technological applications that can be used in the optimal care and treatment of high-risk pregnancies, and inform the patient and her family about high-risk situations. Nurses should take responsibility for the administration of appropriate doses of drugs in the optimal care of high-risk pregnant women, and have information about their indications and side effects (9).

Concerns about the health of the pregnant woman can expose complex feelings about pregnancy and increase the level of anxiety. Proper and appropriate care provided by healthcare professionals positively affects the pregnancy and hospital stay experience. Interventions, especially to provide psychosocial support, of the nurses, who have the most interaction with high-risk pregnant women in the hospital compared to other health professionals, will have a key role in the care. Celebrations can be held at the hospital on days such as the 28th or 32nd week of pregnancy. A special meal for the pregnant woman and her family can be planned so that they can spend time together. Varied/flexible visiting hours, support and group therapies can be beneficial to reduce feelings of isolation and depression. In order to reduce the boredom of the pregnant woman, she should be encouraged to plan activities such as waking up at the same time of the day, eating, reading a book or magazine, listening to music and exercising. In order for the pregnant woman to feel better during the day, she should be supported in wearing different clothes and caring for her hair instead of standing in pajamas all day. Since the feeling of staying in a foreign environment will increase the stress of the pregnant woman, she should be allowed to bring her familiar and loved things from her home to the hospital. Counseling should be given in a multidisciplinary approach to help the pregnant woman express her fears and provide psychological support (10). Nurses also take part in pharmacological treatments as well as providing psychological support to the pregnant woman hospitalized. Hypnotic agents, which are frequently prescribed for hospitalized high risk pregnant women, are not recommended for pregnant women due to their adverse effects on the fetus. If these agents are used in treatment, attention should be paid. Nurses should also perform their treatments with this awareness (3). Nurses should know that

Table 2. BETTER sleep program in hospitalized pregnant women with high-risk pregnancy

Hospital room	Light, noise and temperature in the room affect the pregnant woman's sleep. Try eye masks and earplugs for better sleep. White noise is very effective in blocking the corridor noise. If you have a private bathroom in the room, there might be a fan you can leave at night for a white sound source. Ask your nurse for a battery powered fan or sound machine. The fan also keeps you cool and helps relieve nausea. The sound machine should be at the lowest possible volume. Try the "wind" setting first, avoid water sounds (ocean, thunderstorm, rain) if you have frequent urination.
Exercise	Some daily activities are important for a good night's sleep. Ask your healthcare provider what physical activity is allowed. If you are at bed rest, you can consult your physical therapist about exercises you can do while in bed.
Stress	Ease your stress with relaxing activities in the evening to help you fall asleep. The relaxing activity can be reading a novel or solving a puzzle. Ask your nurse for reading material or a crossword book. Imagine lying on a sandy beach-feel the sun, rest your head on a beach towel, feel the hot sand on your legs and toes, listen to the waves. You can have a relaxation app you can try on your mobile phone or use the soothing options on your sound machine.
Time to try to sleep	You should give yourself the opportunity to sleep at least eight hours a night. Ask your nurse or doctor to put the "do not disturb" sign on the door of your room.
Eating and drinking	A light protein snack or warm milk can help you relax and sleep better. Have light foods like crackers, peanut butter, and yogurt at the bedside. Avoid using caffeine (chocolate, cola, coffee, tea) at night. Decaffeinated herbal tea can make it easier for you to fall asleep thanks to its soothing effect.
Rhythm	A consistent schedule for day/light and night/dark is essential for your brain's sleep chemistry and better sleep. Take some light from your window during the day. Avoid exposure to light at night. Ask your nurse to cover the monitors with a pad. Go to bed at the same times every day to sleep and wear your eye mask. Send signals to your brain that it's time to sleep, turn off your television, cell phone, and other unnecessary light sources when you're ready to go to sleep.

complementary therapies and behavioral approaches can be used in addition to pharmacological treatment in the treatment of high-risk pregnant women, and they should lead these practices to participate in the care process in cooperation with other health professionals (10). In the literature, Schlegel et al. (11) examined the effects of acupuncture, heat application and massage on pain and anxiety in hospitalized high-risk pregnant women, and it was found that the pain score was decreased from 84.5% to 61.4% and anxiety decreased by 70.9%.

Models/Theories That can be used in Optimal Care

Models/theories can be used in the care and management of high-risk pregnancy, which is a complex process. The most important purpose of using a model/theory is to obtain a harmonious whole from parts by establishing a relationship between concepts. Each conceptual model/theory reflects a different perspective on the nursing discipline and offers the researcher a different roadmap, framework and methodological rules (10). Models/theories used in the care and management of many diseases can be useful in strengthening the self-care of pregnant women in high-risk pregnancies, increasing maternal sensitivity, providing comfort, eliminating sexual problems, increasing maternal satisfaction, adaptation of the mother to the hospital and pain management. Orem's Self-Care Deficit Theory, Roy Adaptation Model, Rogers/Unitary Human Theory, Comfort Theory, Functional Health Patterns Model, PLISSIT Model and Pender's Health Promotion Theory are among the models/theories that can be used in the care and management of high risk pregnancies (12). Orem's Self-Care Deficit Theory includes helping the individual in situations where she/he has difficulty in meeting her/his own care needs. Orem's Self-Care Deficit Theory can be used in providing/maintaining self-care of high-risk pregnant women who need to stay in a hospital or are on bed rest at home (13). The purpose of the Roy Adaptation Model is to help the individual to behave in harmony during the health and illness processes. It may be useful in helping high-risk pregnant women to adapt to the process physiologically and psychologically (14). According to Rogers/Unitary Human Theory, the interaction in the field of environment and human is continuous, reciprocal, simultaneous and spontaneous. This theory can be used to adapt high-risk pregnant women who are hospitalized (15). The Comfort Theory expresses relief, relaxation and the ability of the individuals to overcome their problems, depending on the type of individual needs that are not met. This theory can be used to provide and maintain the comfort of pregnant women in high-risk pregnancies (16). The Functional Health Patterns Model is used to collect data from the patient about the disease and to organize the obtained information. The Functional Health Patterns Model can be used in the early diagnosis and treatment of high-risk pregnancies, in the management of the treatment process, and in the follow-up of pregnant women for whom home visits are planned (17). Sexual counseling provided by the PLISSIT Model enables high-risk pregnant women to cooperate with health professionals. The model based on understanding and respecting the beliefs, value judgments and decisions of the patient can be used to help the sexual problems of high-risk pregnancies (18). Pender's Health Promotion Theory aims to improve the health of the individual, to increase his/her control over improving his/her own health. In high-risk pregnancies, this theory can be used to include pregnant women in care and treatment and to maintain the acquired healthy lifestyle behaviors (19). In the literature, there is no finding about which model/theory is more effective in the care of high-risk pregnancies. It has been reported that the use of a model/theory for the needs of high-risk pregnant women is appropriate (17-19).

Patient Safety Practices

Patient safety is an important issue of quality in healthcare services and is one of the important indicators of providing qualified service. The purpose of patient safety is to prevent the harm caused by health care services to individuals and to create a suitable physical and psychological environment for patients, relatives and healthcare professionals by ensuring that employees take the necessary precautions (20). Hospitalized individuals experience problems about patient safety arising from identity errors, communication problems, errors arising from patient delivery and failure to comply with safe surgical steps, errors related to drug safety, falls, healthcare-related infections, errors caused by inappropriate and misuse of medical devices, errors due to patient transfer and medical errors. When high-risk pregnant women who have to stay in the hospital are exposed to other complications, especially problems caused by falls, both their and their babies' lives are threatened (21). In the literature, it is reported that if falls are not prevented, health care costs will increase due to complications arising from falls. It is estimated that the cost of fall injuries will be 55 million dollars annually until 2020 (22). Today, it is stated that the most common cause of non-obstetric maternal deaths is trauma during pregnancy, and the most common form of trauma is falling (25%) (23). This rate was found to be 54.9% in a study conducted in our country (24). The reason for hospitalization of approximately 24% of pregnant women due to injury during pregnancy is falls (25). In a study evaluating postural balance and falls during pregnancy, an increase was observed in falls due to impaired posture, especially in the third trimester (26). In a study conducted with working pregnant women, it was determined that 26.6% of 2847 pregnant women fell at least once during their pregnancy and 6.3% of these falls occurred in the workplace. Walking on slippery ground, carrying heavy objects, and being in a hurry were shown to be among the main causes of falls (27). These results reveal how common falls are a problem in pregnant women and the importance of patient safety in hospitalized high-risk pregnancies.

The Joint Commission International prepared a report for all healthcare professionals, including nurses, to reduce falls and ensure patient safety (22). It was stated in the report that every individual hospitalized in the hospital should be evaluated in terms of fall risk and individuals in the high risk group should be followed up more closely. In the report, it was emphasized that nurses should be sensitive to determine the risky group by filling the fall risk assessment scale developed for pregnant women in pregnancy outpatient clinics, maternal and child health centers, emergency or services where high-risk pregnant women were

hospitalized. A four-leaf clover symbol should be hung at the entrance of the room of pregnant women with high risk of falling. Hospitalized pregnant women should be informed about the use of the bed and about the location and use of the bathroom and call bell. When a pregnant woman wants to move or stand up, she should be informed about not getting up alone and asking for help from her nurse, and help with needs such as hygiene and toilet (28). In addition to these, nurses have responsibilities such as determining the history of falls, the risky drugs used, the balance status during pregnancy and the physical problems, raising awareness of the pregnant woman and her family about the risks of falling, and evaluating the data about falls. It is very important to determine the falling risks of high-risk pregnant women and to plan and implement appropriate interventions for these risks. Even if falls cannot be completely prevented, these scales should be used when diagnosing pregnant women, as falls can be reduced with effective protective measures and effective fall risk assessment scales (28).

Home Care and Mobile Applications

Providing health care in a natural environment at home allows the individual to feel more decisive in her/his life and at the same time to receive safer health care. Recent developments in information provision and communication technology have been used to increase the quality and speed of service delivery (29). Cockcroft et al. (30) examined the effects of home visits on maternal and infant health in 300 high risk pregnant women in a randomized controlled experimental study in Nigeria, which had the highest maternal mortality rates in the world. Three home visits were made during pregnancy and educational videos were used during the visits. As a result of the study, it was determined that in the group where home visits were organized, pregnancy and birth complications were less, benefiting from health services in one year after birth was more, and born children were healthier. In addition, higher level of knowledge, more use of health services, higher level of knowledge about pregnancy danger signs and higher rates of receiving home care were found in the group with home visits. It was determined that home trainings reduced the risk of preterm birth and facilitated learning about healthy lifestyle behaviors. In addition, home care reduced the duration and cost of hospital stay. In another study, it was determined that pregnant women who received home care in addition to routine prenatal care had fewer complications such as spontaneous premature rupture of membranes, preterm birth and hypertension compared to patients treated only in hospital. In addition to this, it was stated in the study that in home care services, healthcare providers would enable them to provide care in an environment where they could feel more comfortable and meet other family members. However, it was stated that today, the increasing workloads of healthcare professionals and developing new technologies emphasized the use of mobile health applications instead of constant home visits in home care of high-risk pregnancies (30).

World Health Organization defines mobile health (mHealth) as "Supporting public health and medical applications with personal digital devices, monitors, mobile phones and other mobile devices with wireless internet access" (31). Mobile health applications are used in many areas such as training of healthcare personnel and patients, follow-up of patients in the diagnosis and treatment process, protection and improvement of health, and storage of health data (32). In recent years, the increasing use of mobile phones and other technological tools and applications suggests that mobile health will be a force in improving maternal health services. During the prenatal period, the period in which mobile health applications are most frequently used is the pregnancy period. Mobile health applications are used to monitor and evaluate the health status of pregnant women and fetuses, to monitor high-risk situations occurring during pregnancy, to inform pregnant women about the pregnancy process and to gain healthy lifestyle behaviors (33). Tele ultrasound, Fetal Heart Rate Monitoring System/Mobile Integrated Doppler Device, The Pregnancy and Newborn Diagnostic Assessment (PANDA), Prenacell, telemedicine and telecare are among the most used mobile applications in the care of high risk pregnancies.

Tele Ultrasound

It is an up-to-date service useful in determining and preventing risk in high risk pregnancies. Examination with ultrasound in prenatal care has an important place in terms of fetus health and it maintains its importance from past to present. As a result of the ultrasound examination, an abnormality can be determined in the fetus, and findings regarding the continuation of the pregnancy can be revealed in genetic tests. However, access to ultrasound may not always be possible for all pregnant women. Pregnant women may have difficulties in accessing healthcare services, especially in rural areas due to transportation problems. Tele-ultrasound, which is one of the technological applications of today, enables a specialist doctor to evaluate the ultrasound from another location, especially in rural settlements and regions with insufficient resources (33).

Fetal Heart Rate Monitoring System/Mobile Integrated Doppler Device

The use of Non-stress Test (NST) devices is limited to the hospital environment. But today, it is possible to transfer instant data of the well-being of the fetus to the hospital database from mobile phone outside the hospital environment with the mDoppler device, without going to the hospital. The mDoppler device can be used from the 25th week, just like the NST devices used routinely (34).

The Pregnancy and Newborn Diagnostic Assessment (PANDA)

One of the applications that can be used in antenatal care of high risk pregnancies is PANDA, a mobile health application that evaluates pregnant women and newborns. This mobile application consists of four modules: Personal information, medical history, follow-up, health education and birth plan. Medical supplies such as thermometer, measuring tape, sphygmomanometer, urine kit, glucometer, stethoscope, rapid tests for screening HIV and syphilis, and gloves are included in the care bag (35).

Prenacell

In primary health care services, it is difficult for health service providers to include practices that improve health care services due to the workload. It has been reported in the literature that mobile applications such as SMS will be useful in the protection and improvement of health, in antenatal pregnancy follow-up and care. Prenacell is a mobile application designed to distribute content related to antenatal care, pregnancy and baby development via SMS. These SMS messages include antenatal care, pregnancy and delivery physiology, postpartum care and contraception, and psychological support during pregnancy and postpartum period (36).

Tele Medicine and Tele Care

Tele medicine is a technology that aims to improve the quality of patient care, increase access to medical care for rural and difficult-to-transport areas, and reduce patient transfer and treatment costs. Tele care is considered as a subcategory for tele medicine. In the field of perinatology, the purpose of using tele care is to identify problems in the early stages, to provide treatment recommendations to prevent further complications and preterm births, to improve the outcomes of high-risk pregnancies, to reduce the number of newborns hospitalized in the neonatal intensive care unit and to reduce the number of hospital visits. For example, the tele care short message service (SMS-based) can be used to care for diabetic pregnant women and better access to maternal and neonatal health services. In a study aiming to reveal the results regarding the care of high-risk pregnant women living in rural areas of Tanzania through home visits, it was found that the rate of receiving two or more cares from healthcare workers and giving birth in hospital was higher in the group that received care and support through messages sent to their smart phones (37).

Contribution of Mobile Applications to the Care of High Risk Pregnancies

Taking advantage of mobile health applications enables pregnant women to participate in their own health care practices and to ensure that the cost of care is effective. Benefiting from mobile health applications in the care of high-risk pregnancy, which is a complex and versatile process, facilitates the work of nurses who take an active role in every stage of care (38). Mobile applications in the field of nursing provide support in the care process of high-risk pregnancy by facilitating communication between healthcare professionals who cannot be found in the same place. It facilitates the monitoring and follow-up of high risk pregnant women who do not have a health unit nearby or who cannot reach the health unit for various reasons. Mobile health applications also ensure that the care and counseling services to be provided by nurses are standardized. In addition, with mobile applications, nurses can train their high-risk pregnant women, provide consultancy and provide a safe care with continuous communication (39).

Counseling and Health Education for Improving Maternal and Fetal Health in High Risk Pregnancies

The pregnancy process includes psychosocial, physiological, economic, educational and family structure changes that do not cause unwanted situations in most cases. Although the pregnancy process is a physiological event, the risks related to pregnancy continue until this period ends. Some women may have pregnancy complications and for this reason they have "high risk" compared to other pregnant women. For this reason, it is very important for pregnant women to pay attention to their own health and the health of their babies, even for pregnant women classified as "low risk" in order to detect the presence of pregnancy complications. If there is any risk during pregnancy, the risks should be detected early, necessary planning should be made and appropriate interventions should be taken. Risk management in high risk pregnancy should be a dynamic process, not a static process. Nurses have important responsibilities in determining the educational needs of high-risk pregnant women and providing education in this care process. Nurses should establish closer relationships with pregnant women in a multidisciplinary health team compared to other health professionals, and provide their care with a holistic and comprehensive approach (40). Nurses should guide and support high-risk pregnant women using plain and understandable language, and encourage high-risk pregnant women to ask questions during health education. In addition, a hospitable and safe communication environment should be provided in health education groups through in-depth focus group meetings (41).

In the care of high-risk pregnant women, an individualized systematic care should be planned, facilitating the adaptation of pregnant women to the hospital and coping strategies should be developed. The use of mobile applications in the care of high-risk pregnant women will increase the feelings of trust and privacy of pregnant women during the delivery process (42). Pregnant women who are planned to be hospitalized during pregnancy should be informed about the hospitalization, their concerns should be understood and solutions should be sought. This interaction will ensure that high-risk pregnant women establish a stronger bond with the healthcare team and feel safe for themselves and their babies. In addition, high-risk pregnant women included in the process will feel more self-confident with the awareness of taking responsibility. Therefore, in coping with high risk pregnancies, healthcare professionals should listen actively to pregnant women and include the pregnant woman and her family in the care process. High-risk pregnant women should be given as much information as possible about pregnancy, adequate nutrition, delivery, postpartum period, breastfeeding and neonatal care before delivery (43). Coping with the crisis caused by high-risk pregnancy, which is a complex and stressful process, is a very difficult situation for both the family and the pregnant woman. Nurses should learn about the coping mechanisms used by pregnant women and their families in the past, and they should aim to bring them new coping mechanisms. It should not be forgotten that in high-risk pregnancy, individualized care should be provided to the pregnant woman in hospital or at home.

Conclusion

Nurses, who take an active role in the health care team, have important roles in the care and management of high risk

pregnancies. Today's developing and changing scientific and technological applications also affect nursing care. Nurses are involved in the protection of health in preventive health services, in the implementation of treatment in therapeutic services and in the rehabilitation process. Providing and maintaining optimal care and patient safety is essential in preventive healthcare services in high-risk pregnancies. In this context, nurses should facilitate the communication of team members in a multidisciplinary team and aim for the pregnant woman to receive care in a safe environment. The nurse should follow the current literature as a curative service, be aware of the effects of drugs and inform the pregnant woman and her family. New technological applications can be used in home care of high risk pregnancies. Nurses should know mobile applications that can be used in the diagnosis and treatment of high risk pregnancies, and should include them in care as much as possible. Home care of high-risk pregnant women can be included in rehabilitative practices. The nurse should develop, implement and evaluate a home care plan by including the pregnant woman and her family in care. The nurse should provide psychological support to the pregnant woman and help her find activities that will make her feel good.

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References

1. Holness N. High-risk pregnancy. Nursing Clinics 2018;53:241-51.
2. World Health Organization. 2018. Available from: Maternal mortality. Available from: URL: http://www. who.int/mediacentre/factsheets/fs348/en/ (19.09.2019).
3. Majella MG, Sarveswaran G, Yuvaraj Krishnamoorthy KS, Arikrishnan K, Kumar SG. A longitudinal study on high risk pregnancy and its outcome among antenatal women attending rural primary health centre in Puducherry, South India. J Edu Health Promot 2019;8:12-9.
4. Eunice Kennedy Shriver National Institute of Child Health and Human Development. 2018. United States of America: National Institutes of Health.Available from: URL: https:// www.nichd.nih.gov/health/topics/high-risk/conditioninfo/pages/factors.aspx. (17.09.2019)
5. Lennon SL. Risk perception in pregnancy: A concept analysis. J Adv Nurs 2016;72:20-9.
6. Rubarth LB, Schoening AM, Cosimano A, Sandhurst H. Women's experience of hospitalized bed rest during high-risk pregnancy. J Obstet Gynecol Neonatal Nurs 2012;41:398-407.
7. Lee KA, Gay CL. Improving sleep for hospitalized antepartum patients: A non-randomized controlled pilot study. J Clin Sleep Med 2017;13:1445-53.
8. Errico D, Bicalho G, Oliveira D, Martins F. The work of nurses in high-risk prenatal care from the perspective of basic human needs. Rev Bras Fisioter 2018;71:1257-64.
9. Alves C, Castro M, Souza R, Lira S, Sampaio R, Pereira P. Group of high-risk pregnant women as a health education strategy. Rev Lat Am Enfermagem 2019;40:1-8.
10. Dagklis T, Tsakiridis I, Chouliara F, Mamopoulos A, Rousso D, Athanasiadis A, et al. Antenatal depression among women hospitalized due to threatened preterm labor in a high-risk pregnancy unit in Greece. J Matern Fetal Neonatal Med 2018;31:919-25.
11. Schlegel ML, Whalen JL, Williamsen PM. Integrative therapies for women with a high risk pregnancy during antepartum hospitalization. MCN Am J Matern Child Nurs 2016;41:356-62.
12. Okuyan Y, Tuna N, Can, HÖ. Theory and model based theses in midwifery practice areas. Life Sci 2018;14:20-9.
13. Rezaeean SM, Abedian Z, Latifnejad Roudsar R, Mazloom SR, Dadgar S. Application of Orem's theory for promotion of self-care behaviors of pregnant women at risk for preterm delivery: A clinical trial. IJOGI 2017;20:68-77.
14. Isbir GG, Mete S. Experiences with nausea and vomiting during pregnancy in Turkish women based on roy adaptation model: A content analysis. Asian Nurs Res 2013;7:175-81.
15. Reis PJ, Alligood MR. Prenatal yoga in late pregnancy and optimism, power, and well-being. Nursing Sci Q 2014;27:30-6.
16. Ünsan A. Hemşireliğin dört temel kavramı: İnsan, çevre, sağlık, hastalık, hemşirelik. Ahi Evran Sağlık Bilimleri Dergisi 2017;1:11-25.
17. Erbaş N, Demirel G. Kadın sağlığının değerlendirilmesinde bir model: Fonksiyonel sağlık örüntüleri. Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi 2016;5:84-91.
18. Uslu E, İnfal S, Ulusoy MN. Cinsel sorunların çözümünde Plissit modelinin etkisi. Psikiyatride Güncel Yaklaşımlar 2016;8:52-63.
19. Shin Y, Jang H, Pender NJ. Psychometric evaluation of the exercise self-efficacy scale among Korean adults with chronic diseases. Res Nurs Health 2001;24:68-76.
20. Korkmaz AÇ. Geçmişten günümüze hasta güvenliği. İnönü Üniversitesi Sağlık Hizmetleri Meslek Yüksek Okulu Dergisi 2018;6:10-9.
21. Bilgiç D, Şahin NH. Obstetride hasta güvenliği ve hemşirenin rolü. Turkiye Klinikleri 2018;4:118-30.
22. The Joint Commission International. National Patient Safety Goals Effective January 2019. Nursing Care Center Accreditation Program, 2019.p.1-9.
23. El Kady D. Perinatal outcomes of traumatic injuries during pregnancy. Clin Obstet Gynecol 2007;50:582-91.
24. Üstünyurt E, Akaltun C. Gebelikte minör travma: 173 olgunun değerlendirilmesi. J Clin Anal Med 2015;6:349-52.
25. Kuo C, Jamieson DJ, McPheeters ML, Meikle SF, Posner SF. Injury hospitalizations of pregnant women in the United States, 2002. Am J Obstet Gynecol 2007;196:161-6.

26. Inanir A, Cakmak B, Hisim Y, Demirturk F. Evaluation of postural equilibrium and fall risk during pregnancy. Gait Posture 2014;39:1122-5.
27. Dunning K, LeMasters G, Levin L, Bhattacharya A, Alterman T, Lordo K. Falls in workers during pregnancy: Risk factors, job hazards, and high risk occupations. Am J Ind Med 2003;44:664-72.
28. Oksel E. Düşmeye hemşire bakışı ve değerlendirilmesi. Ege Tıp Bilimleri Dergisi 2018;1:140-2.
29. Cockcroft A, Omer K, Gidado Y, Gamawa AI, Andersson, N. Impact of universal home visits on maternal and infant outcomes in Bauchi state, Nigeria: protocol of a cluster randomized controlled trial. BMC Health Serv Res 2018;18:510-21.
30. Rastegari Z, Yarmohammadian MH, Mohammadi F, Kohan S. A comprehensive home-care program for health promotion of mothers with preeclampsia: Protocol for a mixed method study. Reprod Health 2019;16:32-8.
31. Kay M, Santos J, Takane M. mHealth: New horizons for health through mobile technologies. World Health Organization, 2011.p.66-71.
32. Overdijkink SB, Velu AV, Rosman AN, Van Beukering MD, Kok M, Steegers-Theunissen RP. The usability and effectiveness of mobile health technology-based lifestyle and medical intervention Apps supporting health care during pregnancy: Systematic review. JMIR Mhealth Uhealth 2018;6:e109.
33. Nader Z, Sandlin AT, Kevin A, Barber M, Wendy N, Magann EF. Tele ultrasound how accurate are we?. J Ultrasound Med 2017;36:2329-35.
34. Yüksel MU. Fetal kalp hızı monitörizasyon sistemi (FKHMS) ve mobil entegre doppler (M-DOPPLER) (Yüksek Lisans Tezi). İstanbul: İstanbul Aydın Üniversitesi Fen Bilimleri Enstitüsü, 2017.
35. Borsari L, Stancanelli G, Guarenti L, Grandi T, Leotta S, Barcellini L, et al. An innovative mobile health system to improve and standardize antenatal care among underserved communities: A feasibility study in an Italian hosting center for asylum seekers. J Immigr Minor Health 2018;20:1128-36.
36. Ciabati L, Alves D, Barbosa-Junior F, Vieira EM, Souza JP. SISPRENACEL–mHealth tool to empower PRENACEL strategy. Procedia Comput Sci 2017;21:748-55.
37. Hackett K, Lafleur C, Nyella P, Ginsburg O, Lou W, Sellen D. Impact of smartphone-assisted prenatal home visits on women's use of facility delivery: Results from a cluster-randomized trial in rural Tanzania. PloS One 2018;13:e0199400.
38. Ngabo F, Nguimfack J, Nwaigwe F, Mugeni, C, Muhoza D, Wilson DR, et al. Designing and implementing an innovative SMS-based alert system (rapidSMS-MCH) to monitor pregnancy and reduce maternal and child deaths in Rwanda. Pan Afr Med J 2012;13:1-15.
39. Silva A, Mascarenhas A, Araújo M, Machado S, Santos D, Andrade R. Mobile technologies in the nursing area. Rev Bras Fisioter 2018;71:2570-8.
40. Chuang ST, Liu YF, Fu ZX, Liu KC, Chien SH, Lin CL, et al. Application of a smartphone nurse call system for nursing care. Telemed J E Health 2015;21:105-9.
41. Alves C, Castro EM, Souza R, Lira S, Sampaio R, Pereira P. Group of high-risk pregnant women as a health education strategy. Rev Lat Am Enfermagem 2019;40:1-7.
42. Pereira SB, Diaz G, Backes S, Ferreira L, Backes S. Good practices of labor and birth care from the perspective of health professionals. Rev Bras Enferm 2018;71:1313-9.
43. Gama SG, Viellas EF, Torres JA, Bastos MH, Brüggemann OM, Theme Filha MM, et al. Labor and birth care by nurse with midwifery skills in Brazil. Reprod Health 2016;13:123-32.

Case Report

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Report of a Case of Signet Ring Carcinoma Presenting as Gastric Mucosal Thickening: A Diagnostic Dilemma

Farklı Tanı Yöntemlerine Rağmen Teşhis Konulamayan Taşlı Yüzük Hücreli Karsinom- Olgu Sunumu

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ABSTRACT

The number of cancer cases has been increasing worldwide. Early diagnosis and tumor resection remain as the most effective treatments for gastric cancer. However, early diagnosis is not always possible as it is frequently not possible to make treatment decisions without pathologic diagnosis in patients with clinically suspected cancer. This causes delays in diagnosing cancer. We presented a 58 years old woman with gastric signet ring cell carcinoma that could not be diagnosed despite using four different methods of stomach biopsies. We aimed to emphasize that despite the use of advanced methods, if clinical cancer in non-diagnosed cases is suspected, we should be more aggressive for early diagnosis.

Keywords: Gastric mucosal thickening, diagnostic dilemmas, signet ring cell carcinoma

ÖZ

Kanser olgularının sayısı dünya çapında artmaktadır. Erken tanı ve tümör rezeksiyonu, mide kanseri için hala en etkili tedavi olarak kabul edilmektedir. Ancak erken tanı koymak her zaman mümkün değildir. Klinik olarak kanser şüphesi olan hastalarda patolojik tanı olmaksızın tedavi kararı vermek çoğu zaman mümkün değildir. Bu durum kanser teşhisinde gecikmelere neden olur. Dört farklı yöntem ile mide biyopsi yapılmasına rağmen tanı konulamayan 58 yaşında mide taşlı yüzük hücreli karsinom olgusunu sunduk. İleri yöntemler kullanılmasına rağmen, tanı konulamayan olgularda klinik kanser şüphesi varsa erken teşhis için daha agresif davranmamız gerektiğini vurgulamak ve çelişkilere dikkat çekmek istedik.

Anahtar Sözcükler: Gastrik mukozal kalınlaşma, tanı zorlukları, taşlı yüzük hücreli karsinom

Introduction

The number of patients diagnosed with early-stage gastric cancer increases with technology development, increasing access to medical system and level of consciousness in people (1). High-definition endoscopic technology and various sampling and histological processing methods are primary in the early diagnosis of cancer (2). However, challenging cases remain, and such cases lead to difficulties and uncertainty in the clinician's approach to diagnosis and treatment (3). Repeated biopsies and follow-ups to achieve diagnosis may reduce the chance of early treatment for these patients. We aimed to present a case with an increased thickness in the stomach wall wherein a definitive diagnosis could

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not be made despite multiple diagnostic methods. In this case, we ought to emphasize that more aggressive decisions should be made if a pathological diagnosis has not been attained despite the use of several different methods.

Case Report

A 58-year-old female patient was admitted to the outpatient clinic (İstanbul, Turkey) with history of abdominal bloating, constipation, and weight loss (20 kg) within 2 months. The patient did not have significant health problems until that time. Physical examination did not reveal any abnormality. Moreover, biochemical test and complete blood count results were within the normal range (Table 1). Abdominal sonography was unremarkable. At the first gastroscopy (January 30, 2017), an infiltrative lesion extending from the cardia to the antrum was detected (Figure 1). Multiple forceps biopsies were obtained. However, histology did not reveal malignancy in the first tissue samples taken. Despite these results, gastroscopy and endoscopic US (EUS) were planned due to the doubt of malignancy. In the EUS examination, the stomach wall was significantly thickened up to 13 mm. Physiologic layering of the wall was noted to disappear. Fine-needle aspiration was performed with a 19 G needle from several sites (Figure 2) (February 20, 2017). Histological sections of the second biopsies showed no evidence of lymphoid or other malignancies. There was no infiltrative pathology in the superficial submucosa in endoscopic mucosal resection (EMR) specimens. It was determined to be hypertrophic gastropathy characterized by an increase in inflammatory glands. However, the patient's laboratory (e.g., hypoalbuminemia, hypochlorhydria and eosinophilia) and clinical features (e.g., peripheral edema, anemia) were not characteristic of Menetrier's disease. A definitive diagnosis could not be made despite the second biopsy, and the patient had to be readmitted to the hospital. Contrast-enhanced upper abdominal computed tomography (CT) revealed diffuse thickening in the stomach wall at a thickness of 14 mm. The 18 fluorodeoxyglucose (FDG) positron emission tomography/CT (PET/CT) showed slightly increased FDG uptake (SUVmax, 7) in the cardia, fundus, and corpus regions of the stomach. No other hypermetabolic lesion was observed in any other site (Figure 3). The tumor markers such as AFP (1.93 ng/mL), CEA (0.90 ng/mL), and CA 19-9 (2.45 U/mL) were found to be within normal ranges. It was concluded that deeper biopsies should be carried out with EUS in the area with gastric mucosal thickening.

The patient underwent gastroscopy and EUS (03.20.2017) for the third time, and a 9-mm irregular thickening on the stomach wall was detected and smear and cell block were prepared by an aspiration with 19-Gauge needle. Histological examination reported no atypical cells in thick-needle biopsies taken for the third time. With the patient's consent, tissue biopsy including all endoscopic layers with the aid of an EUS was decided. The patient was readmitted and a full-layer-thickness biopsy was taken from the corpus of the stomach with duodenal endoscopic examination for the fourth time (May 8, 2017). The pathology revealed mucous epithelium in the superficial focal region, few glandular structures in the lamina propria, dense polymorphonuclear leukocytes among fibrin in a large area, and presence of inflammatory cells within the irregular muscle tissue and highlighted the absence of tumor cells (Figure 4). Re-evaluation of the specimens by two different pathologists did not change the result. Laparoscopic evaluation was recommended with the joint decision of a general surgeon, pathologist, hematologist, gastroenterologist, and oncologist. The patient was transferred for surgery, and total gastrectomy was performed. Frozen gastric resection material showed tumoral

Table 1. Laboratory results of the patient

Date	01.16.2017	03.14.2017	05.01.2017	Normal range
WBC (10*^{3}/uL)	6.1	4.82	9.9	4.6-10.2
Hgb (g/dL)	12.8	11.7	11	12.2-16.2
Hct (%)	37	32.3	32.3	35.5-48
Plt (10*^{3}/uL)	291	232	234	142-424
Glikoz (mg/dL)	95	94	103	70-105
AST (U/L)	11	10	11	5-34
ALT (U/L)	8	9	6	0-55
T. bilirubin (mg/dL)	0.73	0.23	0.29	0.2-1.2
Creatinine (mg/dL)	0.79	0.75	0.67	0.57-1.11
CRP (mg/dL)	0.07	<0.02	2.9	<0.5
ESR (mm/h)	19	10		0-20
Albumin (g/dL)	4.4	3.5	3.5	3.5-5
LDH (U/L)	159	134	142	125-220
Na (mmol/L)	138	139	137	135-145
K (mmol/L)	4.57	4.21	4.43	3.5-5.1
Ca (mg/dL)	9.6	8.9	8.5	8.4-10.2

WBC: White blood cell, Hgb: Hemoglobin, Hct: Hematocrit, Plt: Platelet, AST: Aspartate transaminase, ALT: Alanine transaminase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase

cells in signet ring morphology with a diffuse spread pattern and infiltrated appearance up to the serosa. Immunohistochemically, tumor cells were stained positively with pancytokeratin, and the final specimen finding was poorly differentiated signet ring cell adenocarcinoma of the stomach (Figure 5). The patient had an uncomplicated course after surgery and was then scheduled to receive chemotherapy.

Discussion

There are various difficulties in diagnosing stomach tumors at an early stage. Early diagnosis is difficult because majority of patients are asymptomatic. Sometimes, no laboratory abnormalities are detected in patients with dyspeptic complaints; hence, they are treated symptomatically and further tests are not performed (4). Despite the presence of dyspeptic complaints in our case, no pathology was detected in laboratory tests. However, since weight loss was one of the alarm symptoms, further examinations were immediately performed, and gastroscopy was performed to obtain biopsies from multiple lesion sites due to the preliminary differential diagnoses of Menetrier disease, lymphoma, or linitis plastica. Although it is common practice that the histopathological diagnosis is made with the first biopsy in most cases, we could not reach a diagnosis in this case; hence, EMR, multi-deep biopsy, and full-thickness biopsy were performed. The inability to make the diagnosis despite various methods used resulted in delay in taking decisions for prompt treatment in our case. The reason for this is that the treatment of each disease

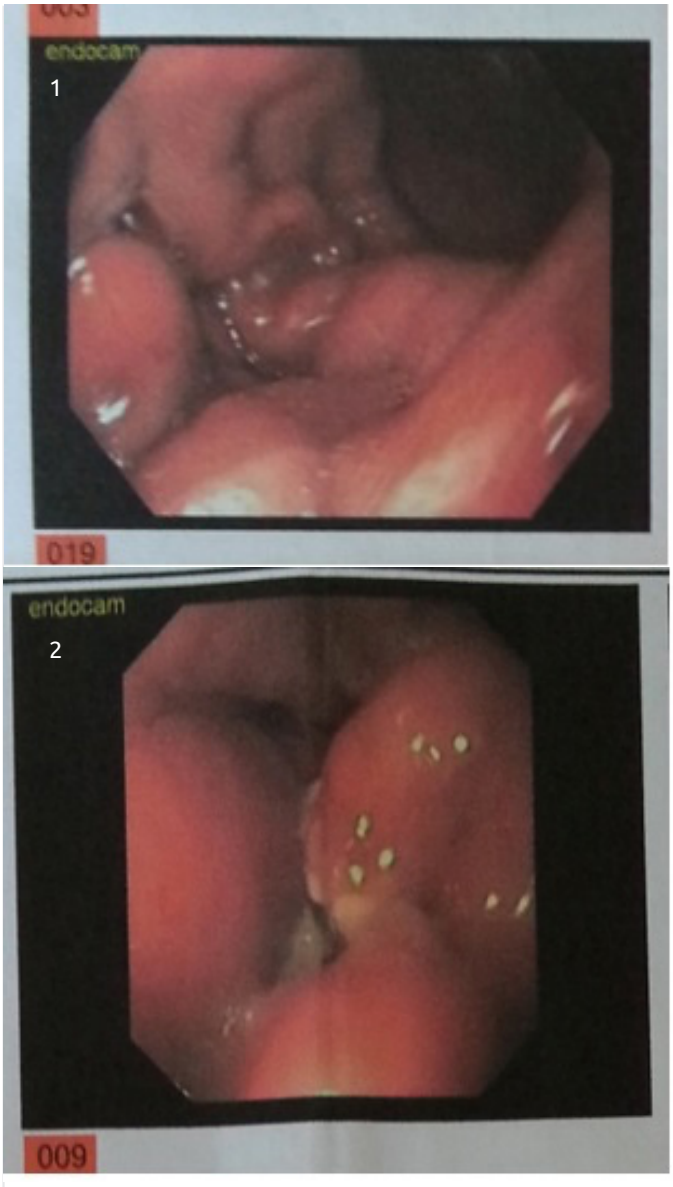

Figure 1-2. First gastroscopic image, second gastroscopic image

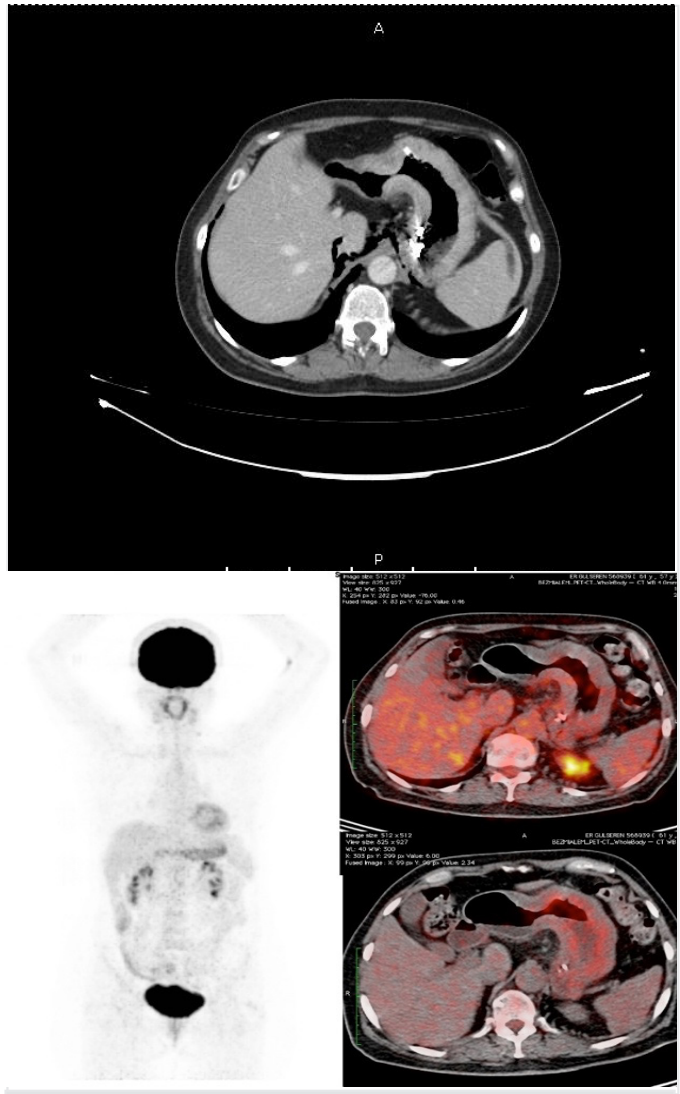

Figure 3. CT and 18 FDG PET/CT images: Contrast-enhanced upper abdominal CT revealed diffuse thickening in the stomach wall at a thickness of 14 mm. The 18 FDG PET/CT images of the patient showed diffuse thickening of the stomach wall showing a slightly increased FDG uptake (SUVmax, 7) in the fundus and corpus region of the stomach. No other hypermetabolic lesions were observed in the other regions of the body

CT: Computed tomography, PET/CT: Positron emission tomography/computed tomography, FDG: Fluorodeoxyglucose

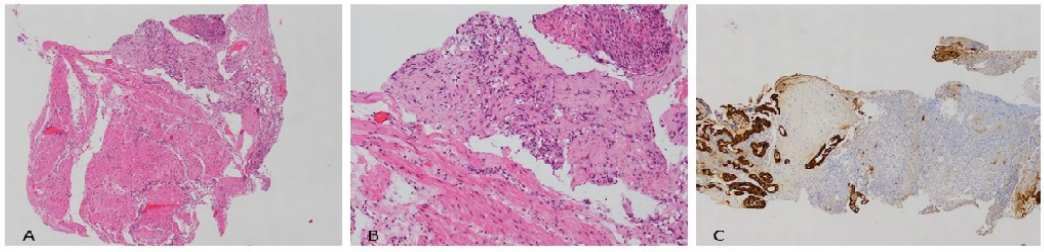

Figure 4. Inflammatory cell infiltration in the fibrin and muscle tissue (A,B-HEx100). Immunohistochemical examination pancreatin staining in surface epithelium and glands (C-HEx100)

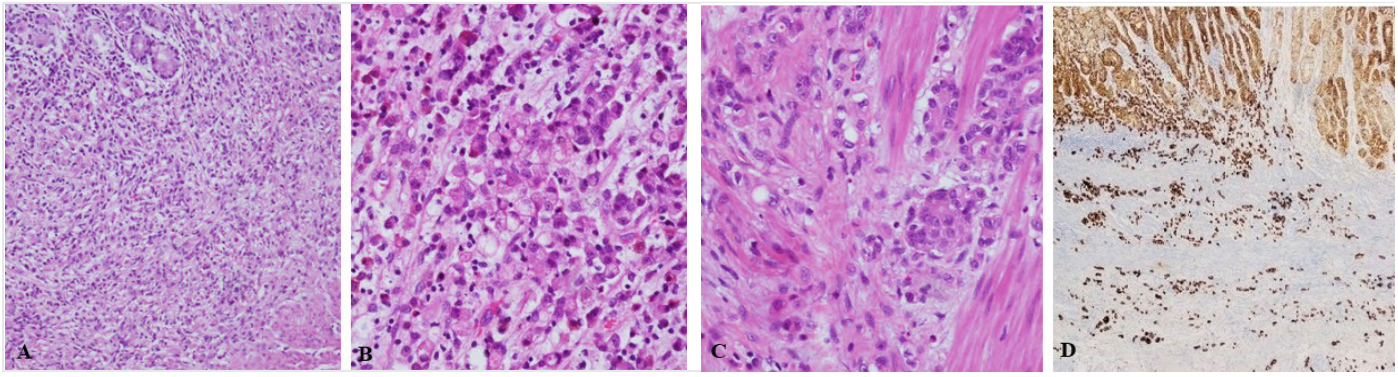

Figure 5. Signet ring cell carcinoma infiltration among inflammatory cells in the mucosa (A-HEx100, B-HEx200). In the muscle tissue, signet ring cells and carcinoma infiltration with glandular appearance (C-HEx200). Positive staining of individual infiltrated tumor cells within the mucosa and submucosa with pancytokeratin (D-HEx100)

differs according to the preliminary diagnosis. If the diagnosis is lymphoma, the treatment should be chemotherapy, radiotherapy, and immunotherapy, whereas the treatment for Menetrier's disease was different (5,6). If linitis plastica is determined as the preliminary diagnosis, surgery should be performed before spread to the lymph nodes and surrounding tissues occurs (7). It is difficult to convince the patients and their relatives to proceed with the operation due to the extensive nature of the surgery and it requiring a wide range of surgical margins and the lack of a pathological diagnosis. Similarly, a pathological diagnosis is warranted before surgery can be done.

Literature on pathologically undiagnosed gastric cancer is scarce. In a meta-analysis, the rate of missed diagnosis of gastric cancer was 10%. It was observed that the majority of patients with missed diagnosis were women under 55 years of age and the final diagnosis was adenocarcinoma. Our patient's case was consistent with that of this group and is compatible with this study (8). In a study from England, endoscopy results of those diagnosed with gastric cancer within 3 years before the diagnosis were screened, and it was found that in 8.3% of the patients, the diagnosis of gastric cancer was missed at endoscopy, and the most common diagnosis at a previous endoscopy was benign gastric ulcer (9). Despite this awareness of cancer, in our case, four different modalities of endoscopy were performed; however, a definitive diagnosis could not be reached. Our case is significant as to our knowledge, there is no similar case report in the literature.

These unknowns distress the clinician and the patient. In this case, although we were a reference hospital and endoscopy center, we could not attain a definitive diagnosis. We considered the lack of a guide in such challenging situations as a limitation.

In conclusion, there may be cases in which the diagnosis cannot be reached despite the use of advanced technology and experienced doctors. Intermittent follow-up in these cases may cause treatment delay and lead to cancer progression. Therefore, we suggest that more invasive interventions should be performed in cases wherein malignancy is suspected (especially in the presence of alarm symptoms/signs) and the diagnosis cannot be obtained with the usual diagnostic modalities.

Informed Consent: With the patient's consent, tissue biopsy including all endoscopic layers with the aid of an EUS was decided.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.A., H.Ş., Concept: C.K., Design: C.K., H.M.T., Data Collection or Processing: G.Ç., N.Ş., Analysis or Interpretation: A.A., H.Ş., G.Ç., N.Ş., H.M.T., Literature Search: C.K., H.M.T., Writing: C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Zhou Y, Abel GA, Hamilton W, Pritchard-Jones K, Gross CP, Walter FM, et al. Diagnosis of cancer as an emergency: a critical review of current evidence. Nat Rev Clin Oncol 2017;14:45-56.
2. Ngamruengphong S, Abe S, Oda I. Endoscopic Management of Early Gastric Adenocarcinoma and Preinvasive Gastric Lesions. Surg Clin North Am 2017;97:371-85.
3. Marin-Gabriel JC, Martos-Vizcaino E, Diaz-Tasende J, Alonso-Riano M, Perez-Carreras M, Rodriguez-Munoz S, et al. Endoscopic submucosal dissection (ESD) of antral subepithelial lesion suspected of malignancy. Rev Esp Enferm Dig 2015;107:380-3.
4. Hudler P. Challenges of deciphering gastric cancer heterogeneity. World J Gastroenterol 2015;21:10510-27.
5. Ikoma N, Badgwell BD, Mansfield PF. Multimodality Treatment of Gastric Lymphoma. Surg Clin North Am 2017;97:405-20.
6. Burdick JS, Chung E, Tanner G, Sun M, Paciga JE, Cheng JQ, et al. Treatment of Menetrier's disease with a monoclonal antibody against the epidermal growth factor receptor. N Engl J Med 2000;343:1697-701.
7. Agnes A, Estrella JS, Badgwell B. The significance of a nineteenth century definition in the era of genomics: linitis plastica. World J Surg Oncol 2017;15:123.
8. Pimenta-Melo AR, Monteiro-Soares M, Libanio D, Dinis-Ribeiro M. Missing rate for gastric cancer during upper gastrointestinal endoscopy: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2016;28:1041-9.
9. Chadwick G, Groene O, Riley S, Hardwick R, Crosby T, Hoare J, et al. Gastric Cancers Missed During Endoscopy in England. Clin Gastroenterol Hepatol 2015;13:1264-70e1.