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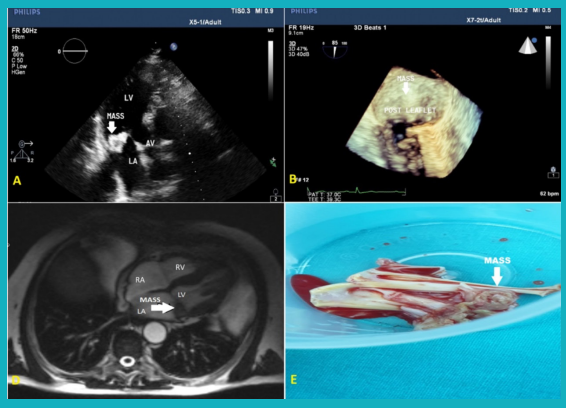

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2. Presentations in image / static image format: JPG, GIF, TIFF, BMP

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4. The file size should be a maximum of 100 MB.

5. The file size should be no more than 10 minutes.

6. Main text should not exceed 500 words.

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9. There should be no identification of patient / physician / institution / city / country in pictures and especially video images.

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Book Section: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine.St Louis: Mosby; 1974.p.273-85.

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CONTENTS

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CONTENTS

BEZMIALEM VAKIF UNIVERSITY 1845

BEZMİÂLEM science

EDITORIAL

Dear readers,

We are here with the first issue of the new year. As we mentioned in our previous issue, we would be here with 6 issues in 2022. On this occasion, we will bring you more research articles. Although the increasing demand recently and the high number of articles sent to us make us happy, they have increased our rejection rates. In order to be able to publish more of your articles, we rearranged the number of our publications as every two months and increased our annual number of publications to 6 issues. In addition, we will have 2 special issues. As a university, we attach great importance to the participation of our students in scientific studies and turning of their studies to publications. One of these issues will be consisted of the studies presented in our university student congress. Our other issue, as I have announced before, will be technology-oriented and will cover studies on scientific technology. I would like to remind you that if you have existing patents, there will be an opportunity to publish them.

We chose the cover art for this issue from the article titled “Cardiac Calcified Amorphous Tumor Presenting with Thromboembolism in a Patient Under Apixaban Treatment” by Çınar T. and his colleagues. If you have original images, we both publish them and choose one of them for our cover.

We are very happy to be together once again with beautiful topics in this issue. “Correlation of Body Composition Analysis with Anthropometric Measurements in Peritoneal Dialysis Patients” by Artan et al., “Investigation of The Effectiveness of Plant Based Algan Hemostatic Agent in a Rat Model of Femoral Arterial Bleeding” by Ekici, and “Evaluation of Patients’ Awareness Levels Regarding Implant And Implant-Supported Prosthesis Who were Admitted to Bezmialem Vakıf University Faculty of Dentistry” by Davut et. are our featured articles in this issue.

Dear readers,

Scientific developments continue to be a beacon of hope against the negativities experienced in the world. We understand once again that it is important to continue scientific studies even during periods of widespread disease and pandemic, and that scientific solutions to problems must be found. This pandemic period has once again proven that science without evidence is worthless. We must continue and we do continue our educational and scientific studies for the coming days and a livable world.

On this occasion, I congratulate your New Year and wish it to be a blessing for our country and our world. All the best, see you again in our next issue.

Best regards,

Prof. Dr. Adem AKCAKAYA
Editor-in-Chief

Comentary

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Staging Laparoscopy in Stomach Cancer
Mide Kanserinde Evreleme Laparoskopisi

Adem AKÇAKAYA

Bezmialem Vakıf University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

Dear Colleagues,

In this issue, I will talk about a method that surgeons dealing with gastric cancer (GC) have to resort to in order to detect the spread to the peritoneum, which they see as a problem despite advances in technology and imaging methods: Diagnostic laparoscopy for staging in GC.

GC is an important health problem worldwide and the only curative treatment is surgery. It has been reported that the morbidity can reach 39% in GC surgery, and it is considered a high-risk surgery in Europe and other Western countries. Therefore, surgical planning and postoperative follow-up are of great importance (1) The right surgical intervention for the right patient and the planning of neoadjuvant chemotherapy (NAC) for the necessary patients play an important role in determining the patient's survival. For which patients the diagnostic laparoscopy will be applied in the staging used for this purpose and the timing of the surgery planning are still controversial.

Staging laparoscopy has been included in the diagnostic methods in advanced GC for years. Some treatment guidelines even recommend doing it routinely before surgery. When we look at its historical development, we see that there are different opinions (1,2). Some surgeons state that there is no need for laparoscopy since a significant portion of the patients will require palliative surgery (3). The majority of the surgeons states that it is beneficial. Diagnostic laparoscopy in GC allows imaging of the peritoneum and organs. Peritoneal spread, ascites, mesenteric or omental spread can be diagnosed with computed tomography, but the diagnostic accuracy is low (4). The rate of diagnosis can be increased with laparoscopy. It also allows taking samples for cytological examination. Detection of peritoneal spread changes the surgical approach because it means a jump in the phase of the disease. These patients are considered as having stage 4 disease and if there are no signs of bleeding or obstruction, systemic chemotherapy is given priority.

It was shown that peritoneal spread was more common in tumors in the esophagogastric region, in those involving the entire stomach, in those with lymphadenopathy (LAP) on computed tomography, in poorly differentiated adenocarcinomas, and in tumors of T3-T4 stage. The rate of peritoneal involvement was found to be statistically significantly higher in patients with esophagogastric or whole stomach involvement and in patients with LAP detected by using imaging methods (2). In another study, a significant difference was found in tumors larger than 4 cm (5).

Although laparoscopy is a more invasive method than some imaging methods, it has advantages such as detection of 5 mm or smaller metastases that cannot be demonstrated by other methods, evaluation of peritoneal surfaces, liver surface and lymph nodes, and taking samples for peritoneal cytology in terms of micrometastases. Our experience in these patients has shown that although they are defined as having locally advanced disease in imaging methods, peritoneal involvement may not be detected in some patients (6). As a matter of fact, peritoneal metastasis is detected in approximately 20-30% of patients with GC, although there is no finding on imaging. In a study conducted by the Memorial Sloan Kettering Cancer Center, 657 patients with potentially resectable gastric adenocarcinoma underwent laparoscopic staging over a 10-year period and metastatic disease was detected in 31% of the patients (7,8). The risk of occult peritoneal metastasis is higher especially in surgical stage (T4) tumors of advanced gastrointestinal system cancers and in patients with the appearance of linitis plastica (9). Staging laparoscopy to be performed in these patients will increase morbidity in a significant part of the patients and will prevent radical surgical interventions that will not contribute to survival. In a study evaluating the diagnostic contribution of additional PET/CT and diagnostic laparoscopy in patients with locally advanced disease (T3-4 or N+) detected by standard staging methods, endoscopic ultrasound (EUS) and high-resolution CT, and without distant

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metastasis findings; distant metastases were detected by using PET/CT in 10% of patients, and peritoneal metastases were detected in 19% by using laparoscopy (10). Diagnostic laparoscopy can be used for accurate staging and treatment in patients who are thought to have T2 or more advanced lesions with EUS, who do not have evidence of stage 4 disease, who do not need palliative gastrectomy due to local symptoms, and who are planned for neoadjuvant treatment. It is helpful in choosing the most appropriate treatment.

Patient selection for laparoscopy is still controversial. According to the results of the REGATTA trial, palliative gastrectomy should not be performed in patients with peritoneal invasion. Therefore, staging laparoscopy is recommended to detect peritoneal spread during laparoscopy, to avoid non-therapeutic laparotomy, and to shorten the time to initiation of chemotherapy (11).

In a study conducted in Japan (JCOG0405), staging laparoscopy was made to detect occult peritoneal involvement. If LAP and paraaortic lymph nodes were detected in the patients, extended surgery was performed after NAC (12). Peritoneal involvement was reported to be positive in 21% of this patient group. In these patients, restaging laparoscopy was performed to decide on surgery after chemotherapy. In another study in Japan, the false negative rate was reported to be 10%. This rate varied between 0-17% in different publications (2). In order to reduce this rate, careful exploration was recommended. In the publications recommending repetitive laparoscopy after chemotherapy applied after the first staging laparoscopy, positivity was detected in 12% of the patients, and there were some who stated that repeated staging laparoscopy was more beneficial in poorly differentiated tumors and linitis plastic (13). It was also stated that the survival of these patients was not good, although they responded well to neoadjuvant treatment.

In practice, the entire abdomen and the bursa omentalis should be explored. A good exploration will reduce false negative rates. When the results of the Japanese groups and Western countries are compared in the studies, it is seen that the false-negative rates are lower in Western countries, and it is stated that the reason for this is indications for laparoscopy (2).

Laparoscopy is also used for the evaluation of tumor resectability and is superior to other radiological methods in this respect (4). The most important problem is to determine when laparoscopic staging is necessary and to decide on its timing. There is no clear consensus on whether it should be performed immediately before surgery or as a separate intervention. However, in patients with more advanced disease (T3, T4 or linitis plastica), laparoscopy is required before laparotomy to rule out occult intraperitoneal metastases. In this way, it was reported that it was possible to avoid unnecessary laparotomy in almost 60% of the patients (1,9).

Staging laparoscopy is considered a safe procedure that is performed under general anesthesia in an average of one hour. Intestinal injury was reported in some publications. It was reported that this rate was quite low and around 0.4% (2).

In conclusion, diagnostic laparoscopy for GC staging is useful in detecting occult metastases. Cytological testing of peritoneal fluid allows identification of occult carcinoma. Chemotherapy provides a statistically significant improvement in survival in patients with positive cytological tests. If there is no bleeding or obstruction in patients with positive peritoneal cytology, the role of surgery is unclear and chemotherapy should be prioritized. The patient group to be selected should include patients with T3 and/or N+ tumors detected in preoperative imaging. In this way, it will be possible to detect occult metastatic disease. The timing of laparoscopy is slightly different from the West in our country, considering the density of our hospitals. Patients should be planned before curative surgery and surgery should be performed if appropriate.

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Original Article

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Correlation of Body Composition Analysis with Anthropometric Measurements in Peritoneal Dialysis Patients

Periton Diyalizi Hastalarında Vücut Kompozisyonu Analizi ile Antropometrik Ölçümlerin Korelasyonu

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ABSTRACT

Objective: This study investigates correlations between different methods for diagnosis of protein energy malnutrition (PEM) in peritoneal dialysis patients.

Methods: Twenty four patients were included. Patients with amputations, infections, peritonitis, malignancies and PD duration less than three months were excluded. Physical examination findings, laboratory results and anthropometric measurements were recorded. Body composition analysis was performed with multi-frequency bioimpedance analyzer. Dialysis malnutrition score (DMS) was calculated. The correlations of different parameters were searched.

Results: Eleven patients were female and 13 patients were male. Mean age was 58.9±12.6 years. Median dialysis duration was 25 (interquartile range: 14) months. Protein percentage was negatively correlated with fat percentage (r=-0.785; p<0.001), triceps skinfold thickness (SFT) (r=-0.641; p<0.001), biceps SFT (r=-0.685; p<0.001), body mass index (BMI) (r=-0.867; p<0.001), mid-arm circumference (r=-0.680; p=0.001). Fat percentage was positively correlated with BMI (r=0.780; p<0.001), biceps SFT (r=0.817; p<0.001), triceps SFT (r=0.901; p<0.001) and mid-arm circumference (r=0.558; p=0.005)

Albumin was negatively correlated with DMS (r= -0.439; p=0.032). DMS and albumin were not correlated with bioimpedance and anthropometry.

Conclusion: Albumin is a marker of PEM in PD patients. Malnutrition scores may be used as adjunct methods. Increase

ÖZ

Amaç: Çalışmada, periton diyalizi (PD) hastalarında protein enerji malnütrisyonu değerlendirmesinde kullanılan yöntemlerin birbiriyle korelasyonunun araştırılması amaçlandı.

Yöntemler: Çalışmaya 24 hasta alındı. Ekstremite ampütasyonu, enfeksiyon, peritonit, aktif malignite ve PD süresinin üç aydan kısa olması dışlanma kriteri sayıldı. Fizik muayene bulguları, laboratuvar verileri ve antropometrik ölçümler kaydedildi. Multi-frekans biyoempendans ile vücut kompoziyon analizi yapıldı. Diyaliz malnütrisyon skoru (DMS) hesaplandı. Farklı parametrelerin birbirleriyle korelasyonu incelendi.

Bulgular: Hastaların 11'i kadın, 13'ü erkekti. Ortalama yaş 58,9±12,6 yıl, ortanca diyaliz süresi ise 25 (çeyreklerarası aralık: 14) aydı. Protein oranı; yağ oranı (r=-0,785; p<0,001), triseps deri katman kalınlığı (DKK) (r=-0,641; p<0,001), biseps DKK (r=-0,685; p<0,001), vücut kitle indeksi (VKİ) (r=-0,867; p<0,001) ve orta kol çevresi (r=-0,680; p<0,001) ile negatif koreleydi. Yağ oranı; biseps DKK (r=0,817; p<0,001), VKİ (r=0,780; p<0,001), triseps DKK (r=0,901; p<0,001) ve orta kol çevresi (r=0,558; p=0,005) ile pozitif koreleydi. Albümin, DMS (r=-0,439; p=0,032) ile negatif korele bulundu. DMS ve albümin düzeyinin biyoempedans tekniği ve antropometrik ölçümler ile anlamlı bir korelasyonu saptanmadı.

Sonuç: Albümin periton diyaliz hastalarında malnütrisyon göstergesidir. Malnütrisyon testleri, serum albümin düzeyine ek yardımcı yöntem olarak kullanılabilir. Periton diyaliz hastalarında yağ kitlesi ve yağ oranının artışı antropometrik ölçümlerin yorumunu etkileyebilir.

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in fat mass and percentage may influence the interpretation of anthropometric measurements.

Keywords: Anthropometric measurements, dialysis malnutrition score, multi-frequency bioimpedance analysis, peritoneal dialysis, protein energy malnutrition, serum albumin

Anahtar Sözcükler: Antropometrik ölçümler, diyaliz malnütrisyon skoru, multi-frekans biyoimpedans analizi, periton diyalizi, protein enerji malnütrisyonu, serum albümin

Introduction

Protein energy malnutrition (PEM) is a common complication in dialysis patients. Malnutrition is associated with deterioration in quality of life, increased morbidity, cardiovascular and infection-related mortality and total mortality (1). According to one view, underlying comorbidities and inflammatory processes are responsible for both malnutrition and increased morbidity and mortality (2). According to another view, inflammation and malnutrition are independently associated with cardiovascular and all-cause mortality (3). According to the International Society of Renal Nutrition and Metabolism, diagnostic criteria for PEM are as follows: Biochemically; low serum albumin (<3.8 g/dL) or prealbumin (<30 mg/dL) or total cholesterol (<100 mg/dL), in terms of body mass; low body mass index (BMI) (<23 kg/m^2) or decreased body fat (<10%) or unintended weight loss (more than 5% in 3 months), in terms of muscle mass; reduction in muscle mass (more than 5% at 3 months) or lower middle arm muscle circumference or reduction in protein equivalent of nitrogen appearance (PNA); in terms of dietary intake; involuntary insufficient protein or energy intake. PEM is diagnosed with the presence of at least 3 of these criteria (4).

According to the latest data, the frequency of PEM varies between 28% and 60% in hemodialysis and peritoneal dialysis (PD) patients (1). Malnutrition may develop due to many factors in patients with end-stage renal disease. Among the identified causes are; loss of appetite due to uremia, decrease in dietary calorie intake, dietary restrictions, chronic inflammation, proteinuria, other comorbid diseases, and the dialysis process itself, which causes loss of amino acids and proteins (5).

Due to its clinical importance, malnutrition should be carefully monitored. With early diagnosis, progression of malnutrition and muscle wasting are prevented. Many methods are used for clinical diagnosis. Among them; clinical evaluation, weight monitoring, biochemical tests (serum albumin, prealbumin, creatinine and lipid levels), and anthropometric measurements can be counted in the first stage (6). There are also various questionnaires evaluating malnutrition. Among them, subjective global assessment (SGA), malnutrition inflammation score (MIS), dialysis malnutrition score (DMS) also called modified-SGA(m-SGA) score, and mini-nutritional assessment (MNA) (7). Dual energy X-ray absorptiometry and multi-frequency bioelectrical impedance analysis are also among the available. methods that can be used for diagnostic purposes (5). None of these methods is sufficient alone in the detection of malnutrition. The methods have been used in various combinations.

In our clinic, monthly albumin and C-reactive protein (CRP) measurements and anthropometric measurements are performed every six months in the malnutrition evaluation of PD patients. Patients' complaints such as loss of appetite and weight loss are taken into account in this evaluation.

In this study, we aimed to investigate which methods gave more accurate results in the cross-sectional evaluation of malnutrition in PD patients. We applied anthropometric measurements, bioimpedance analysis, biochemical parameters and DMS test together in our patients and investigated the relationship between the methods.

Method

Our study was approved by the ethics committee of our university (ethics committee file number: 22/420), and the principles stated in the Declaration of Helsinki were complied with. Written and verbal consent was obtained from all patients.

Patient Selection: The study included 24 patients followed up in the PD outpatient clinic, either in the automated PD or continuous ambulatory PD program. Patients who refused to give written consent, patients with limb amputation, active infection, peritonitis or active malignancy, and patients with dialysis duration shorter than three months were excluded. Patients with cured malignancy or in remission in terms of malignancy were included in the study.

Study Parameters: Demographic and physical examination findings: Age, gender, duration of dialysis, primary kidney disease and comorbidities of all patients were recorded. Physical examinations were performed, systolic and diastolic blood pressures were recorded, and the presence of edema was evaluated.

Laboratory parameters: Daily urine amount (mL/day), proteinuria amount (mg/day), albumin (g/dL) and CRP (mg/L) levels were measured. The kt/V value as an indicator of dialysis adequacy, and normalized protein catabolic rate (nPCR) were recorded as an indicator of protein catabolism.

Anthropometric Measurements: All anthropometric measurements were made by the same investigator from the nondominant side and repeated twice. Mid-arm circumference was measured with a tape measure, and triceps and biceps skinfold thicknesses (SFT) were measured using a "skinfold caliper".

DMS or m-SGA: The m-SGA scores of all patients were calculated using the form developed by Kalantar-Zadeh (8,9). In this scoring system, which is developed based on the SGA test, 7 criteria are evaluated with scores ranging from 1 to 5.

These criteria are weight loss, dietary intake, gastrointestinal symptoms, functional capacity, decreased fat stores on physical examination or signs of decreased subcutaneous fat and muscle wasting in the last six months. One point is considered normal and five points are considered severe malnutrition. Final scoring is done with the sum of the 7 components. The score obtained varies between 7-35. Seven points represent normal nutritional status and 35 points represent severe malnutrition (8,9).

Body Composition Analysis: Body composition analysis was performed with the TANITA MC 780 (Tanita Corporation, Tokyo, Japan). This technique performs bioimpedance analysis using 6 frequency currents (multi-frequency BIA-MF BIA). Basal metabolic rate, total body water and percentage (%), fat mass, fat percentage, muscle mass, muscle percentage, bone mass, protein percentage were measured and recorded.

Statistical Analysis

The distribution of the data was analyzed with the Shapiro-Wilk test. The relationship between numerical variables was examined by Spearman Correlation analysis. Descriptive statistics of the data were given as n (%) for categorical variables, and as median (interquartile range) for non-normally distributed numerical variables. All statistical analyzes were analyzed and reported at the α=0.05 significance level in the IBM SPSS Statistics 22.0 program.

Results

Twenty-four patients were included in the study, of whom 11 were female and 13 were male. The mean age was 58.9±12.6 years, and the median dialysis time was 25 months (interquartile range: 14).

Primary kidney disease was diabetic nephropathy in 5 (20.8%) patients, autosomal dominant polycystic kidney disease in 3 (12.5%) patients, chronic glomerulonephritis in 3 (12.5%) patients, and nephrosclerosis in 2 (8.3%) patients. Urological causes were present in 1 (4.2%) patient and the etiology was unknown in 10 (41.7%) patients.

Of the patients, 21 (87.5%) had hypertension, 9 (37.5%) diabetes mellitus, 7 (29.2%) hyperlipidemia, 7 (29.2%) coronary artery disease, and 4 (16.7%) had a history of malignancy. Two patients had untreated prostate cancer, 1 patient had cured laryngeal cancer, and 1 patient had breast cancer in remission with ongoing hormonal therapy. There was no patient with metastatic malignancy.

The median systolic and diastolic blood pressures were 120 mmHg (IRQ: 28) and 80 mmHg (IRQ: 28), respectively. While 8 patients were using one type of antihypertensive drug, 9 patients were using 2 drugs, and 5 patients were using 3 drugs. Two patients did not need antihypertensive medication. Edema was detected in 6 patients.

Demographic and clinical characteristics, physical examination findings, and laboratory tests of the patients are summarized in Table 1.

The median albumin level was 3.6 (IRQ: 0.5)g/dL, it was ≤3.5 g/dL in 7 (29.2%) patients, 3.6-4 in 14 g/dL (58.3%) patients, and >4 g/dL in 3 (12.5%) patients. The median CRP level was 3.25 mg/L (IRQ: 7.63) and was above the reference values in 9 patients. The median urine volume was 905 mL/day (IRQ: 646), and the median proteinuria was 327.88 mg/day (IRQ: 944.88). The median weekly creatinine clearance, median kt/V, and median nPCR were 67.46 mL/min (AUC: 25.82), 2 (IRQ: 0.66) and 0.76 g/kg/day (IRQ: 0.29), respectively.

The median BMI was 28.30 kg/m2 (IRQ: 9.25). The median middle arm circumference was 28.50 cm (IRQ: 6.75). Median

Table 1. Demographic, clinical characteristics and physical examination and laboratory findings of the patients
***given as median and interquartile range**

	Patients n=24
Age (mean, standard deviation)	58.9±12.6
Gender (female)	11/24
Dialysis time*	25 (14)
Etiology of chronic kidney disease (%)	20.8% diabetic nephropathy, 12.5% autosomal dominant polycystic kidney disease, 12.5% chronic glomerulonephritis, 8.3% nephrosclerosis, 4.2% urological causes, 41.7% unknown etiology,
Hypertension (%)	87.5
Diabetes mellitus (%)	29.2
Coronary artery disease (%)	29.2
Malignancy (%)	16.7
Systolic blood pressure* (mmHg)	120 (28)
Diastolic blood pressure* (mmHg)	80 (10)
Edema (%)	25
Albumin* (g/dL)	3.60 (0.50)
CRP* (mg/L)	3.25 (7.63)
Urine volume* (mL/day)	905 (646)
Proteinuria* (mg/day)	327.88 (944.88)
Creatinine clearance* (mL/min)	67.46 (25.82)
Kt/V*	2 (0.66)
nPCR*(g/kg/day)	0.76 (0,29) g/kg/day
Body mass index* (kg/m^2)	28.30 (9.25)

CRP: C- reactive protein

biceps and triceps SFTs were measured as 10 mm (IRQ: 12.25) and 16 mm (IRQ: 18.50), respectively. The median DMS score was 11 (IRQ: 4.75); while it was normal in 16 (66.7%) patients, it was compatible with moderate malnutrition in 8 (33.3%) patients.

Body composition analysis results are presented in Table 2.

Correlation Analysis Results: Muscle mass was positively correlated with bone mass (r=0.970; p<0.001) and fluid percentage (r=0.514; p=<0.010); and it was negatively correlated with fat percentage (r= -0.462; p=0.023) and Kt/V (r= -0.612; p=0.001).

Protein percentage was positively correlated with fluid percentage (r=0.681; p<0.001), and it was negatively correlated with fat percentage (r=-0.785; p<0.001), fat mass (r=-0.833; p<0.001), triceps SFT (r=-0.641; p<0.001), biceps SFT (r=-0.685; p<0.001), BMI (r=-0.867; p<0.001), and middle arm circumference (r=-0.680; p=0.001).

Fat content was negatively correlated with fluid percentage (r=-0.867; p<0.001), and it was positively correlated with protein percentage (r=-0.833; p<0.001); BMI (r=0.940; p<0.001), biceps SFT (r=0.874; p<0.001), triceps SFT (r=0.855; p<0.001), and middle arm circumference (r=0.705; p<0.001) .

Fat percentage was negatively correlated with fluid percentage (r=-0.977; p<0.001), and it was positively correlated with BMI (r=0.780; p<0.001), biceps SFT (r=0.817; p<0.001), triceps SFT (r=0.901; p<0.001) and mid-arm circumference (r=0.558; p=0.005).

Albumin level was positively correlated with creatinine clearance (r=0.561; p=0.004) and urine volume (r=0.566; p=0.004), and it negatively correlated with age (r=-0.464; p=0.022) and DMS score (r=-0.439; p= 0.032).

Table 2. Bioimpedance analysis results

	Mean ± standard deviation
Bone mass (kg)	2.78±0.40
Fat mass (kg)	22.94±9.77
Fat percentage (%)	28.86±9.43
Liquid amount (kg)	38.93±6.78
Liquid percentage (%)	50.38±6.71
Muscle mass (kg)	52.12±8.55
Protein percentage (%)	16.16±2.70

The nPCR level was positively correlated with kt/V (r=0.617; p=0.001) and proteinuria (r=0.494; p=0.014). The relationship between classification according to albumin level and nutritional assessment according to DMS is presented in Table 3.

There was no significant correlation of DMS with bioimpedance technique and anthropometric measurements. There was no significant correlation of albumin level with bioimpedance technique and anthropometric measurements.

Discussion

Malnutrition is an important complication of end-stage renal disease (ESRD) and a marker of mortality. Detection of weight loss, anthropometric measurements, evaluation of biochemical markers such as serum albumin and prealbumin level are used in the diagnosis (6). In our study, a negative correlation was found between DMS and albumin level. DMS and albumin levels were not associated with body composition analysis and anthropometric measurements. SFT and middle arm circumference were found to be associated with the amount and percentage of fat, and they were found to be negatively correlated with the protein percentage.

It has been shown that albumin level is a strong marker of malnutrition in patients with ESRD (10). However, there are some limitations in clinical use. Since albumin is also a negative acute phase protein, it is decreased in inflammatory states. In addition, it is affected by many factors such as its loss in urine and dialysate, and its decreased synthesis, and these factors reduce the power of albumin level in the assessment of malnutrition (4,11).

The mean albumin level of our patients was found to be 3.62±0.33 g/dL. In our study, a negative correlation was found between DMS and albumin level (r=-0.439; p=0.032). The patients with normal albümin level also had normal nutritional status when evaluated according to the DMS. It can be interpreted that the albumin level and DMS are in parallel.

The median CRP level was found to be 3.25 mg/L (IRQ: 7.63). Since the CRP level was within normal limits in 62.5% of the patients and patients with acute infection or active malignancy were excluded, it was thought that serum albumin level was less affected by the inflammatory state in our study and gave a sufficient result in reflecting malnutrition in this respect.

DMS is an adaptation of the SGA developed by Kalantar-Zadeh in 1999. In a study conducted with 41 patients, it was found that DMS showed statistically significant negative correlation

Table 3. Relationship between albumin levels and nutritional status assessed by dialysis malnutrition score

		Nutritional status by dialysis malnutrition score		
		Normal nutritional status	Moderate malnutrition	Total
Albumin level	<3.5	3 (43%)	4 (57%)	7
	3.6-4	11 (78%)	3 (22%)	14
	>4	2 (67%)	1 (33%)	3
Total		16	8	24

with mid-arm circumference, mid-arm area, BMI, biceps SFT, serum albumin, and total protein (9). In later studies, it has been shown that the DMS is associated with anthropometric measurements and serum albumin level in the detection of malnutrition (12,13). In our study, DMS was used because of its simplicity, ease of application and fast application. The negative correlation between DMS and albümin in our study was found to be compatible with other studies using DMS (9,12,13).

There are several studies showing a strong association of not only DMS but also various other nutritional tests with serum albumin level, which is consistent with the results of our study. In a study conducted by Visser et al. in 1999, SGA was found to be associated with albumin, BMI, mid-arm circumference and fat percentage in 22 hemodialysis and PD patients (14). In a study conducted by Sezer et al. with 100 PD patients, similar to our study, it was found that serum albumin levels were found to be significantly lower in patients who were determined to be malnourished according to the SGA (15).

Anthropometric measurements are inexpensive and relatively easy tests that have been applied for many years. Studies to standardize these measurements are limited. Since measurements take a long time to change, they are insufficient to show the effects of short-term nutritional interventions on patients (16). In one study, patients were separated according to albumin level and SGA score. While anthropometric measurements were found to be related with SGA score in patients with PEM; no correlation was found between anthropometric measurements and low albumin level in these patients (17). In our study, DMS and albumin were not associated with body composition analysis and anthropometric measurements.

Bioimpedance analysis is a fast, non-invasive and safe technique. Its advantages are that it is independent of the user and provides information about the patient's hydration status. The negative aspect is that it is not available in every center.

According to the study of Passadakis et al. (18) on 47 PD patients, the phase angle was found to be compatible with the results of the SGA. In another study performed in the pediatric age group, it was reported that findings of bioimpedance analysis were correlated with nutritional assessment according to SGA and that findings of bioimpedance analysis were found to be associated with survival (19,20).

In our study, no correlation was found between bioimpedance methods and albumin, DMS and anthropometric measurements.

In the publication of Oe et al. (21), SFT and bioimpedance analysis were compared in 4 areas before and after dialysis in hemodialysis patients. Lean body mass and body fat mass were evaluated. The two techniques were correlated with each other in determining body fat and lean body mass. In another study, 100 hemodialysis patients were evaluated according to MNA, bioimpedance and biochemical parameters, and the reliability of bioimpedance analysis in terms of diagnosis of malnutrition was investigated. According to this study, albumin level was found to be higher in the group without malnutrition but at risk of malnutrition than in the group with malnutrition. Fat percentage, fat mass, muscle mass and lean body mass were found to be significantly higher in the non-malnutrition group than in the malnourished and risky group, and it was concluded that bioimpedance analysis could be used in the diagnosis (22). In our study, the patients were classified according to their DMS and albumin levels, and the anthropometric measurements of these subgroups were compared. No significant difference was found. Compared to the other studies mentioned, the higher BMI of our patients and the low number of patients whose malnutrition was detected by other methods could be counted among the reasons for the difference in our findings.

In PD patients, weight change may not be correlated with lean body mass. In the study of Schmidt et al. in which they followed up PD patients, weight loss was found in only 36% of the patients, and 49% had a reduction in lean body mass (23). A decrease in lean body mass was found in 24% of 64 patients whose weight was found to be increased. In another study, it was reported that there was a significant increase in BMI, body fat mass and body fat mass and a significant decrease in lean body mass in PD patients (24). Mid-arm circumference was found to be a moderately reliable indicator of lean mass and amount of adipose tissue (25,26). Again, in a one-year follow-up study conducted in PD patients, BMI was found to be significantly associated with mid-arm circumference, biceps SFT, and visceral and subcutaneous fat detected by abdominal tomography in the initial evaluation. In one-year follow-up, it was found that the amount of visceral and subcutaneous fat and biceps SFT increased significantly (27). This study is similar to the findings of our study in terms of the relationship between anthropometry and fat percentage. In our study, SFT and mid-arm circumference were found to be significantly associated with the amount of fat, and a strong negative correlation was found between SFT and mid-arm circumference, and the amount of protein. This may be associated with the possibility of altered tissue distribution in PD patients. Possible reasons for this change are continuous glucose absorption from dialysate, increase in body fat percentage and protein malnutrition due to protein loss from dialysate (28,29). It was thought that anthropometric measurements in PD patients could not be interpreted similarly to healthy adults, and biceps SFT and mid-arm circumferences, which reflected both subcutaneous fat and lean body mass, showed more fat percentage in PD patients.

The relationship between malnutrition indicators and clinical outcome in geriatric hemodialysis patients was investigated. SGA, low serum albumin level, MIS and hand grip strength were found to be associated with hospitalization; and SGA, MIS, calf circumference and BMI were found to be associated with mortality (30). No relationship was found between the mid-arm circumference and triceps SFT, which were also used in our study, with hospitalization and mortality. As seen in that study example, serum albumin level and malnutrition tests are more effective methods in estimating clinical outcomes than mid-arm circumference and SFT.

In conclusion, several nutritional diagnostic methods used in the clinic were evaluated together in our study. Serum albumin and nutritional tests have a definite place in the diagnosis of malnutrition, as shown in many other studies. Anthropometric measurements and bioimpedance analysis are routine tests based on healthy people. According to the results of our study, the interpretation of these tests in PD patients should be done carefully. However, considering the strong correlation between anthropometry and bioimpedance analysis in terms of fat mass, we think that it can be included in the malnutrition assessment routine.

Study Limitations

The main limitations of our study were the small number of patients and its cross-sectional nature.

Conclusion

Albumin is an indicator of malnutrition in PD patients. Examination and laboratory data remain valuable in nutritional assessment. Malnutrition tests (DMS) can be used as an auxiliary method in addition to serum albumin level in PD patients in the examination of malnutrition. Evaluation of body composition and anthropometric measurements may not be informative enough cross-sectionally. Serial assessments can be stimulus for detecting malnutrition.

Ethics

Ethics Committee Approval: Our study was approved by the ethics committee of our university (ethics committee file number: 22/420), and the principles stated in the Declaration of Helsinki were complied with.

Informed Consent: Written and verbal consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.S.A., Concept: A.S.A., M.G., R.G., Design: M.G., A.Y., R.K., Data Collection or Processing: A.S.A., M.G., Ö.C.E., A.Y., Analysis or Interpretation: A.S.A., Ö.C.E., A.Y., Literature Search: A.S.A., Ö.C.E., Writing: A.S.A., M.G., R.K.

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Original Article

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Effects of Perturbation Training on Balance, Walking, and Lumbar Stabilization in Patients with Multiple Sclerosis: A Pilot Study

Multipl Skleroz Hastalarında Pertürbasyon Eğitiminin Denge, Yürüyüş ve Lumbar Stabilizasyon Üzerine Etkisi: Pilot Çalışma

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ABSTRACT

Objective: To investigate the effect of perturbation training (PT) on balance, walking, and lumbar stabilization in patients with multiple sclerosis.

Methods: Ten patients were given manual PT twice a week for 6 weeks. Romberg (RT), Sharpened Romberg (SR), and single leg stance test (SLST) were performed for static balance. Dynamic balance was assessed with functional reach test (FRT), lateral reach test [dominant (LRT-D) and non-dominant (LFR-ND)], and four square step test (FSST). The Falls Efficacy Scale International (FES-I) was used to evaluate the fear of falling. Timed up and go (TUG) test and pressure biofeedback stabilization were used to assess the functional mobility and lumbar stabilization.

Results: The results of SR and SLST were significantly increased after the treatment ($p<0.05$). However, the RT duration had no differences between pre and post-treatments ($p>0.05$). Significant differences were found in the values of FRT and LRT-ND. The results of LRT-D and FSST were not changed with the treatment. The fear of falling decreased after the treatment but was not statistically significant ($p>0.05$). After the treatment, the TUG duration improved in participants ($p=0.01$). No difference was found in the PBS duration between the pre and post-treatment ($p>0.05$).

ÖZ

Amaç: Multipl skleroz hastalarında pertürbasyon eğitiminin (PE) denge, yürüme ve lumbal stabilizasyon üzerine etkisini araştırmak.

Yöntemler: On hastaya 6 hafta boyunca haftada iki kez manuel PE verildi. Statik denge için Romberg Test (RT), Keskinleştirilmiş Romberg (KR), Tek Bacak Duruş Testi (TBDT) yapıldı. Dinamik denge Fonksiyonel Uzanma Testi (FUT)'yle, Lateral Uzanma Testi (dominant, non-dominant; LUT-D, LUT-ND)'yle ve Dört Kare Adım Testi (DKAT)'yle değerlendirildi. Düşme korkusunu değerlendirmek için Düşme Etkinliği Skalası (DES) kullanıldı. Fonksiyonel mobilite ve lumbal stabilizasyonu değerlendirmek için sırasıyla Zamanlı Kalk ve Yürü (ZKY) testi, Basınçlı Biofeedback Stabilizer (BBS) kullanıldı.

Bulgular: SR ve SLST sonuçları tedaviden sonra anlamlı olarak arttı ($p<0,05$). Ancak RT süresi için tedavi öncesi ve sonrası arasında fark yoktu ($p>0,05$). FUT ve LUT-ND değerleri arasında önemli fark vardı. Tedavi ile LUT-D ve DKAT sonuçları değişmedi. Tedavi sonrasında bireylerin düşme korkusu azalsa da, istatistiksel analize yansımadı ($p>0,05$). Tedaviden sonra ZKY süresinde iyileşmeler kaydedildi ($p=0,01$). Tedavi öncesi ve sonrası arasında BBS süresi bakımından fark yoktu ($p>0,05$).

Sonuç: Bu çalışma, klinikte bilgisayarlı sistemler olmadan manuel PE'nin statik ve dinamik dengeyi, yürüyüşü, düşme korkusunu

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Conclusion: This study revealed that manual PT without computerized systems in the clinic may improve static and dynamic balance, walking, and fear of falling. Additionally, the effect of PT on lumbar stabilization in MS was not determined in our study. Major conclusions were limited by the small sample size; however, the observed results may contribute to designing future trials.

Keywords: Gait, multiple sclerosis, postural balance, rehabilitation

iyileştirebileceğini göstermiştir. Ayrıca çalışmamızda PE'nin multipl sklerozda lumbal stabilizasyon üzerine etkisi saptanmadı. Önemli sonuçlarımız küçük örneklem büyüklüğü ile sınırlıydı; ancak, gözlemlenen sonuçlar gelecekteki çalışmaların tasarlanmasına katkıda bulunabilir.

Anahtar Sözcükler: Yürüyüş, multipl skleroz, postural denge, rehabilitasyon

Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune neurological disease that is characterized by myelin destruction in the central nervous system (CNS), grey matter, and axonal loss (1). The damage within the CNS slows the nerve conduction and decreases motor activation that coincides with impaired motor performance (2). Altered balance, walking dysfunction, muscle weakness, reduced core stabilization, and fatigue are symptoms of impaired motor performance (3,4). Especially, core muscle strength is necessary for skilled movement and function (5). Physiotherapy and rehabilitation training includes strength and stretch and balance and coordination exercises for patients with MS in the baseline. Recently, task-oriented training and whole-body vibration have proved benefits in patients with MS (6). Perturbation training (PT) has been incorporated into balance training (7). Anticipatory (APAs) and compensatory postural adjustments (CPAs) are the two main postural mechanisms used by the CNS to maintain and restore balance during perturbations (8). APAs are responsible for postural muscle activation in a feed-forward manner before perturbations (9). Predicted or small perturbations can only be counteracted with APAs (10). Unexpected or large perturbations can be counteracted with CPAs (10). Perturbations develop an automatic postural response, which is known as the primary component of postural control (11). PT is aimed to improve reactive balance control, step quality, and reduce the risk of falling (12,13). The inefficient APAs cause fear of falling, slow mobility, and poor balance in older adults (14). The muscle activity during APAs was smaller and delayed than healthy persons, even in the early phase of MS (15). Additionally, few studies investigated the effect of PT on lumbar stabilization (16), which revealed that external perturbations increased intramuscular electromyography signals, especially the transversus abdominis (17). Unexpected perturbation to the transversus abdominis plays a key role in lumbar stabilization compared to other trunk muscles (16).

The effects of PT are shown in different areas in different diseases, in the elderly, e.g., stroke, Parkinson's disease, and anterior cruciate ligament ruptures (12,18-20). PT stimulated the neuromotor system, improved sensorimotor skills, and prevented falling (21). Lateral perturbations were improved in the magnitude of CPAs for patients with Parkinson's disease to develop balance and reduce falls (14). Perturbations provide information on the strategies of adjustments, but the effects of PT were not clearly understood in patients with MS (22). The effects of perturbations on the fear of falling are still unknown. Thus, investigating the effect of PT on MS is necessary. This study aimed to investigate the effect of PT on balance, walking, and lumbar stabilization.

Method

This is a pilot study that was approved by Hasan Kalyoncu University, Clinical Researches Ethics Committee in June 2017 (number: 2017/255). Informed consent was obtained from all participants.

Participants

This study included 10 patients with MS between July and December 2017 (Figure 1). The inclusion criteria were (1) Mc Donald's MS diagnosis following the 2010 criteria, (2) ages 18-45 years, (3) and Expanded Disability Status Scale (EDSS) score of 3-5.5. The exclusion criteria were (1) 3 or higher scores in spasticity according to Modified Ashworth Scale, (2) psychological, orthopedic, and other neurological disorders, and (3) attacks in the last 3 months.

Procedure

All patients attained a physiotherapy program. Perturbations were manually applied, and precautionary measures were taken to avoid the risk of injuries. PT was carried out in different positions that included standing, kneeling, and sitting. Manual perturbations in each position were applied 10-12 times, and individuals were allowed to rest for 10 s between each position at a sitting position. Perturbations were applied for 5 min, along with 10 s break between two successive sets. Perturbations were performed in both right and left sideways, backward and forward in each of positions, and at the pelvis and shoulders in different directions. The duration of one session was 45 min. Treatment was given twice a week for 6 weeks (23). Participants did not receive any other treatment or physiotherapy application. The treatment and assessment tests were carried out by the same physiotherapist.

Measurements

Statics Balance Tests

Romberg (RT), Sharpened Romberg (SR), and single leg stance test (SLST) were performed and their duration was recorded. RT was performed on patients with eyes closed and feet together. The test was terminated when the participant held it in one place, oscillations began or were likely to fall (24). RT maximum duration was 120 s. SR was performed on a straight line with one

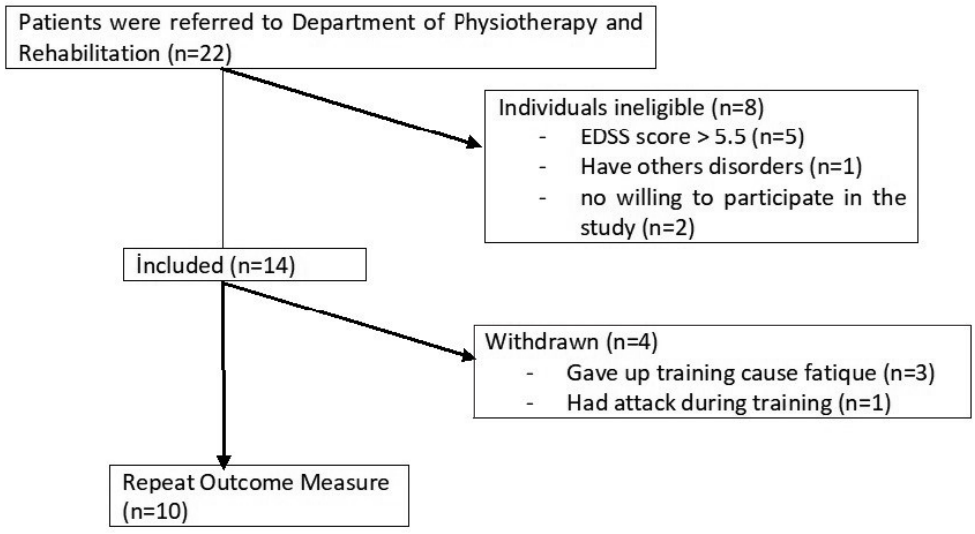

Figure 1. Follow-up diagram

leg behind the other leg, eyes open, and leaving the arms sagging, without impairing the balance. Duration stop criteria were defined as the time that took a participant to dislocate the foot, reach the maximal duration of 30 s, and contact the observer to avoid falling (25). An SLST was measured in a standing position with dangling arms. The duration was stopped when the participant re-positioned his/her supportive foot, touched their feet to the ground, sought support from the observer, and reached the maximum duration of 30 s (16).

Dynamic Balance Tests

Dynamic balance was assessed with functional reach test (FRT), lateral reach test (LRT), and four square step test (FSST). FRT was performed by reaching forward and lateral without taking a step. The level of the metacarpal bone was marked in the start position and final position. The difference between these levels was measured (26). LRT was performed with both sides that included dominant and non-dominant sides (27). LRT is a reliable and valid measure for lateral stability limits and mediolateral balance in the MS population (28). FSST measured dynamic balance and included all directions, e.g., backward, forward, right, and left (29). The time of the test was recorded while the participant rapidly stepped in clockwise and counter-clockwise rotations (30).

Walking

A timed up and go (TUG) test was used for functional mobility that was related to falling risk. Individuals in TUG were asked to stand from the sitting position, walk 3 m, turn back, and sit back on the chair again (31).

Lumbar Stabilization Test

Core muscle performances were assessed with a Pressure Biofeedback Stabilizer (PBS) (Chattanooga, Australian) (32). Individuals were positioned to stand with their comfortable foot distance and their back resting on the wall. The stabilizer's pressure cell was placed under L3-4 spinous processes and was inflated to a baseline pressure of 40 mmHg. All individuals were asked to have a stable baseline pressure. The duration without moving their spine or pelvis was recorded. Three trials were performed and the best scores were recorded (5).

Fear of Falling

Falls Efficacy Scale International (FES-I) was used to evaluate the level of concern related to falls during 16 activities of daily living. This questionnaire quantifies the level of concern about falling while performing each activity on a 4-point scale (1= not at all; 2= somewhat; 3= quite a lot; and 4= very). The total score is between 16 and 64, in which a higher score indicates more concern about falling (33).

Statistical Analysis

Statistical Package for the Social Sciences version 22.0 software was used for statistical analyses. G*power application was used to calculate the necessary minimum sample size. The sample size was calculated to be 19 subjects with 5% type 1 and 10% type 2 error limits before and after treatment to provide 90% working power, gain 0.80 of effect size, and 95% confidence interval. The frequency in percent (%) and mean ± standard deviation (X ± SD) of necessary variables were calculated for the descriptive analyses. Normality of distribution was tested with the Skewness-Kurtosis and histogram graphic. Paired samples t-test was used for the comparison of two measurements; pre and post-treatment. Differences were assumed significant at p-values of <0.05.

Results

The demographic characteristics of participants are shown in Table 1. All participants had a Relapsing-Remitting type of MS. The diagnosis period of participants varied between 2 and 15 years. The average EDSS score was 1.87. All participants were right-handed. Two participants have no history of falling,

whereas three participants fell one time or two times in the last year and five participants have >2 histories of falls in the last year.

SR and SLST, which were used to test the static balance, significantly increased after the treatment ($p<0.05$) (Table 2); however, RT had no differences between the pre and post-treatment periods ($p>0.05$) (Table 2). Significant differences were found in FRT and LRT-ND (Table 2). FSST dynamic balance test was not changed with the treatment period ($p>0.05$) (Table 2). The fear of falling decreased after the treatment, without statistically significant analysis ($p>0.05$) (Table 2). After the treatment, TUG improved in participants ($p=0.01$) (Table 2). However, no differences were found in PBS between the pre- and post-treatment periods ($p>0.05$) (Table 2).

Discussion

This study aimed to investigate the effect of PT on balance, walking, and lumbar stabilization in patients with MS. A significant effect of PT was recorded on balance and walking. However, the improvement in fear of falling was observed to be clinically but not statistically significant. Investigating the effect of PT on balance, walking, lumbar stabilization, and fear of falling is effective in long-term MS.

Table 1. The demographics characteristics in participants

Characteristics	Mean ± SD (min-max)
Age (year)	**37.12±7.21 (26-45)**
Years since diagnosis	**6.00±4.27 (2-15)**
Expanded disability status scale (scores)	**1.87±1.95 (1-5.50)**
Gender	
Female	**8**
Male	**2**
Fall history	
No	**2**
1-2 in the last year	**3**
>2 in the last year	**5**

Perturbations are known to improve CPAs and APAs and positively affect balance and walking in the elderly (19,34). Both gait and fear of falling are affected by gender. Functional walking categories revealed that walking performance changed according to age and gender in patients with MS (35). Therefore, the effects of PT according to age and gender should be compared in a larger sample. The range of age and the number of participants were limited in our study. As this is a pilot study, the effects of age or gender were not determined. Further studies might focus on investigating the response of PT according to age and gender.

Studies investigated the perturbation direction in the literature. Morrison et al. (36) showed that persons with MS exhibited greater sway in the mediolateral direction compared to the anteroposterior direction. The comparison of the elderly revealed that mediolateral sway was greater in MS, which increased the falling risk and affected the activity in daily life (36). Cortesi et al. (37) determined that their treatment improved not only the mediolateral balance but also the anteroposterior balance. Additionally, Salcı et al. (11) demonstrated that proprioceptive neuromuscular facilitation techniques should be applied for motor strategy training, and balance, and especially posterior perturbations should be preferred. This study performed perturbations in all directions. The mediolateral balance was thought to be more difficult to develop since it was more affected according to the FSST and LRT results. A more intensive treatment program may be required to improve the mediolateral balance.Perturbations disturb individual stability and supply feedback postural control, thus they improve the balance (38). However, perturbations should be sufficient to improve reactive balance control (39). The amount of perturbations is unclear. A study showed that it should be 24 perturbations at one session and another argued that it should include approximately 80 perturbations over four sessions (40,41). Some studies determined approximately 700-1,150 perturbation overall training (42,43). This study performed approximately 75 perturbations in one session that includes three positions (i.e., sitting, stand, and tandem positions) 10-12 times in each position for two successive sets. The number of perturbations was thought to be sufficient to improve the

Table 2. Pre-post outcome measures: balance, walking, lumbar stabilization, and fear of falling

Measurements	Pre-treatment	Post-treatment	p-value
Romberg Test (sec)	78.21±57.78	98.54±41.74	0.285
Sharpened Romberg Test (sec)	9.28±11.5	46.65±34.91	0.018*
Single Leg Stance Test (sec)	5.02±3.46	18.1±22.76	0.05*
Functional Reach Test (cm)	25.58±5.43	33.18±4.44	0.011*
Lateral Reach Test-D (cm)	20.56±8.59	25.29±6.79	0.098
Lateral Reach Test-ND (cm)	18.5±2.48	22.25±4.32	0.044*
Four Square Step Test (sec)	10.7±2.26	9.85±1.59	0.235
Timed Up and Go test (sec)	9.23±1.92	7.41±1.04	0.01*
Pressure Biofeedback Stabilizer (sec)	26.67±13.47	33.02±16.92	0.45
Fear Efficacy Scale International (Score)	40.63±24.04	25.00±16.89	0.06

P<0.05, X ± SD: Mean ± standard deviation, Lateral Reach Test-D: Lateral Reach Test on Dominant Side, Lateral Reach Test-ND: Lateral Reach Test on Non-Dominant Side

balance and gait of MS. More studies are needed to determine the exact amount in patients with MS.

van Duijnhoven et al. (13) determined that perturbations improved the quality of stepping in patients with chronic stroke but not the speed of gait. Another study applied PT on the treadmill and revealed that PT improved the dynamic balance and walking in the elderly (34). Further, another study investigated the effect of PT on gait in Parkinson's disease using the 6-meter walk test and TUG (44). Compared with the control group, PT was determined to improve the performance in TUG but remained unchanged in the 6-meter walk test duration (44). Our primary findings indicate that PT might support improvements in walking performance in patients with MS. Our study findings were similar to the literature. To our knowledge, performing PT in MS is the original feature of our study. However, our study investigated only the speed of walking in MS. Other studies in literature investigated the gait in detail. Aruin et al. (22) determined that perturbations improved CPAs and APAs and changed gait initiation in MS. Tajali et al. (14) showed that external perturbations change in core muscle activity during walking in MS. Thus, the effect of PT on walking can be investigated in detail like electromyography activity.

After perturbations, improved balance and accurate stepping are essential strategies to prevent falling and reduce the fear of falling (34). PT focuses on response to improve reactive balance and reduce the risk of falling (12). PT was performed in 10 sessions for patients with chronic stroke in a study and showed increased activity-specific confidence, but no statistically significant differences (13). However, the increased activity-specific confidence after 6 weeks was greater than the post-treatment. Thus, the effect of PT on the fear of falling became apparent in the follow-up period. Our study revealed a decreased fear of falling with PT training following the literature. However, the effect of treatment is thought to be better in the long term. Fear is known as a psychogenic composite parameter and fear is affected by psychosocial factors. Thus, the fear of falling is thought to be follow-up as long term in patients.

Freeman et al. (16) emphasized the effect of unexpected perturbations on core stabilization that is directly controlled by CNS and PT supplied feedback and proprioception for deficits in neuromuscular control of stabilization; therefore, PT improved lumbar stabilization (45). Vera-Garcia et al. (46) showed that trunk perturbations increased preactivation of core muscles and trunk stability and reduced lumbar displacement. Another study proved that high-intensity perturbations increased neuromuscular activity (47). However, no significant differences were found in PBS. Future studies are necessary to investigate the effect of PT on lumbar stabilization that includes more intense training. The effect of PT on patients with MS remains unclear.

Study Limitations

This study had several limitations, such as the small sample size that has no control group. Future studies that investigate the effect of PT in the long term are needed to understand the effect of PT on MS.

Conclusion

This study revealed that PT may improve static and dynamic balance, walking, and fear of falling. The balance was insufficiently developed in the mediolateral direction with the PT. Additionally, the effect of PT on lumbar stabilization in MS was not determined in our study. Major conclusions were limited by the small sample size; however, the observed results may contribute to designing future trials.

Ethics

Ethics Committee Approval: This is a pilot study that was approved by Hasan Kalyoncu University, Clinical Researches Ethics Committee in June 2017 (number: 2017/255).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: T.M., H.Y., Y.Y., A.A., Concept: T.M., H.Y., Design: T.M., H.Y., Data Collection or Processing: T.M., A.A., Analysis or Interpretation: T.M., H.Y., Y.Y., A.A., Literature Search: T.M., H.Y., Writing: T.M., H.Y., Y.Y., A.A.

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Original Article

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Reliability of High-Alert Medications Questionnaire in Turkish Healthcare Professionals

Sağlık Çalışanlarında Yüksek Riskli İlaç Bilgi Anketinin Güvenilirliği

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ABSTRACT

Objective: This study aimed to evaluate the reliability of the High-Alert Medications (HAM) Questionnaire in Turkish healthcare professionals.

Methods: This methodological study was conducted between December 2017 and January 2018 in a private university hospital. The healthcare professionals, including nurses, health service technicians, and pharmacists, who are older than 18 years old were eligible for this study. After following the appropriate translation and cultural adaptation process, the internal consistency of the HAM Questionnaire using the Kuder-Richardson 20 coefficient and test-retest reliability was evaluated.

Results: Among 146 healthcare professionals, the mean age was 25.40±5.16 years, wherein 76% were females. Most participants were nurses (69.9%) and other healthcare professionals were health service technicians (28.1%) and pharmacists (2.0%). The mean total score of the HAM Questionnaire was 70.00±19.50. The Kuder-Richardson 20 was 0.815. A statistically significant correlation was found between the scores of the HAM Questionnaire at baseline and after 15 days, which confirmed the test-retest reliability (r=0.527; p<0.01). A statistically significant correlation was found between the HAM Questionnaire score and advanced age (r=0.310; p<0.001) and higher professional year (r=0.445; p<0.001).

Conclusion: The Turkish version of the HAM Questionnaire could

ÖZ

Amaç: Sağlık çalışanlarında Yüksek Riskli İlaç Bilgi Anketi'nin anketinin güvenilirliğinin değerlendirilmesi amaçlanmaktadır.

Yöntemler: Bu metodolojik çalışma Aralık 2017 ile Ocak 2018 tarihleri arasında özel bir üniversite hastanesinde gerçekleştirilmiştir. Çalışmamıza 18 yaşından büyük hemşireler, sağlık teknisyenleri ve eczacılar dahil edilmiştir. Uygun çeviri ve adaptasyon sürecini takiben, Kuder-Richardson 20 katsayısı kullanılarak yüksek riskli ilaçlar hakkında bilgi anketinin iç tutarlılığı ve test-tekrar test güvenilirliği değerlendirilmiştir.

Bulgular: Çalışmamıza dahil edilen 146 sağlık çalışanının yaş ortalaması 25,40±5,16 olarak hesaplanmış ve katılımcıların %76'sı kadındır. Katılımcıların meslekleri, hemşire (%69,9), sağlık teknisyenleri (%28,1) ve eczacıdır (%2). Sağlık Çalışanlarında Yüksek Riskli İlaç Bilgi Anketi'nin toplam puan ortalaması 70,00±19,50 olarak hesaplanmıştır. Anket güvenilirliği için Kuder Richardson 20 değeri 0,815 olarak bulunmuştur. Test-retest güvenilirliğini doğrulamak için, başlangıçta ve 15 gün sonra Yüksek Riskli İlaç Bilgi Anketi puanları arasında istatistiksel olarak anlamlı bir korelasyon bulunmuştur (r=0,527; p<0,01). Sağlık Çalışanlarında Yüksek Riskli İlaç Bilgi Anketinin puanı ile ileri yaş (r=0,310; p<0,001) ve mesleki tecrübe yılı (r=0,445; p<0,001) arasında istatistiksel olarak anlamlı bir korelasyon bulunmuştur.

Sonuç: Sağlık Çalışanlarında Yüksek Riskli İlaç Bilgi Anketinin

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be used to assess healthcare professionals' knowledge about high-alert medications.

Keywords: High-risk medication, healthcare professional, medication safety, pharmacist, nurse, knowledge

Türkçe versiyonu sağlık çalışanlarının yüksek riskli ilaçlar hakkındaki bilgilerini değerlendirmek için kullanılabilir.

Anahtar Sözcükler: Yüksek riskli ilaçlar, sağlık çalışanları, ilaç güvenliği, eczacı, hemşire, bilgi seviyesi

Introduction

The Institute for Safe Medication Practices (ISMP) has been published and periodically updated a list of high-alert medications (HAM), which are defined as medications that could cause significant patient harm when erroneously used in variable settings. The HAM list was determined through ISMP Medication Errors Reporting Program, current literature, and input from practitioners and safety experts (1). HAM has a narrow margin of safety or causes severe adverse events. The frequency of medication errors related to HAM varies. Previous studies revealed that medication errors were due to HAM with a rate of 55% (2) and 33% (3). Medication errors with these medicines may lead to devastating consequences, such as death (4).

Insufficient knowledge about HAM was one of the significant causes of medication errors (5,6). Health care professionals should be aware of the risks of HAM and develop strategies to improve safety about the administration of such medications. Knowledge improvement of healthcare professionals by developing educational interventions would be one of the strategies to reduce the risk of HAM. Therefore, the assessment of knowledge related to HAM is essential and is required when developing and implementing educational training programs about HAM for healthcare professionals (7,8).

To our best knowledge, there is no reliable scale in Turkish to evaluate the knowledge of healthcare professionals regarding HAM. Therefore, this study aimed to evaluate the reliability of the HAM Questionnaire; which is developed by Hsaio et al. (9), in Turkish healthcare professionals.

Method

This methodological study was conducted between December 2017 and January 2018 in a private university hospital. The study population includes healthcare professionals who have a direct responsibility in preparing and applying medications (nurse, pharmacist, and health service technician) aged over 18 years old and who worked in a 350-bed private university hospital located in Istanbul, Turkey. According to previous studies (10,11), the minimum sample size was determined as 200. Convenience sampling was used for selecting the study population. Self-reported survey tools were distributed to all participants and collected within the week. The ethical committee approval was obtained from Acıbadem Mehmet Ali Aydınlar University with approval number of 2017-18/9. An informed consent form was obtained from all participants.

Demographic and professional data and their self-assessment regarding their knowledge level and training needs about HAM have been collected. The HAM Questionnaire was generated in Taiwan, and the Turkish version was adapted with permission from the developers (9). It includes a total of 20 items regarding basic and important knowledge of HAM usage. This questionnaire consisted of items regarding administration, delivery route and dosage of medications, and medication regulation. Each item was ranked as true or false by participants. After the true and false/unknown responses scored as 1 and 0, respectively, the total score was multiplied by 5. The minimum and maximum scores were ranged from 0 to 100. The higher score represented better knowledge of HAM (9). The Turkish translation and cultural adaption have been performed before applying the questionnaire to the participants based on the World Health Organization guidelines (12). The original questionnaire included a high concentration of potassium chloride, which was not available in Turkey. This concentration was substituted with the highest concentration of potassium chloride available in Turkey.

Statistical Analysis

The descriptive statistic was represented with number and percentage and mean with standard deviation or standard error of the mean, as appropriate. The Kuder-Richardson test, which is more appropriate for questionnaires with a dichotomous response, was used for internal consistency. According to the findings of the Kolmogorov-Smirnov test, the Spearman correlation was performed between the total score of the questionnaire and other continuous variables, such as age, a profession of health care, and test-retest score. The Mann-Whitney U test for two independent groups, such as age and profession, and the Kruskal-Wallis test for more than two groups, such as education level, perception of knowledge level, and necessary training for HAM, was conducted to compare the total knowledge score between each group. The statistical significance was obtained if the p-value was <0.05.

Results

Among the 200 distributed questionnaires, 159 were returned, and among the 159, 13 had missing data. Thus, the analysis was done in 146 fully-filled questionnaires. The mean age was 25.40±5.16 years. Of them, 76.0% were female. The rate of nurses, pharmacists, and health service technicians were 69.9%, 2.0%, and 28.1%, respectively. Of them, 47.3% had a bachelor's degree. Participants worked in various wards and 45.2% of them worked in the surgery ward. The mean professional experience years were 3.29±5.05 (minimum-maximum: 0-37).

The demographic and professional experience of health care professionals was presented in Table 1.

A moderate correlation was found between the scores of the HAM Questionnaire at baseline and after 15 days, which confirm the test-retest reliability (r=0.527; p<0.01). The internal consistency reliability was acceptable (Kuder-Richardson 20: 0.815). If the item was deleted, the Kuder-Richardson 20 ranged from 0.798 to 0.821. The mean total score was 70.00±19.50. Most participants gave the correct response to the following items: "for convenience, heparin and insulin should be stored together in the refrigerator" (89.7%), "7.5% KCl is frequently used, thus it should be easily and freely accessed by nurses" (91.1%), and "for pediatric dose, use teaspoon for dose expression" (89.7%). Most participants did not give the correct response for the questions about dose calculation for chemotherapy (75.3%), fast IV push 10% calcium chloride at 10 mL in 1-2 min when an emergency happens (63.7%), and potassium can be administered orally instead of IV route if patients can tolerate (62.3%). The rate of correct responses to each item in the questionnaire, corrected item-total correlation, and Kuder-Richardson 20 coefficients if item deleted was presented in Table 2.

Of them, 65.1% agreed that their knowledge was sufficient, and 63.7% agreed to the need for training about HAM. The participants' self-assessment on their knowledge level and training needs about HAM is presented in Table 3.

Increased age was moderately correlated with higher knowledge level (r=0.310, p<0.001). More professional experience also moderately correlated with higher knowledge level (r=0.445, p<0.001) (Table 4).

Table 1. Demographic and professional experience of health care professionals (n=146)

Age (mean ± standard deviation)	25.40±5.16
Female n (%)	111 (76.0%)
Male n (%)	35 (24.0%)
Health care professional n (%)	
Nurse	102 (69.9%)
Health service technician	41 (28.1%)
Pharmacist	3 (2.0%)
Education n (%)	
High school	35 (24.0%)
Two-year degree	37 (25.3%)
Bachelor of science	69 (47.3%)
Specialist	5 (3.4%)
Workplace n (%)	
Surgery	66 (45.2%)
Intensive care unit	41 (28.1%)
Internal medicine	17 (11.6%)
Pharmacy	15 (10.3%)
Emergency department	4 (2.7%)
Missing data	3 (2.1%)
Professional experience (years) (mean ± standard deviation)	3.29±5.05

Male participants had a higher knowledge score compared with the females. However, this difference was not found statistically significant (p>0.05). No statistically significant difference was found between the groups based on their education level (p>0.05). Participants who thought they had sufficient knowledge about HAM had a higher knowledge score compared to participants who did not (p<0.01). No statistically significant difference was found between the groups based on their opinions regarding training need for HAM (p<0.05). Factors related to their knowledge about HAM was presented in Table 5.

Discussion

After the test-retest analysis and assessment of the Kuder-Richardson 20 value, the Turkish version of the HAM Questionnaire could be used to assess the knowledge of healthcare professionals about HAM. Relationships were found between their HAM-related knowledge and advanced age and higher professional year.

The Kuder-Richardson value of the original HAM Questionnaire was found as 0.74 in the previous study (9). Similar to Hsaio et al.'s (9) study, the internal reliability of the Turkish version of the questionnaire is sufficient to evaluate the knowledge levels of healthcare professionals in Turkey. Similar to our study, Hsaio et al. (9) also found a correlation between their HAM-related knowledge level and age and experience. In their study with increasing age and experience, HAM-related knowledge was also increased.

One of the most common wrong responses about HAM in our study was the intravenous (IV) administration of electrolytes, such as 3% NaCl, 7.5% KCl, 10% Ca-gluconate, and 10% CaCl. Our findings were similar to other studies in the literature (9,13,14). Hsaio et al. (9) pointed out that 30% of nurses were administrating electrolytes in an improper way. The present study revealed that almost half of the healthcare professionals gave accurate responses to the question of "Fast IV infusion of 3% NaCl of 500 mL for patients who have low sodium level," which is similar to Zyoud et al. (13) results, where they pointed out that only 50.4% of participants were able to answer correctly.

It is well-known that 7.5% KCl should not be stored in the wards or nursing units and free access to 7.5% KCl should be discouraged (9,13,14). This recommendation was made because IV bolus administration may cause fatal outcomes (9,13-15). Contrarily, our participants agreed with keeping 7.5% KCl away in easily accessible places and 91.1% properly respond to these questions (9). Zyoud et al. (13) revealed that 76.8% of nurses agreed with not administering the 7.5% KCl as fast IV push. Contrarily, Hsaio et al. (9) revealed that only 46.9% of participants were familiar with this warning. Similar to the study conducted by Hsaio et al. (9), our study revealed that 58.9% of participants were able to correctly answer the question regarding 7.5% KCl as fast IV push. Additionally, the Turkish healthcare professionals had much lower knowledge about calcium-containing solutions compared with their knowledge about sodium and potassium-

Table 2. The rate of correct response to each item in the questionnaire, corrected item-total correlation, and Kuder–Richardson 20 coefficients if item deleted

	Correct response	The rate of correct response (%)	Corrected item-total correlation	Kuder-Richardson 20 coefficients if item deleted
"cc" or "mL" is the dosage expression for insulin injection"	F	80.1%	0.544	0.799
"When an emergency, such as ventricular fibrillation happens, push fast 7.5% KCl at 10 mL into IV"	F	58.9%	0.540	0.798
"Fast IV infusion of 3% NaCl of 500 mL for patient who has low sodium level"	F	51.4%	0.483	0.802
"Port-A route can be used for blood withdrawal and drug injection generally"	F	84.2%	0.277	0.813
"Insulin syringe can be replaced by 1 mL syringe"	F	84.9%	0.317	0.811
"Fast IV push 1:1000 epi at 1 amp for patient who has mild allergic reaction"	F	63.7%	0.559	0.797
"10% Ca-gluconate and 10% $CaCl_2$ are the same drug and interchangeable"	F	74.0%	0.518	0.800
"7.5% KCl better added to Ringer's solution for rapid infusion"	F	52.1%	0.532	0.798
"When an emergency happens, fast IV push 10% $CaCl_2$ 10 mL in 1-2 minutes"	F	36.3%	0.488	0.801
"For chemotherapy dose calculation in adult is based on BW, whereas BSA in children"	F	24.7%	0.133	0.821
"Taken fentanyl skin patch as regulated narcotic"	T	82.9%	0.208	0.816
"Use distinctive labeling on look-alike drugs"	T	93.2%	0.012	0.821
"For convenience, heparin and insulin should be stored together in the refrigerator"	F	89.7%	0.400	0.808
"Use "Amp" or "Vial" for dose expression instead of "mg" or "gm"	F	87.7%	0.483	0.804
"If a ward stores atracurium for tracheal intubation, the drug should be stored with other drugs and easily accessed by nurses"	F	71.2%	0.369	0.808
"7.5% KCl is frequently used, so it should be easily and freely accessed by nurses"	F	91.1%	0.410	0.808
"If the patient can tolerate, potassium can be administered orally instead of IV route"	T	37.7%	0.264	0.815
"Each drug better has multiple concentrations for nurse to choose"	F	79.5%	0.375	0.808
"For pediatric dose, use teaspoon for dose expression"	F	89.7%	0.277	0.812
"Use 'U' instead of 'unit' for dose expression"	F	67.1%	0.396	0.807

T: True, F: False, KCl: Potassium chloride, Ca: Calcium, NaCl: Sodium chloride, Epi: Epinephrine, $CaCl_2$, Calcium chloride, IV: Intravenous, BW: Body weight, BSA: Body surface area

Table 3. The participants' self-assessed knowledge level and training needs on high-alert medications (n=146)

	Strongly agree/agree n (%)	Neither agree nor disagree n (%)	Strongly disagree/disagree n (%)
Knowledge level	95 (65.1%)	34 (23.3%)	17 (11.6%)
Training need	93 (63.7%)	29 (19.9%)	24 (16.4%)

Table 4. Correlation between total knowledge score and age and professional experience

	Total knowledge score Spearman's rho-correlation coefficient (r)
Age (years)	0.310***
Professional experience (years)	0.445***

***p<0.001

containing solutions. Our results were consistent with the literature in terms of fast IV administration of $CaCl_2$ (13,16). Additionally, less than one-third of them were not aware that Ca-gluconate and $CaCl_2$ are not interchangeable, which was also consistent with the literature (13,16).

Hypoglycemic effects of insulin put insulin into the HAM list. Due to specific features, insulin should be expressed in units and a 1 mL syringe should be used during administration. The present study revealed that the majority of participants gave an accurate

Table 5. Factors related to their knowledge about high-alert medications (n=146)

	n	HAM Questionnaire score (mean ± SEM)	p-value
Gender			
Female	111	69.46±1.84	
Male	35	71.71±3.41	>0.05
Education			
High school	35	69.86±3.32	
Two-year degree	37	71.89±3.66	>0.05
Bachelor of science degree/specialist	74	69.12±2.11	
Knowledge level regarding high-alert medication			
Strongly agree/agree	95	74.05±1.92a*	
Neither agree nor disagree	34	63.38±2.91b*	<0.05
Strongly disagree/disagree	17	60.59±5.49b*	
Training need for high-alert medications			
Strongly agree/agree	93	68.12±2.01	
Neither agree nor disagree	29	72.76±3.33	>0.05
Strongly disagree/disagree	24	73.96±4.39	

SEM: Standard error of the mean, *there was statistically significant difference between different letters

response for insulin dosage and administration. A concordance was found compared with previous studies (9,13). Additionally, the abbreviation 'U' should be used instead of the unit to prevent misreads such as "0," "11," or "cc" (9,17).

Chemotherapeutical medications are considered one of the most toxic and harmful medications. Medication errors in a chemotherapeutical medication, such as paclitaxel, vincristine, cisplatin, etc., or even dose calculation mistakes may cause devastating results. Our results obtained the lowest correct response rate with chemotherapeutical calculation. Only almost one-fourth of them were aware that during the dose calculation of chemotherapy, the body surface area should be used in adults, whereas the bodyweight for children. Our findings were in-line with previous studies (9,13).

Medication errors are common and life-threatening. Thus, HAM usage and administration need comprehensive knowledge and perception level (18). Medication errors related to HAM may be fatal (19). The evaluation of HAM-related knowledge of nurses, pharmacists, and prescribers, most did not receive any education about HAM during their education and the rest who were educated about HAM were firstly educated during the job training (19). Lack of education and knowledge about HAM increases medication error incidence and patient harm (9,19,20). In this study, more than half of the healthcare professionals agreed to the need for education regarding HAM, which suggests continuing education programs. A follow-up study made by Sullivan et al. (8) revealed that the education program and labeling of HAM increased the knowledge and perception level of healthcare personnel. This education should be executed in nurses, pharmacists, and prescribers. In addition to education, other environmental resources, such as safeguards, should also be reinforced. Systematic risk reduction strategies should be applied, such as barcode medication administration and/or computerized physician order (19).

A randomized controlled trial showed that interventions to prevent medical errors were statistically significant (7). After 1 hour of education about HAM, participants were able to get significantly better results compared with the control group. Furthermore, participants of this education were more motivated, self-confident, and had increased awareness about HAM administration and handling (7).

Identifying the barriers, which let healthcare professionals commit medical errors, is important to prevent the medical errors and cope with them. In the literature, the most common barriers that healthcare professionals encounter are listed as conflicting opinions between the pharmacist, nurse, and prescriber, confused perception, and illegible prescriptions while administering HAM (13,17).

The solution to these problems between pharmacists, nurses, and physicians includes improving communication skills, reliable documentation, computerized drug systems, and supervision. Each institution needs standard operating procedures for the handling and administration of HAM (13,21). These standard operating procedures should be modified according to the need of the institution and regularly updated according to evidence-based data. In addition to standard operating procedures, increased safeguards, a structured interprofessional education, should be ensured regularly for the healthcare worker.

Study Limitations

Our study had some limitations. The generalizability of the results is limited as the sample was taken from a single center. The

distribution of sample size mostly consisted of nurses. Another limitation was that the study findings were based on a reliability study rather than an observational study.

Conclusion

To the best of our knowledge, this is the first study, which evaluated the reliability of a HAM Questionnaire in Turkish healthcare professionals. Institution-specific education and operating model should be created to prevent medication errors. Prevention of medication errors and patient safety should be assured by a collaborative multidisciplinary team, including the clinical pharmacists, nurses, and physicians. A clinical pharmacist should be in charge of medicine use and administration and also supervise the whole process in each unit.

Education and training of healthcare professionals should be placed in the undergraduate curriculum and also maintained with continuing education programs. A system containing standard operating procedures, regular audit, and supervision should be constituted within every institution. Additionally, the administration of safe storage and dispensing of HAM should also be regulated.

Ethics

Ethics Committee Approval: The ethical committee approval was obtained from Acıbadem Mehmet Ali Aydınlar University with approval number of 2017-18/9.

Informed Consent: An informed consent form was obtained from all participants.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: F.Ö., Ö.A., M.S., B.O., Design: F.Ö., M.S., B.O., Data Collection or Processing: F.Ö., Analysis or Interpretation: Ö.A., M.Y.B., B.O., Literature Search: Ö.Ö., B.T., M.Y.B., B.O., Writing: F.Ö., Ö.A., B.T., M.Y.B., M.S., B.O.

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Original Article

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The Effects of Genetic Characteristics on the Survival in Myelodysplastic Syndrome

Myelodisplastik Sendromda Genetik Özelliklerin Sağkalım Üzerine Etkisi

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ABSTRACT

Objective: This study aimed to evaluate the effects of genetic characteristics on the survival in patients with myelodysplastic syndrome (MDS).

Methods: This retrospective study reviewed the data on epidemiological features, main laboratory tests, International Prognostic Scoring System (IPSS) and revised-IPSS risk categories, genetic anomalies, genetic risk categories, and survival in patients who are diagnosed with MDS in our center. According to the IPSS risk categories, patients were classified into three groups as follows: "low risk," "intermediate-1," and "intermediate-2 risk and high risk." The groups were compared using the ANOVA and Kruskal-Wallis tests.

Results: The study reviewed the data of 99 patients. The mean age was 66±11.6 years. A genetic anomaly was detected in 30.3%, of which the most common was del20q (26.7%). The median survival was 61 months [95% confidence interval (CI): 50.9-71] in the study population. The 5-year survival rate was calculated as 64%, 41%, and 33% in "low risk," "intermediate-1," and "intermediate-2 risk and high risk" groups, respectively. The predicted median survival rate was 96 months (95% CI: 47.7-144.2), 56 months (95% CI: 34.1-77.8), and 18 months (95% CI: 15.1-20.8), respectively, which indicate a significant difference (log-rank chi-square: 6.6; p=0.035). The risk for mortality was 3.3-folds higher in the "intermediate-2 and high risk" group compared to the "low risk" group (RR: 3.3; 95% CI: 1.2-8.6; p=0.017).

ÖZ

Amaç: Çalışmamızın amacı, myelodisplastik sendrom (MDS) hastalarındaki genetik özelliklerin, sağkalım üzerine etkisini değerlendirmektir.

Yöntemler: Çalışma, retrospektif olarak tasarlandı. Merkezimizde MDS tanısı alan ve takip edilen hastaların epidemiyolojik özellikleri, temel laboratuvar testleri, Uluslararası Prognostik Skorlama Sistemi (IPSS), R-IPSS risk kategorileri, genetik anomali ve genetik risk kategorileri ve sağ kalım bilgileri kaydedildi. Hastalar IPSS risk kategorisine göre 3 gruba ayrıldı; "düşük risk", "orta-1 risk" ve "orta-2 ve yüksek risk". Gruplar tek yön ANOVA ve Kruskal-Wallis testleri kullanılarak karşılaştırıldı.

Bulgular: Çalışmamızda 99 hasta değerlendirildi. Medyan yaş 66±11,6 yıl bulundu. Hastaların %30,3'ünde bir genetik anomali saptandı. En sık görülen anomali del20q (%26,7) idi. Tüm hastalar için medyan sağkalım 61 ay [%95 güven aralığı (GA); 50,9-71] bulundu. Beş yıllık genel sağkalım "düşük risk", "orta-1 risk" ve "orta-2 ve yüksek risk" gruplarında sırasıyla; %64, %41 ve %33 hesaplandı. Tahmini medyan sağkalım ise sırasıyla 96 ay (%95 GA; 47,7-144,3), 56 ay (%95 GA; 34,1-77,8) ve 18 ay (%95 GA; 15,1-20,8) olup sağkalım farklılığı istatistiksel olarak anlamlı bulundu (Long Rank ki-kare:6,6, p=0,035). "Düşük risk"li grupla karşılaştırıldığında ölüm riski "orta-2 ve yüksek risk"li hastalarda anlamlı olarak 3,3 kat yüksek bulundu (RR: 3,3 %95 GA; 1,2-8,6, p=0,017).

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Conclusion: Our study supports that risk groups that are determined by several parameters, including genetic characteristics, provide predictive information about survival in MDS.

Keywords: Myelodysplastic syndromes, prognosis, genetics, survival

Sonuç: Çalışmamız, genetik özellikler başta olmak üzere çeşitli parametreler ile belirlenen risk gruplarının MDS'de sağkalım hakkında prediktif bilgi verdiğini desteklemektedir.

Anahtar Sözcükler: Myelodisplastik sendromlar, prognoz, genetik, sağkalım

Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disease, which is characterized by cytopenias due to ineffective erythropoiesis (1). The annual incidence is 12.6:100,000, which is increased in advanced age and reaches up to 50:100,000 (2). It is diagnosed after evaluations for unexplained cytopenias, particularly anemia, in older patients. Genetic characteristics are diagnostic for MDS, which also affect the identification of subtype, thus its classification. The French-American-British classification that relies on morphological characteristics is replaced with the World Health Organization (WHO) classification by cytogenetic and molecular advances. At this point, isolated 5q deletion is suggested as a distinct subtype in the 2008 WHO classification (3). Additionally, genetic findings suggest disease progression. Therefore, the International Prognostic Scoring System (IPSS), revised IPSS (R-IPSS) that included details for genetic findings and cytopenias, and WHO-PSS were developed (4,5). Thus, these are reflected in the 2016 update and nomenclature for subtypes that were changed despite the unchanged primary definitions for MDS (6). No standard therapeutic approach is available for MDS treatment. Prognostic assessment and molecular evaluations offer a wide therapeutic spectrum from drug-free observation to immunomodulatory and hypomethylating agents and even allogeneic stem cell transplantation (7).

Herein, presented the genetic characteristics of patients with MDS and their clinical implications.

Method

This study was approved by the Ethics Committee on Medicinal Product and Non-Medical Device Research of Necmettin Erbakan University, Medicine School (approval: 14567952-050/1566-27.11.2020). Patients who were followed in our center were retrospectively reviewed. The epidemiological characteristics (age, gender, and date of diagnosis), disease-related risk scoring and risk groups, genetic characteristics, complete blood count at the time of diagnosis, biochemical tests, and survival were recorded. Survival time was defined as the time from diagnosis to death for non-survivors and time from diagnosis to final assessment for survivors.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 22.0. Descriptive statistics are given as mean ± standard deviation. Categorical variables are presented as percentages (%) and were assessed using the chi-square test. The ANOVA and Kruskal-Wallis tests were used to compare the groups. The survival time was calculated using the Kaplan-Meier analysis and compared between groups using the log-rank test. P-values of <0.05 [95% confidence interval (CI)] was considered as statistically significant.

Results

This study retrospectively evaluated 99 patients, wherein 48 were females (48.5%) and 51 were males (51.5%). The mean age was 66.0±11.6 years in the study population. Table 1 presents the disease subtype, IPSS, R-IPSS, genetic risk groups, and the employed first-line treatment modalities.

A genetic anomaly was detected in 30 (30.3%) patients. The most common anomaly detected was del20q as seen in 8 (26.7%) patients. Multiple anomalies were detected in 3 (10%) patients, all of which showed complex karyotype features. Acute myeloid leukemia (AML) transformation was detected in 3 (3.1%) patients of the study population. These patients were male, with loss of Y chromosome in 1. Figure 1 presents the type and frequency of the genetic anomalies.

The median survival was 61 months (95% CI: 50.9-71) in the study population. According to IPSS, 9 patients were in the intermediate-2 and 1 in the high-risk group, thus the survival analyses were performed in 3 groups as "low risk," "intermediate-1," and "intermediate-2 and high risk" groups. The 5-year survival rate was calculated as 64%, 41%, and 33% in "low risk," "intermediate-1," and "intermediate-2 risk and high risk" groups, respectively. A significant difference was found in the predicted median survival time (log-rank chi-square: 6.6; p=0.035). Table 2 presents median survival in 3 groups. Figure 2 presents the survival plot. Effects of risk groups on survival were assessed using the Cox regression analysis.

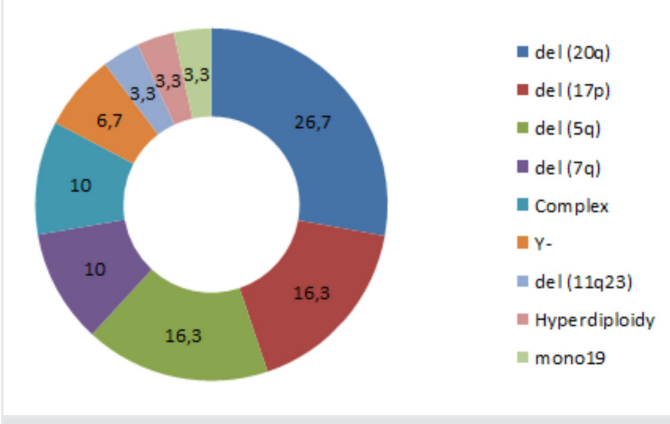

Figure 1. Frequency of genetic abnormality (%)

Table 1. Subtype and risk groups of patients (N=99)

	n	%
MDS-subtypes		
MDS-SLD	41	41,4
MDS-MLD	29	29,3
MDS-RS	3	3
MDS-EB-1	14	14,1
MDS-EB-2	8	8,1
Isolated del5q	4	4
R-IPSS		
Very low	27	27,3
Low	46	46,1
Intermediate	19	19,2
High	6	6,1
Very high	1	1
IPSS		
Low	41	41,4
Intermediate-1	48	48,5
Intermediate-2	9	9,1
High	1	1
Genetic risk		
Very good	3	3
Good	82	82,8
Intermediate	10	10,1
Poor	1	1
Very Poor	3	3

*SLD: Single lineage dysplasia, MLD: Multilineage dysplasia, RS: Ring sideroblast, EB: Excess blast, IPSS: Internationale Prognostic Scoring System, R-IPSS: Revised IPSS

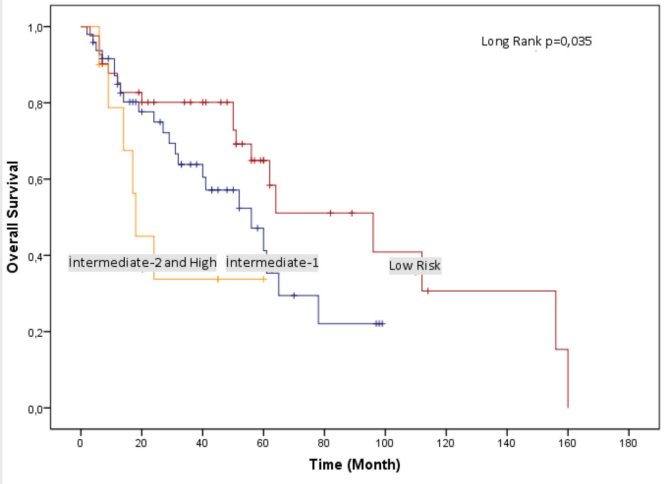

Figure 2. Overall survival according the IPSS risk groups

The risk for mortality was found as 3.3-folds higher in patients in "intermediate-2 and high risk" (RR: 3.3; 95% CI: 1.2-8.6; p=0.017), whereas 1.7-folds higher in the "intermediate-1" risk group (RR: 1.7; 95% CI: 0.9-3.5; p=0.98) compared to "low risk" group. No significant difference was found among the 3 groups in gender and MDS subtypes.

Table 2. Results of the overall survival according to the IPSS

IPSS-risk groups	Estimated median survival (month)	5-years OS (%)	p-value
Low	96 (95% CI; 47.7-144.3)	64	
Intermediate-1	56 (95% CI; 34.1-77.8)	41	**0.035***
Intermediate-2 ve high	18 (94% CI; 15.1-20.8)	33	

*Long rank, IPSS: Internationale Prognostic Scoring System, OS: Overall survival, Cl: Confidence interval

The median survival time was 51 months (95% CI: 27.1-74.8) in patients with genetic anomalies, whereas 62 months (56.5-67.4) in those without genetic anomaly, regardless of genetic risk group; however, the difference did not reach a statistical significance (log-rank chi-square: 1.3; p=0.242).

Discussion

MDS is a clonal bone marrow disorder that is diagnosed in advanced ages. The literature suggested that 80% of cases are diagnosed at >60 years old (1). Some patients are diagnosed at younger ages and cases aged <50 years can be associated with several mutations, including SFSR2 (8). Our study revealed that the mean age was 66±11.6 years, which correlates with the literature. Additionally, 8 (8.1%) patients were aged <50 years.

In the two decades, the effects of genetics have become more apparent on prognosis, treatment selection, and survival time that have been elucidated by better characterization of genetics in MDS. Some genetic anomalies, such as 5q, 7q, and 20q deletions, and chromosome anomalies that have been introduced into the diagnostic criteria and MDS with 5q deletion have been defined as a distinct subtype among the morphological subtypes (6).

Different frequency rates have been reported for genetic anomalies in MDS; however, a genetic anomaly is detected in 80% of patients with MDS (9). Particularly, alterations at the micro-RNA level and epigenetic mutations can be detected using Next Generation Sequencing (10,11). Hosono (11) reported that chromosomal anomaly was detected in 50-60%, whereas repeated somatic mutations in >50 genes were detected in 80-90% of patients. A study by Haferlach et al. (12) detected at least one mutation in 845 (89.9%) of 944 patients. In addition, a mutation was detected in 104 different genes, with TET2, SF3B1, ASXL1, SRSF2, DNMT3A, and RUNX a more common and RNS splicing mutations as the most common (12). In our center, chromosomal analysis was performed by conventional G banding method and a panel was evaluated including del (5q), del (7q), del (17p), del (20q), del (p53), del (11q23), t (15:17) fusion, and t (8:'1 by Fluorescence In Situ Hybridization. In our study, a genetic anomaly was detected in 30.3%. The lower rate in our study results is thought to be due to genetic technology limitations in our center.

In our patients, the most common genetic anomaly was del (20q), which comprise 26.7% of cases with genetic anomalies.

The primary DNA sequence, termed TERRA, is localized at 20q in the human genome and protects telomeres. Previous studies revealed that del (20q) leads to telomere loss; thus, DNA damage (13), which is not specific to MDS and can be seen in AML and other myeloproliferative diseases (14).

Cytogenetic features were classified as good, intermediate, and poor cytogenetic properties in the IPSS, whereas they were defined in more detail by adding very low and very high-risk groups in the R-IPSS (6). Del (20q) is one of the anomalies that indicate good cytogenetic characteristics (15). Our study revealed that 82.8% of cases had good cytogenetic characteristics. A large case series reported this rate at approximately 70% (5). Our analysis revealed that a lack of significant difference in patients with or without cytogenetic anomaly regardless of the risk group supports that different cytogenetic anomaly has distinct effects on prognosis. Some diagnostic features, other than cytogenetic, affect the prognosis. For instance, Malcovati et al. showed that survival was shorter in patients who are transfusion-dependent and patients with increased blast ratio (16). Thus, risk scores include cytopenia and blast ratio in addition to cytogenetic features. Moreover, the WHO-PSS also considers the MDS subtype (17). Survival is heterogeneous in MDS, which can be defined as a group of heterogeneous diseases with its clinical, laboratory, and cytogenetic characteristics. Our study found the median survival time as 61 months in the study population; however, the literature reported a survival time of 36 months and others reported a longer survival time (18).

In MDS, prognostic scoring systems are predictive for both survival and AML transformation. A multicenter study in 7,012 patients by Greenberg et al. (5) revealed that the median survival time is 8.8 years in the low-risk group and 0.8 years in the high-risk group according to the R-IPSS, whereas according to the IPSS it was 7, 3.6, 1.5, and 0.7 years in the low-risk, intermediate-1 risk, intermediate-2 risk, and high-risk groups, respectively. Our study revealed 1 patient in the high-risk group according to the IPSS and 7 patients in intermediate-2 and high-risk groups according to R-IPSS, thus the intermediate-2 and high-risk groups were assessed as one group. Based on the grouping, the median survival time was 18 months in the "intermediate-2 and high risk" group, whereas 56 and 96 months in "intermediate-1" and "low risk" groups, respectively. The shorter 5-year overall survival time by increasing risk correlates with the literature. Additionally, the risk for mortality was significantly higher (by 3.3 folds) in the "intermediate-2 and high risk" group compared to the "low risk" group. Mortality risk was 1.7-fold higher in the "intermediate-1" risk group compared to the "low risk" group. These findings support that risk assessment in MDS has a significant effect on survival.

AML transformation occurs in 20-30% of patients with MDS, of which the majority are high risk (19). Additionally, time to transformation is shorter in the high and very high-risk groups according to the R-IPSS (17). Our study revealed 3 patients with AML transformation in the "low risk" group regarding the genetic and prognostic aspects.

The MDS subtypes were assessed, the most common subtype was MDS with single lineage dysplasia (MDS-SLD) by 41.4%. The current literature reported that the incidence of MDS-SLD was approximate 7-20% (20). MDS registry that includes 7,012 patients by Della Porta et al. (17) revealed that the most common subtype was MDS with multi-lineage dysplasia by 29.6%.

Study Limitations

Our study revealed the AML transformation in the "low risk" group and the most common MDS subtype was inconsistent with the literature. This is attributed to the single-center design and smaller sample size, which is also the main limitation of our study. Other limitations include combining "intermediate-2 and high risk" groups in the survival analysis, insufficient survival analysis according to R-IPSS groups, and failure to assess the treatment modalities and their effects on survival.

Conclusion

However, our study can contribute to the literature by detecting the cytogenetic characteristics despite limited technical sources and emphasizing the effects of risk assessment on survival.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee on Medicinal Product and Non-Medical Device Research of Necmettin Erbakan University, Medicine School (approval: 14567952-050/1566-27.11.2020).

Informed Consent: It has taken.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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Original Article

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A Novel External Fixator Designed for a More Comfortable and Secure Hip Arthroscopy

Daha Rahat ve Güvenli Kalça Artroskopisi için Yeni Bir Eksternal Fiksatör Tasarımı

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ABSTRACT

Objective: To evaluate the functional results of a novel external fixator (EF) designed for joint distraction and prevention of traction table-related hip arthroscopy complications

Methods: After obtaining promising results in a cadaveric study, 21 hips of 20 patients underwent EF-assisted arthroscopic hip surgeries for femoroacetabular impingement (FAI) and/or labral tear treatments. Patients were operated on a standard operating table in the supine position. A novel EF was used to distract the joint for central hip arthroscopy. The time needed for EF application and joint distraction and the amount of joint distraction were recorded. Preoperative functional scores were retrospectively compared to the postoperative 5-year follow-up results using the Harris Hip and Western Ontario and McMaster Universities Index scores.

Results: All patients underwent peripheral and central arthroscopy. The mean time for EF application and joint distraction was 19 min (range: 8-21). The mean amount of joint distraction was 13.2 mm (range: 12-18). None of the arthroscopic procedures had to be converted to open surgery. Functional results of all patients were improved at the 5-year follow-up ($p<0.01$). Only one patient required hip arthroscopy revision due to residual FAI. No other major or minor complication was found that is related to the EF or arthroscopy itself.

Conclusion: Mid-term outcomes following EF-assisted hip arthroscopy demonstrate significant improvement in the functional outcomes without traction table-related complications. EF can be used as an alternative to traction table to maintain adequate hip

ÖZ

Amaç: Kalça artroskopisinde traksiyon masası ile ilişkili komplikasyonların önlenmesi ve eklem distraksiyonu için tasarlanmış yeni bir eksternal fiksatörün (EF) fonksiyonel sonuçlarını araştırmaktır.

Yöntemler: Kadavra çalışmasında ümit verici sonuçlar elde ettikten sonra 20 hastanın 21 kalçasına femoroasetabuler sıkışma (FAS) ve/veya labral yırtık tedavisi için EF destekli kalça artroskopi cerrahisi uygulandı. Hastalar sırtüstü pozisyonda standart ameliyat masasında opere edildi. Santral kalça artroskopisinde eklemin distraksiyonu için yeni tasarım EF kullanıldı. EF uygulanması ve eklem distraksiyonu elde edilmesi için gereken süre ile distraksiyon miktarı kaydedildi. Ameliyat öncesi Harris Kalça ve WOMAC fonksiyonel skorları ameliyat sonrası beş yıllık takip sonuçları ile retrospektif olarak karşılaştırıldı.

Bulgular: Tüm hastalara periferik ve santral kalça artroskopisi uygulandı. EF uygulaması ile eklem distraksiyonu için gereken ortalama süre 19 dakikaydı (dağılım: 8 ila 21). Eklem distraksiyonunun ortalama miktarı 13,2 mm (dağılım: 12-18) idi. Artroskopik prosedürlerin hiçbirinde açık cerrahiye geçilmek zorunda kalınmadı. Ameliyat sonrası beş yıllık takipte tüm hastaların fonksiyonel sonuçları ameliyat öncesine göre iyileşti ($p<0,01$). Sadece bir hastada rezidüel FAS nedeniyle revizyon kalça artroskopisi yapıldı. EF veya artroskopinin kendisi ile ilgili başka bir majör veya minör komplikasyon görülmedi.

Sonuç: EF destekli kalça artroskopisini takiben traksiyon masası ile ilişkili komplikasyon riski olmaksızın fonksiyonel sonuçlarda

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distraction in arthroscopic hip surgery. In addition to the rotation, a novel designed EF allows hip joint flexion during distraction contrary to traction table.

Keywords: Arthroscopy, external fixator, hip, traction, complication

anlamlı düzelme görülmektedir. EF artroskopik kalça cerrahisinde yeterli distraksiyon sağlanması amacıyla traksiyon masasına alternatif olarak kullanılabilir. Yeni tasarım EF distraksiyon sırasında kalça ekleminin rotasyonuna ek olarak fleksiyona da izin verir.

Anahtar Sözcükler: Artroskopi, eksternal fiksatör, kalça, traksiyon, komplikasyon

Introduction

Hip arthroscopy was firstly performed in 1931; however, arthroscopic hip surgery has been popularized in the last two decades with the development of specific instruments, arthroscopic tools, and better hip joint pathology understanding (1-4). The anatomical of hip joint constraints make its scope more challenging than the other joints. Adequate joint distraction should be obtained and maintained to visualize the joint inside, especially the central compartment, and to intervene inside the hip (5-8). Therefore, traction tables are widely used. However, some specific complications, such as pudendal nerve palsy and perineal soft tissue necrosis, which are directly related to the distraction or increase perineal post pressure on the skin, have been reported (6,9). Additionally, traction or perineal post-related nerve dysfunction after hip arthroscopy is an under-reported complication (10). Another disadvantage of the traction table is its limitation on the hip joint motions during the surgery. These difficulties and complications make this procedure more challenging. Thus, an external fixator (EF) is designed to eliminate the complications due to traction table and to allow hip flexion and rotation during distraction to perform a more secure and comfortable hip arthroscopy.

A two-stage retrospective study was designed to evaluate the safety and outcomes of our novel external distraction device for patients undergoing hip arthroscopy. The first stage was a cadaveric study and the second stage was the application of EF in patients.

The study hypothesized that joint distraction with the use of an EF can be a safe and alternative method to a traction table with similar success rates and less risk of traction table-related complications in arthroscopic hip surgeries. This study aimed to evaluate the effectiveness and safety of a novel EF for joint distraction in the arthroscopic treatment of hip pathologies.

Method

After a satisfactory cadaveric study, instructional review board and local ethical committee approvals were obtained for the clinical retrospective study. Detailed information about the surgical interventions was provided to all patients and each patient signed an informed consent form, including the treatment alternatives, operative technique, and complications.

Patient Selection

Between December 2010 and October 2012, 36 consecutive patients undergoing hip arthroscopy were proposed to participate in this study. Patients, who were informed about the study and then accepted the EF application, were included. Patients over 60 years old were excluded due to possible fracture risk around the Schanz screws secondary to osteoporosis. Twenty-seven patients fulfilled the inclusion and exclusion criteria mentioned above and agreed to participate in our study and seven patients were lost to follow-up. Of 20 consecutive patients (10 male and 10 female) with a mean age of 34.1 (range: 19-46) years, 21 hips (10 right and 11 left) underwent EF-assisted arthroscopic hip surgery. The etiologies include isolated cam-type femoroacetabular impingement (FAI) in six patients, cam-type FAI and concomitant labral tear in five patients, pincer type FAI in one patient, mixt type (cam + pincer) FAI and concomitant labral tear in three patients, and isolated labral tear in six patients.

Only cam resection was performed in six patients, cam resection and labral tear debridement in five patients, pincer resection in one patient, labral repair with suture anchors and cam and pincer resection in three patients, and labrum debridement in six patients with an isolated labral tear.

External Fixator

The EF was made of stainless steel, weighing 1,750 grams, 280 mm in width, 235 mm in height at the distal part, 130 mm in height at proximal part, and 83 mm in depth. The novel EF can carry an 800 N (80 kg) load and can be distracted up to 105 mm with the help of a distraction device. The fixator has two hinge clickers, one in the proximal and one in the distal part, a vertically oriented clamp on its proximal part for the insertion of two or three half-pins to the supra acetabular region, and a T-shaped clamp on its distal end for fixation of the Schanz screws to the femoral diaphysis (Figure 1).

Preliminary Cadaveric Study

A preliminary cadaveric study was performed with this novel designed EF to check if it easily works and provides an adequate hip joint distraction. Four hips of two male fresh frozen cadavers (with ages 54 and 64 years) were prepared. According to the plain radiographs, the cadavers without obvious degeneration or arthrosis signs in their hip joints were included and those with hip deformity were excluded. The EF was fixed to the pelvis on the supra acetabular region and the mid diaphysis of the femur using two half-pins for each region. Turning the distractor of the fixator under fluoroscopic control resulted in increased femoroacetabular distance. After obtaining an adequate amount

of joint space, central and peripheral regions were evaluated through standard arthroscopic portals.

Surgical Technique

Patients were placed in a supine position on a standard operating table, and the fluoroscopic view of the operative hip joint was checked under general or regional anesthesia. Fluoroscopy, image intensifier screening, and arthroscopy system were placed on the opposite side of the operative leg that faces the surgeon. Two 6 mm half-pins were applied, 2 cm above the supra acetabular region joint in about 30˚ abducted position to prevent impingements of the arthroscopy instruments to the Schanz screws around the hip and reach into the central compartment easily (Figure 2). The screws were fixed to the proximal clamp of the fixator. Another two 6 mm half-pins were inserted perpendicular to the mid diaphysis of the femur after 30˚ abduction of the operative leg and predrill in the insertion site of the screws, and they were fixed to the T-clamp of the fixator.

After EF application, the EF distractor was rotated in a counter-clockwise direction until the adequate widening of the hip joint, under the fluoroscopic control, was obtained (Figures 3 and 4). Subsequently, the central and peripheral regions of the hip joints were evaluated, and arthroscopic intervention was performed through standard arthroscopic portals. To reach far areas in the peripheral or central compartment, flexion or rotational movements of the distracted hip joint were possible with the novel EF (Figure 5). After carrying out the operation in the central compartment, the distractor was released and intervention in the peripheral compartment was performed without distraction as standard. The EF and half-pins were removed at the end of the arthroscopic procedure and arthroscopy portals and screw entry sites were sutured using absorbable monofilament materials.

Operation Findings Assessment

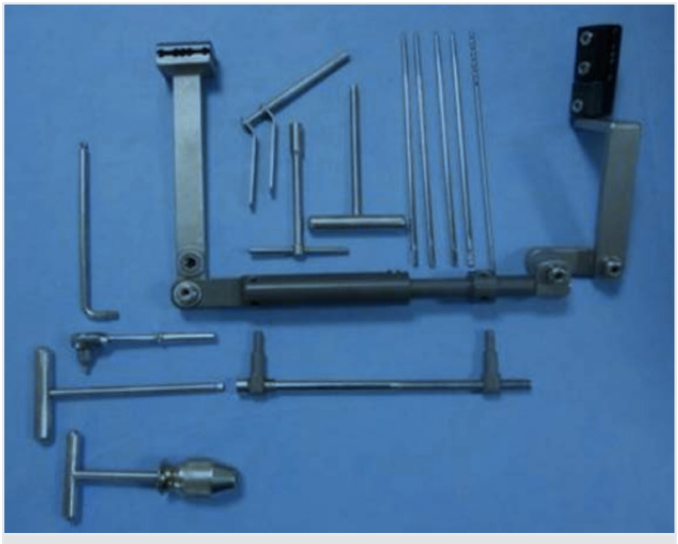

Figure 1. The novel designed EF, its distractor, half-pins, and other instruments for the set-up
EF: External fixator

The outcome parameters include the required time for EF application and adequate distraction and the amount of joint distraction. The distance between the most superolateral edge of the acetabulum and the femoral head was measured on the fluoroscopy images before and after the distraction in the same leg position. The radius of the 6 mm Schanz screws placed at the supra acetabular area was also measured on the fluoroscopy images and the rate of magnifier was found for each patient. The difference between the post- and preoperatively measured lengths was multiplied with the magnifier ratio and the corrected distraction value was found.

Functional Outcome Assessment

The Harris Hip Score (HHS) and the Western Ontario and McMaster Universities Index (WOMAC) scores were evaluated

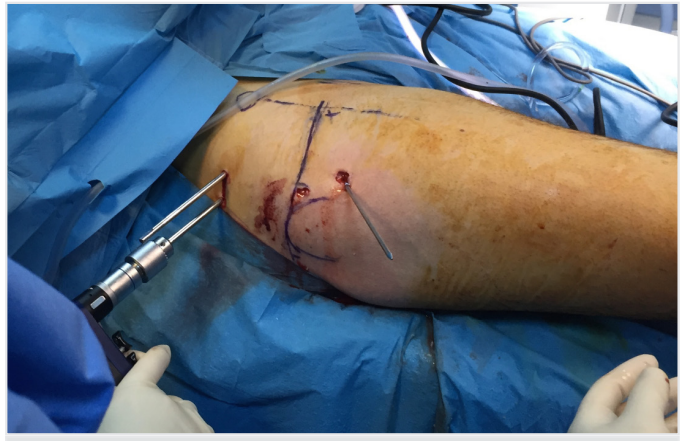

Figure 2. Application of the proximal Schanz screws to the supra acetabular region

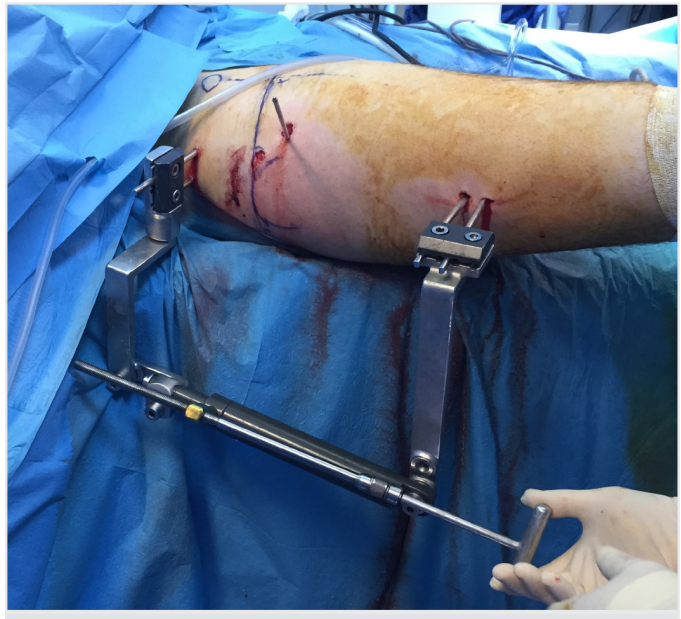

Figure 3. After the Schanz screw insertion and EF set-up, the distractor was rotated in a counter-clockwise direction to achieve joint distraction using its T-handle
EF: External fixator

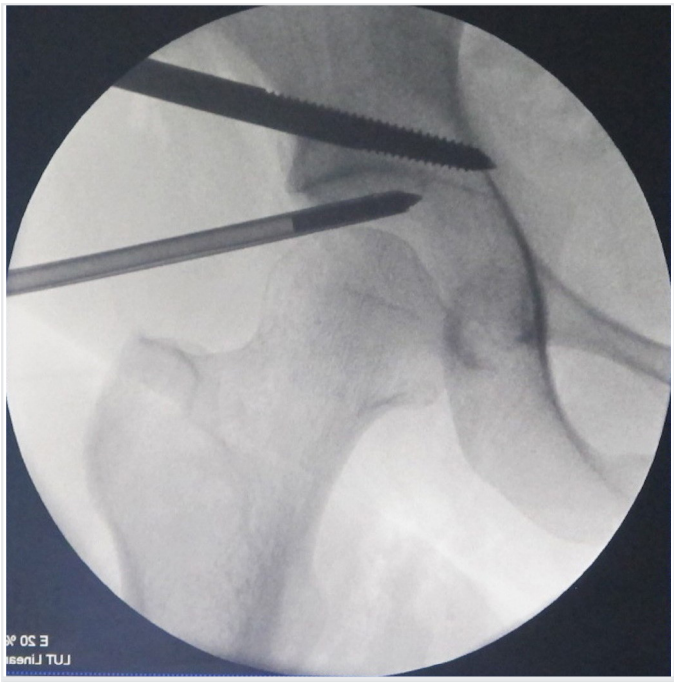

Figure 4. The amount of distraction, half-pin positions, bony integrity under distraction forces, and arthroscopy instrument placement controlled under fluoroscopy

by a research physiotherapist without prior knowledge of the surgical reports and radiological imaging pre- and postoperatively at the 5-year follow-up. Pre- and postoperative functional results were statistically compared.

Follow-up Protocol

Postoperative rehabilitation protocol included an immediate range of motion (ROM) exercises with the help of a continuous passive motion device for the first 2 days. All patients were discharged on the second day of surgery with a home rehabilitation protocol, which include hip joint ROM exercises and strengthening exercises for the musculature around the hip. Patients, who underwent cam or pincer resection, were allowed non-weight bearing walking with crutches for the first 3 weeks and partial weight-bearing with crutches between the third and sixth week of surgery. After 6 weeks, full weight-bearing was allowed. Full weight-bearing without crutches was allowed for patients who underwent labral debridement alone, whereas patients who underwent labrum repair were allowed non-weight bearing with crutches for the first 6 weeks as standard.

Statistical Analysis

All statistical analysis was performed using the Statistical Package for the Social Sciences statistical software package (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The Shapiro-Wilk test was used to determine the concordance of the continuous data to normal distribution. Continuous data were presented as median (minimum-maximum) and mean ± standard deviation values. Preoperative and postoperative functional results were statistically compared using the paired t-test. Results were reported as 95% confidence intervals and related p-values, wherein $p<0.05$ was considered statistically significant.

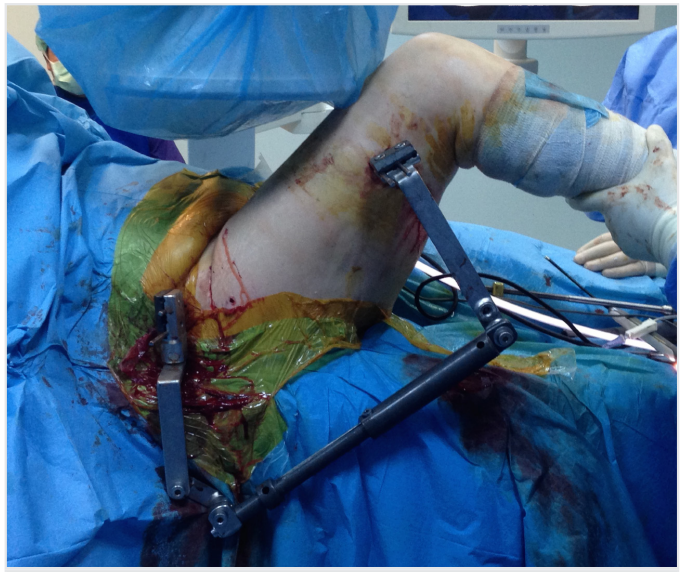

Figure 5. The novel EF allows up to 60 degrees of hip flexion as required
EF: External fixator

Results

Both central and peripheral compartment evaluations and interventions were easily performed in all patients. None of the arthroscopic procedures had to be converted to open surgery.

The mean total amount of required time for EF application and adequate joint distraction was 19 min (range: 8-21). A single fluoroscopy shot was taken at each stage of surgery to control ideal pin placement and effective distraction in all operations. The mean number of fluoroscopy shots was 22 (range: 18-28). The mean amount of effective joint distraction was 13.2 mm (range: 12-18). The mean HHS was improved from 57.1±15.3, preoperatively to 86.5±15.1, postoperatively ($p<0.001$). The mean WOMAC index was increased from 40.4±15, preoperatively to 89±7.3, postoperatively ($p<0.001$). During the surgeries, a minimum of 30˚ external and internal rotations was obtained using the EF while distraction was maintained.

One female patient had complaints of continuing hip pain and impingement symptoms similar to her preoperative status that was diagnosed as residual FAI due to inadequate cam resection required arthroscopic surgery revision. Almost all patients (19 of 20) had lateral hip pain around the pinholes of the supra acetabular and femoral regions. Their complaints were over in 3 days with postoperative anti-inflammatory drug treatment. No other complication related to arthroscopic hip surgery, such as neurological complications, soft tissue problems, heterotopic ossification, or osteoarthritis, was noted.

Discussion

Hip joint distraction is essential for arthroscopic hip procedures (11). Most surgeons place patients in the supine position on the traction table; however, these procedures can be also performed

in the lateral decubitus position (5,7). Meanwhile, successful results of joint distraction with the help of an EF were already reported (12).

This study introduces a novel EF design for joint distraction as part of the arthroscopic hip surgeries, which was considered to eliminate traction table or perineal post-related complications. Additionally, surgery becomes easier using the EF since it allows hip flexion and rotation while maintaining joint distraction. Dienst et al. reported that better hip joint distraction was achieved at 20 degrees of flexion without abduction (13). Therefore, we designed the novel EF and test it in a preliminary cadaveric study. After getting easy and adequate hip joint distractions on the cadavers, a clinical study was started, which obtained satisfactory results without EF-related complications.

Several complications that are directly related to the traction table usage were reported, such as neuropraxia (transient or permanent pudendal, sciatic or common peroneal nerve injuries), soft tissue problems (genitoperineal skin necrosis and vulvar hematoma), crush syndrome, or well-leg compartment syndrome (6,9,11). Ankle fracture, skin irritations, foot and ankle paresthesias, and vascular obstruction at the level of the ankle joint directly related to tight foot fixation in the traction device boot have been reported (14-16), mainly due to traction misuse, inappropriate perineal post use, and hemilithotomy position for the well-leg. Positive correlations were well-presented in several studies between the pudendal nerve palsy incidence and perineal post size, and amount of the traction force (9,17,18). The current study revealed no complications, most probably due to the use of EF and no traction table. Only one patient required hip arthroscopy revision due to the continuing impingement symptoms. In her second look arthroscopy, a residual cam was observed and arthroscopic re-resection was performed. Her complaints were over at the 5-year follow-up. However, the number of patients in our study is too low to conclude that this technique prevents complications.

A prospective study by Flecher et al. (12) described the use of hip distractor in the arthroscopic treatment of FAI and reported the functional results of 23 patients. They indicated no complication in their consecutive series and concluded that using a distractor during hip arthroscopy is a reproducible and reliable technique in FAI treatment. Their hip distractor showed similarities with the novel EF in our study. However, novel EF differs with its ability to allow flexion and rotational movements of the hip joint while maintaining distraction. Moreover, Schanz screw application to the femoral diaphysis provides a wider working area around the hip joint, which facilitates the use of accessory arthroscopic portals when required. Another difference in their study is that all operations were performed in the lateral decubitus position, whereas the patients in our series were operated in a supine position. Additionally, in their study hip arthroscopies were performed only for FAI treatment, whereas ours is not only for FAI but also for labral tears.

Contrarily, Merrell et al. (19) used a deflated beanbag instead of the perineal post to reduce the complications due to the perineal post. They used pillows, blankets, and tape to secure the patient to the beanbag and table. They reported that their technique provides sufficient stability for adequate traction and good visualization while minimizing the risk of pudendal nerve palsy. However, the beanbag that wraps around the abdomen may slip in patients with obesity during surgery. Details of 30 patients in their study were not provided.

Study Limitations

This study has several limitations, including its retrospective nature and lack of a control group. Another limitation is the small number of patients with heterogeneous etiologies and interventions. Some potential EF-related complications, such as fractures or visceral proximal half-pin penetration, may occur in larger series, which was not experienced in our case series. All surgeries were performed by a single senior surgeon and the experience of different surgeons was not included in the study may be another limitation point.

Conclusion

In conclusion, mid-term outcomes of EF-assisted hip arthroscopy demonstrate significant improvement in the functional outcomes with the advantage of avoiding traction table-related complications. EF can be used as a safe, reliable, and reproducible alternative to traction tables to obtain adequate joint distraction in arthroscopic hip surgery. Novel EF allows hip joint rotation and flexion during the distraction, as well as supine position operation. Further prospective randomized controlled comparative studies that involve more patients are necessary to determine which joint distraction technique might be superior in complication rates for arthroscopic hip procedures.

Ethics

Ethics Committee Approval: After a satisfactory cadaveric study, instructional review board and local ethical committee approvals were obtained for the clinical retrospective study.

Informed Consent: Detailed information about the surgical interventions was provided to all patients and each patient signed an informed consent form, including the treatment alternatives, operative technique, and complications.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.T., Concept: F.Y., Design: A.P., Data Collection or Processing: V.U., Analysis or Interpretation: V.U., Literature Search: A.P., Writing: İ.T.

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

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Original Article

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Bezmialem Science 2022;10(1):35-43

Ultrasound-guided Venous Catheterization Experiences in Pediatric Burn Cases in Our New Burn Center

Yeni Yanık Merkezimizde Pediatrik Yanık Olgularında Ultrason Eşliğinde Venous Kateterizasyon Deneyimlerimiz

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ABSTRACT

Objective: This study aimed to convey our experience in opening the central venous catheter (CVC) with ultrasound (US) in children under 18 years old who came to our clinic between September 01, 2018, and December 15, 2019.

Methods: This study included 20 patients with a body burn surface of ≥15% due to electrical, chemical, and inhalation burns, of which vascular access is impossible despite at least 5 years of experienced assistant health personnel. Patients with thrombocytopenia and coagulopathy, whose catheter could not be opened with the US and were not allowed to be operated on by their parents were excluded from the study.

Results: Included patients were determined to be equal in gender. The mean age values of patients were calculated as 39.45±39.10 months, and the average burn percentage was 27.25±8.95%. The cause of burns examination revealed that 13 (65%) patients had hot water, 1 (5%) had hot tea, 4 (20%) had hot milk, and 2 (10%) had flame burns. The examination for the CVC opening indication revealed that 14 patients (70%) were tried by experienced medical staff, but the CVC was observed to be opened for 6 patients (30%) due to the prevention of hypovolemia.

Conclusion: Our study results showed that the CVC opening performed with the help of the US in the pediatric patient group should be the preferred method of choice for patients with burns since it has both fewer complications and a higher chance of success.

Keywords: Central venous catheterization, ultrasonography, burn

ÖZ

Amaç: 01.09.2018 ve 15.12.2019 tarihleri arasında kliniğimize gelen 18 yaş altı yoğun bakım takibi gereken çocuklarda ultrasonografi (USG) eşliğinde santral venöz kateter (SVK) açma deneyimlerimizi aktarmayı amaçladık.

Yöntemler: Bu çalışmada vücut yanık yüzeyi ≥%15 olan, elektrik, kimyasal ve inhalasyon yanığı olan, en az 5 yıllık deneyimli yardımcı sağlık personeli çabasına rağmen damar yolu ulaşımı sağlanamayan 20 hasta dahil edildi. Trombositopenisi ve koagulopatisi olan, USG ile katater açılamayan ve ebeveynleri tarafından işleme izin verilmeyen hastalar çalışma dışı bırakıldı.

Bulgular: Çalışmaya dahil edilen hastalar cinsiyet açısından eşit tespit edildi. Hastaların ortalama yaş değerleri 39,45±39,10 ay olarak hesaplandı. Hastaların ortalama yanık yüzdesi %27,25±8,95 bulundu. Hastalar yanık nedeni açısından incelendiğinde 13 hastada sıcak su yanığı (%65), 1 hastada sıcak çay yanığı (%5), 4 hastada sıcak süt yanığı (%20) ve 2 hastada alev yanığı (%10) olduğu saptandı. Hastalar SVK açma endikasyonu açısından incelendiğinde 14 hastaya (%70) deneyimli sağlık personeli tarafından denenmesine rağmen damar yolu bulunamadığı için, 6 hastaya (%30) hipovolemi önlenmesi nedeniyle CVP açıldığı gözlendi.

Sonuç: Çalışma sonuçlarımız gösterdi ki pediatrik hasta grubunda USG yardımıyla açılan CVP işlemi hem daha az komplikasyona hem de daha yüksek başarı şansına sahip olması nedeniyle yanık hastalarında öncelikli tercih edilen yöntem olmalıdır.

Anahtar Sözcükler: Santral venöz punksiyon, ultrasonografi, yanık

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Introduction

Burns occurring in children is a health problem that must be examined in all aspects, as they cause severe physical and psychological trauma in patients, as well as high mortality and morbidity due to dehydration and metabolic events. The World Health Organization has determined that the number of injuries caused by burns is 6.6 million people each year and the number of deaths caused by burns is 300,000 (1).

When the patients are examined by age groups, childhood and newborn period constitute a high-risk group in burns. Studies in the literature show that 50% of patients with burn are from the patient group in these two periods (1).

The examination of patients with burns in terms of their causes revealed that hot water and milk burns are frequently observed, especially in childhood, whereas flame burns are more frequently observed in the adult group. These causes are followed by electrical and chemical Some burns in our clinic are shown in Figure 1,2.

The most important indicators of mortality in burns that are observed in the childhood and newborn period are the amount of burn surface, fluid-electrolyte disturbances that develop in patients, acute renal failure, and infections. Therefore, effective fluid management, appropriate antibiotherapy, and nutritional correction are the most important parameters in preventing mortality.

Based on the loss of fluid observed due to burns and the width of the burn area, vascular access problem in the pediatric patient group poses a serious problem for healthcare professionals. Therefore, opening an appropriately sized central venous catheter (CVC) in the early period was the primary preference in patients undergoing intensive care in most centers.

The literature has shown fewer complications and higher success rates after CVC opening with the use of ultrasonography; however, routine ultrasonography (US) has not been used during CVC opening in many clinics (3,4).

A study conducted in the United States of America revealed that the rate of US aiming at CVC in burn centers is <50% (5). Many factors have been found effective in low rates of US use. Primarily, because US device is still unavailable in most clinics, the procedure duration due to the use of US is extended, which causes the clinicians not to prefer the US, and the ability to use the US is insufficient.

This study aimed to convey our experiences of opening the CVC accompanied by the US in children under 18 years in intensive care, who came to our clinic between September 01, 2018, and December 15, 2019.

Method

Our study was conducted in our burn center with 13 clinical beds and 5 intensive care beds. The study started after the approval from our hospital ethics committee dated May 15, 2020, with approval number 478. Approximately, 715 patients with burns were applied to the burn center of our hospital during the study. Of these, 20 patients with a body burn surface of ≥15%, with electrical, chemical, and inhalation burns, and whose vascular access could not be achieved despite the efforts of experienced medical personnel, were included. Patients with thrombocytopenia and coagulopathy, whose catheter could not be opened with the US, and who were not allowed to be operated on by their parents, were excluded from the study.

In our burn center, routine US is used during the CVC opening. Patients' images and data are recorded on our computers. Patient data were accessed through the electronic data recording system and anesthesia forms of our hospital. Demographic data of each patient, total body burn percentage, burn type and grade, burn zone, CVC opening indication, CVC shape opened, CVC size used, number of trials, complications during the procedure, urea and creatine values before and after CVC opening, hospitalization duration, and mortality status were recorded.

The burn percentage was given in percentage of the total body surface area and the calculation was made using the "Lund-Browder Scale" (6) (Figure 3). In the grading, the depth of the burn was evaluated and classification was made between 1 and 4 degrees. First-degree burns were defined as superficial burns, of which the depth did not exceed the epidermis. Second-degree burns are those with a depth exceeding the epidermis but not more than half the dermis. Third-degree burns depth was defined as burns with dermis passing through the full layer and affected by the reticular dermis. Fourth-degree burns were defined as burns extending to the subcutaneous fascia that contains muscle or bone. Since first-degree isolated burns were treated in an outpatient clinic in our hospital, they were excluded from our data.

The length of hospital stay was evaluated in days and was recorded as the time between the day of hospital admission and the day of discharge.

When choosing the CVC region, the distance from the burn area was preferred as far as possible from the burn site to reduce the risk of infection. Before the procedure, 1 mcq/kg of fentanyl, 0.1 mg/kg of midazolam, or 1-2 mg/kg of ketamine were given for sedation. During the procedure, patients were monitored for heart rate, rhythm, respiratory rate, and peripheral oxygen saturation. After the sterile dressing and taking necessary medical barrier measures (mask, sterile gloves, disposable sterile gowns, and goggles), the treatment area was cleaned with 10% povidone-iodine (Poviiodex). During the procedure, a routine linear US probe (7.5 MHz) was used (Mindray DP-50). Technically, the plane technique was preferred. Before the procedure, the venous structures in the appropriate CVC regions were evaluated with the US, and regions with an anatomical variation or thrombus were excluded. Arterial and vein localization was determined and the image was taken on the midline in the image of the US. "Seldinger Technique" was preferred when inserting the catheter (7) (Figure 4,5). After the catheter was placed, the use of the CVC was started after both the US and posterior-anterior chest X-ray were seen in the distal superior vena cava or right atrium entrance.

Statistics Analysis

Numerical data that were obtained in the study were expressed as arithmetic mean ± standard deviation, and categorical data were expressed as frequency (percent). Statistical analyzes were performed using the Statistical Package for the Social Sciences version 16.0 (Chi. Ill. USA). Compliance of numerical data to normal distribution was tested with the Shapiro-Wilks and homogeneity with the Levene test. For statistical analysis, the chi-square, Student's t independent, one-way analysis of variance, and post hoc Tukey-HSD tests were used. P-values of <0.05 value were accepted for statistical significance.

Results

The examination of patients in terms of gender revealed that 10 (50%) were female and 10 (50%) were male (Table 1).

The mean age values of patients were calculated as 39.45±39.10 months (minimum: 10 months, maximum: 154 months).

The average burn percentage of patients was 27.25±8.95 (minimum: 15%, maximum: 45%).

The examination of patients in terms of the degree of burns revealed that 10 patients were followed due to second-degree burns (50%), 9 for third-degree burns (45%), and 1 for fourth-degree burns (5%).

The examination for the cause of burns revealed that 13 (65%) patients had hot water, 1 (5%) had hot tea, 4 (20%) had hot milk, and 2 (10%) had flame burns.

The examination in the length of hospital stay revealed that the average length of hospital stay was 10.10±3.93 days.

The examination for the CVC indication revealed that vascular access was not found; however, 14 (70%) patients were tried by experienced medical personnel and observed that 6 (30%) patients had opened CVC due to hypovolemia (Table 2).

The examination of the CVC opening region revealed that the femoral region was preferred in 10 (50%) patients and the internal jugular region was preferred in another 10 (50%) patients.

The evaluation of the used CVC diameter revealed that 10 (50%) patients opened 5 F CVC and another 10 (50%) patients opened 4 F CVC.

The examination of the procedure duration revealed that the average duration of the procedure was 11.05 (±6.37) (minimum: 4, maximum: 30) min.

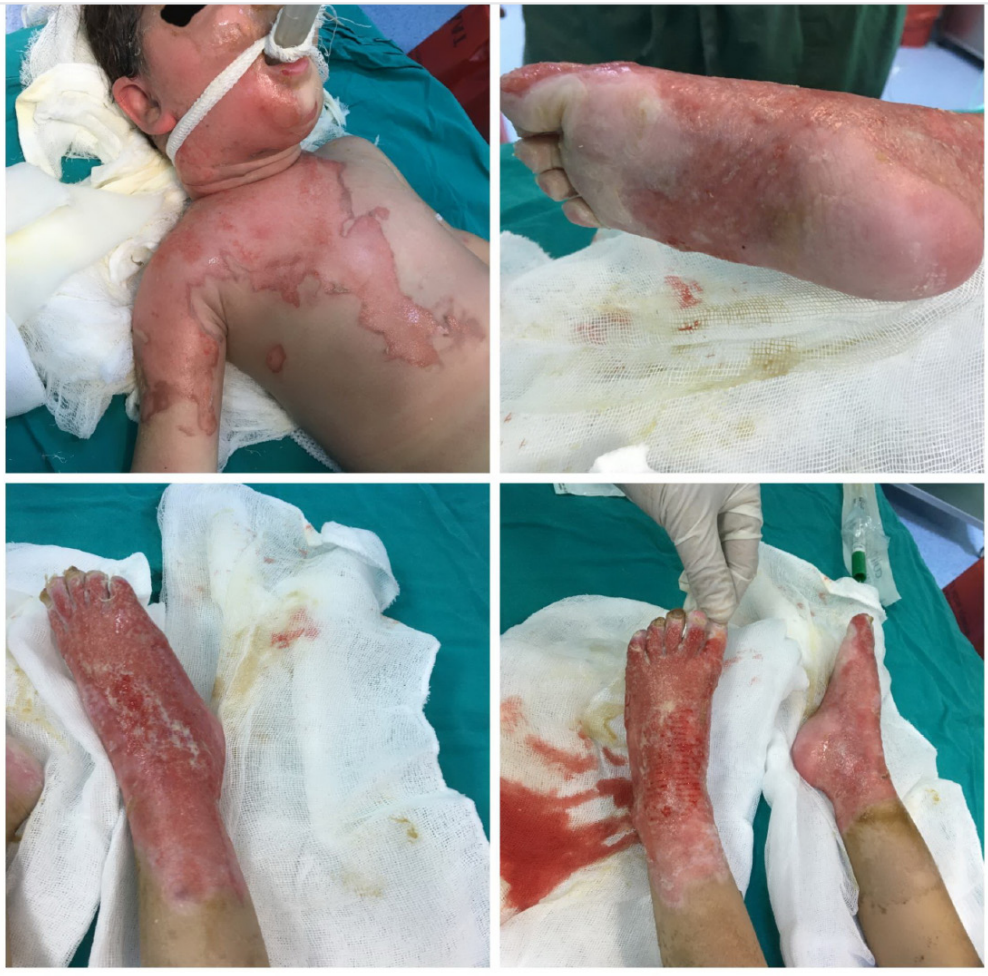


Figure 1. Pediatric patient developing scalding burn after pouring hot water

The examination of the number of trials during CVC opening revealed that the average number of trials was 1.70 (±0.92) (minimum: 1, maximum: 4) times.

The examination of complications during the procedure revealed that complications were observed in 2 (10%) patients, of which both were intraarterial punctures and were effectively controlled after 5 min of compression.

None of the patients included in the study was exitus.

The examination of the urea values (urea 1) before the CVC opening revealed a mean value of 27.6±8.15 mg/dL. Whereas the creatinine means value (cre 1) was 33.30±2.90 mg/dL.

The examination of the urea values (urea 2) after the CVC opening and adequate fluid resuscitation revealed a mean value of 12.15±5.43mg/dL. Whereas, the creatinine mean value was 20.35±3.41 mg/dL.

The comparison of urea value before fluid resuscitation was 15.45±9.05 mg/dL (p=0.000), whereas the creatinine value was 12.93±15.58 mg/dL (p=0.001) (Table 3).

No symptoms of acute kidney injury were observed in any patients in the study.

Discussion

This study aimed to present a retrospective evaluation of our CVC catheter opening experiences in patients under 16 years old in our burn center intensive care unit and with a burn percentage of ≥15 and contribute to the literature on the subject.

Table 1. Demographic and burn-related data

Characteristics	Categories	N (%)
Gender	Female	10 (%50)
	Male	10 (%50)
Age (month)	39.45 (±39.10)	
Burn type	Hot water	13 (%65)
	Hot tea	1 (%5)
	Hot milk	4 (%20)
	Flame	2 (%10)
Burn degree	1. degree	0 (%0)
	2. degree	10 (%50)
	3. degree	9 (%45)
	4. degree	1 (%5)
Total body burn percentage	27.25% (±8.95)	
Hospital stay (days)	10.10 (±3.93)	

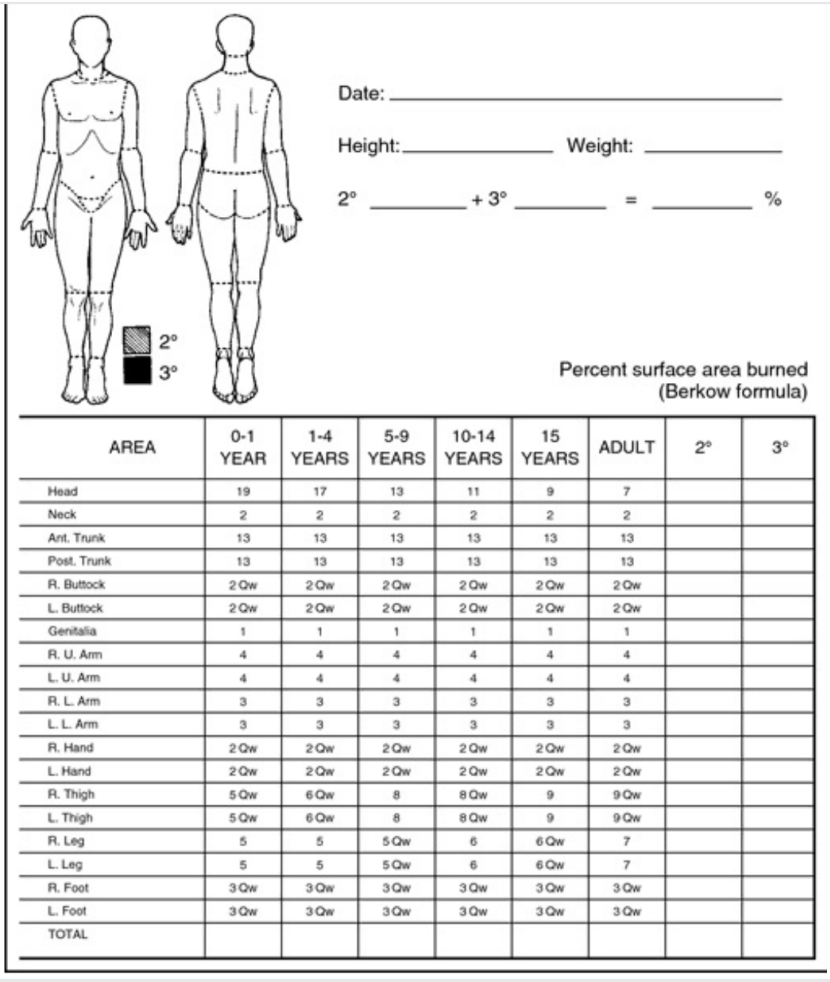
Figure 2. Pediatric patient developing scalding burn after pouring hot milk

Table 2. Process evaluation		
Characteristics	Categories	n (%)
CVC indication	Hypovolemia	6 (30%)
	No vascular access	14 (70%)
CVC region	Femoral	10 (50%)
	Internal jugular	10 (50%)
CVC F	4 F	10 (50%)
	5F	10 (50%)
Processing time (min)	11.05 ± 6.37	
Number of attempts	1.70 ± 0.92	
Complication	Intraarterial puncture	2 (10%)
Mortality		0 (0%)

Younghwan et al. (8), in their study with burn patients over the age of 18 years, found the ratio of male to female as 1.81/1, whereas Austin et al. (9) found this rate as 1.11/1. Our study revealed this rate as 1/1. Compared to other studies, we associate this difference between the gender distributions with the different age groups of the studies. The frequency of burns increases in male as the age increases since most studies in the literature are conducted with adults and the frequency of working in risky jobs in males are higher than in females (8,9).

The literature review revealed that the incidence of burns in newborns and children is higher than that of adults (10,11). Our study preferred the group of patients under 16 years old with a higher risk of severe injury to the burn, as both burns are more frequent and the body surface area is larger than adults.

Table 3. Urea/creatinine values analysis				
	Mean ± SD	Minimum	Maximum	P-value
Urea 1-Urea 2	15.45± 9.05	11.21	19.68	0.000
Cre 1-Cre 2	12.93 ± 15.58	5.64	20.23	0.001
SD: Standard deviation				



AREA	0-1 YEAR	1-4 YEARS	5-9 YEARS	10-14 YEARS	15 YEARS	ADULT	2°	3°
Head	19	17	13	11	9	7		
Neck	2	2	2	2	2	2		
Ant. Trunk	13	13	13	13	13	13		
Post. Trunk	13	13	13	13	13	13		
R. Buttock	2 Qw	2 Qw	2 Qw	2 Qw	2 Qw	2 Qw		
L. Buttock	2 Qw	2 Qw	2 Qw	2 Qw	2 Qw	2 Qw		
Genitalia	1	1	1	1	1	1		
R. U. Arm	4	4	4	4	4	4		
L. U. Arm	4	4	4	4	4	4		
R. L. Arm	3	3	3	3	3	3		
L. L. Arm	3	3	3	3	3	3		
R. Hand	2 Qw	2 Qw	2 Qw	2 Qw	2 Qw	2 Qw		
L. Hand	2 Qw	2 Qw	2 Qw	2 Qw	2 Qw	2 Qw		
R. Thigh	5 Qw	6 Qw	8	8 Qw	9	9 Qw		
L. Thigh	5 Qw	6 Qw	8	8 Qw	9	9 Qw		
R. Leg	5	5	5 Qw	6	6 Qw	7		
L. Leg	5	5	5 Qw	6	6 Qw	7		
R. Foot	3 Qw	3 Qw	3 Qw	3 Qw	3 Qw	3 Qw		
L. Foot	3 Qw	3 Qw	3 Qw	3 Qw	3 Qw	3 Qw		
TOTAL								

Figure 3. Lund-Browder Burn Scale (Since the scale is an international commonly used general scale, it has been taken from scientific publication sources.)*
*Lund Charles C. The estimation of areas of burns. Surg Gynecol Obste 1944:79;352-8.

Burn width is defined as the percentage of burn area to total body area. The 9's rule, which is used very often in adults, is only suitable for children in adolescence. Thus, our study chose the Lund-Browder Scale for calculating the percentage of burns since this scale handles each age group individually due to the varying head and limb ratios during growth and development, thus giving more accurate results in children (6).

Previous studies revealed a positive correlation between mortality and total body burn surface. Mortality was found to be between 0.9% and 10.5% based on the percentage of burn. A study conducted with patients with a burn percentage of 40% or more revealed that mortality was 60% (10,12). Our study results showed that 2 (10%) patients had 45% of total body burn, whereas the average burn area of patients was 27.25% (±8.95), but we did not have any exitus patients. This result is a great success for our clinic; however, we believe that it would be better to conduct a longer study with a larger patient group to obtain clearer results regarding mortality.

Yastı et al. (13), in their study with children with burns, determined the average burn area percentage of patients as 16.91±12.63%, and the average length of hospital stay as 12.41±10.03 days. In their study, Albayrak et al. (10) determined the average burn area percentage of the patients as 16.91±12.63% and the average length of hospital stay as 12.1±8.8 days. Our study revealed that the average length of hospital stay was 10.10 (±3.93) days. Our study revealed that the average burn area percentage of patients was 27.25% (±8.95%); however, the length of hospital stay was relatively short since the majority of patients were patients with second-degree burn, and burn covers were used, such as skin equivalent, in our clinic at an early stage, together with effective fluid resuscitation and early beginning of nutrition period.

Additionally, a study that evaluated hypovolemia and hypothermia in patients with burns emphasized two parameters as a marker of mortality, which includes the absence of vascular access after burns and associated hypovolemia (13,14). Our study evaluation of the CVC indications revealed that the most

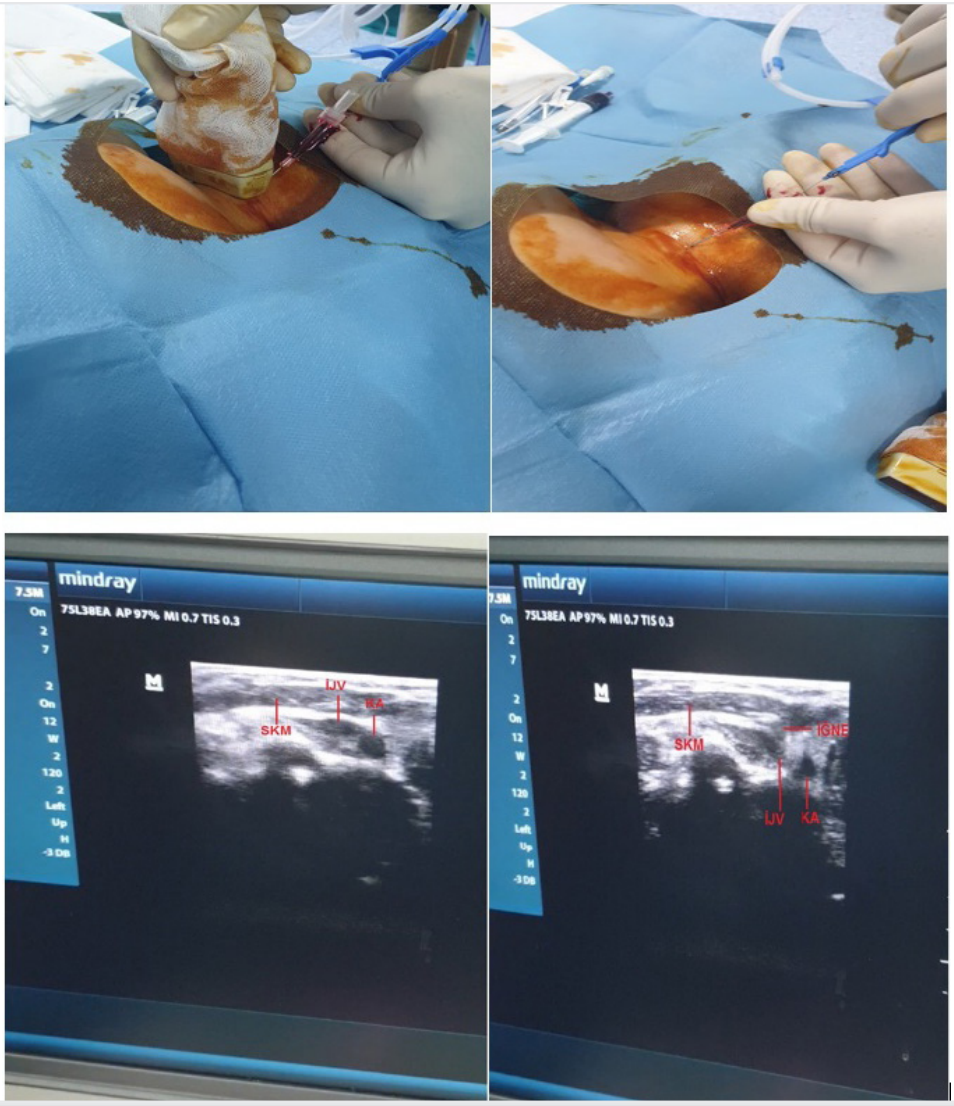


Figure 4. Jugular central venous catheterization with the US
US: Ultrasonography

common two reasons for CVC opening in the early period are the absence of vascular access and hypovolemia due to losses secondary to the burn site. The opening of the US-assisted early CVC was believed to contribute to the low mortality rate.

Burn depth is affected by age as well as factors, such as the temperature of a hot agent, contact time, anatomical region, and early intervention time (15). Due to the thinner skin tissue in childhood, the same factor can cause deeper burns. Burns caused by hot water in short-term contact often cause first-degree burns in adults but cause second and third-degree burns in children (15). Our study supports this data by the burns observed in 95% of the patients, which were second and third degree, although the majority of patients (65%) had hot water burns.

Studies that examined the causes of childhood burns revealed that hot water burns and tandoor (oven made in an underground hole to bake bread in Turkey) burns are the most common causes that lead to the treatment of burns in children who are hospitalized in Turkey (10,16) (Figure 6). Our study result examination revealed compatibility with the literature, and hot water burns (65%) in boiling style were observed most frequently.

Tolunay et al. (17), in their study on US-assisted CVC in children in the intensive care unit, the femoral region, and jugular region selection rates were found to be 45.7% and 54.3%, respectively, and this rate was 1/1 in our study. Previous studies that are conducted on pediatric patients concluded that the risk of infection was higher in the CVC procedure opening from the femoral region, but no relationship was found between the infection development and region selection in the large-scale studies that are conducted by Reyes and his friends in 4512 patients (18). Additionally, the current Centers for Disease Control and Prevention guidelines stated that no suggestions can be made for any region in reducing infection rates (19).

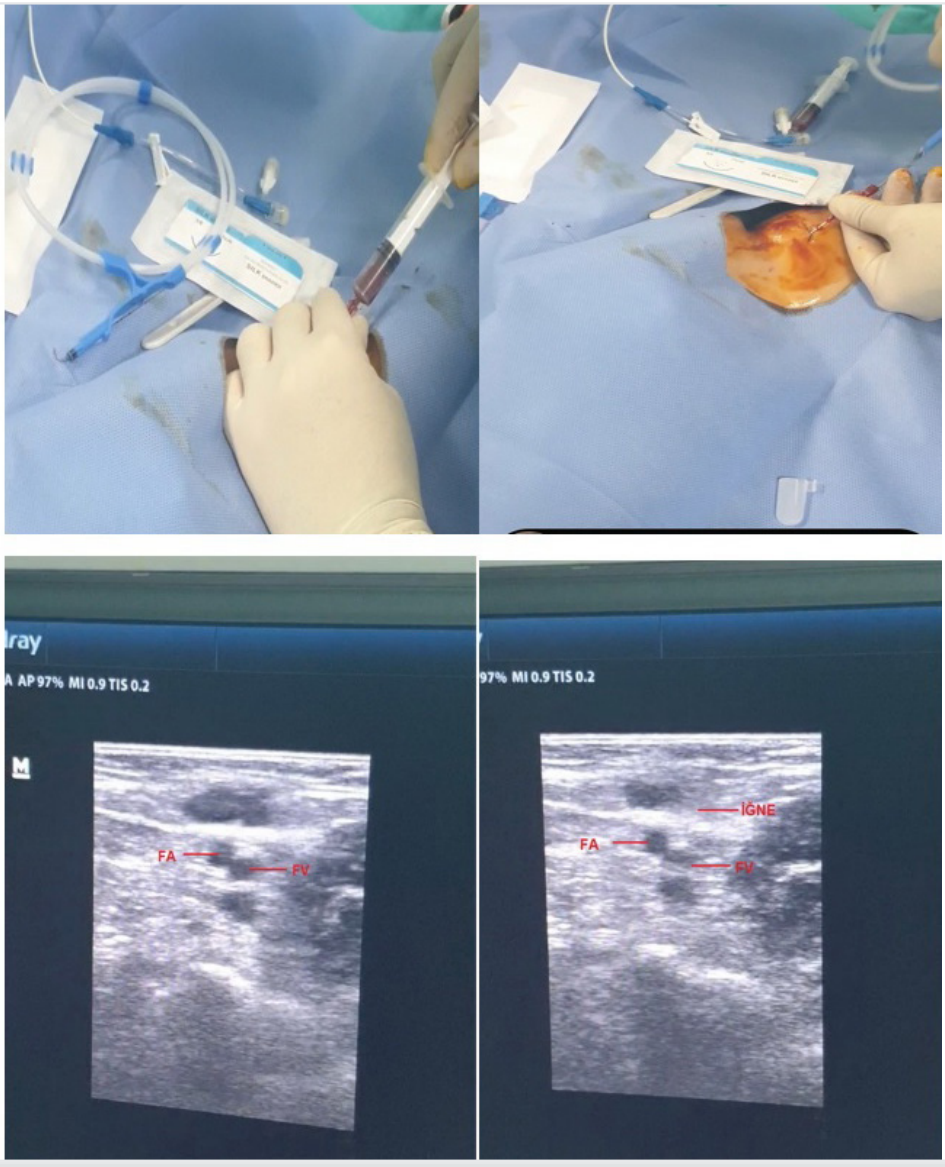


Figure 5. Femoral central venous catheterization with the US
US: Ultrasonography

The maintenance of the infection risk was suggested to be performed well and the catheter should not be used for >20 days. Patients in our study were a burn group, thus we aimed to stay away from the burn area as primary as possible in the selection of the region to reduce the infection rates. This proportional difference was believed to be related to the burn area diversity. Additionally, our hospitalization times are no >20 days in any patient and the empirical antibiotherapy that was initiated by the consultant infectious diseases specialist in the early period contributes to the absence of infection.

A meta-analysis compared the use of the US and the CVC opening process with the landmark method and revealed that the chance of success was higher and the complication rates were lower in the US-assisted CVC opening (20). The patients in our study were under 16 years old and had burns; however, we were able to successfully attach CVC to all our patients with a low complication rate of 2% and an average procedure time of 11.05±6.37 min. Our patients did not develop pneumothorax and hemothorax; however, intraarterial puncture occurred in 2 of our patients.

Studies have shown that acute kidney damage that is observed in risky patient groups is associated with increased mortality, morbidity, and length of hospital stay (21). The study by Colpaert et al. (22) reported that depending on the age, burn percentage, sepsis, and multiorgan dysfunction, acute kidney injury was observed in 1/4 and 1/3 of patients with major burns.

Study Limitations

Our study could not detect acute kidney damage in any of the patients, and we link this to many factors. The most important is that we open an appropriate CVC in the early period, calculate fluid losses and perform proper fluid replacement according to the Parkland method, start early nutritional support following the hypermetabolism that develops due to burns, and effectively fight infection with our empirical antibiotherapy. However, as in our study, the evaluation of acute kidney damage with serum creatinine value in patients with pediatric groups and patients with low muscle mass may cause false results. Another limitation is that patients with different muscle masses may have the same glomerular filtration rates although their serum creatinine value is higher (23). Serum creatinine values that were measured due to hemodilution that can develop secondary to fluid resuscitation, which is vital for burn patients, is another obstacle to our correct acute kidney damage assessment. Therefore, the changes in the urea creatinine levels are statistically significant; however, we believe that it is necessary for the literature with large-scale studies in which more patients and more parameters are evaluated together in the evaluation of acute kidney damage.

Figure 6. Jugular central venous catheterization with the US
US: Ultrasonography

Conclusion

Moreover, our study results revealed that the CVC opening with the help of the US in the pediatric patient group should be the preferred method of choice in patients with burns since it has both fewer complications and higher chances of success.

Ethics

Ethics Committee Approval: Our study was conducted in our burn center with 13 clinical beds and 5 intensive care beds. The study started after the approval from our hospital ethics committee dated May 15, 2020, with approval number 478.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B., F.S., H.A., S.K., Concept: M.B., H.A., S.K., Design: M.B., H.A., S.K., Data Collection or Processing: M.B., F.S., H.A., S.K., Analysis or Interpretation: M.B., F.S., H.A., S.K., Literature Search: M.B., F.S., H.A., S.K., Writing: M.B.

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

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Original Article

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Prevalence of Premenstrual Syndrome Among University Students: Associated Factors and Comfort Level

Üniversite Öğrencilerinde Premenstrüel Sendrom Prevelansı, İlişkili Faktörler ve Konfor Düzeyi

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ABSTRACT

Objective: Premenstrual syndrome (PMS) is a combination of behavioral, somatic, emotional, and cognitive symptoms that are very common in women during reproductive age. The worldwide prevalence of PMS varies between 12% and 98%. Thus, this study aimed to determine the prevalence of PMS and its associated factors and comfort level in a group of university students who stay in a dormitory.

Methods: This cross-sectional study was conducted in Yozgat Sürmeli Girls' Dormitory, which is located within Yozgat Bozok University Erdoğan Akdağcampus. A total of 1162 students are staying in the dormitory, and the study was completed with 935 students who stayed in the dormitory and volunteered to participate in the study without sample selection. The study collected data using the Participant Information Form that consist of 30 questions prepared by the researchers, the premenstrual syndrome scale (PMSS), and the general comfort scale (GCS). Percentage, mean, chi-square, t-test, correlation, and logistic regression analysis were used for data evaluation.

Results: The mean age of the students was 20.81±1.487 years. The total score of the PMS scale was 115.21±41.615. On the scale, the highest score is 20.203±7.493 from the depressive affection dimension and the lowest score is 7.854±3.771 from the sleep change dimension. PMS was found in 34.2% of students. The total GCS score of the students was 2.43±0.35, and scores obtained from the sub-dimensions and GCS levels were lower in students with PMS. A weak and negative relationship was found between

ÖZ

Amaç: Premenstrüel sendrom (PMS), üreme çağındaki kadınlarda çok sık görülen davranışsal, somatik, duygusal ve bilişsel semptomların bir kombinasyonudur. Dünya çapında PMS prevalansı %12 ile %98 arasında değişmektedir. : Bu çalışmada, yurtta kalan bir grup üniversite öğrencisinde premenstrüel sendrom (PMS) prevelansı, ilişkili faktörler ve konfor düzeyinin belirlenmesi amaçlanmıştır.

Yöntemler: Kesitsel tipteki bu çalışma, Yozgat Bozok Üniversitesi Erdoğan Akdağ Kampüsü içerisinde yer alan, Yozgat Sürmeli Kız Öğrenci Yurdu'nda yapılmıştır. Yurtta 1.162 öğrenci kalmakta olup, örneklem seçimine gidilmeksizin yurtta kalan, çalışmaya katılmaya gönüllü olan öğrencilerin tamamının araştırmaya alınması planlanarak 935 öğrenci ile çalışma tamamlanmıştır. Araştırmada veriler; araştırmacılar tarafından hazırlanan 30 sorudan oluşan katılımcı bilgi formu, premenstrüel sendrom ölçeği (PMSÖ) ve genel konfor ölçeği (GKÖ) kullanılarak toplanmıştır. Verilerin değerlendirilmesinde yüzdelik, ortalama, ki-kare, t-testi, korelasyon ve logistik regresyon analizi kullanılmıştır.

Bulgular: Öğrencilerin yaş ortalaması 20,81±1,487'dir. PMS ölçeğinin toplam puanı 115,21±41,615'tir. Ölçekte depresif duygulanım boyutundan en yüksek puan 20.203±7.493, uyku değişikliği boyutundan en düşük puan 7,854±3,771'dir. Öğrencilerin %34,2'inde PMS saptandı. Öğrencilerin toplam GKÖ puanı 2,43±0,35 olup, PMS'li öğrencilerde alt boyutlardan ve GKÖ düzeylerinden elde edilen puanlar daha düşüktür. PMSS ve GKÖ arasında zayıf ve negatif bir ilişki bulundu. On üç yaş ve öncesinde

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the PMSS and the GCS. The risk of PMS increased by 1.366 times (p=0.036) in students with menarche at the age of 13 years and younger, whereas, in students with chronic diseases, it was 2.512 times higher (p=0.001). The use of salt without tasting the food and daily coffee consumption increased the risk of PMS by 1.626 times (p=0.004) and 1.882 times (p=0.000), respectively. The risk of PMS was 2.026 times (p=0.000) higher in students with dysmenorrhea, whereas 1.614 times higher in students who used any method to cope with dysmenorrhea (p=0.004).

Conclusion: PMS is an important problem among women. A weak and negative relationship was found between PMS and comfort level. Considering the results of this study, menarche before the age of 13, the presence of chronic disease, dysmenorrhea, excessive salt use, and coffee consumption increases the risk of PMS. Many factors lead to the occurrence of PMS. Interventional studies are necessary to reduce the risk factors for PMS that significantly affect the women's health or its risk factors.

Keywords: Premenstrual syndrome, prevalence, comfort level

menarş olan öğrencilerde PMS görülme riski 1,366 kat artarken (p=0,036), kronik bir hastalığa sahip olan öğrencilerde PMS görülme riski 2,512 kat daha fazladır (p=0,001). Yemeğin tadına bakmadan tuz kullanımı PMS riskini 1.626 kat (p=0,004), günlük kahve tüketme alışkanlığı 1,882 kat artırmaktadır (p=0,000). Dismenore yaşayan öğrencilerde PMS görülme riski, 2,026 kat (p=0,000), dismenore ile baş etmek için herhangi bir yöntem kullanan öğrencilerde 1,614 kat daha fazladır (p=0,004).

Sonuç: PMS kadınlar arasında önemli bir sorundur. PMS ile konfor düzeyinin negatif yönde, zayıf bir ilişkisi olduğu bulunmuştur. Bu çalışmanın sonuçları dikkate alındığında; 13 yaşından önce menarş olma, kronik hastalık varlığı, dismenore, fazla tuz kullanımı, kahve tüketimi PMS görülme riskini artırmaktadır. Birçok faktör PMS'nin ortaya çıkmasına neden olur. Kadın sağlığını önemli ölçüde etkileyen PMS risk faktörlerini veya risk faktörlerini azaltmak için girişimsel çalışmalara ihtiyaç vardır

Anahtar Sözcükler: Premenstrüel sendrom, prevelans, konfor düzeyi

Introduction

Premenstrual syndrome (PMS) is a combination of behavioral, somatic, emotional, and cognitive symptoms that occur during the luteal phase of the menstrual cycle, which is quite common among women during reproductive life, and rapidly improve with the onset of menstruation (1). More than 200 symptoms occur during the first 7-10 days of menstruation. The most frequent symptoms are headache, fatigue, bloating, back pain, breast tenderness, appetite changes, fatigue, anxiety, nervousness, impaired interpersonal communication, and depression (2). Determining the true prevalence of PMS with so many symptoms is difficult (3). Studies revealed different results in the prevalence of PMS depending on the diagnostic criteria and methodology (4). The systematic review and meta-analysis study that was conducted by Direkvand-Moghadam et al. (5) revealed that the prevalence of PMS varied between 12% and 98%. The examination of countries in this study reported that the lowest prevalence was in France (12%) and the highest prevalence was in Iran (98%). Two studies on Turkish women were also included in this meta-analysis and stated that the prevalence of PMS varied between 32.6% and 69.9% (5). The studies that were conducted with university students in our country revealed that the prevalence of PMS varied between 36.4% and 91.8% (6-9). University students, who are among the groups that are most affected by PMS, indicated that this period negatively affected their academic achievements, emotional states, social activities, and family relationships (10). Considering the negative effects of PMS on daily life, conducting scientific studies is very important to determine the frequency of PMS and its affecting factors (11). The cause of PMS is unknown; however, hormonal changes are frequently affected by diet, stress, and lifestyle changes (12). Studies examined the status of PMS in some variables, such as the quality of life, lifestyle changes, healthy lifestyle behaviors, smoking, alcohol, and carbohydrate intake (7,13-16). University students have to change their living environments and even cities due to their education, their lifestyles are changed and they encounter many stressful situations. The literature reported no studies on the comfort level of students who stay in dormitories; however, a study indicated that the prevalence of PMS was 4.19 times higher among students who stay in dormitories (17). PMS is considered to change the comfort level by changing the experience of performing activities of daily living with many

Table 1. Sub-dimensions and total mean scores of the PMSS and GCS

PMSS sub-dimensions	Min	Max	Mean	SD
Depressive affection	7	35	20.203	7.493
Anxiety	7	35	14.726	6.915
Fatigue	6	30	17.124	6.599
Nervousness	5	25	14.065	5.966
Depressive thoughts	7	35	16.632	8.049
Pain	3	15	8.088	3.671
Change in appetite	3	15	8.576	3.710
Sleep change	3	15	7.854	3.771
Bloating	3	15	7.946	3.896
Total scale score	44	218	115.21	41.615
Comfort scale levels				
Relief	1	4	2.67	0.45
Ease	1	4	2.25	0.38
Transcendence	1	4	2.36	0.38
Comfort scale sub-dimensions				
Physical	1	4	2.39	0.41
Psychospiritual	1	4	2.39	0.38
Sociocultural	1	4	2.53	0.40
Environmental	1	4	2.37	0.40
Total scale score	1	4	2.43	0.35

Min: Minimum, Max: Maximum, SD: Standard deviation, PMSS: Premenstrual syndrome scale, GCS: General comfort scale

symptoms. Comfort is a concept that an individual feels while performing activities of daily living, including relaxation, peace, and the experience of overcoming the problem (18). Comfort is affected by many biological, psychological, social, and cultural factors, as in PMS. No study on PMS and comfort level was found in the literature. Thus, this study aimed to determine the prevalence of PMS and its associated factors and comfort level in a group of university students who stay in a dormitory.

Research Questions

What is the prevalence of PMS among students?

What are the factors that affect the occurrence of PMS among students?

Is there a relationship between PMS and general comfort level among students?

Method

Type and Place of the Study

This cross-sectional study was conducted in Yozgat Sürmeli Girls' Dormitory, which is located within Yozgat Bozok University Erdoğan Akdağcampus.

Ethical Aspect of the Study

Approval was obtained from Gazi University Ethics Committee for the Research (no: 2020-162). Permission was obtained from the Provincial Directorate of Youth and Sports and the Directorate of Yozgat Sürmeli Girls' Dormitory for the institution where the study was conducted. The aim of the study was explained to all students who would participate in the study and informed consent was obtained. Permission was obtained from the authors for the scales used in data collection.

Population and Sample of the Study

This study included 1,162 students staying in Yozgat Sürmeli Girls' Dormitory. Reaching the entire population without sample selection was planned in the study. However, 4 of 1,162 students were foreign nationals who do not speak Turkish and 123 students refused to participate in the study, thus the study was completed with 935 (80%) students.

Data Collection Tools

The Participant Information Form prepared by the researchers, the premenstrual syndrome scale (PMSS), and the general comfort scale (GCS) were used as data collection tools in this study.

Participant Information Form: The Participant Information Form, which was prepared following the literature, included the questions that determine the socio-demographic characteristics of females with PMS (age, school, department, grade, place of residence, income status, employment status, characteristics related to height and weight, and history of chronic disease and drug use), lifestyle (smoking, alcohol, and exercise habits), menstruation, and history of PMS (age of menarche, frequency and duration of menstruation, and family history of PMS) (7,19,20). The Participant Information Form consisted of a total of 30 questions.

PMSS: It was developed by Gençdoğan (21) based on the Diagnostic and Statistical Manual of Mental Disorders-III and DSM-IV-R diagnostic criteria in 2006. The Cronbach alpha coefficient of the scale is 0.75. The scale is a 44-item 5-point Likert type. While scoring the scale, the "None" option is evaluated as 1 point and the "Continuous" option is evaluated as 5 points. PMSS consists of 9 sub-dimensions. The scale scores range from 44 to 220 points. The theoretical cut-off point is used for the diagnosis of PMS. The presence of PMS is evaluated according to the condition of exceeding 50% of the score obtained from each sub-dimension of the scale. The Cronbach alpha coefficient of the scale is 0.75 (21). This study revealed that the Cronbach alpha coefficient of the scale was 0.97. Written permission was obtained from Gençdoğan (21) to use PMSS in this study.

GCS: The Turkish validity and reliability study of the GCS, which was developed by Katharina Kolcaba in 1992, was performed by Kuğuoğlu and Karabacak (22). The scale is 4-point Likert type consists of a total of 48 items. The comfort levels of the scale are a relief (16 items), ease (17 items), and transcendence (15 items). The scale consists of positive and negative items in the mixed form. The reverse-coded items in the scale evaluation are presented in the table below. The highest and lowest scores that are obtained from the scale are 192 and 48, respectively. The scale is determined with a value between 1 and 4 by dividing the total score by the number of items. The comfort level increases as the scale score approach 4. The Cronbach alpha coefficient of the scale was found to be 0.85 in the validity and reliability study (22). This study revealed that the Cronbach alpha coefficient of the scale was 0.88. Written permission was obtained from Kuğuoğlu and Karabacak (22) to use GCS in this study.

Statistical Analysis

Statistical Package for the Social Sciences 21.0 (SPPS-PC Version 21.0) package program was used for the statistical analysis of the data. Number, percentage, arithmetic mean, t-test, chi-square, logistic regression, and correlation analysis were used for data evaluation.

Results

The mean age of the students who participated in the study was 20.81 years. Students who study daytime education accounted for 76.8% and 46.5% were 3rd-grade students. Additionally, 78.8% of students had a nuclear family structure, and mothers of 54.4% and fathers of 36.8% were primary school graduates. Moreover, 54.2% indicated that their income was less than their expenses.

Chronic disease was determined in 11.9% of students, thus use drugs, whereas 18.4% experienced polycystic ovarian syndrome symptoms and 4.3% have obesity.

Students who added salt without tasting the food account for 73.5% and 31.3% had the habit of consuming coffee daily. Of

those who consumed coffee, 54.3% consumed 2 cups or more of coffee daily. Smokers accounted for 13% of students and 4.3% consumed alcohol. Of the smoker students, 45.1% had been smoking for 4 years or more and 41.8% smoked 6 cigarettes or more a day. Of the students, 9.1% had regular exercise, of whom 52.9% regularly exercised 1-3 times a week and only 32.9% had exercise duration of 31 min or more.

The history of first menstruation of 54.8% of students was at the age of 13 years and younger, 77.8% had dysmenorrhea, and 26.2% used any method, such as painkiller and hot application, to cope with dysmenorrhea. Dysmenorrhea was determined in 57.2% of students in one or more of their mothers and sisters and 49.2% of these people had the symptoms of PMS.

The total score of the PMSS was 115.21±41.615, wherein the highest score is 20.203±7.493 from the depressive affection dimension and the lowest score is 7.854±3.771 from the sleep change dimension.

The total score of the GCS was 2.43±0.35. The highest value of the sub-dimensions of the comfort scale is 2.53±0.40 in the sociocultural dimension. The highest value among the levels of the scale was found at the relief level by 2.67±0.45.

PMS by the scoring of 132 points and above was determined in 34.2% of students.

A weak and negative relationship was found between the PMSS and the GCS.

The examination of the comfort levels according to the presence of PMS revealed lower comfort scores in students with PMS. A statistical significance was found at the relief and transcendence levels of the scale compared to those with and without PMS ($p<0.01$). Physical, sociocultural, and environmental dimensions of the scale were statistically significant compared to students with and without PMS ($p<0.01$).

A statistically significant relationship was found between PMS and the age of menarche, chronic disease, presence of polycystic ovarian syndrome symptoms, drug use, use of salt without tasting the food, daily coffee consumption, smoking, having dysmenorrhea, using dysmenorrhea coping methods, and dysmenorrhea and PMS in first-degree relatives ($p<0.05$).

The risk of PMS was higher in students with menarche at age 13 years or younger (1.366 times, $p=0.036$), who had the chronic disease (2,512 times, $p=0.001$), a high salt use (1.626 times, $p=0.003$), a high daily coffee consumption (1,882 times, $p=0.000$), had dysmenorrhea (2,026 times, $p=0.000$), and used any method to cope with dysmenorrhea (1,614 times, $p=0.003$).

Discussion

This study aimed to determine the prevalence of PMS and its associated factors and comfort level in a group of students who stay in a dormitory and revealed that 34% of students had PMS. The study of Güvenç et al. revealed that the prevalence of PMS was 36%, which is similar to our study results. The prevalence of PMS was 62% in the study of Bakır and Yangın (7) and 57% in the study of Kısa et al. (19) The prevalence of PMS was 60% in the study of Silva et al. (23) and 84% in the study of Houston et al. (24). A wide range of results was obtained in studies on the prevalence of PMS. Many factors, such as the presence of different evaluation criteria, different attitudes of different cultures, and different forms of health service delivery, can make the determination of the true prevalence difficult. Additionally, the same scale is used in the studies conducted in our country; however, calculations according to different cut-off points led to different results in PMS prevalence. Our study used 132 as the cut-off value of the scale, and the prevalence of PMS was found to be 34.2%.

Our study revealed that the total score of PMSS was 115.21±41.615. The highest score on the scale was in the depressive affection dimension and the lowest was in the sleep change dimension. The study by Topatan and Kahraman (16) with university students revealed that the total score of the PMSS was 118.4±32.4. Similarly, the highest score was obtained from the depressive affection dimension (18.21±7.42) and the lowest score from the sleep change dimension (7.85±2.96) (16). Another study revealed that the mean total score from the PMSS was 122.14±32.60 (25). This study revealed that the highest score was from the depressive thought sub-dimension (20.42±6.76) and the lowest score was from the pain sub-dimension (8.10±3.27). The study results of Tanrıverdi et al. (26) are also similar to the study of Aba et al. (25) and differ from the results of this study.

The study revealed a statistically significant relationship between the menarche age of the students and the PMSS and observed that the risk of PMS was 1,366 ($p=0.036$) times higher in students whose menarche age was 13 years and younger. The literature reported studies that revealed the relationship between PMS and menarche age as statistically insignificant (4,14,25,27).

No statistically significant relationship was found between the body mass index and PMS in the literature (4,25,28). The results on body mass index in this study are also consistent with the literature.

PMS coexists with dysmenorrhea in many women, and premenstrual symptoms alternate with dysmenorrhea at the beginning of menstruation (7,14,25,29). Our study revealed that 77.8% of the students had dysmenorrhea and that the risk of PMS was 2.026 times higher in students with dysmenorrhea. The study conducted by Bakır and Yangın revealed this value to be 1.62. The study on Japanese students that was conducted by Yamamoto et al. (30) revealed a relationship between dysmenorrhea and PMS. Studies also reported different results from our study. The study that was conducted by Rupani and Lema (31) and Freeman et al. (32) revealed no relationship between dysmenorrhea and PMS.

Our study revealed that the risk of PMS was 1.882 times higher in students who consumed coffee daily. Several studies that were conducted with university students revealed that the chi-square analysis of coffee consumption was statistically significant;

Table 2. Prevalence of PMS

	Number	Percentage (%)
Those with premenstrual syndrome	320	34.2
Those without premenstrual syndrome	615	65.8
Total	935	100

PMS: Premenstrual syndrome

Table 3. Correlation of the PMS scale and the GCS

Scale	Comfort scale
	rp
Having PMS	-0.1920.001

PMS: Premenstrual syndrome, GCS: General comfort scale

Table 4. Evaluation of the presence of PMS and comfort levels in students

Comfort levels	PMS <132	PMS ≥132	t-test*	p
Relief	2.757±0.466	2.526±0.376	8.194	**0.000**
Ease	2.254±0.400	2.260±0.339	-0.249	0.803
Transcendence	2.387±0.414	2.317±0.327	2.792	**0.005**
Comfort sub-dimensions				
Physical	2.466±0.431	2.258 ± 0.345	8.013	**0.000**
Psychospiritual	2.400±0.400	2.382 ± 0.346	0.680	0.497
Sociocultural	2.567±0.429	2.482 ± 0.358	3.232	**0.001**
Environmental	2.405±0.418	2.327 ± 0.385	2.795	**0.005**
GCS total score	2.463±0.377	2.367 ± 0285	4.365	**0.000**

*Independent sample t-test, PMS: Premenstrual syndrome

however, the presence of PMS in the logistic regression analysis was not statistically significant (7,14). A study conducted with university students in Thailand revealed a relationship between coffee consumption and PMS symptoms (33). The study conducted by Moon-Soo et al. (34) with university students in Korea revealed a statistically significant difference in coffee consumption between the group with moderate to severe PMS and the group with mild PMS. Another study revealed no statistically significant relationship between the consumption of tea, coffee, and cola-containing caffeine and the PMS (13,15). The study conducted by Çelik et al. (35) revealed no significant relationship with coffee consumption, whereas a statistically significant relationship between cola and tea-drinking variables. A study on high-caffeine coffee intake conducted with nurses revealed no significant relationship between PMS and caffeine intake (36).

The literature reported many studies on the presence of PMS in smoking and alcohol use. A study conducted with Japanese adolescent students revealed that smoking and alcohol use increased problems, such as concentration disorders, behavioral changes, fluid retention, and negative affection, in the premenstrual period (37). Studies revealed statistically significant results in the chi-square tests on alcohol, smoking, and PMS (14,15,38). The study of Pinar et al. (14) revealed that the risk of PMS was 0.4 times higher in smoker students compared to non-smokers. Studies by Demir et al. (13) and Çelik et al. (35) revealed a statistically significant relationship between smoking and PMS. Deuster et al. (39) also revealed that the prevalence of PMS was higher in those who smoked for >5 years. The study on PMS that was conducted by Bakır and Yangın (7) revealed no association with smoking, whereas results of the chi-square analysis of alcohol use were significant and regression results were statistically insignificant. Our study revealed no relationship between alcohol use and the presence of PMS; however, a relationship was found with smoking. A recent case-control study on smoking and PMS determined that smoking and PMS are correlated (40).

The literature reported studies that reveal the relationship of PMS with genetic factors (7,13-15). The square test in our study revealed the presence of PMS and dysmenorrhea in the mother, elder sister, or younger sister, which was statistically significant. A study in Malaysia determined that PMS was more common in people with any relative complaints of PMS (4). A study conducted in Turkey revealed that PMS was highly detected in people with PMS complaints in their mothers or sisters (13). The study of Bakır and Yangın determined that the risk of PMS was 2.27 times higher in students whose mothers had PMS complaints. Another study found that the presence of PMS in mothers of students increased the risk of PMS by 1.68 times (8).

Another PMS symptom is edema. Salt intake increases the formation of edema in the body (41). Our study revealed that 26.5% of students used salt without tasting the food. Our analysis on the risk of PMS was 1.626 times higher in students who used salt without tasting the food. The study of Aşcı et al. (8) revealed that 35.6% of students used salt without tasting the food, and the PMSS score was found significantly (p=0.021) higher in students who used salt. The study conducted by Hashim et al. (28) found that the use of salt increased the risk of PMS. Şahin et al. (20) revealed that the risk of PMS was 1,982 times higher in students who used salt, whereas Bakır and Yangın (7) found this value as 2,415. The study conducted by Pinar et al. (14) determined that salt was not a factor that increased the risk of PMS.

Exercise is also used to relieve PMS by increasing serotonin levels (25,41). Şahin et al. (20) revealed that the risk of PMS was 1.710 times higher in those who did not exercise. Our study revealed no significant relationship between exercise and PMS prevalence. The literature reported similar results (8,13,25). A low number of students, who exercised regularly in the studies with similar results to our study, and this study, may have caused the statistics to be insignificant.

Table 5. Examination of the factors affecting the presence of PMS among students

Variables		PMS <132		PMS ≥132		Test value	
Age	Number (%)	n	%	n	%	X2	p
18-20 years	389 (41.6)	259	66.6	130	33.4	0.192	0.661
21 years and above	546 (58.4)	356	65.2	190	34.8		
Type of education							
Daytime education	718 (76.8)	482	67.1	236	32.9	2.525	0.112
Evening education	217 (23.2)	133	61.3	84	38.7		
Age of menarche							
13 years and below	512 (54.8)	320	62.5	192	37.5	**5.393**	**0.022**
14 years and above	423 (45.2)	295	69.7	128	30.3		
Body mass index							
Slim (18.4 and below)	116 (12.4)	78	67.2	38	32.8	0.592	0.744
Normal (18.5-24.9)	664 (71.0)	439	66.1	225	33.9		
Overweight and fat (25.0 and above)	155 (16.6)	98	63.2	57	36.8		
Chronic disease							
Yes	111 (11.9)	49	44.1	62	55.9	26.180	**0.000**
No	824 (88.1)	566	68.7	258	31.3		
Symptoms of polycystic ovarian syndrome							
With	172 (18.4)	99	57.6	73	42.4	6.322	**0.012**
Without	763 (81.6)	516	67.6	247	32.4		
Drug use							
Yes	111 (11.9)	58	52.3	53	47.7	10.232	**0.001**
No	824 (88.1)	557	67.6	267	32.4		
Use of salt without tasting the food							
Yes	248 (26.5)	139	56.0	109	44.0	14.186	**0.000**
No	687 (73.5)	476	69.3	211	30.7		
Daily coffee consumption							
Yes	293 (31.3)	156	53.2	137	46.8	29.775	**0.000**
No	642 (68.7)	459	71.5	183	28.5		
Smoking							
Yes	122 (13.0)	65	53.3	57	46.7	9.734	**0.002**
No	813 (87.0)	550	67.7	263	32.3		
Alcohol use*							
Yes	40 (4.3)	21	52.5	19	47.5	2.684	0.101
No	895 (95.7)	594	66.4	301	33.6		
Regular exercise							
Yes	85 (9.1)	59	69.4	26	30.6	0.549	0.459
No	850 (90.9)	556	65.4	294	34.6		
Having dysmenorrhea							
Yes	727 (77.8)	448	61.6	279	38.4	25.030	**0.000**
No	208 (22.2)	167	80.3	41	19.7		
Use of a method for coping with dysmenorrhea							
Yes	245 (26.2)	137	55.9	108	44.1	14.329	**0.000**
No	690 (73.8)	478	69.3	212	30.7		

Table 5. Continued

Variables		PMS <132		PMS ≥132		Test value	
Presence of dysmenorrhea in the mother, elder sister, younger sister							
Yes	535 (57.2)	325	60.7	210	39.3		
No	144 (15.4)	106	73.6	38	26.4	14.166	**0.001**
Do not know	256 (27.4)	184	71.9	72	28.1		
Presence of PMS in the mother, elder sister, younger sister							
Yes	460 (49.2)	271	58,9	189	41.1		
No	154 (16.5)	115	74.7	39	25.3	19.456	**0.000**
Do not know	321 (34.3)	229	71.3	92	28.7		

*0 cells (0%) have expected count <5. The minimum expected count is 13.69 continuity correction

PMS: Premenstrual syndrome

Our study revealed that 18.4% of students had polycystic ovarian syndrome symptoms. A statistical significance was found between having the symptoms of the polycystic ovarian syndrome and PMSS scores. The fluctuation in hormonal levels in polycystic ovarian syndrome and PMS causes the exacerbation of PMS syndromes and the emergence of short-term mixed mood changes (42). Our study revealed that the risk of PMS was 2,512 times higher in people with any chronic disease compared to those without chronic disease. The study conducted by Arslantaş et al. (15) revealed a statistically significant difference between those with and without chronic diseases other than gynecological diseases and the presence of PMS was. The study conducted by Acikgoz et al. (38) revealed that PMS was 2.35 times higher in students with chronic diseases. Our study results were consistent with the literature. Our study revealed a statistical significance between regular drug use for chronic diseases and PMSS score, whereas no statistically significant difference in the regression analysis.

Study Limitations

Our study revealed a weak and negative relationship between GCS and PMSS. The mean scores in each level and dimension of the GCS were lower in students with PMS. The relief and ease levels in the GCS were significantly lower in people with PMS. The scores of the students with PMS in the physical, sociocultural, and environmental dimensions of the scale sub-dimensions were significantly lower. No study on the relationship between comfort level and PMS was reported in the literature; however, it can be said that PMS negatively affects the comfort level of students.

Conclusion

Of the university students who participated in the study, 34.2% had PMS. The total score of the GCS of the students was 2.43±0.35, and based on the scores from the subscales and levels of GCS, the comfort levels of students with PMS were found to be lower. Considering our study results, menarche age under 13 years, presence of chronic disease, dysmenorrhea, salt use, and coffee consumption increased the risk of PMS. Many factors lead to the occurrence of PMS. Interventional studies are necessary to reduce the risk factors for PMS that significantly affect the women's health or the effects of these risk factors.

Table 6. Logistic regression analysis of the factors that affect the presence of premenstrual syndrome in students

Variables	ß	SH	Wald	P	0R	95% CI for EXP (B)	
						Lower	Upper
Constant	-2.109	0.212	99.244	0.000	0.121		
Age of menstruation (1)	0.312	0.148	4.411	**0.036**	1.366	1.021	1.827
Have a chronic disease (1)	0.921	0.273	11.360	**0.001**	2.512	1.470	4.292
Polycystic ovarian syndrome (1)	0.313	0.185	2.868	0.090	1.367	0.952	1.963
Drug use (1)	0.012	0.276	0.002	0.966	1.012	0.590	1.736
Use of salt (1)	0.486	0.162	8.988	**0.003**	1.626	1.183	2.233
Coffee consumption (1)	0.632	0.157	16.210	**0.000**	1.882	1.383	2.560
Smoking (1)	0.346	0.213	2.645	0.104	1.413	0.932	2.143
Dysmenorrhea (1)	0.706	0.200	12.518	**0.000**	2.026	1.370	2.995
Coping with dysmenorrhea (1)	0.479	0.163	8.637	**0.003**	1.614	1.173	2.222

CI: Confidence interval

Ethics

Ethics Committee Approval: Approval was obtained from Gazi University Ethics Committee for the Research (no: 2020-162). Permission was obtained from the Provincial Directorate of Youth and Sports and the Directorate of Yozgat Sürmeli Girls' Dormitory for the institution where the study was conducted.

Informed Consent: The aim of the study was explained to all students who would participate in the study and informed consent was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: D.Y.G., Concept: D.Y.G., N.B., Design: D.Y.G., N.B., Data Collection or Processing: D.Y.G., Analysis or Interpretation: D.Y.G., N.B., Literature Search: D.Y.G., N.B., Writing: D.Y.G., N.B.

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Original Article

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Awareness Level Evaluation of Dental Professionals on Zoonoses

Diş Hekimlerinin Zoonotik Hastalıklar Konusunda Farkındalığının Değerlendirilmesi

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ABSTRACT

Objective: This study aimed to evaluate the awareness level of dental professionals on zoonoses and surveys and raise their awareness of the "one health" concept, which is a key policy that was adopted by veterinarians, physicians, and other health professionals to attain definitive outcomes in the fight against zoonoses.

Methods: The study included dental professionals working at the state, private universities, and private clinics in Turkey who completed an 18-item online survey between March and April 2020.

Results: This study included 603 dental professionals who completed the survey form. Participants that were specialized in pedodontics, oral and maxillofacial radiology, and restorative dentistry had a significantly higher level of knowledge about the types of zoonoses compared to nonspecialized participants. Similarly, participants who were specialized in oral and maxillofacial radiology had a significantly higher level of knowledge about the types of zoonoses compared to participants who were specialized in oral and maxillofacial surgery, orthodontics, prosthetic dentistry, and endodontics. Nevertheless, no significant difference was established among other fields of specialty about the knowledge level on the types of zoonoses. Contrarily, 96.19% of participants reported no knowledge about the "one health" concept.

Conclusion: Activities on zoonoses should be promoted and training schemes should be conducted to inform dental professionals and other health professionals on zoonoses.

ÖZ

Amaç: Diş hekimlerinin zoonozlar konusundaki farkındalık düzeyini değerlendirmek ve aynı zamanda, veteriner hekimler, hekimler ve diğer sağlık profesyonelleri tarafından zoonotik hastalıklar ile mücadelede kesin sonuçlara ulaşmak için benimsenen anahtar bir politika olan "Tek Sağlık" kavramı hakkında araştırma yapmak ve farkındalıklarını artırmak.

Yöntemler: Türkiye'de kamu, üniversite ve özel kliniklerde çalışan diş hekimlerine tanımlayıcı 18 soruluk anket Mart-Nisan 2020 tarihlerinde uygulanmıştır. Katılımcılara demografik bilgileri ve zoonotik hastalıklar konusundaki farkındalıklarını değerlendirecek sorular sorulmuştur.

Bulgular: Toplamda 603 diş hekimliği uzmanı anket formunu doldurdu ve çalışmaya dahil edildi. Pedodonti, oral ve maksillofasiyal radyoloji ve restoratif diş hekimliği alanlarında uzmanlaşmış katılımcılar, uzman olmayanlara göre zoonotik hastalıklar hakkında önemli ölçüde daha yüksek bilgi düzeyine sahiptiler. Benzer şekilde, oral ve maksillofasiyal radyoloji konusunda uzmanlaşmış katılımcılar, ağız ve çene cerrahisi, ortodonti, protez diş hekimliği ve endodonti alanlarında uzmanlaşmış katılımcılara kıyasla zoonoz türleri hakkında önemli ölçüde daha yüksek bilgi düzeyine sahipti. Bununla birlikte, zoonoz türleri hakkında bilgi düzeyi açısından diğer uzmanlık alanları arasında önemli bir farklılık tespit edilmemiştir. Öte yandan, katılımcıların %96,19'u "Tek Sağlık" kavramı hakkında hiçbir bilgisi olmadığını belirtmiştir.

Sonuç: Diş hekimleri ve diğer tüm sağlık çalışanlarının zoonoz hastalıklar konusunda bilgilendirilmesine ve bu konu hakkında

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Additionally, dental professionals and other health professionals need to learn about and adopt the "one health" concept.

Keywords: Dentistry, zoonotic disease, "one health" concept

yapılacak çalışmalara ihtiyaç duyulmaktadır. Ayrıca özellikle zoonoz hastalıklar konusunda "Tek Sağlık" konseptinin benimsenmesi gerekmektedir.

Anahtar Sözcükler: Diş hekimliği, zoonotik hastalıklar, "Tek Sağlık" konsepti

Introduction

The link between human and animal medicine has been a major concern among researchers for more than 150 years. As a pioneering proponent, German physician and pathologist, Rudolph Virchow, proposed that there is and will be no clear-cut distinction between human and animal medicine and coined the term "zoonosis," which means a disease that can be transmitted from vertebrate animals to humans, based on his animal experimentation on the life cycle of *Trichinella spiralis* (1).

Zoonoses account for up to 60% of all known human infections and >75% of the emerging pathogens. These diseases are mostly classified based on the nature of the pathogen, animal host, disease severity, and the mode of transmission among animals or humans (2,3). The infection in zoonotic diseases results from the exposure of a sensitive population to the pathogenic microorganism. Contrarily, zoonoses may spread across the world during the mass immigration of infected humans or animals (3,4). Moreover, these diseases may be transmitted by contact with all contaminated animals, including poultry, birds, rodents, pets, cattle, bovines, sheep-goats, wild animals, and prey animals (5).

Zoonoses show wide variation due to the variation of microorganisms and transmission modes (animal-animal, animal-human, human-human, and human-animal). Among the most common zoonoses reported in Europe in 2016, *Campylobacter* was the most frequently seen infection since 2005 and accounted for up to 70% of all cases, followed by *Salmonella*, *Yersinia*, *Escherichia coli*, *Listeria*, Q fever, tularemia, *Echinococcus*, and brucellosis (6). In addition to bacterial pathogens, viral, fungal, and parasitic agents can also be a cause of zoonoses. Common zoonoses include rabies, tuberculosis, bird flu, severe acute respiratory syndrome (SARS), leishmaniasis, capillariasis, anthrax, Crimean-Congo hemorrhagic fever (CCHF), and human immunodeficiency virus (HIV) (7).

Zoonoses are a leading cause of death from infectious diseases worldwide (8,9). A previous study that investigated the global effect of zoonoses on morbidity and mortality revealed that zoonoses are responsible for approximately 2.7 million human deaths and 2.5 billion cases of human illness annually worldwide (10). Zoonoses in Turkey, particularly, including CCHF, anthrax, rabies, and brucellosis, remain a significant public health problem. Besides their adverse public health impact, zoonoses also lead to large economic losses due to productivity loss and death in animals (11,12). Complete eradication of zoonoses seems unlikely; however, their spread can be prevented by taking appropriate measures (13).

Dr. Calvin W. Schwabe established the "One Health" concept in the 1960s, calling upon all health professionals, including veterinarians, to collaboratively work against zoonoses (14). In 2004, the "One World-One Medicine-One Health" concept was established based on the "One Medicine" concept and advocated a collaborative fight against zoonoses by a combination of human and animal medicine (14,15). As a concept involving both ecosystem and wildlife health, the "One Health" concept comprises a global strategy that emphasizes the need for a holistic and interdisciplinary approach and incorporates multisector expertise in coping with the health of mankind, animals, and the ecosystem (15,16).

Dental professionals can be exposed to numerous pathogenic microorganisms, including viruses and bacteria that infect the oral cavity and respiratory tract. Additionally, both dental professionals and dental care settings invariably have an increased risk of infection due to the specificity of their procedures that involve face-to-face communication with patients, contact with saliva, blood, and other body fluids, and the use of sharp tools (17,18). Contrarily, pathogenic microorganisms can be transmitted in dental settings through inhalation of airborne microorganisms that can remain suspended in the air for long periods (19). These notions indicate that dental practices facilitate the human–human transmission of zoonoses. The present study aimed to evaluate the awareness level of dental professionals on zoonoses and survey and raise their awareness of the "One Health" concept, which is a key concept in the transmission and distribution of zoonoses (20).

Methods

An accuracy test was performed using a serial approach to assess the validity and reliability of the survey that is used in the study (21). The survey questions were prepared as authentic, reliable, and valid items. Data were collected using an online survey created by Google Forms that was administered to dental professionals working at the state, private universities, and private clinics in Turkey between March and April 2020. The survey was administered to dentists who were actively working in Turkey who either had a bachelor's degree or had been specialized in any subfield of dentistry. The target participants were informed about the survey via text messages and emails and were requested to participate in the study. This study included 603 dental professionals who completed the survey form. The survey consisted of 18 items that probe participants' demographic features (e.g., professional setting, the year of starting to work), knowledge on zoonoses (sources, causes, transmission modes of zoonoses, and methods of knowledge acquisition), and their

awareness level about the implementation of the "One Health" concept against zoonoses (Table 1). Before the study, approval was obtained from Fırat University Non-interventional Clinical Research Ethics Committee (approval date: March 5, 2020; no: 2020/05-08). Each participant was informed about the goals and anticipated outcomes of the study.

Statistical Analysis

Data were analyzed using International Business Machines Statistical Package for the Social Sciences Statistics Version 25 (Armonk, NY: IBM Corp.). Nominal variables were compared using the Chi-square test. RxC tables were analyzed using Pearson's chi-square test with Monte Carlo simulation. Differences between group means of data with nonnormal distribution were assessed using the Mann-Whitney U test and Kruskal-Wallis H test followed by a *post hoc* test. A p-value of <0.05 was considered significant.

Results

The survey form was completed by 603 dental professionals, wherein 63.18% were female and 36.82% were male. Of all participants, 1.33% graduated before 1990, 1.49% in 1990-1994, 1.82% in 1995-1999, 39.47% in 2000-2014, and 55.89% in 2015-2019. Additionally, 34.49% were working at a private clinic, 25.87% in a specialty program or doctoral degree, 25.7% at an oral and dental health clinic, and 13.93% as an academician at a university. Moreover, 51.08% were nonspecialized, whereas 11.94% had a specialty in oral and maxillofacial surgery, 7.79% in prosthetic dentistry, 6.8% in endodontics, 6.63% in pedodontics, 4.81% in orthodontics, 4.15% in periodontology, 3.65% in restorative dentistry, and 3.15% in oral and maxillofacial radiology.

As presented in Tables 1 and 2, the most common reply provided to the question "Are zoonoses transmitted from animals to humans?" was "Rarely" (56.38%), to the question "Can zoonoses be transmitted by a healthy animal?" was "Yes" (65.3%), and to the question "Are zoonoses transmitted human-to-human?" was "Yes" (89.1%). Similarly, the most common reply provided to the question "Are zoonoses life-threatening?" was "Yes" (97.35%), to the question "Can zoonoses be eradicated?" was "Partially" (52.07%), and to the question "What/who is the primary source of information you would apply to in a case of a health problem related to zoonoses?" was "Relevant specialists" (83.08%).

Table 2 presents the participants' perceived level of knowledge regarding zoonoses. Of all participants, 62.35% believed that dental professionals have a role in the treatment of zoonoses and 96.35% stated no problems regarding zoonoses during their professional practice.

In the question "Which of the following well-known diseases are zoonoses (rabies, tuberculosis, bird flu, SARS, tularemia, yersinia, leishmaniasis, capillariasis, brucellosis, anthrax, malaria, CCHF, salmonella, and HIV)?," each correct reply was scored as 1 point, and thus the maximum score was determined as 14, and the participants that had a score of 14 were considered as having a knowledge level of 100%. Accordingly, the mean score of participants was 8.02, which corresponded to a knowledge level of 58.57%. In the question "Which animals can zoonoses be transmitted by (poultry, birds, rodents, pets, bovines, sheep-goats, wild animals, and prey animals)?," the maximum score was determined as 8, and the mean score of the participants was 7.47, which corresponded to a knowledge level of 93.37%. In the question "What are the transmission modes of zoonoses (animal-human, animal-animal, human-human, and human-animal)?," the maximum score was determined as 4, and the mean score was 2.58, which corresponded to a knowledge level of 64.5%.

Rabies, CCHF, anthrax, bird flu, and brucellosis were the most commonly selected zoonoses by the participants; however, 3.2% and 11.3% of participants misidentified hepatitis B virus (HBV) and tetanus as zoonoses, respectively. Moreover, 84.4% of participants responded to the question "Which animals can zoonoses be transmitted by?" as "All". Moreover, the question "What are the transmission modes of zoonoses?" was answered by 99.8% of participants as "animal-human," 69.3% as "animal-animal," 66% as "human-human," and 23.5% as "human-animal".

The question "What agents can zoonoses be caused by (bacterial, viral, parasitic, fungal)?" was answered by 87.2% of the participants as "viral," 85.7% as "parasitic," 79.1% as "bacterial," and 44.6% as "fungal." Furthermore, 40.4% of the participants believed that all four agent types were responsible for zoonoses, 27.53% believed that three of them were responsible, 19.24% believed that two of them were responsible, and 12.44% believed that only one of them was responsible.

Participants who were specialized in pedodontics, oral and maxillofacial radiology, and restorative dentistry had a significantly higher level of knowledge about the types of zoonoses compared to non-specialized participants ($p<0.05$). Similarly, participants who were specialized in oral and maxillofacial radiology had a significantly higher level of knowledge about the types of zoonoses compared to participants who were specialized in oral and maxillofacial surgery, orthodontics, prosthetic dentistry, and endodontics ($p<0.05$). However, no significant difference was established among other fields of specialty about the knowledge level on the types of zoonoses ($p>0.05$). The specialized participants provided a higher number of correct replies compared to the nonspecialized participants; however, no significant difference was found between the two groups in the level of knowledge about zoonoses, the animals that could transmit zoonoses, and the transmission modes of zoonoses ($p>0.05$ for all) (Table 3).

Participants who were working in a private clinic had a lower level of knowledge regarding zoonoses compared to participants who were enrolled in a specialty program or doctoral degree ($p<0.05$). However, no significant difference was found among the professional settings of participants in the level of knowledge about the animals that could transmit zoonoses and transmission modes of zoonoses ($p>0.05$ for both) (Table 4).

Contrarily, 96.19% of the participants reported no knowledge about the "One Health" concept. Similarly, 99% indicated that they had received no training on this concept. Additionally, no significant relationship was found between the knowledge level and the acquisition of the training on the "One Health" concept and the participants' year of graduation, professional setting, and field of specialty ($p>0.05$). Similarly, no significant relationship was found between the participant's views on the role of dental professionals in the fight against zoonoses and their year of graduation, professional setting, and field of specialty ($p>0.05$).

Discussion

Zoonoses have become more prevalent within the last five decades due to the large-scale changes in ecological and anthropogenic factors, which equally increased the potential risk of zoonoses for public health (22-25). Additionally, almost 60% of all human pathogens are zoonotic and the number of novel pathogens continually increased, which indicates the seriousness of zoonoses and the socioeconomic losses caused by these diseases (26). Previous studies evaluated various serious zoonoses in Turkey, including toxoplasmosis, tuberculosis, anthrax, hydatid cyst, and rabies, and predominantly investigated their transmission modes, sources, and the number of infected individuals (27-30). Kakkar et al. (30) examined the level of awareness among medical and veterinary students on zoonoses. Nevertheless, to our knowledge, no study had evaluated the knowledge level of dental professionals regarding zoonoses and their level of awareness on the "One Health" concept.

Zoonotic pathogens can be transmitted in either direction between humans and animals (31). Our study revealed that most of our participants (99.8%) declared that zoonoses are transmitted from animals to humans and 89.05% considered that zoonoses are transmitted from humans to humans. Body fluids play an important role in the transmission of zoonoses from humans to humans. Droplets and aerosols are commonly known to be generated during most dental clinical procedures (32). Meaningfully, inhaling or direct contact with these particles leads to the human-to-human transmission of zoonoses (17). Therefore, dental professionals need to have high-level awareness of the transmission of zoonoses and take necessary precautions.

Our study revealed that 23.5% of the participants considered that zoonoses are transmitted from humans to animals. However, only several zoonoses, including *Mycobacterium tuberculosis*, *Staphylococcus* infections (predominantly methicillin-resistant *Staphylococcus aureus*), and *Cryptosporidium parvum* are known to be rarely transmitted from humans to animals (33). Contrarily, most participants (56.38%) indicated that zoonoses are rarely transmitted from animals to humans, which indicates their low level of knowledge regarding this transmission mode. Meaningfully, this low level of knowledge could be attributed to the fact that the transmission of zoonoses to animals is a major field of interest among veterinarians.

Practitioners, physicians, nurses, health technicians, and other healthcare professionals need to undergo continuing vocational training (CVT) schemes that provide extensive information on access to information sources, dynamic zoonoses prevention, and public protection against zoonoses. Furthermore, studies that are conducted in Turkey and other countries showed that the administration of CVT schemes can prevent economic losses in healthcare services and reduce professional risks associated with zoonoses (25,27).

Taştan et al. (27) evaluated the knowledge level of nurses regarding zoonoses and revealed that the most common reply provided to the question "What/who is the primary source of information you would apply to in a case of a health problem related to zoonoses?" was "Relevant specialists" (40.5%), followed by "Internet" (27.9%), and the least common reply was "Television" (0.4%) (27). These findings were consistent with our findings since "Relevant specialists" (83.08%) was also the most common reply provided by our participants, followed by "Internet" (28.05%), "Colleagues" (28.5%), and the least common reply was "Books" (8.3%). Çilingiroğlu et al. (11) evaluated the knowledge, opinions, and behaviors of adults regarding CCHF and revealed that television (94%) was the most common information source among the participants, followed by healthcare professionals (7.4%), health centers (6.4%), and internet (4%). These findings were inconsistent with our findings, which could be attributed to the fact that our participants were dental professionals, and the participants in the study by Çilingiroğlu et al. (11) consisted of non-healthcare professionals who had a higher potential of television viewing.

Taştan et al. (27) revealed that 59% of their nurse participants had insufficient knowledge about zoonoses. Similarly, 60.86% of our participants revealed that they had insufficient knowledge about zoonoses. These low knowledge levels are highly important in protective health services, risk management in public health services, health economy, and efficiency. Therefore, both dental professionals and other healthcare professionals should undergo multidisciplinary training on zoonoses, as well as intensive training schemes that provide updates on emerging zoonoses.

Taylor et al. (34) conducted a systematic review and identified 1,415 species of infectious organisms that are known to be pathogenic to humans, including 538 bacteria and rickettsia, 353 parasites, 307 fungi, and 217 viruses and prions. However, the participants in our study identified viral pathogens (87.2%) as the most common cause of zoonotic infections, followed by parasitic (85.7%), bacterial (79.1%), and fungal (44.6%) pathogens. These differences could be attributed to the worldwide impact of the widespread coverage of Coronavirus disease-2019 (COVID-19) on mass media and social media on the decisions of participants.

Our study revealed a significantly lower knowledge level of participants working in private clinics about zoonoses than those enrolled in a specialty program or doctoral degree ($p<0.05$). Contrarily, the specialized participants provided a higher number of correct replies compared to nonspecialized participants; however, no significant difference was found between the two groups in the level of knowledge about zoonoses ($p<0.05$).

These findings were consistent with the findings of studies that compared the knowledge level of specialized and nonspecialized dental professionals about other issues (35-37).

Zoonoses, particularly rabies, tuberculosis, bird flu, brucellosis, SARS, leishmaniasis, capillariasis, anthrax, malaria, CCHF, and HIV, remain a serious public health problem both in Turkey and other countries (7,12). Hundal et al. (38) evaluated the awareness, knowledge, and risks of zoonoses among livestock farmers and revealed that the most commonly identified zoonosis among the participants was bird flu (92.4%), followed by rabies (84.8%), brucellosis (46.0%), tuberculosis (32.8%), and anthrax (4.61%). Molineri et al. (39) evaluated the awareness levels of freshmen entering the veterinary school about zoonoses and revealed that the most commonly identified zoonoses among the participants were rabies, tuberculosis, and leptospirosis. Our study revealed that the mean score of the participants for the question "Which of the following well-known diseases are zoonoses?" was 8.02, which corresponded to a knowledge level of 58.57%. Additionally, rabies was found to be the most well-known zoonosis among our participants, followed by CCHF (87.6%), bird flu (85.7%), and anthrax (85.1%). These findings were consistent with those reported in the literature. Contrarily, HIV, which has a cross-contamination potential due in dental clinics, was identified as a zoonosis by 14.1% of our participants. We believe that HIV should be better known than rabies by dental professionals. Additionally, HBV, which is a non-zoonotic disease and a critical entity in dental clinical practice, was identified as a zoonosis by 3.2% of the participants. These findings implicate the need for health professional education.

Table 1. Questions in the survey

Question 1:	What is your gender?
Question 2:	What year did you graduate?
Question 3:	Where do you work?
Question 4:	What is your area of expertise?
Question 5:	Is disease transmitted from animals to humans?
Question 6:	Does zoonotic diseases threaten life?
Question 7:	Can zoonotic diseases be eliminated?
Question 8*:	Which are the Zoonosis Diseases?
Question 9*:	Are the zoonotic diseases transmitted from which animals?
Question 10*:	Can zoonotic diseases be transmitted with which transitions?
Question 11:	Can zoonotic diseases be transmitted from person to person?
Question 12*:	What do pathogens cause zoonotic diseases?
Question 13*:	Which information source do you first apply to when you have a health problem with zoonotic diseases?
Question 14:	Have you ever had a problem with zoonotic diseases during professional practices?
Question 15:	Do you think you have sufficient knowledge about zoonotic diseases?
Question 16:	Do you know the one health concept?
Question 17:	Have you received any education on the one health concept?
Question 18:	Do you think the dentist has a role in the treatment of zoonotic diseases?

*In these questions, the participants were able to mark more than 1 option

Zoonoses may be transmitted by contact with all contaminated animals, including poultry, birds, rodents, pets, cattle, bovines, sheep-goats, wild animals, and prey animals (5). Our study revealed that the mean score of participants for the question "Which animals can zoonoses be transmitted by" was 7.47, which corresponded to a knowledge level of 93.37%. This finding indicates that participants did not know all the types of zoonoses; however, they had sufficient knowledge on which animals had the potential to transmit these diseases.

Zoonoses are a leading cause of death from infectious diseases worldwide (8,9). Among these, SARS and bird flu that emerged in the 2000s and the current COVID-19 pandemic that influences the entire world remain the most fatal zoonoses (17,40,41). The present study revealed that 97.35% of participants identified zoonoses as life-threatening. Accordingly, raising the awareness of dental professionals, particularly, on the zoonoses that are transmitted via airborne droplets and particles, and supporting the measures to be taken against these diseases are of prime importance.

The "One Health" concept emerged as an internationally significant phenomenon that follow the outbreak of bird flu in the early twenty-first century (42). Zoonoses can emerge in any part of the world, thus worldwide measures need to be taken to keep track of, prevent, and cope with these diseases (43). A previous study by Wong and Kogan evaluated the views of second to fourth-year veterinary medicine students at the Colorado State University College of Veterinary Medicine and Biomedical Sciences on the needs and attitudes regarding the "One Health" concept. The students were involved in educational activities that included interdisciplinary interactions with health professionals and revealed that most of the students were highly interested in the activities and that this model was remarkably effective (44). Such activities are considered to become widespread both in Turkey and worldwide.

Our study revealed that 99% of participants received no training on the "One Health" concept and 96.19% had no prior knowledge about this concept. Additionally, 62.35% considered that dental professionals had a role in the treatment of zoonoses. The lack of knowledge about the "One Health" concept among dental professionals, as well as other health professionals, results from their lack of training on these diseases. Accordingly, activities on zoonoses are considered to be promoted, and training schemes should be conducted to eliminate deficiencies in the systems to prevent these diseases. The present study aimed to elucidate zoonoses and the application of the "One Health" concept in dental practice, as well as raise awareness in clinical practice and contribute to the relevant literature.

Table 2. The distribution of given answers

Questions	Answers	n	%
Is disease transmitted from animals to humans?	Never infect	0	0
	Often infects	232	38.47
	Rare infection	340	56.38
	Always infected	26	4.31
	No idea	5	0.83
	Total	603	100
Does zoonotic diseases threaten life?	Yes	587	97.35
	No	16	2.65
	Total	603	100
Can zoonotic diseases be eliminated?	Yes	170	28.19
	No	46	7.63
	Partially	314	52.07
	I do not know	73	12.11
	Total	603	100
Can zoonotic diseases be transmitted from person to person?	Yes	537	89.05
	No	66	10.95
	Total	603	100
What do pathogens cause zoonotic diseases?	1 of 4 correct	75	12.44
	2 of 4 correct	116	19.24
	3 of 4 correct	166	27.53
	4 of 4 correct	246	40.8
	Total	603	100
Which information source do you first apply to when you have a health problem with zoonotic diseases?	Experts	501	83.08
	Colleagues	72	11.94
	Internet	172	28.52
	Books	50	8.29
Have you ever had a problem with zoonotic diseases during professional practices?	Yes	22	3.65
	No	581	96.35
	Total	603	100
Do you think you have sufficient knowledge about zoonotic diseases?	Absolutely enough	2	0.33
	Enough	10	1.66
	Partly enough	224	37.15
	Partially insufficient	166	27.53
	Absolutely insufficient	201	33.33
	Total	603	100
Do you know the one health concept?	Yes	23	3.81
	No	580	96.19
	Total	603	100
Have you received any education on the one health concept?	Yes	6	1
	No	597	99
	Total	603	100
Do you think the dentist has a role in the treatment of zoonotic diseases?	Yes	376	62.35
	No	227	37.65
	Total	603	100

Table 3. The result of the analysis on the difference between the areas of expertise

Questions	The areas of expertise	n	Mean	Median	Min	Max	SD	Kruskal-Wallis H testi		
								Mean Rank	H	p
Are the zoonotic diseases transmitted from which animals?	Pediatric dentistry	40	8.87	9	4	14	2.27	356.73	19.654	**0.012**
	Oral, dental and maxillofacial surgery	72	8.24	8	3	13	2.25	316.15		
	Orthodontics	29	8	8	4	12	2.31	295.07		
	Prosthetic dental treatment	47	7.89	8	2	13	3.04	304.27		
	Periodontology	25	8.32	8	4	13	2.38	324.1		
	Mouth. tooth and jaw radiology	19	9.47	10	5	12	2.25	409.71		
	Restorative dental treatment	22	8.86	9	6	13	2.01	361		
	Endodontics	41	7.76	8	2	12	2.59	286.93		
	None	308	7.74	8	2	13	2.21	281.25		
	Total	603	8.02	8	2	14	2.35			
	Pediatric dentistry	40	7.48	8	3	8	1.47	308.1	6.298	0.614
	Oral, Dental and maxillofacial surgery	72	7.6	8	4	8	1.06	307.06		
	Orthodontics	29	7.41	8	3	8	1.45	295.59		
	Prosthetic dental treatment	47	7.23	8	2	8	1.59	272.79		
	Periodontology	25	7.56	8	3	8	1.29	310.86		
	Mouth, tooth and jaw radiology	19	7.26	8	4	8	1.48	283.87		
	Restorative dental treatment	22	7.77	8	3	8	1.07	332.5		
	Endodontics	41	7.32	8	2	8	1.72	300.45		
	None	308	7.49	8	1	8	1.4	303.51		
	Total	603	7.47	8	1	8	1.4			
Can zoonotic diseases be transmitted with which transitions?	Pediatric dentistry	40	2.75	3	1	4	1.08	331.58	13.752	0.088
	Oral, dental and maxillofacial surgery	72	2.82	3	1	4	0.91	341.01		
	Orthodontics	29	2.45	3	1	4	1.09	282.48		
	Prosthetic dental treatment	47	2.3	2	1	4	1.02	252.78		
	Periodontology	25	2.4	2	1	4	1.04	271.16		
	Mouth, tooth and jaw radiology	19	2.26	2	1	4	0.99	247.39		
	Restorative dental treatment	22	2.5	2	1	4	0.86	281.18		
	Endodontics	41	2.71	3	1	4	0.98	324.96		
	None	308	2.59	3	1	4	0.97	302.69		
	Total	603	2.58	3	1	4	0.99			

Min: Minimum, Max: Maximum, SD: Standard deviation

Conclusion

Zoonoses will exist as long as humans and animals persist. The emergence of novel diseases may not be preventable; however, humans can be protected by the prevention of the spread of zoonoses. Therefore, dental professionals and other health professionals need to learn about and adopt the "One Health" concept. Further larger-scale studies with larger numbers of participants are needed to substantiate our findings.

Raising the awareness of all dentists about diseases that can be transmitted by airborne particles and droplets, particularly about zoonoses, and supporting the measures to be taken against zoonoses in dental practices is of great importance.

In addition to the clinical medical courses that are delivered in dentistry education, a course, such as infectious diseases, can be added, or regular training seminars can be organized to increase awareness on the duties of dentists in zoonoses and their transmission paths, prevention methods, and treatment methods.

Table 4. Analysis result regarding the difference between the places studied in terms of knowledge scores

Questions	Workplace	n	Mean	Median	Min	Max	SD	Kruskal-Wallis H testi		
								Mean Rank	H	p
Which are the zoonosis Diseases?	University (academician)	84	7.83	7	2	14	2.99	290.85	9.504	0.023
	University (doctoral student)	156	8.5	9	2	13	2.11	337.47		
	Oral and dental health clinic	155	7.98	8	2	13	2.25	297.71		
	Private clinic	208	7.76	8	2	13	2.28	283.1		
	Total	603	8.02	8	2	14	2.35	4-2		
Are the zoonotic diseases transmitted from which animals?	University (academician)	84	7.25	8	2	8	1.65	288.5	1.85	0.604
	University (doctoral student)	156	7.49	8	2	8	1.32	299.96		
	Oral and dental health clinic	155	7.51	8	3	8	1.34	306.2		
	Private clinic	208	7.52	8	1	8	1.38	305.85		
	Total	603	7.47	8	1	8	1.4			
Can zoonotic diseases be transmitted with which transitions?	University (academician)	84	2.54	3	1	4	1.06	293.58	1.873	0.599
	University (doctoral student)	156	2.67	3	1	4	0.97	315.51		
	Oral and dental health clinic	155	2.51	3	1	4	1	291.46		
	Private clinic	208	2.6	3	1	4	0.96	303.12		
	Total	603	2.58	3	1	4	0.99			

Min: Minimum, Max: Maximum, SD: Standard deviation

Ethics

Ethics Committee Approval: Before the study, approval was obtained from Fırat University Non-interventional Clinical Research Ethics Committee (approval date: March 5, 2020; no: 2020/05-08).

Informed Consent: Each participant was informed about the goals and anticipated outcomes of the study.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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Original Article

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The Evaluation of Urethritis in Men Caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*: Ten-year Retrospective Data from Turkey

Neisseria gonorrhoeae, *Chlamydia trachomatis*, *Ureaplasma urealyticum* ve *Mycoplasma hominis*'in Etken Olduğu Erkek Üretrit Olgularının Değerlendirilmesi: Türkiye'den On Yıllık Retrospektif Veri

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ABSTRACT

Objective: Sexually transmitted diseases are one of the most important health issues that cause economic and social problems. Urethritis is one of the most common clinical manifestations. Patients who are especially asemptomatically infected with resistant microorganisms continue to infect others; thus, surveillance is important. Our study retrospectively evaluated urethritis cases in males over 10 years for causative agents and their antibiotic susceptibilities.

Methods: This study included 748 male patients with urethritis. Urethral discharge swab and ejaculation samples were examined for isolation and antibiotic susceptibilities of *N. gonorrhoeae* (Biomerieux, France), *M. hominis*, and *U. urealyticum* (Mycoplasma IES, Autobio). Additionally, rapid chromatographic immunoassay (Ultimed) was used for *C. trachomatis* antigen detection.

Results: Of 748 patients, 166 (22.2%) were positive for at least one microorganism, whereas 28 showed a mixed infection. The most prevalent microorganism was *U. urealyticum* (114 patients, 58.8%), followed by *N. gonorrhoeae* (43 patients, 21.6%), *M. hominis* (24 patients, 12.4%), and *C. trachomatis* (10 patients, 5.2%). Most of the *N. gonorrhoeae* strains were susceptible (92.3-100%) to cefuroxime,

ÖZ

Amaç: Cinsel temasla bulaşan hastalıklar (CTBH), ekonomik ve sosyal problemlere yol açan en önemli halk sağlığı sorunlarından biridir. Üretrit en sık karşılaşılan CTBH'lerden biridir. Bu nedenle, dirençli mikroorganizmalarla özellikle asemptomatik olarak infekte kişiler enfeksiyonlarını diğer kişilere de bulaştırmaya devam edeceğinden bu etkenlerin izlenmesi çok önemlidir. Çalışmamızda 10 yıllık dönemde üretritli erkek hastalardaki etkenler ve antibiyotiklere duyarlılıkları retrospektif olarak değerlendirilmiştir.

Yöntemler: Yedi yüz kırk sekiz üretritli erkek hasta çalışmaya dahil edilmiştir. Üretral akıntı ve ejekülat sıvısı örneklerinde *N. gonorrhoeae* (Biomerieux, Fransa), *M. hominis* ile *U. urealyticum* (Mycoplasma IES, Autobio) varlığı ve antibiyotiklere duyarlılıkları araştırılmıştır. Ayrıca *C. trachomatis* (Ultimed) antijeni varlığı da hızlı kromatografik yöntem ile araştırılmıştır.

Bulgular: Yedi yüz kırk sekiz hastanın 166'sının (%22,2) incelenen etkenlerin en az biri ile infekte olduğu bulunmuş; hastaların 28'inde mikst enfeksiyon saptanmıştır. En sık saptanan etken *U. urealyticum* (114 olgu-%58,8) olmuştur; *N. gonorrhoeae* (43 olgu-%21,6), *M. hominis* (24 olgu-%12,4) ve *C. trachomatis* (10 olgu-%5,2) onu izlemiştir. *N. gonorrhoeae* suşları genellikle sefuroksim, seftriakson,

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ceftriaxone, penicillin, levofloxacin, ciprofloxacin, and tetracycline. The great majority of *U. urealyticum* strains were resistant to clindamycin (89.6%) and ciprofloxacin (78.5%). *M. hominis* strains were resistant to erythromycin (100%), clarithromycin (90%), clindamycin (70%), and ciprofloxacin (43.8%).

Conclusion: This study revealed that these microorganisms and their antibiotic resistance patterns remain a major public health concern for the last decade.

Keywords: Urethritis, *N. gonorrhoeae, C. trachomatis, M. hominis, U. urealyticum*, antibiotic resistance

penisilin, levofloksasin, siprofloksasin ve tetrasikline duyarlı bulunmuştur. (%92,3-100). *U. urealyticum* suşlarının büyük bir çoğunluğu klindamisin (%89,6) ve siprofloksasine (%78,5) dirençli bulunmuştur. Bunlara ilave olarak *M. hominis* suşları eritromisin (%100), klaritromisin (%90), klindamisin (%70) ve siprofloksasine (%43,8) dirençli bulunmuştur.

Sonuç: Sonuçlar, geçtiğimiz on yılda da etkenlerin ve antibiyotik direnç modellerinin hala önemli bir halk sağlığı sorunu olduğunu göstermiştir.

Anahtar Sözcükler: Üretrit, *N. gonorrhoeae, C. trachomatis, M. hominis, U. urealyticum*, antibiyotik direnci

Introduction

Urethritis is one of the most common sexually transmitted diseases (STDs) that is also defined as urethral inflammation (1-4). Some common clinical signs, such as stinging or itching mucoid, mucopurulent, and/or purulent discharge, dysuria and penile irritation, and urethritis can often be asymptomatic. Urethritis may occur due to infectious or non-infectious causes, such as using condoms or spermicide and mechanical traumas (1,2,4).

N. gonorrhoeae is the agent of gonococcal urethritis (GU), which is still the most important agent in developing countries, whereas *Chlamydia trachomatis, Ureaplasma urealyticum*, *Mycoplasma* species, *Trichomonas vaginalis*, *Herpes simplex virus,* and Adenoviruses are the causes of non-GU (NGU) in developed countries. More commonly microorganisms than *N. gonorrhoeae* are detected (1,3-6).

Penicillins, tetracyclines, fluoroquinolones, and oral third-generation cephalosporins are recommended for *N. gonorrhoeae* therapy (7-10). Macrolides, tetracyclines, and quinolones are antibiotics of choice for the treatment of *Chlamydia*, *Mycoplasma,* and *Ureaplasma* due to the emergence of resistance, and antibiotic susceptibilities should also be tested (11,12).

This study aimed to report the distribution of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum,* and *Mycoplasma hominis* and the antibiotic resistance rates in clinical specimens obtained from male patients with urethritis in a third-step hospital between 2010 and 2019.

Method

Patient Population and Study Design

Between 2010 and 2019, 748 male patients with urethritis having clinical complaints and admitted to İstanbul Yeni Yüzyıl University, Medical Faculty Gaziosmanpaşa Hospital were evaluated. Male patients were 20-74 (mean; 38) years old. Patients had clinical signs, such as urethral discharge and/or dysuria. Urethral discharge, swab, and ejaculation samples were collected after the clinical examination using sterilized cotton swabs and placed in transport agar (SEEDSWAB ΥNo2, Eiken Chemical Co. Ltd. Tokyo, Japan). All samples were dyed with Gram's stain and all preparations were examined for the presence of polymorph nuclear leukocytes and microorganisms.

N. gonorrhoeae, *M. hominis,* and *U. urealyticum* were isolated and their antibiotic susceptibilities were also tested. The antibiotic testing panels are changed in diagnostic kits over 10 years; thus, not all isolated strains could be tested for the same groups of antibiotics. The immune chromatographic method was used to detect *C. trachomatis* antigen.

Isolation of *N. gonorrhoeae* and Antibiotic Susceptibility Testing

All samples were cultivated on the Thayer-Martine agar and incubated for 24-48 h at 35 °C in 5% CO_2 atmospheric conditions to isolate *N. gonorrhoeae*. The identification was performed using VITEK-2. The antimicrobial susceptibility testing was performed by disc diffusion method for cefuroxime, ceftriaxone, penicillin, levofloxacin, ciprofloxacin, and tetracycline according to the recommendations of Centers for Disease Control and Prevention (2005) and Clinical & Laboratory Standards Institute (2012) (13,14). During the antimicrobial susceptibility testing, our results were confirmed with the results of clinical *N. gonorrhoeae* strains that were performed in an accredited laboratory to validate the internal quality of our test conditions.

Isolation of *M. hominis* and *U. urealyticum* and Antibiotic Susceptibility Testing

A quantitative commercial test (Mycoplasma IES, Autobio) was used to identify and test the antibiotic susceptibility (roxithromycin, clarithromycin, erythromycin, ofloxacin, tetracycline, ciprofloxacin, clindamycin, and levofloxacin) of *M. hominis* and *U. urealyticum*. This test detects urease and arginase activities by releasing NH_3 to identify *Ureaplasma* and *Mycoplasma*, respectively. The positive results were determined with color changes in the wells that contain antibiotics, wherein changes mean that the bacterium is resistant. The tests were performed following the manufacturer's recommendations.

Detection of *C. trachomatis* Antigen

A rapid chromatographic immunoassay (Ultimed) was used to detect *C. trachomatis* antigen. The test was performed according to the manufacturer's recommendations.

Results

Distributions of Patients, Clinical Samples, and Detected Microorganisms

A total of 987 patients with prediagnosed urethritis were evaluated. To determine the prevalence and antibiotic resistance rates of causative microorganisms, 748 (75.8%) male patients were included in the present study, wherein 165 (22.05%) were positive for at least one investigated microorganism. Among 165 patients with urethritis, 28 (16.9%) have mixed infection (infected with more than one causative agent). A total of 194 different microorganisms were detected. Except for one urine and three ejaculate samples, the majority of the clinical samples were urethral swabs.

The distributions of positive patients for urethritis according to years were shown in Table 1; in years 2015 and 2017 the positivity was the highest. In 2011, only eight patients were found to be infected with the investigated microorganisms.

U. urealyticum (114 patients) was revealed as the most prevalent microorganism over a 10-year period, which was followed by *N. gonorrhoeae* (43 patients), *M. hominis* (24 patients), and *C. trachomatis* (10 patients) (Figure 1).

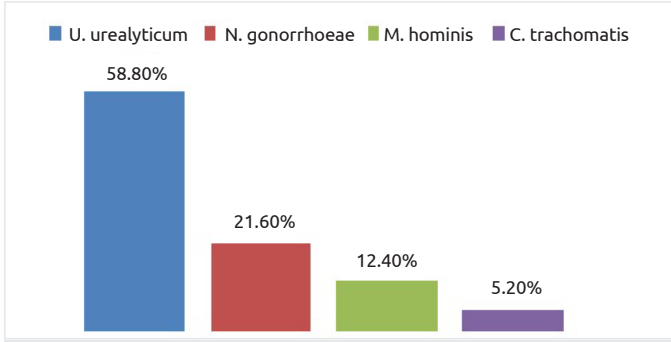

Figure 1. Microorganism detected in samples obtained from patients

Antibiotic Susceptibility Results

All 42 *N. gonorrhoeae* strains isolated over the 10-year period were susceptible (92.3-100%) to all six tested antibiotics (Table 2).

The resistance rate of *U. urealyticum* strains to clindamycin was 89.6%, followed by ciprofloxacin (78.5%) and tetracycline (43.9%). Strains were also intermediate resistant to ofloxacin (47.5%) (Table 3).

All *M. hominis* strains were resistant to erythromycin, followed by clarithromycin (90%), clindamycin (70%), and ciprofloxacin (43.8%) (Table 4).

Discussion

Urethritis is the most common syndrome among STDs, which are globally important public health concerns (3,5,15,16). Early diagnosis and treatment were implicated. Increasing resistance rates in agents of STDs is also very important and can cause treatment failure (3,17,18).

N. gonorrhoeae and *C. trachomatis* remain as the most important causative agents of urethritis in male patients (2,4,5,8). Asymptomatic cases are frequent and important for infection transmission (19-21). The body of evidence suggests that *N. gonorrhoeae* has a great capacity to develop antibiotic resistance, and in many countries, resistance rates are very high to penicillin, macrolides, tetracycline, and quinolones; therefore, ceftriaxone (extended-spectrum cephalosporin) has become an important antibiotic (17,18,22). The World Health Organization and CDC have emphasized the importance of surveillance studies performed by culture and antibiotic susceptibility testing to prevent the dissemination of multidrug-resistant *N. gonorrhoeae* strains (18).

Previous studies from India, Kuwait, Zimbabwe, and the United States reported that the detection rates of *N. gonorrhoeae* and *C. trachomatis* from male patients range 23.9-81.9% and 12.4-31.4%, respectively according to different geographical regions (17,23-25).

A study reported from France analyzed 1,944 cases of urethritis in male patients during 10 years and 38% of patients were found

Table 1. Distributions of the detected microorganisms from clinical samples in 10 years

Years	Number of patients	Number of microorganisms detected from the patients			
		U. urealyticum	*N. gonorrhoeae*	*M. hominis*	*C. trahomatis*
2010	14	12	2	5	0
2011	8	5	4	2	0
2012	14	10	4	2	0
2013	15	10	4	4	0
2014	13	9	4	1	0
2015	34	23	14	4	0
2016	20	11	4	1	5
2017	22	11	6	3	4
2018	9	9	0	0	1
2019	16	14	1	2	0

Table 2. Antibiotic susceptibilities of *N. gonorrhoeae* strains

Antibiotics	Strains tested (n)	Susceptible (%)	Resistant (%)
CRO	36	100	0
CXM	36	100	0
P	30	93.3	6.6
LEV	29	93.1	6.9
CİP	36	91.6	8.3
TET	26	92.3	7.7

CXM: Cefuroxime, CRO: Ceftriaxone, P: Penicillin, LEV: levofloxacin, CIP: Ciprofloxacin, TET: Tetracycline

Table 3. Antibiotic susceptibilities of *U. urealyticum* strains

Antibiotics	Strains tested (n)	Susceptible (%)	Resistant (%)	Intermediate (%)
ROX	95	85.3	6.3	8.4
E	81	90.1	9.8	0
CLAR	80	83.6	11.3	5
CLIN	77	6.5	89.6	3.9
CIP	107	9.3	78.5	12.1
OFX	101	23.7	28.7	47.5
LEV	78	78.2	11.5	10.3
TET	82	36.6	43.9	19.5

ROX: Roxithromycin, CLAR: Clarithromycin, E: Erythromycin, OFX: Ofloxacin, TET: Tetracycline, CIP: Ciprofloxacin, CLIN: Clindamycin, LEV: Levofloxacin

to be infected with *C. trachomatis* while the isolation rate of *N. gonorrhoeae* was 32.5%. Additionally, 6.7% of the patients were found to be co-infected (5). Our study also includes strains that are isolated from the samples obtained in male patients in the last 10 years. Our isolation rates were 21.6% and 5.2% for *N. gonorrhoeae* and *C. trachomatis,* respectively, and the difference between isolation rates can be associated with the number of included patients and techniques used to detect microorganisms.

Many literature reports on antibiotic susceptibility were also investigated. As an example, Hamasuna et al. (26) reported that the majority of *N. gonorrhoeae* strains were resistant to ciprofloxacin in Japan. The prevalence of fluoroquinolone resistance rates of *N. gonorrhoeae* has been reported to reach almost 70% (26-28).

A study by Buder et al. (18) in Germany revealed that a total of 537 *N. gonorrhoeae* strains were isolated during an extended surveillance program in the whole country, wherein none of the strains were found to be resistant to ceftriaxone but with resistance rates to azithromycin and ciprofloxacin of 10.8% and 64.9%, respectively. Consistent with Buder et al. (18), Latif et al. (17) reported that all *N. gonorrhoeae* strains were susceptible to ceftriaxone and cefixime, but resistance to ciprofloxacin and kanamycin were 18.6% and 2%, respectively. Contrarily, many literatures reported the susceptibility rates of *N. gonorrhoeae* strains showed to be decreased to cefixime (29,30).

Yeshanew and Geremew (15) found in Ethiopia that, among

Table 4. Antibiotic susceptibilities of *M. hominis* strains.

Antibiotics	Strains tested (n)	Susceptible (%)	Resistant (%)	Intermediate (%)
ROX	14	71.4	14.2	14.2
E	10	0	100	0
CLAR	10	10	90	0
CLIN	10	30	70	0
CIP	16	37.5	43.8	18.8
OFX	14	78.6	7.1	14.3
LEV	10	80	10	10
TET	10	90	0	10

ROX: Roxithromycin, CLAR: Clarithromycin, E: Erythromycin, OFX: Ofloxacin, TET: Tetracycline, CIP: Ciprofloxacin, CLIN: Clindamycin, LEV: Levofloxacin

207,044 gonorrhoeae suspected patients, 20.8% were confirmed to be infected with *N. gonorrhoeae*. All isolated strains were resistant to tetracycline (100%) and penicillin (100%), and resistance rates to ciprofloxacin, ceftriaxone, and cefoxitin were 52%, 48%, and 44%, respectively (15).

Some studies revealed that *N. gonorrhoeae* strains are found resistant to various antibiotics, even to ceftriaxone (15,26-28); however, in our study, none of the strains were resistant to ceftriaxone and cefuroxime and even penicillin-resistance rates were found to be low (6.6%).

In Turkey, Balıkçı and Aydın (31) reported that 1,226 *N. gonorrhoeae* strains were found to be susceptible to ceftriaxone, cefuroxime, and cefoxitin. However, resistance rates of penicillin, tetracycline, and ciprofloxacin were 62%, 61%, and 33%, respectively (31). Another study from Turkey revealed that, among 78 *N. gonorrhoeae* strains, the resistance rate was 64% for penicillin and 75.7% for tetracycline, whereas doxycycline, azithromycin, and ciprofloxacin were found to be the most effective antibiotics (22). In the present study, resistance rates to penicillin (6.6%), tetracycline (7.7%), and ciprofloxacin (8.3%) were much lower as mentioned above.

U. urealyticum and *M. hominis* is well known to colonize the genital tract when people were born, colonization rates increase up to 60% of the population after puberty, and that they can be responsible for some clinical manifestations, such as NGU, cervicitis, and cystitis (20,32). Generally, the prevalence of *U. urealyticum* in patients with NGU is nearly 6-60%, and infections are associated with socioeconomic status and education levels of the population (17,31).

Authors from Switzerland, China, Cuba, Africa, and Serbia informed that isolation rates of *Ureaplasma* and *Mycoplasma* from patients with urethritis range 13-89% according to different geographical regions (34-38).

Various reports from Turkey showed that isolation rates of *U. urealyticum* and *M. hominis* reached up to 82% and 30%, respectively (33). Pelit et al. (16) reported that *U. urealyticum* was the most prevalent (32%) microorganism that is isolated from the

urethral discharges of 140 male patients followed by *M. hominis* (10.7%), *C. trachomatis* (8.6%), and *N. gonorrhoeae* (8.6%). Our study revealed that the isolation rate of *U. urealyticum* (58.8%) was higher than *N. gonorrhoeae* (21.6%), thus our results appear to support previous studies.

Quinolone resistance of *Ureaplasma* (0-62.5%) and *Mycoplasma* (17.6-41.2%) strains is increasing (32,39-41). Resistance rates of *Mycoplasma* and *Ureaplasma* strains to doxycycline, roxitromycin, and tetracycline were reported as 0-8%, 0-30%, and 19-50%, respectively. Thus doxycycline, clarithromycin, and azithromycin are most recommended antibiotics (42).

Our results revealed that resistance rates of *U. urealyticum* strains to clindamycin, quinolones, and tetracycline were 89.6%, 47.5-78.5%, and 43.9%, respectively. Additionally, *Ureaplasma* strains were susceptible to erythromycin (90.1%), roxithromycin (85.3%), and clarithromycin (83.6%). Similar to *U. urealyticum*, resistance rates of *M. hominis* strains were high to clindamycin (70%) and ciprofloxacin (43.8%). Tetracycline was also effective to *Mycoplasma* strains (90%) but not to *Ureaplasma* strains (36.6%). Therefore, roxithromycin was the most effective antibiotic against both *Ureaplasma* and *Mycoplasma* strains, with resistance rates of 14.7% and 28.6%, respectively.

Study Limitations

Limitations of our study include insufficient demographical data, knowledge about recent antibiotic usage and serological test results (anti-HIV, anti-syphilis, etc.), and the number of sexual partners or unprotected sexual intercourse. We also failed to perform antibiotic susceptibility testing for *C. trachomatis*.

Additionally, our training hospital is a third-step hospital, and patients are mostly admitted after a prior antibiotic therapy and due to financial difficulties, all diagnostic procedures could not be performed to clearly define urethritis etiology. Therefore, our number of positive cases, such as *N. gonorrhoeae*, is lower than some of the reported studies. The low prevalence rates could be the reason for lower resistance rates compared with previous studies.

Conclusion

Our results proved that, among the four major STD agents, *U. urealyticum* was the most common for the last decade in symptomatic male patients with urethritis. Roxithromycin is found to be the most effective antibiotic for both *Ureaplasma* and *Mycoplasma* strains. As mentioned in previous studies, *N. gonorrhoeae* strains were susceptible to mostly used therapeutic agents.

Ethics

Ethics Committee Approval: Ethical approval has been obtained from İstanbul Yeni Yuzyıl University Medical Faculty Research Ethics Committee (meeting date: 2020/04-05).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: D.B.T., Concept: D.B.T., Design: D.B.T., D.G., F.K.Y., Data Collection or Processing: D.B.T., D.G., F.K.Y., Analysis or Interpretation: D.G., F.K.Y., Literature Search: D.G., F.K.Y., Writing: D.G., F.K.Y.

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Original Article

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The Effect of Long Public Holidays on Healthcare-associated Infection Rate

Uzun Tatillerin Hastane Enfeksiyonları Üzerine Etkisi

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ABSTRACT

Objective: Healthcare-associated infections (HAIs) are infections that cause serious mortality and morbidity. This study aimed to investigate the effect of long public holidays on HAIs rates in the intensive care units (ICUs).

Methods: The study was conducted in tertiary university education and research hospital, from January 2014 to October 2015. All ICUs are monitored daily by the infection control team by the active surveillance method. In this study, LPH and normal working periods (NWT) that develop HAIs, the bacterial factors that cause HAIs, between periods mortality rates, and overall mortality rates were compared. All data were analyzed with the Epi-Info program (Atlanta, USA) and p-values of <0.05 were considered statistically significant.

Results: During the study period, 3082 patients in the ICU were followed up. The HAI rate was 3.5% in NWT and 16.5% in LPH (p=0.001). The examination of bacterial distribution that causes HAIs revealed significantly higher gram-negative bacterial infections in LPH than in NWT [13.7% and 2.4%, respectively (p=0.001)]. The mortality rate examination revealed no significant difference in the overall mortality rates between study periods (p=0.769); infection-related mortality rates were significantly higher in LPH (7.3%; p=0.002).

Conclusion: HAIs are affected by LPH. All employees should be motivated to prevent HAIs and should be trained for infection control measures before and after the holidays.

Keywords: Long public holidays, healthcare-associated infections, intensive care unit

ÖZ

Amaç: Sağlık bakımı ilişkili enfeksiyonlar (SBİE) ciddi mortalite ve morbiditeye neden olan enfeksiyonlardır. Bu çalışmada yoğun bakım ünitelerinde (YBÜ) uzun tatil dönemlerinin (UTD) SBİE oranları üzerine etkisi araştırıldı.

Yöntemler: Çalışma, Ocak 2014 ile Ekim 2015 arasında üçüncü basamak bir eğitim ve araştırma hastanesinde yapıldı. Tüm YBÜ, enfeksiyon kontrol ekibi tarafından günlük olarak aktif gözetim yöntemi ile izlenmektedir. Bu çalışmada, UTD ve normal çalışma dönemlerinde (NÇD) gelişen SBİE, SBİE'ye neden olan bakteriyel etkenler, dönemler arası mortalite oranları ve genel mortalite oranları karşılaştırıldı. Tüm veriler Epi-Info programı (CDC, Atlanta, ABD) ile analiz edildi ve p<0,05 değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışma döneminde YBÜ'de 3.082 hasta takip edildi. NÇD'de SBİE oranı %3,5 ve UTD'de %16,5 idi (p=0,001). SBİE'ye neden olan bakteriyel dağılım incelendiğinde, Gram-negatif bakterileri enfeksiyonları UTD'de NÇD'ye göre anlamlı olarak yüksekti [sırasıyla; %13,7; %2,4 (p=0,001)]. Mortalite oranları incelendiğinde, çalışma periyotları arasında toplam mortalite oranları arasında anlamlı bir fark yokken (p=0,769); enfeksiyona bağlı mortalite oranları UTD'de anlamlı olarak daha yüksek saptandı (%7,3; p=0,002).

Sonuç: SBİE UTD'den etkilenmektedir. Tüm çalışanlar SBİE'nin önlenmesi için motive edilmeli, tatilden önce ve sonra enfeksiyon kontrol önlemleri konusunda eğitilmelidir.

Anahtar Sözcükler: Uzun tatil dönemi, sağlıkla ilişkili enfeksiyonlar, yoğun bakım ünitesi

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Introduction

Healthcare-associated infection (HAI) is an important health problem. Today, many complicated procedures and invasive procedures are frequently performed. These situations increase the risk of HAI. HAIs can cause functional impairment, decreased quality of life, and deaths. Additionally, prolonged hospital stay increased antibiotic consumption, isolation costs, workload, and economic losses (1-3).

Some days are official holidays in Turkey, such as April 23 (National Sovereignty And Children's Day), May 19 Commemoration of Atatürk, Youth and Sports Day), August 30 (Independence Day), and October 29 (Republic Day), as well as some religious holidays, such as Ramadan and Qurban (Literally, "sacrifice"). Sometimes, on these official and religious festivals, long public holidays (LPH) are granted by the government, and allowances are sometimes extended up to 9 days. The LPH, which includes long working hours, disruptions, and problems that occur in transportation, communication, security, and health services. Hospitals are one of the most affected institutions from LPH because primary healthcare centers are closed (4,5). In our country, the most social mobility is seen during these holidays. Patients are generally admitted to the emergency services in LPHs. As both primary healthcare centers are closed and patients can only apply to the emergency department of hospitals, working as a hospital healthcare personnel during these periods becomes difficult. Moreover, the workload of the health care practitioner is also higher in LPHs than normal working hours (5-7). Contrary to the workload, more inexperienced personnel are employed during the LPH. Furthermore, these inexperienced staffs are working on duty for a long time and are exhausted (5-8). Therefore, infection control was thought to be easily compromised from the measures of these exhausted personnel (9). Moreover, many employees with controlled duties are permitted in those periods. Thus, staffs who are not concerned about monitoring can ignore infection control measures (6,7,10).

Our research revealed that a study published in English, which investigated the risk of hospital infection during LPHs, is not accessible. Therefore, this study aimed to investigate the effect of LPHs on the risk of infection.

Methods

Working Design and Data Collection

During the study period, reanimation, neurology, cardiovascular surgery, and surgical intensive care unit (ICU) were monitored daily by the active surveillance method of the infection control team.

Study Periods

The study was carried out between January 01, 2014, and October 10, 2015, in tertiary university education and research hospital with a total capacity of 900 beds.

LPH

LPH was defined as public holidays that are ≥4 days including weekends. This study included patients who are hospitalized in the ICUs for >1 day. Upon unit admission, patients who are infected and colonized were excluded from the study. The number of patients, the day of hospitalization, and the developing HAI information were obtained from the surveillance files.

Normal Working Time (NWT)

NWT was defined as normal working periods that do not include any public holidays without weekends. During this period, patients who are hospitalized in the ICU for >1 day, as in LPH, were included in the study, whereas patients who were infected and colonized upon admission were excluded. During NWT, the number of inpatients, patient days, and developing HAI rates were obtained from the surveillance records.

Infection-related Mortality Rate

Patients who died within the first 28 days after the infection diagnosis was accepted as infection-related death. The ınfection-related mortality rate was calculated with this formula: patients who died within 28 days after the infection diagnosis ÷ patients followed up in the relevant period (LPH/NWT) x100.

Overall Mortality Rate

Patients who died from non-infectious causes 28 days after the infection diagnosis were accepted as the overall mortality-related death. The overall mortality rate was calculated with this formula: patients who died from non-infectious causes 28 days after infection diagnosis ÷ patients followed up in the relevant period (LPH/NWT) x100.

Inclusion Criteria

All patients in the ICU of our hospital were included in the study. The infection and colonization discrimination of patients was performed according to the diagnostic criteria of the hospital infection of the Center for Diseases Control (z) (11).

Exclusion Criteria

Patients with colonization and patients under 18 years old were excluded from the study.

Ethical Consent

Ethical approval of this study was obtained from Sakarya University Medical Faculty Ethics Committee with the application dated 04/17/2017: document number: 85/2017.

Statistical Analysis

Data were evaluated in Epi-info (CDC, Atlanta, USA) 6.0 computer program. The Student t-test was used to evaluate quantitative variables, and chi-square and yates corrected chi-square tests were used to evaluate qualitative data. p-values of <0.05 were considered significant.

Results

During the study period, 3082 patients were followed in the ICUs. The number of patients in LPH was 109 and patient days was 993. The number of patients in NWT was 2,973 and patient days was 23,044. The rate of HAI was 16.5% (n=18) in LPH, whereas 3.5% (n=106) in NWT and there was a significant

difference between LPH and NWT [p=0.001, odds ratio (OR): 5.35, 3.00 <OR <9.45). A total of 18 (16.5%) HAI develops in LPH, whereas 16 (3.5%) in NWT (p=0.001). Central venous catheter-related bloodstream infection was the HAIs in LPH. Similarly, the most common HAI in NWT was central venous catheter-related bloodstream infection (Table 1). Table 1 presents the distribution of HAI according to periods. Gram-negative bacteria that are detected as a pathogen of nosocomial infection were more frequently observed in LPH than in NWT [13.7% vs. 2.4%, respectively (p=0.001)] (Table 2). In both LPH and NWT, the most common cause of HAI was Gram-negative bacteria, such as *Klebsiella pneumoniae and Enterococcus* spp. The overall mortality rate was 28.4% (31/109) and 29.7% (883/2,973) in LPH and NWT, respectively (p=0.777). Infection-related mortality rate was significantly higher in LPH [7.3% (8/109)] than in NWT [2.5% (74/2973)] (p=0.001). Mortality rates were given in Figure 1.

Discussion

Hand hygiene and infection control measure compliance has shown an effect in reducing health-related infection rates (12,13). Hand hygiene compliance with a hand hygiene education program was reported to increase from 46% to 69% (p<0.0001) and the nosocomial sepsis rate decreased from 96% to 47% (p<0.0001) (14). Hand hygiene compliance with the hand hygiene program was significantly increased from 25.7% to 57.5% (p<0.001), and the incidence of HAIs was 31.7% from 20.3% (p<0.001) (15). However, if the healthcare personnel are subject to a heavy workload, many infection control measures are compromised, especially hand hygiene (16). This study revealed that more infections may occur if healthcare personnel is exposed to a heavy workload during LWP. Mortality in LPHs is higher than in NWT. This is also evident in infection-related mortality. The increased mortality due to infection is thought to be related to the increased work intensity per employee. A study reported that mortality increased by 3.5 times higher with the nurse bed ratio at <1/2.5 in the same study period. When the doctor/bed ratio was above 1/14, the mortality increased 2 times (20). A retrospective observational study conducted in the United Kingdom with quite a lot of patients (n=38,168) revealed that survival improved as the number of both doctors and nurses increased (21).

One study revealed that infection-related mortality is higher in LPHs than in NWT. Hospital mortality rates were seen higher in LPH than NWT (17). This situation may be related to the amount of work per staff member in LPH. Many staff does not come to work in LPH, thus the services work with full capacity. Healthcare personnel who are obliged to train a specific job at this time can easily abandon the necessity of compliance with hospital cleaning or isolation measures. Additionally, our study revealed that hygiene practices should be monitored in LPH. Acute hospitals provide round-the-clock services, 7 days a week; however, the number of personnel (seniority and number) is seen lower on weekends than on weekdays (22). Nurse inadequacy and increased nursing workload have been associated with an increased risk of adverse patient outcomes (e.g., falls, decubitus, medication administration errors, healthcare-related infections, unplanned extubations, and mortality), as well as nurse burnout and job dissatisfaction (23).

During LPH, intensive care workers are exposed to a heavy workload per capita. The number of experienced staff in LPHs

Table 1. Distribution of healthcare-associated infections according to subgroups of infection in long public holidays and normal working time

Distribution of healthcare-associated infections	Long public holidays (n=109) n (%)	Normal working time (n=2,973) n (%)	p-value
Central venous catheter-related blood circulation infection	11 (10.0)	75 (2.5)	0.001
Laboratory-based blood circulation infection	6 (5.5)	15 (0.5)	0.001
Soft tissue infection	1 (0.9)	0	0.001
Other infections	0	16 (0.53)	0.442
Total	18 (16.5)	106 (3.5)	0.001

Table 2. Bacterial agent distribution of healthcare-associated infections during long public holidays and normal working time

Microorganism	Long public holidays (n=109) n (%)	Normal working time (n=2,973) n (%)	p-value
Gram-positive	**1 (0.9)**	**11 (0.3)**	**0.367**
Enterococcus spp.	1 (0.9)	7 (0.2)	0.169
Staphylococcus aureus	0	2 (0.06)	0.786
Coagulase negative Staphylococcus	0	2 (0.06)	0.786
Gram-negative	**15 (13.7)**	**72 (2.4)**	**0.001**
Acinetobacter baumannii	1 (0.9)	15 (0.5)	0.555
Pseudomonas aeruginosa	2 (1.8)	13 (0.4)	0.039
Klebsiella pneumoniae	6 (5.5)	37 (1.2)	0.0001
Escherichia coli	2 (1.8)	3 (0.1)	0.001
Serratia marcescens	1 (0.9)	2 (0.06)	0.005
Enterobacter cloacae	2 (1.8)	1 (0.03)	0.001
Citrobacter	1 (0.9)	0	0.001
Proteus mirabilis	0	1 (0.03)	0.964
Fungi	**2 (1.8)**	**23 (0.7)**	**0.503**
Candida spp.	2 (1.8)	23 (0.7)	0.503
Total	**18 (16.5)**	**106 (3.5)**	**0.001**

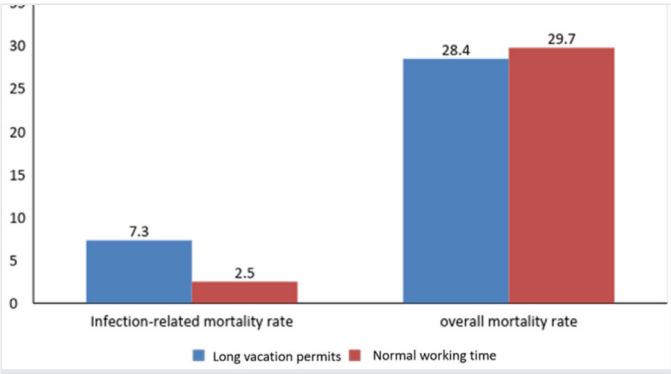

Figure 1. General mortality and infection-related mortality rates during long public holidays and normal working time

is less than the NWT. Additionally, many invasive procedures are performed with less qualified personnel (8). Therefore, the development of infection due to invasive procedures increases, as well as the infection frequency. Moreover, the number of staff in charge of the supervision is decreasing in LPHs. Employees may exhibit sloppy behavior when they feel that they are not being monitored or controlled. Thus, many measures, such as hand washing, wearing gloves, or adapting to isolation measures, may be inconvenient. A study on feedback to the healthcare workers showed a significantly decreased central venous catheter-associated bloodstream infections (17).

Hospital surface cleaning is thought to be much worse in these periods since the number of staff involved in the resettlement is less than the normal period and the unit work volume per staff is much higher. The deterioration of all these functions also brings about deterioration. Significantly, more gram-negative and yeast infections are observed. LPHs understandably had the highest level of contamination due to grove turnover and the greater number of patients and staff workload seemed less sensitive in prioritizing the hygiene in these periods (19). The heavy workload in the work shift also increases the probability of hospital infections (24).

Conclusion

Therefore, LPH is disadvantageous for HAI. Prevention of HAI is a process that begins with a patient's hospital admission. Healthcare personnel should be aware that HAI is preventable. An education plan for infection control measures should be established, training should be made continuous and repeated before and after an LPHs. LPH significantly influences hygiene and infection control, facilitates the spread of pathogenic bacteria, and increases infection-related deaths. Therefore, infection control precautions should be more frequently supervised in LPHs.

Ethics

Ethics Committee Approval: Ethical approval of this study was obtained from Sakarya University Medical Faculty Ethics Committee with the application dated 04/17/2017: document number: 85/2017.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Concept: O.K., G.K., E.G., A.Ö., Design: O.K., G.K., E.G., A.Ö., Data Collection or Processing: O.K., G.K., E.G., A.Ö., Analysis or Interpretation: O.K., G.K., E.G., A.Ö., Literature Search: O.K., G.K., E.G., A.Ö., Writing: O.K., G.K., E.G., A.Ö.,

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Original Article

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Evaluation of Midwifery and Nursing Practices for Maternal and Neonatal Safety in the Delivery Room

Doğumhanede Anne ve Yenidoğan Güvenliğinin Sağlanmasında Ebe ve Hemşirelik Uygulamalarının Değerlendirilmesi

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ABSTRACT

Objective: Delivery rooms are places where problems rapidly develop and decisions are quickly taken. Therefore, patient safety practices are among the most important things. This study was conducted to discover patient safety practices of nurses and midwives who work in the delivery room.

Methods: This descriptive study was conducted with 140 midwives and nurses working in eight hospitals in Ankara. Data were collected with a questionnaire, which was developed by reviewing the literature. Research data were analyzed by number and percentile distribution.

Results: No controlled doors were found in 1/3 of the eight delivery rooms in hospitals, 21.1% of participants did not attach identity wristband while taking mothers to delivery rooms, 34.3% used room/bed numbers in detecting identity, and 63% did not register the given instructions during the emergency-sterile applications. Additionally, 8.6% left mothers and babies alone, 27.9% did not write the date of the birth on the identity wristband, 11.4% did not follow uterus involution.

Conclusion: Our study results revealed that most targets for ensuring maternal and neonatal safety are achieved in delivery rooms. However, deficiencies were found in the application, such as identity control, applications registration, and drug administration. The majority of patient safety applications are routine practices of nurses and midwives. Training for midwives and nurses who work in delivery rooms for the safety of mother–newborn is recommended.

ÖZ

Amaç: Doğumhaneler problemlerin hızlı geliştiği ve kararların hızlı alındığı yerlerdendir. Bu nedenle hasta güvenliği uygulamaları en önemli konular arasındadır. Bu araştırma, doğumhanede çalışan ebe ve hemşirelerin hasta güvenliği uygulamalarını araştırmak amacıyla yapılmıştır.

Yöntemler: Tanımlayıcı nitelikteki bu çalışma, Ankara'da sekiz hastanede çalışan 140 ebe/hemşire ile yürütülmüştür. Araştırma verileri, literatür doğrultusunda oluşturulan bir anket aracılığıyla, yüz yüze görüşülerek toplanmıştır. Veriler sayı ve yüzde ile analiz edilmiştir.

Bulgular: Doğumhanelerin 1/3'ünde "kontrollü kapı" olmadığı, ebe ve hemşirelerin %21,1'inin anneyi servise kabul ederken kimlik bilekliği takmadığı, %34,3'ünün kimlik doğrularken oda/yatak numarası kullandığı, %63'ünün acil-steril uygulamalar sırasında verilen talimatları kayıt altına almadığı belirlenmiştir. Ebe ve hemşirelerin %8,6'sının anne ve bebeği doğumhanede yalnız bıraktığı, %27,9'unun bebeğin doğum tarihini kimlik bilekliği üzerine yazmadığını, %11,4'ünün uterus involüsyonunu takip etmediği bulunmuştur.

Sonuç: Araştırma sonuçlarına göre doğum salonlarında anne ve bebek güvenliğinin sağlanmasına yönelik hedeflerin çoğunun gerçekleştirildiği belirlenmiştir. Ancak uygulamada kimlik doğrulama, kayıt tutma, ilaç uygulama gibi konularda eksiklerin olduğu belirlenmiştir. Doğum salonlarında görev yapan ebe ve

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Keywords: Patient safety, nurse, midwives, delivery room

hemşirelere, anne-yenidoğanın güvenliğine yönelik eğitim verilmesi önerilmektedir.

Anahtar Sözcükler: Hasta güvenliği, hemşire, ebe, doğum salonu

Introduction

The World Health Organization (WHO) defines patient safety as the minimization of the risk of harm in health care (1). Patient safety aims to decrease errors during the presentation to health care services and protect patients from harm due to medical error (2).

By developing medical technologies, many improvements are made within health services; however, medical errors and associated deaths continue to be frequently observed (3). A medical error is a preventable adverse effect of medical care, whether or not it is evident or harmful to the patient (4). The medical errors that commonly occur during health care providers include adverse drug events and improper transfusions, misdiagnosis, under and overtreatment, surgical injuries, wrong-site surgery, falls, infections, suicides, and mistaken patient identities (5). A medical error was determined to rank fourth among the reasons for death after cardiac disease, cancer, and chronic lower respiratory diseases (6). According to estimations of the WHO, 1 out of every 10 people is harmed while receiving health care in developed countries (7). Further, 10 out of every 100 people who are hospitalized in developing countries are exposed to infection while in the hospital, and the risk of exposure to infection could have been reduced using low-cost measures in half of this cases (7). According to reports of the Institute of Medicine, between 44,000 and 98,000 people in the USA lose their lives annually due to medical errors. These reports state that cases cost 17-20 billion dollars each year (8).

Medical errors that threaten patient safety can be frequently seen in many countries. A study that analyzed 60,599 discharged patients who experienced an event that threaten their safety revealed that 4% were exposed to an undesirable experience (falls, medication events, equipment events, etc.) (9). Annually, 24,500 people are estimated to die in Iran due to medical errors. Additionally, more adverse events are experienced in subjects, such as drug preparation, prescribing, and transcribing (10). A study in Canada revealed highly preventable adverse events in 36.9% of patients with adverse events, wherein 9% of these adverse events can be prevented (11). A study carried out in Portugal found that medical errors prolong hospitalization by 10.7 days (12). As a result of common problems, such as death, infection, and financial loss occurring due to medical error, the term patient safety has emerged (13).

Delivery rooms are places where health risks momentarily emerge and quick decisions are necessary; therefore, the risks associated with patient safety are high (14). Throughout the process, from awareness of pregnancy to the delivery room right through until postnatal services, many problems are possible, such as drug administration, identification errors, and patient falls. Patient safety problems are common in delivery rooms, especially when more than one birth takes place at a time (15).

The Canadian Medical Protective Association stated that in 2010-2014, 688 obstetric medical-legal cases took place, and of these cases, 395 pertained to newborn care. Additionally, 6% of gynecologists in Canada are called to the court regarding their practices annually (16). Maternal mortality rates decrease in the global world; however, these rates are still high. In Sub-Saharan Africa, 56% of the 287,000 maternal deaths worldwide that occurred in 2010 in this area were due to obstetric complications (15,17).

According to the 2018 data of the Turkish Demographic and Health Research department, 2.2% of baby deaths are neonatal deaths (18). These results emphasize the importance of care given in the newborn period. The WHO reports that 22-45% of all neonatal deaths occur within the first 24 h. Moreover, 80% of neonatal deaths are due to infection and birth trauma (19).

The National patient safety targets are helpful in the provision of secure health care. These targets involve correct procedures for patient identification, effective communication, drug safety enabling, and correct allocation of the surgery site, decreasing infection risks in health services, and preventing patient harm due to falls (20).

Specific measures should be taken, as well as research in patient safety in delivery rooms. The importance of patient safety is emphasized in many studies; however, literature on patient safety in the delivery room (identity control, infection prevention, drug safety, fall reduction, and first care of the mother and the baby) is restricted. Therefore, evaluating the practices of midwives and nurses regarding patient safety is important. Additionally, our research elucidates the status of applications, such as identity control, drug administration, fall prevention, and provision of mother-baby care for patient safety in the delivery room. Thus, this study will narrow the knowledge gap in the labor and delivery room about patient safety. This study aimed to determine maternal and neonatal safety in the delivery room. Identity control, drug administration, fall prevention, and first care of mother-baby in delivery rooms were determined. In line with these issues, the midwife, and nursing practices were assessed.

This descriptive study was conducted to determine the practices of midwives and nurses in delivery rooms, which is based on the Joint Commission International (JCI) patient safety criteria and affects the safety of mother and newborn.

Methods

Study Design and Participants

This study was descriptively conducted to determine the practices of midwives and nurses who work in eight hospital delivery

rooms on how they maintain the safety of mothers and their babies. This study evaluated the nursing and midwifery practices within the scope of JCI's patient safety criteria.

All non-accredited state hospitals and university hospitals in a city center were included in the study. The universe of the study was composed of 179 midwives and nurses working in eight hospital delivery rooms. Including all midwives and nurses who work in the delivery rooms of all non-accredited state and university hospitals was planned. All nurses and midwives were aimed to be accessed but only 140 midwives and nurses (approximately 80% of the population) agreed to participate. This study excluded 39 midwives and nurses due to their refusal to voluntarily join and they were off work. After the data collection, a power analysis was done with the G*power program, which revealed sufficient research power (power =0.81) and sample size.

Participant Inclusion Criteria

All midwives and nurses who volunteered to participate in the study that speak Turkish and work in the delivery room were included in the study.

Participant Exclusion Criteria

Those who refuse to voluntarily join, on leave, and work in obstetrics and gynecology services are not excluded from the study.

Data Collection

Data were collected with face-to-face interviews that were conducted by the researchers using a questionnaire that was prepared through a literature review (4,7,8). The questionnaire was evaluated by four academic nurses who specialize in gynecology and obstetrics. Necessary changes were made to the questionnaire following the suggestions of these experts. The questionnaire included two sections. The first section has five questions asking about the characteristics of delivery rooms; whereas the second section has seven questions asking about the socio-demographic characteristics of the participants and 56 questions (fewer than seven headings) related to patient safety targets. These questions were about identification checking, communication, drug safety, infection, preventing falls, and initial care of newborns and mothers.

Ethical Considerations

The study protocol was approved by the Turkish Republic Ministry of Health and the Gülhane Military Medical Academy Ethical Committee (no: 169) and Local Ethics Committee (no: 25.02.2011/46136). The study was conducted following the Declaration of Helsinki. The objectives of the study were explained to the participants to comply with ethical considerations. All the participants signed the written informed consent before enrolment. The participants were free to withdraw from the study at any time and stage. All responses were stored safely.

Statistical Analysis

The Statistical Package for Social Sciences ver.15 software was used for statistical analysis. Numbers were shown as percentage, mean, and standard deviation to identify the characteristics of nurses and midwives, as well as descriptive statistics.

Results

Of the midwives and nurses who participated in the study, 55.7% were 33 years old or younger and 51.4% had are both undergraduate and postgraduate. Nurses constituted 42.9% of the total number of participants, whereas midwives made up the remaining 53.5%. Of the midwives and nurses, 55% had 10 years of occupational experience, 49.3% had served in a delivery room for >3 years, and 73.6% worked for 40 h a week (Table 1).

The analyses of safety practices of the midwives and nurses related to identity checking revealed that 97.1% checks the identity when taking the pregnant women to the delivery room and 72.8% checked the protocol number. Of the participants, 78.8% attached the patient identity wristband when taking the patients to the delivery room. When checking identity, 96.4% of the midwives and nurses used to name and surname together, whereas 34.3% used room or bed number and 99.3% checked the identity before any practices (Table 2).

Of the midwives and nurses, 65% did not receive verbal or telephone instructions from doctors apart from during sterile emergency practices. While taking verbal or telephone instructions

Table 1. Distribution of midwives/nurses by their socio-demographic characteristics

Socio-demographic characteristics	Number	%
Age group		
33 years and under	78	55.7
34-37 years	34	24.3
38 years or above	28	20.0
Education level		
Vocational school of health	19	13.6
Associate degree	49	35.0
Undergraduate and graduate	72	51.4
Occupation		
Chief-nurse	5	3.6
Nurse	60	42.9
Midwives	75	53.5
Occupations working time		
Less than 1 year	8	5.7
1-5 years	39	27.9
5-10 years	16	11.4
More than 10 years	77	55.0
Occupational time in the delivery room		
Less than 3 year	71	50.7
3-6 years	42	30.0
More than 6 years	27	19.3
Working hours in a week		
40 hours	103	73.6
45 hours	29	20.7
48 hours or above	8	5.7

from a doctor for sterile emergency practices, 65.4% of midwives and nurses stated that they write down the instructions, 46.3% read the instructions back to the doctor, and 81.6% ask for the instructions to be confirmed by the instructor. While only 37% of midwives and nurses record instructions for sterile emergency practices, 99.3% stated they convey information about patients to the team on night duty during shift changeovers (Table 3).

The analyses of the drug safety practices of midwives and nurses revealed that 98.6% classify drugs according to their names and all store drugs according to a cold chain. Of the midwives and nurses, 86.4% recorded the opening time (date) of the drug, whereas 68.6% record the opening hour of the drug (Table 4).

Of the midwives and nurses, 97.8% obtain data from pregnant women about drugs that they have been using. Moreover, all participants ask the pregnant woman about drug allergies when taking them to the delivery room and adopt eight correct principles of drug practices (Table 4).

Considering the distribution of safety practices to decrease infection risks, 99.3% of midwives and nurses wash their hands before and after practices. Moreover, 58.6% make other staff wash their hands, and 97.1% control maternal blood results for infectious disease. All midwives and nurses apply aseptic techniques during practices and check sterilization dates before they use sterile materials. Additionally, all midwives and nurses open the materials they use without breaking the sterilization and send the materials they used to be sterilized under suitable conditions. Of the midwives and nurses, 8.6% do not give perineum care to mothers in the delivery room (Table 5).

Table 2. Checking identity applications of midwives and nurses

Applications of midwives and nurses	Number	%
Checking identity while taking the pregnant to the delivery room		
Yes	136	97.1
No	4	2.9
Checking the protocol number (n=136)		
Yes	99	72.8
No	37	27.8
Attached patient identity wristband (n=137)		
Yes	108	78.8
No	29	21.2
Checking identity with name + surname		
Yes	135	96.4
No	5	3.6
Checking identity with room/bed number		
Yes	48	34.3
No	92	65.7
Checking identity before any practices		
Yes	139	99.3
No	1	0.7

All participants said they make the length of the obstetric/birth table suitable for the mother to prevent falls. Moreover, all participants use stretchers or wheelchairs to transfer mothers during postpartum and accompany them while they are being transferred to prevent falls. Of the participants, 91.4% do not leave mothers and babies alone in the delivery room. Likewise, 41.4% of midwives and nurses do not use an incubator while transporting a baby (Table 6).

Considering the initial newborn care practices of midwives and nurses in patient safety, 95.7% securely hold the baby (supporting the baby by holding the head and body, monitoring whether the cord goes around the neck of the baby, and keeping the babies level with the vagina) and 98.6% leave the baby in radiant heat as soon as possible after delivery. All participants use a sterile catheter while aspirating the baby.

Of the participants, 85.7% confirm the gender of the baby with its mother and attach wristband to the baby and mother in the same color and code. Nearly all (98.6%) midwives and nurses write the name and surname of the mother and 72.1% write the baby's date of birth on the identity wristband. Most (97.9%) midwives and nurses evaluate the umbilicus regarding bleeding and enable the first contact between mother and baby. Of the participants, 96.4% enable the baby to be breastfed within half an hour after birth and all participants record all their practices.

The analysis of midwives' and nurses' initial care practices for mothers revealed that they monitor the vital signs of mothers

Table 3. Taking order (instructions) verbal/telephone applications of midwives and nurses

Applications of midwives and nurses	Number	%
Taking orders by verbal/telephone except for emergency-sterile applications		
Yes	49	35.0
No	91	65.0
Emergency-sterile applications		
Write the order		
Yes	89	65.4
No	47	34.6
Repeat order		
Yes	63	46.3
No	73	53.7
Confirm the order		
Yes	111	81.6
No	25	18.4
Recording the order in emergency-sterile applications (n=138)		
Yes	51	37.0
No	87	63.0
Convey all patient information during shift changeovers		
Yes	139	99.3
No	1	0.7

and evaluate their pain and fatigue status. Additionally, 99.3% give information to the mother about interventions. Of the total midwives and nurses, 92.9% monitor bleeding, 88.6% monitor uterus involution, and 98.6% meet the hygiene needs of mothers.

As a limitation of our research, the answers to the questions within the scope of the questionnaire were only obtained by the participants' declaration. Conducting observational research, which would strengthen the research results, was impossible.

Discussion

The practices of midwives and nurses are critically important in delivery rooms; however, a review of the existing literature found no studies about maternal and neonatal safety in delivery rooms.

A literature review done with hospital nurses revealed that the use of surnames to check the identity was similar to our results (21). A literature review revealed that nearly half of the staff used surnames to check their identity (22). Our study revealed that one out of three participants uses room or bed numbers to identify patients, which is a known cause of faulty medical practices. Patient identification is an area of high priority in delivery rooms, with an error, or adverse event regarding non-compliance in patient identification. General conformity rates between mother and baby is another problem in delivery rooms. Bates et al. (23) revealed in their study considerably lower general conformity rates, especially in identifying newborns at the delivery room. The study results by Filiz (24) revealed a high rate for using room or bed numbers to identify patients. A literature review with health staff working at hospitals and cottage hospitals is also parallel with our results (23,24). Our study revealed that nearly one-quarter of midwives and nurses do not attach identity wristbands to pregnant women when taking them to the delivery room. Matching the right patient with the right care is an important issue of safe health care. Patient wristbands form a vital link between the patient and the health care system. However, our study revealed that identity wristbands are not generally attached to pregnant women before taking them to the delivery room. This increases the risk of errors in the delivery room.

The study of Henneman et al. (25) in emergency services nurses revealed parallel results with our study. Moreover, in both studies conducted on health personnel, the number of those who do not use identity wristbands was higher than in our results (24,26). Some studies revealed that the rate of errors in the use of identity wristbands was high (25,27). Therefore, the use of identity wristbands instead of room/bed numbers is important to ensure maternal and neonatal safety in the delivery room.

The study of Mrayyan et al. (28) revealed that wrong labeling or classification of drugs is the primary reason for drug error as stated by nurses. Our study revealed that nearly all participants classify drugs according to their names and all maintain drugs according to the cold chain. Fisun et al. (29) revealed are parallel results to

Table 4. Drug safety applications of midwives and nurses

Applications of midwives and nurses	Number	%
Classify drugs according to their names		
Yes	138	98.6
No	2	1.4
Storage in a cold chain		
Yes	140	100.0
No	-	-
Record the following:		
Name of drug		
Yes	134	95.7
No	6	4.3
Opening date of the drug		
Yes	121	86.4
No	19	13.6
The opening hour of the drug		
Yes	96	68.6
No	44	31.4
Asking for the:		
Drugs used by the pregnant women		
Yes	136	97.8
No	3	2.2
Drug allergy		
Yes	140	100.0
No	-	-
Eight correct principles of drug practices		
Yes	140	100.0
No	-	-

Table 5. Applications of midwives and nurses to prevent infection

Applications of midwives and nurses	Number	%
Wash hands before and after practices		
Yes	139	99.3
No	1	0.7
Control hand washing of other staff		
Yes	82	58.6
No	58	41.4
Control maternal blood results for infectious disease		
Yes	136	97.1
No	4	2.9
Applying aseptic techniques		
Yes	140	100.0
No	-	-
Checking sterilization dates		
Yes	140	100.0
No	-	-
Giving perineum care to mothers		
Yes	128	91.4
No	12	8.6

our study. Our study revealed that nearly all participants write the drug name on the injector, but one-third said they do not write the date and time the drug seal was opened. An observational study about the drug practices of nurses revealed that none of the nurses drew the drug left in the vial and all keep it at room temperature. Moreover, 44.7% of the drugs had no opening date or time, and 55.3% of the labeled ones contained imperfect information (30). Our study revealed that all participants asked about drug allergies while taking the patients to the delivery room and apply eight correct drug practice principles. The literature review supports these results (29,30). Therefore, we can say that as a routine practice of nursing, nurses classify drugs according to names and dates. However, they did not write the date and time the drug seal was opened.

Nearly all participants in our study pay attention to washing hands and sterilization_to decrease infection risks in the delivery room. Other studies revealed that health staffs pay attention to hand hygiene and adapt to asepsis rules (31,32). Additionally, the literature emphasized the importance of hand washing and hygiene, and midwives and nurses should be careful with effective management of coronavirus disease-2019 (COVID-19) in the delivery room (33,34).

Risks have been identified through a scale developed in 2010 to prevent falls for newborns (35). Nearly all participants adjusted the delivery table to a suitable height and transferred mothers to prenatal areas using a stretcher or wheelchair. However, nearly half of the participants did not use an incubator while transporting a baby. Another study showed that the use of incubators for this purpose was also quite low (36). Moreover, our study revealed that some participants left mothers and babies alone in the delivery room. These results provide information

Table 6. Applications of midwives and nurses to prevent falls

Applications of midwives and nurses	Number	%
Making the height of the obstetric birth table suitable for the mother		
Yes	140	100.0
No	-	-
Using stretchers/wheelchairs to transfer the mothers		
Yes	140	100.0
No	-	-
Using an incubator to transfer the baby		
Yes	82	58.6
No	58	41.4
Accompanying mother and baby during transfers		
Yes	140	100.0
No	-	-
Not leaving mother and baby alone in the delivery room		
Yes	12	8.6
No	128	91.4

Table 7. Newborn and mother care practices

Applications of midwives and nurses	Number	%
Hold the baby in a secure way		
Yes	134	95.7
No	6	4.3
Leaving the baby in radiant heat		
Yes	138	98.6
No	2	1.4
Using sterile catheter while aspirating the baby		
Yes	140	100.0
No	-	-
For baby		
Confirm the gender		
Yes	120	85.7
No	20	14.3
Attach wristband same color and code		
Yes	139	99.3
No	1	0.7
Write the mother's name-surname on the wristband		
Yes	138	98.6
No	2	1.4
Write baby's birth date on the wristband		
Yes	101	72.1
No	39	27.9
Evaluate the umbilicus for bleeding		
Yes	137	97.9
No	3	2.1
Breastfed within half an hour		
Yes	135	96.4
No	5	3.6
Monitor mother's vital signs, pain, and fatigue		
Yes	140	100.0
No	-	-
Provide information to the mother about interventions		
Yes	139	99.3
No	1	0.7
For mother		
Monitoring bleeding		
Yes	130	92.9
No	10	7.1
Monitoring uterus involution		
Yes	124	88.6
No	16	11.4
Ensuring hygiene		
Yes	138	98.6
No	2	1.4

on the development of midwifery and nursing practices in the prevention of patient falls and life-threatening conditions.

In the United States, 600-1,600 newborns experience hospital falls annually (37). Manson et al. (38) reported that 14 baby fall cases occurred in 888,774 births, of which four happened in the delivery room, thus the importance of the issue was emphasized. Trauma incidents of the newborn that result from falling were found to be 1.6 per 10,000 (38). Our study revealed that nearly all participants paid attention to securely holding the babies to prevent trauma. The majority of midwives and nurses attach color and number-coded identity wristbands for both the mother and baby to prevent mistaking the identity of the baby, as well as writing the name and surname of the mother. However, nearly one-quarter of midwives and nurses did not write the birth date of the baby. The majority of patient safety applications were routinely practiced by nurses and midwives.

All participants monitor the vital signs of mothers before and after birth and evaluate their fatigue status. A study carried out by Lai et al. (39) showed that high levels of fatigue caused difficulties for baby care and falling, and emphasized the importance of attentively evaluating the fatigue of mothers. Our study revealed that nearly all participants evaluate the bleeding of mothers and assist them with body hygiene. Additionally, the majority of midwives and nurses evaluated uterus involution. Another study revealed an 80% rate of midwives and nurses who controlled bleeding in the postnatal period (40). Controlling the bleeding after birth and assisting body hygiene are very important measures to prevent infection and provide patient safety.

Study Limitations

One limitation of our study could be considered as giving the questionnaires to nurses and midwives who may be scared to reveal an improper behavior concerning patient safety due to possible medicolegal consequences. However, as we have assured them the anonymity of the data, we believe that every participant honestly answered the questionnaire. No scale has been developed or used in data collection. Therefore, make validity and reliability is not necessary.

Conclusion

Our study results highlight the deficiencies in maternal and neonatal safety in delivery rooms. Thus, the applications of midwives and nurses including covers identity control, prevention of infections, drug safety, reduction of falls, and the first care of the mother and the baby are suggested to be examined with more comprehensive research along with their results. Additionally, taking measures to prevent COVID-19 infection in the delivery room is also recommended, as well as train nurses and midwives on the subject.

Delivery rooms are places where health risks momentarily emerge and quick decisions are necessary; therefore, the risks associated with patient safety are high. Additionally, more descriptive research/observational studies are needed in this area.

Ethic

Ethics Committee Approval: Turkish Republic Ministry of Health and the Gülhane Military Medical Academy Ethical Committee (no: 169) and Local Ethics Committee (no: 25.02.2011/46136).

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: G.A., G.V., Design: G.A., G.V., Data Collection or Processing: G.A., Analysis or Interpretation: G.A., G.V., K.E.K., Literature Search: G.A., G.V., K.E.K., Writing: G.A., G.V., K.E.K.

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Original Article

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Adaptation and Psychometric Testing of the Turkish Caregiving Competence Scale

Bakım Verme Yeterliliği Ölçeği'nin Türkçe Uyarlaması ve Psikometrik Olarak Test Edilmesi

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ABSTRACT

Objective: This study aimed to adapt the Turkish version and assess the cultural and psychometric properties of the Caregiving Competence Scale (CCS).

Methods: CCS-Turkish form (CCS-TR) was tested in a sample of 337 family caregivers of patients who had a stroke. The explanatory and confirmatory factor analyses were carried out for construct validity. The item-total score correlations, Cronbach's Alpha value, and split-half test were calculated for reliability. The score on the scale was 4-16 points.

Results: The mean age of the caregivers was found to be 47.48 ± 14.52 years, whereas the mean age of patients who had a stroke was 70.34±12.04 years. According to expert opinion, the content validity index score of the scale was 0.83. The result of the confirmatory factor analysis revealed that the single-factor structure revealed a good fit. The Cronbach's Alpha value was 0.83, whereas the split-half reliability value was r: 0.82. The total score of the scale was determined as 11.5±1.74.

Conclusion: This study revealed high validity and reliability values of the CCS-TR, which suggests that the scale can be safely used. The presence of CCS in different languages is an advantage for conducting comparative studies.

Keywords: Caregiving competence, caregiver, validity, and reliability, Turkish

ÖZ

Amaç: Bu çalışmanın amacı Bakım Verme Yeterliliği Ölçeği'nin (BVYÖ) Türkçe'ye uyarlanması ile kültürel ve psikometrik özelliklerinin değerlendirilmesidir.

Yöntemler: BVYÖ-Türkçe formu (BVYÖ-TF) inmeli hastalara bakım veren 337 aile üyesinden oluşan bir örneklemde test edildi. Yapı geçerliliği için açıklayıcı ve doğrulayıcı faktör analizi yapılmıştır. Güvenilirlik için, madde-toplam puan korelasyonları, Cronbach Alpha değeri ve iki yarı testi hesaplandı. Ölçek puanı 4-16 puandır.

Bulgular: Bakım veren aile üyelerinin yaş ortalamasının 47,48±14,52 ve inmeli hastalarının yaş ortalamasının ise 70,34±12,04 olduğu bulunmuştur. Uzman görüşleri doğrultusunda ölçeğin kapsam geçerlilik indeks puanı (S-CVI) 0,83'tür. Doğrulayıcı faktör analizi sonucunda, tek faktörlü yapının iyi bir uyum sağladığı görülmüştür. Cronbach Alpha değeri 0,83 iken, iki yarı güvenirlilik değerinin r=0,82 olduğu belirtilmiştir. Ölçeğin toplam puanı 11,5±1,74 bulunmuştur.

Sonuç: Çalışmada BVYÖ-TF'nin geçerlik ve güvenirlik değerlerinin yüksek olduğu bulunmuştur. Ölçeğin güvenle kullanılabileceği ortaya konulmuştur BVYÖ'nün farklı dillerde mevcut olması karşılaştırmalı çalışmalar yapmak için avantaj sağlamıştır.

Anahtar Sözcükler: Bakım verme yeterliliği, bakım veren, geçerlilik ve güvenirlilik, Türkçe

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Introduction

The members of a family undertake the primary responsibility for long-term care of the individuals having a stroke. The family members undertaking the caregiving responsibility during the hospitalization period also continue to contribute to complex caregiving processes (1). Home-based healthcare services have rapidly developed in Turkey in recent years. Additionally, procedures, such as changing the catheter or wound care, may be performed in a home environment (2). However, the care is dominantly provided by the families; therefore, families should be competent for caregiving. Financial support that is given by the state to the family members and the provision of some of the materials that are necessary for the patient may contribute to the competency of caregivers even if insufficient.

Fulfilling the care required for individuals who are dependent on daily life activities due to stroke is a long and difficult process. Incidents that are suddenly and unexpectedly experienced, like stroke, are difficult to be adopted by patients and caregivers (3). The caregivers trying to adopt caregiving state to the individual who had a stroke experience intense stress between their responsibilities and daily life activities. Within this context, acquiring the caregiving competency for the family or informal caregivers and acceleration, as well as support for process adaptation, are very critical issues (4). The researchers have stated that the negative experiences and caregiving burden on the family members undertaking the primary responsibility for caregiving to the bedbound individuals may be decreased by support and consultancy (5,6). Caregiving competency should be evaluated to determine the training requirements of individuals undertaking the caregiving responsibility (3). Preparation of training events is considered to be provided as a result of caregivers' assessment in a planned manner and through the effective requirements to resolve the problems and meet the requirements (7). Family member preparations for the caregiving process and gaining the required skills and competencies are important for effective process management (4,7).

Valid, reliable, and feasible measurement tools are needed to determine the competency of the family or informal caregivers in patient safety and care surveillance. Scholten et al. (4) has noted that 96 measurement tools were used to evaluate the caregivers, and the number of the items in such tools varied between 4 and 37. Few measurement tools were found to measure the competency of the family caregiver in Turkey (8-10). Various measurement tools that assess the caregivers are reported in the literature; however, the Caregiving Competence scale (CCS) has been used in many studies since it included four items, with a single dimension that is easy to understand, and available in three different languages. Availability of CCS in English (11), Swedish (12), and Chinese (13) versions ease the process of international comparison.

The caregiver's feeling of self-competent affects his/her behavior toward the patient. The CCS developed by Pearlin et al. (11) was used in many studies to evaluate caregiver competency. The CCA was used to measure the levels of caregiving competence perceived by caregivers of patient groups, such as patients with stroke, Alzheimer's, cancer, and dementia, in the literature (14-17).

A study that measures the competency of caregivers applied 6 weeks and 90 min of group training to the caregivers of patients with Alzheimer's. The study revealed an increased competency level of the caregivers and possibly educational and group discussions on various issues that are found difficult by the caregivers (14). Another study stated that psychoeducation that is given to caregivers increased their competency level and problem-solving abilities (15). A study conducted by Quinn et al. (16) with caregivers of patients with dementia revealed that the competency level of the caregivers was low and found a relationship between life quality and satisfaction and caregiver competency.

This study aimed to adapt the Turkish version and assess the cultural and psychometric properties of CCS, as well as assess its compatibility with the Turkish culture and compare it with the translated versions in other languages.

Methods

Design

This study used a methodological design. The universe of the present methodological research consists of all caregivers that refer to neurology clinic and stroke polyclinic of a university hospital between December 1, 2017, and February 10, 2018. The sample included 377 caregivers who met the inclusion criteria. In the literature, different opinions are reported on sample size related to scale studies, wherein 20 participants are recommended per item; however, the number of adequate sample size is expressed as "50: very poor, 100: poor, 200: fair, 300: good, 500: very good, and 1000: excellent" to perform factor analysis (18). Therefore, the sample size of 400 was targeted and the data of 377 participants (participant rate of 94%) who agree to participate were evaluated. Additionally, Kaiser-Meyer Olkin and Bartletts' test indicated that our sample was enough for factor analysis.

Inclusion criteria were as follows:

- To be the primary caregiver of patients who had a stroke
- Dependency level of the patient at 2, 3, and 4 according to Modified Rankin scale (19,20)
- Literate caregiver
- Having no communication problem
- Contribution request of the caregiver to the study

Data Collection tools

CCS-Turkish Form (CCS-TR)

Pearlin et al. (11) developed the CCS consisting of four questions. The Likert-type scale was structured as "not sufficient at all" as 1, "slightly sufficient" as 2, "sufficient" as 3, and "very sufficient" as 4. The lowest score was 4 and the highest score was 16. An increased score on the scale meant an increased caregiving competency (11).

Figure 1. Scree plot for CCS-TR (N=337)

Furthermore, some caregiver and patient characteristics, such as age, gender, and marital status, as well as the income level of the family, kinship with the patient, gender, age of the patient, stroke type, dependency grade, and other chronic diseases, were examined.

Data Collection Method

Written consent of the caregivers was obtained to conduct the research. Furthermore, the questionnaires were completed through personal interviews with the caregivers in the neurology clinic and stroke polyclinic of the university hospital. The data were collected in the stroke polyclinic for 1 week and in the neurology clinic when the researcher was available. The questionnaire was filled through face-to-face interviews of caregivers who met the inclusion criteria by the researcher. The data were collected in an available separate room.

The Adaptation of the Scale and Its Translation

The translation process included a translation panel, opinions of experts, re-translation, and pilot implementation. The independent professional translation was performed by 2 independent translators, 1 neurologist, 2 nurses, and 1 academician who understands and speaks both languages (Turkish-English). The ten experts' opinion stage of the scale was performed by eight professors from the department of nursing, a nurse from the neurology clinic, and an instructor from the Department of Foreign Languages. Re-translation was performed by an instructor from Foreign Languages Department through expert opinions.

CCS-TR was tried as a pilot implementation for comprehensibility and caregivers of 30 patients who had a stroke. Minor revisions were made to avoid any changes in the meaning after the preliminary evaluation. The minor revision was reported to one of the authors, Sample S. J., who developed the CCS via e-mail (e-mail date: 22.03.2018), and his consent was obtained.

Data Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) (Statistical Package for Social Science) 23.0 program. A normality test was performed before statistical analysis. Cronbach Alpha and Split Half Reliability were used for validity and reliability; Kaiser-Meyer Olkin (KMO) and Barlett test for explanatory factor analysis was done in the SPSS program. The Linear structural relations 8.71 package program was used for confirmatory factor analysis. The item-total score correlation and Cronbach Alpha and Split Half Reliability were performed for the reliability of the scale. The test-re-test method was not appropriate for the scale. Therefore, two half reliability method was implemented. The Independent Samples t-test in binary groups was used to analyze the demographic features in CCS-TR scores. The one-way analysis of variance was used in more than two groups.

Ethics

Consent was obtained from the scale developer before initiating the research. Written consents from the Ethical Committee of the University Hospital (01/06/2017-10/07) and of the hospital, where the research was carried out, were obtained. Informed consent was signed by the caregivers who volunteered to participate in the study.

Results

The mean age of the caregivers was 47.48±14.52 years, whereas in patients who have stroke was 70.34±12.04 years. Among the caregivers, 75.7% (n=255) were female and 60.8% (n=205) were male. Married caregivers consisted of 83.1% of all participants; 49.8% (n=168) of them were elementary school graduates and had lower educational levels; and 25.2% (n=85) were unemployed. Almost half of the patients were parents of the caregivers (47.8%, n=308). The majority of patients who had a stroke were diagnosed with ischemic stroke (91.4%, n = 308). The most common concomitant chronic disease of patients who had a stroke was hypertension by 40.4% (n=136) (Table 1).

Content Validity

Each item was evaluated by 10 specialists as "not adequate" as 1, "slightly adequate" as 2, "very adequate" as 3, and "very adequate" as 4. Content Validity index (CVI) of the scale was 0.83. CVI values of the items were determined as 0.07, 0.06, 0.08, and 0.09, respectively.

Construct Validity

The exploratory factor analysis revealed that 66.675% variance of the scale is at a single dimension. Variance analysis KMO of 0.81 indicated that the sample size was very good and the significance of the Bartlett test showed that the data was adequate for factor analysis (χ^2=491.133; p=0.000). No rotation was performed since the scale had a single-factor structure (Figure 1). Excellent compliance of the single-factor structure was found as a result of confirmatory factor analysis [root mean square error of approximation (RMSEA) =0.00, normed fit index =0.00, comparative fit index (CFI) =0.00, incremental fit index =0.00, relative fit index =0.99, goodness of fit index (GFI) =0.00, and adjusted goodness of fit index =0.99] (Table

Table 1. Demographic characteristics of family caregivers and patients who had a stroke (N=337)

Characteristic	Mean ± SD or n (%)	
	Caregivers	Stroke patients
Age ($\bar{X}$ ± SD)	47.48±14.52	70.34±12.04
Gender		
Caregiver, female	255 (75.7)	205 (60.8)
Stroke patient, male		
Marital status		
Married	280 (83.1)	
Single	57 (16.9)	
Educational level		
Primary or less	168 (49.8)	
Secondary	57 (16.9)	
Tertiary or above	112 (33.3)	
Employment status		
(being employed)	85 (25.2)	
Type of stroke		
Ischemic		308 (91.4)
Hemorrhagic		29 (8.6)
Relatives of the family		
Father-mother		161 (47.8)
Spouse		89 (26.4)
Children		17 (5.0)
Sibling		15 (4.5)
Others		55 (16.3)
Most prevalent health problems		
Hypertension		136 (40.4)
Diabetes		24 (7.0)
Hypertension and diabetes		101 (30.0)
Others		76 (22.6)
Modified Rankin scale (0-5)		
2 (Slight disability)		62 (18.4)
3 (Moderate disability)		119 (35.3)
4 (Moderately severe disability)		156 (46.3)

SD: Standard deviation

Table 2. Confirmatory factor analysis of CCS-TR

Index of compliance	Abbreviation	Caregiving competence scale	Excellent compliance limit*
Degrees of freedom	Df	2	-
P value	P	0.54	0.05≤ p ≤1
Chi-square/ degrees of freedom	χ^2/df	1.22/2 =0.61	Should be smaller than χ^2/df =3 or lower
Root mean square error of approximation	RMSEA	0.00	=0.000 and <0.050
Normed fit index	NFI	0.00	0.95 and over
Comparative fit index	CFI	0.00	0.97 and over
inceremental fit index	IFI	0.00	0.95 and over
Relative fit index	RFI	0.99	0.95 and over
Goodness of fit index	GFI	0.00	0.90 and over
Adjusted goodness of fit index	AGFI	0.99	0.90 and over

*Excellent compliance limits were determined according to (25).

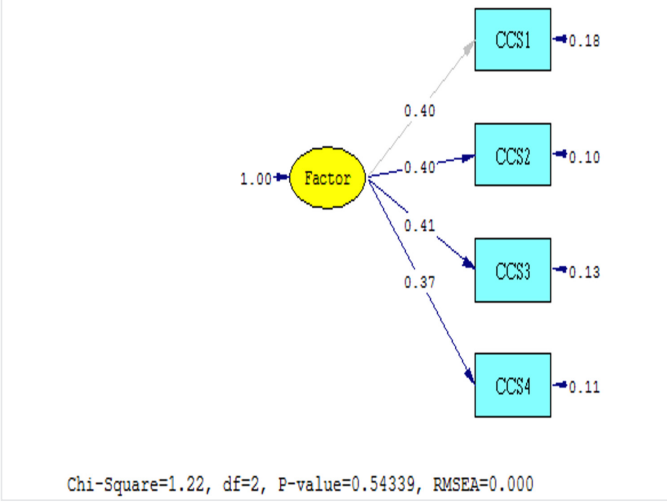

Figure 2. Factor loading for CCS-TR (N=337)

2, Figure 2).

Reliability

Corrected item-total correlation values of the scale were 0.620, 0.698, 0.666, and 0.659 (Table 3). The Cronbach Alpha value was 0.83. The value of the two-half reliability was r=0.82.

Table 3. Factor loading, item analysis, and item-total correlations for four items in the CCS-TR (N=337)

Caregiving competence scale item	Factor loading	Item mean (SD)	Corrected item-total correlation	Cronbach's alpha if item deleted
1. How much do you believe that you've learned how to deal with a very difficult situation?	0.842	2.76±0.58	0.620	0.807
2. How much do you feel that all in all, you are a good caregiver?	0.822	2.90±0.50	0.698	0.769
3. How competent do you feel?	0.816	2.84±0.54	0.666	0.782
4. How self-confidence do you feel?	0.785	3.04±0.49	0.659	0.787
Caregiving competence scale (X ± SD) (min-max, 4-16)		11.5±1.74		

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

Table 4. The Evaluation of the average definitive characteristics of caregiver score of the CCS-TR

		n	%	Mean	P
Gender	Female	255	75.7	7.65±1.72	>0.05
	Male	82	24.3	7.51±1.55	
Type of stroke	Ischemic	308	91.4	7.62±1.62	>0.05
	Hemorrhagic	29	8.6	7.58±2.30	
Marital status	Married	280	83.1	7.52±1.56	>0.05
	Single	57	16.9	8.07±2.16	
Previous experience of caregiving for patients	Yes	80	23.7	**8.03±1.70**	**<0.05***
	No	257	76.3	**7.48±1.66**	
Person providing support in terms of patient care	Available	236	70	7.61±1.69	>0.05
	None	101	30	7.63±1.67	
Person receiving care except for the patient	Available	46	13.6	7.78±1.54	>0.05
	None	291	86.4	7.59±1.71	
Patients dependence level Modified Rankin Scale (0-5)	Slight disability	62	18.4	**7.77±1.45**	**<0.05****
	Moderate disability	119	35.3	**7.92±1.70**	
	Moderately severe disability	156	46.3	**7.32±1.72**	
Employment status	Being employed	85	25.2	7.51±1.62	>0.05
	No	244	72.4	7.65±1.72	
	Retired	8	2.4	7.37±1.06	
Educational level	Primary or less	28	5.9	7.25±1.97	>0.05
	Primary	140	43.9	7.43±1.42	
	Secondary	57	16.9	7.54±1.47	
	Tertiary	66	19.6	8.12±1.96	
	Graduate and over	46	13.6	7.71±2.04	

*Independent samples t-Test, **One-way ANOVA/Tukey have used for post hoc analysis

The distribution of the effect of the descriptive characteristics of caregivers on the average score of the care competency scale was presented and revealed that previous experience of caregiving and level of dependence of the patient affected caregiver competency ($p<0.05$) (Table 4).

Discussion

CCS was adapted into the Turkish version linguistically and culturally appropriate. The validity of the content was performed in the compliance among specialist opinions after the translation process at the language adaptation phase of the measurement tool (19). The grade of scale comprehensibility and the measured qualifications between the specialists were similar to the Chinese version (12) (CVI =0.83). Scope validity values of the four items for I-CVI were 0.07 and 0.09 and were similar to the Chinese version values (13).

The Adaptation of the CCS was developed by Pearlin et al. (11) and adopted into English as well as Chinese and Swedish and into Turkish was found to be valid and reliable. The majority of participants were female, elementary school graduates, and

unemployed. Such profile was found to be similar to the profile of females, with low educational level, and unemployed in other countries (10,13). The validity and reliability of CCS in a group indicated that it can be used in a wider population. CCS was performed on caregivers of 337 patients who had a stroke, whereas the English version was implemented to caregivers of 326 patients with dementia by Perlin et al. (11) and Swedish and Chinese versions were performed on caregivers of 124 patients with cancer (12) and 118 patients who had a stroke (20), respectively. Multi-centered studies and comparative analyses may be carried out by confirming the validity and reliability of CCS.

The caregivers expressed the caregiving competency perceived in the scale. Two scoring types were found in the literature. Moreover, the original scale score was observed to vary between 4 and 16, and 0 and 12 in other scoring types. The average score of the CCS-TR was 11.5, Cheng et al. (20) at 12.5, and Cheng et al. (20) found the score as 12.3. Chan et al. (21) found such score as 11.4, whereas Henriksson et al. (12) detected a score of 6 with the lowest score compared with other studies. The reason was that scoring was performed according to 0 and 12.

Confirmatory factor analysis presented excellent compliance. Therefore, any modification is unnecessary (Figure 2). Factor analysis was similar to the study by Henriksson et al. (12). Despite the cultural difference, similar results have indicated that the problems of the caregivers are similar. The result has revealed that the need is universal and the perceived caregiving competence should be improved.

The situation to be considered in the evaluation of confirmatory factor analysis is the ratio of the chi-square value to the degree of freedom. Civelek (23) considers this ratio to be below 3 as a sign of perfect harmony. This value was found 0.61 in CCS-TR, which shows a perfect fit. The RMSEA value of the scales with confirmatory factor analysis should be close to or equal to 0, whereas the GFI and CFI values close to 1 increased the level of compliance. The CFI value of CCS-TR was 0.00, the GFI was 0.00, and the RMSEA was 0.00. Considering all these criteria, the adaptation study was successful according to the exploratory and confirmatory factor analyzes results of the scale (Table 2). This situation was similar to the original CCS (11) and Chinese (12) and Swedish (13) language versions.

Factor loads of items under a single-factor ranged between 0.785 and 0.842. Concurrently, the breaking point was examined on the screen plot, and the scale showed a single-factor structure from the breaking point (Figure 1). CCS-TR explained 66.675% of the variance of the single-factor structure. Orçun (24) stated the requirements of the variance that was explained in the measuring scale at 52% and over.

The Cronbach Alpha was frequently used to determine internal consistency in scale development studies. The Cronbach Alpha level varies between 0 and 1. The lowest score should be 0.70 and over in scale studies (25). The present study revealed a Cronbach Alpha of 0.83, which is sufficient. The Cronbach Alpha level in the original scale was 0.74, whereas Henriksson et al. (12) revealed it at 0.86 and Cheng et al. (13) at 0.81. The reliability values of the scale were found close to each other. The Cronbach Alpha value of the present study was determined as higher than the original value, due to the performance of the study in 1990. The healthcare system improvement within the years and increased options associated with the care and educational levels of the individuals may be related to the increased knowledge on competence concept by the caregivers.

Study Limitations

Our study revealed that the caregivers with previous experience of care in moderate disability of patients who had stroke increased the caregiver competency (Table 4). Contrarily, the moderate dependence of patients increased the caregiver competency. Another study that was conducted with caregivers of patients who had a stroke revealed that the ability of caregivers to deal with problems affected their competency (15). The study of Llanque et al. (14) noted that stress and fun affected the caregiving competency. The literature revealed that efforts made for caregivers of patient groups, such as stroke, Alzheimer, and dementia, increased the caregiver competency (14-16), whereas no increase in the caregiver competency was found in a randomized controlled study, where psychoeducation was applied to caregivers of patients with cancer in palliative care (17). This result could be due to the high mortality in patients with cancer and the duration and content of these efforts.

Conclusion

The validity and reliability values of the CCS-TR were similar to the English, Swedish, and Chinese versions. The validity and reliability values of the CCS-TR were high, which revealed its safety. The presence of CCS in different languages provided an advantage for conducting comparative studies, whereas the fact that the scale was a short and easy tool provided an advantage for its use in the field by healthcare professionals.

Ethics

Ethics Committee Approval: Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," (protocol no: 10/07, date: 01.06.2017).

Informed Consent: The caregivers were informed about the study and their written consents were obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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Appendix

Caregiver competence scale

	Not at all	Just a little	Fairly/somewhat	Very/very much
1 How much do you believe that you've learned how to deal with a very difficult situation?				
2.How much do you feel that all in all, you're a good caregiver?				
3 How competent do you feel?				
4 How self-confident do you feel?				

Original Article

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Investigation of The Effectiveness of Plant Based Algan Hemostatic Agent in a Rat Model of Femoral Arterial Bleeding

Ratlarda Femoral Arter Kanama Modelinde Bitki Bazlı Algan Hemostatik Ajanın Etkinliğinin Araştırılması

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ABSTRACT

Objective: The aim of this study is to evaluate the efficacy of the Algan Hemostatic Agent (AHA) available in three different physical form (liquid, powder and sponge absorbed) in the femoral artery incision model in rats.

Methods: A total of sixty-four 5-7 weeks old rats were used in the study. Rats were randomly divided into 8 groups each consisting of eight rats (4 groups heparinized and 4 groups non-heparinized). An experimental femoral artery incision was created. As a control, physiological saline absorbed sponge was applied. AHA liquid, AHA powder and AHA sponge absorbed forms were applied to the experimental groups.

Results: Upon application to the bleeding sites, all the AHA forms stopped bleeding in a significantly shorter time compared to the control group ($p<0.05$). In contrast, bleeding in control group could not be controlled within 4 minutes. The best result was in AHA powder form and it was able to control bleeding in the non-heparinized group at 87.5% in the first minute and 12.5% in the second minute. In the heparinize group, the AHA powder form was able to control the bleeding at 62.5% in the first minute and 37.5% in the second minute.

Conclusion: This study shows that AHA is a highly effective and promising hemostatic agent in bleeding control.

Keywords: Algan, hemostasis, femoral artery, rat

ÖZ

Amaç: Bu çalışmanın amacı, sıçanlarda femoral arter insizyon modelinde üç farklı fiziksel formda (sıvı, toz ve spança emdirilmiş) bulunan Algan Hemostatik Ajanın (AHA) etkinliğini değerlendirmektir.

Yöntemler: Çalışmada toplam 64 adet 5-7 haftalık rat kullanıldı. Ratlar rastgele olarak her biri sekiz rattan oluşan 4 gruba (4 grup heparinize ve 4 grup nonheparinize) ayrıldı. Deneysel femoral arter insizyonu oluşturuldu. Kontrol olarak serum fizyolojik emdirilmiş spanç uygulandı. Deney gruplarına AHA sıvısı, AHA tozu ve AHA sıvısı emdirilmiş spanç formları uygulandı.

Bulgular: Kanama bölgelerine uygulanan tüm AHA formları kontrol grubuna göre anlamlı olarak daha kısa sürede kanamayı durdurdu ($p<0.05$). Buna karşılık, kontrol grubunda kanama 4 dakika içinde kontrol edilemedi. En iyi sonuç AHA toz formundaydı ve heparinize olmayan grupta kanamayı birinci dakikada %87,5 ve ikinci dakikada %12,5 oranında kontrol edebildi. Heparinize grupta AHA toz formu birinci dakikada %62,5, ikinci dakikada ise %37,5 oranında kanamayı kontrol edebildi.

Sonuç: Bu çalışma, AHA'nın kanama kontrolünde oldukça etkili ve umut verici bir hemostatik ajan olduğunu göstermektedir.

Anahtar Szöcükler: Algan, hemostaz, femoral arter, rat

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Introduction

Acute excessive bleeding is still considered the leading preventable cause of death in modern medical practice. Recent efforts in preoperative car- and trauma-related hemorrhages have provided some improvements in minimizing undesired incidences. Uncontrolled hemorrhage due to large vascular damage is the most commonly known cause of death in patients with serious trauma. Additionally, the incidence of death as a consequence of uncontrolled bleeding is preventable with appropriate intervention measures in a short period before an excessive blood loss occurs, as trauma-related death incidences occur within the first 6 h of trauma (1). Therefore, quick but effective bleeding control is critically important to minimize the mortality rate. In addition to conventional techniques, such as cauterization, pressure application, and ligation to stop bleeding, the use of fast-acting local hemostatic agents provides additional therapeutic advantages. Many studies have been conducted to reveal the effect and safety of locally acting hemostatic agents over the last decades (2-7).

Nowadays, several hemostats in different physical forms, e.g., powder, liquid, and gel, are commercially available in the market worldwide. Active hemostatic agents (Active HAs) contain a drug active substance, such as thrombin, which is available either as a sole agent or in a combination with a medical device, a mechanically acting hemostat. A gelatin sponge carrying thrombin is an example of a combination product that can be directly applied to bleeding sites (8-10). Thrombin containing active HA releases a high concentration of thrombin to the bleeding site. Thrombin converts fibrinogen to fibrin that facilitated the deposition of a fibrin clot at the bleeding site (1). Due to thrombin's role in the coagulation cascade, thrombin containing active HAs can be ideal treatment options for patients with coagulopathies including clotting factor deficiencies other than those with hypofibrinogenemia, platelet dysfunction, or antithrombotic medications (11). Thrombin source is critically important. For instance, bovine thrombin has been associated with immunologic reactions. Additionally, the use of human or animal-sourced thrombin carries out the risk of contamination with infectious disease agents such as bovine spongiform encephalopathy (11,12). Immunological reactions due to human and bovine-derived topical thrombin products have been reported in several studies that focus on cardiothoracic surgery (13,14).

Mechanical HAs (MHAs) exert their function by forming a physical barrier matrix at bleeding sites. Collagen, oxidized cellulose, polysaccharide spheres, and gelatin products are among the well-known MHAs available in the market (1,11). The matrix formed by MHAs over the bleeding site activates the extrinsic clotting pathway and facilitates additional setting for platelet aggregation, which in turn accelerates clot formation (13). Additionally, polysaccharide beads absorb free water that facilitates the accumulation of proteins and platelets in wound edges vicinity (13,15). Therefore, MHAs should be kept in place until clot formation occurs and gently removed to avoid clotting disturbance and bleeding recurrence (11,16). Due to the absence of an active substance as a coagulation factor, MHAs were considered the most effective first-line treatment option for minimal bleeding. The use of MHAs is only appropriate in patients with an adequately functioning coagulation system (6,16).

Despite the major advances in medicine and many hemostatic products available in the market, an ideal hemostatic product has not been introduced into the market yet, thus developing an effective hemostatic product is necessary. An ideal hemostatic product should be effective with a fast-acting mechanism, safe, cost-effective, and easy to use.

Algan hemostatic agent (AHA) is a polysaccharide-based herbal extract. Several studies tested the efficacy of hemostatic products in a model of femoral artery bleeding in animals (17). This study aimed to evaluate the effectiveness of AHA in a rat model of femoral artery bleeding.

Methods

Animals

This study was conducted following the Local Ethics Committee of Animal Experiments as specified in the literature (Kırıkkale University Animal Experiments Local Ethics Committee, protocol number: 2018/16). This study used 64 180-210 grams and 5-7 weeks old rats. Rats were fed ad libitum and were housed under standard laboratory conditions with a 12-12-hour dark-light cycle.

The rats were first divided into two groups of random heparinized and non-heparinized, each include 32 animals. The subjects were then divided into eight groups each consisting of 8 randomly selected subjects (Table 1). The heparinized group received heparin intraperitoneally at 640 IU/kg daily for 3 days. No other procedure has been performed.

The procedures were performed under general anesthesia that is induced with a combination of ketamine hydrochloride (100 mg/kg) and xylazine hydrochloride (10 mg/kg). At the end of the study, the rats were killed with 100 mg/kg intravenous sodium thiopental (Pental Sodium®, I.E. Ulagay).

Bleeding Test

The right inguinal region of the rats was shaved and wiped with Batticon, and the femoral vein and artery were exposed by cutting

Table 1. Animal groups

Groups	Explanation
Group 1	Non-heparinized control
Group 2	Heparinized control
Group 3	Non-heparinized AHA powder
Group 4	Heparinized AHA powder
Group 5	Non-heparinized AHA liquid
Group 6	Heparinized AHA liquid
Group 7	Non-heparinized AHA liquid impregnated sponge
Group 8	Heparinized AHA liquid impregnated sponge

AHA: Algan Hemostatic Agent

the skin and subcutaneous tissues. The bleeding duration was evaluated according to the literature protocol (18). The femoral artery was damaged by a green-colored injector tip. As soon as the bleeding began, another person pressured the area with a sponge for 10 s. Once the sponge is removed, the AHA powder, liquid, and AHA-impregnated or saline-impregnated sponges were applied to this area and light pressure was applied to the region. Bleeding was checked after 1 min of time initiation. If bleeding stopped, it was recorded as "first minute-controlled bleeding."

If the bleeding continues in the first application, the same amount of material was added, and the compression was continued for another minute. The bleeding was checked and was recorded as "controlled bleeding at the second minute" if the bleeding stopped. If bleeding continues, the same procedure was performed for the third time and waited for 2 min. The applications are shown in Figures 1-4. Finally, if the bleeding stopped, it was recorded as controlled bleeding at the fourth minute. If the bleeding persists after the fourth minute, it was recorded as unsuccessful. After the application in the form of AHA liquid, the bleeding area was not pressed and was left open. In addition to the results of the second and fourth minutes, the time of bleeding was measured with the stopwatch.

Statistical Analysis

The Statistical Package for the Social Sciences software version 22.0 (SPSS Inc., Chicago, IL) was used to analyze the data. The bodyweight and bleeding time were calculated, and the mean values were compared among the four groups using variance analysis. The Duncan test was used for multiple comparisons in case of differences. The results were evaluated at a 95% confidence interval. A p-value of <0.05 was considered significant.

Results

No differences were found among the groups in terms of body weight. The AHA powder form gave the best result in the heparin-free group in achieving hemostasis at 87.5% and 12.5% success in the first and second minutes, respectively. This rate was 62.5% and 37.5% in the heparinized group in the first and second minutes, respectively. AHA powder, liquid, and sponge forms were found to be more effective in bleeding control than the control group (P<0.05). Additionally, the AHA powder form was more effective in bleeding control than the AHA fluid and AHA sponge form (P<0.05). Results were given in Table 2 and Figures 1, 2, 3, 4.

Discussion

AHA is a plant-based hemostat that is produced in various forms and used in case of many types of bleeding. The AHA powder, sponge absorbed, and liquid forms used in this study were very effective in hemostasis in a rat model of femoral artery bleeding.

A variety of hemostatic agents with varying contents and mechanisms of action are available (19). An active substance, e.g., thrombin

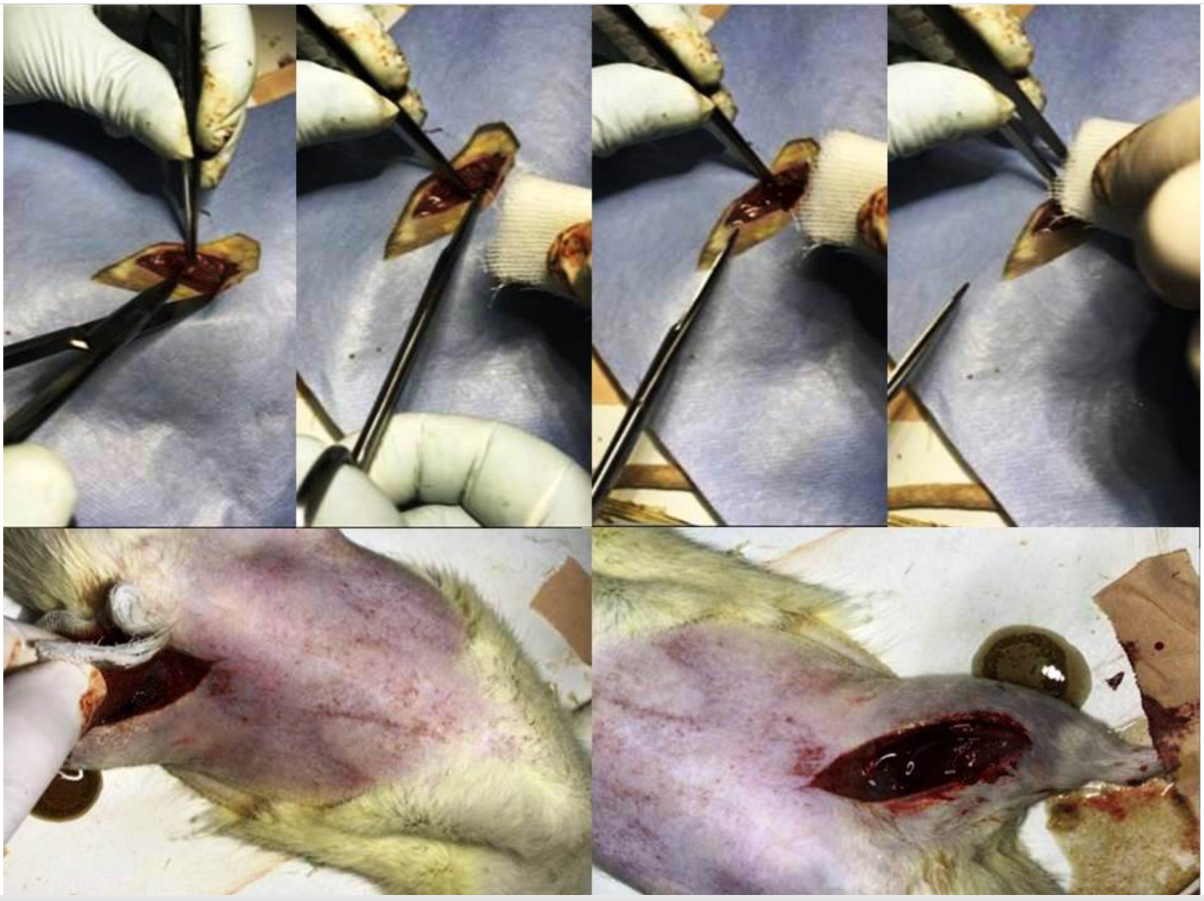

Figure 1. Dry sponge application after bleeding in the control group. Bleeding continues with removal of sponge

Table 2. Homeostasis times of groups

		Bleeding controlled at 1 minutes.	Bleeding controlled at 2 minutes.	Bleeding controlled at 4 minutes.	Unsuccessful
Non-heparinized	Control	0 (0%)	0 (0%)	0 (0%)	8 (100%)
	AHA powder	7 (87.5%)a	1 (12.5%) a	0 (0%) a	0 (0%)
	AHA liquid	3 (37.5%)b	4 (50%) b	2 (12.5%) b	0 (0%)
	AHA sponge	2 (25%) b	4 (50%) b	2 (25%) b	0 (0%)
Heparinized	Control	0 (0%)	0 (0%)	0 (0%)	8 (100%)
	AHA powder	5 (62,5%)d	3 (37,5%) d	0 (0%)d	0 (0%)
	AHA liquid	1 (12.5%)e	5 (62.5%) e	2 (25%)e	0 (0%)
	AHA sponge	2 (25%)e	4 (50%) d	2 (25%)e	0 (0%)

a, b, c, d, e, f Mean within in the same column with different letters are statistically significant (P<0.05)

containing HAs, releases thrombin to the bleeding sites in a high concentration that directly converts fibrinogen into a fibrin clot (11,20). Active HAs are probably the best option to intervene in bleeding in patients with coagulation factor deficiencies (13). However, thrombin has side effects, such as fostering infection and facilitating immunological reactions (11,12). Several immune reaction developments are reported as a consequence of hemostats produced of human or bovine thrombin (13,14). A prospective observational study investigating the immunogenicity of topical use of bovine thrombin has reported the presence of antibodies in patients who have undergone coronary artery bypass graft and valvar cardiac surgery (13). Patients who had cardiothoracic surgery have postoperatively increased anticardiolipin antibodies within 4-8 weeks of operation in 56% of patients who receive bovine thrombin, but anticardiolipin antibodies postoperatively increased only in 9% of patients without topical thrombin (14). Observing the establishment of successful hemostasis within 3-10 min in cardiothoracic surgery, a randomized clinical trial reported a similar success rate of hemostasis for topical human-derived (Evithrom) and bovine-derived thrombin (Thrombin-JMI). However, the number of patients who used Thrombin-JMI (13%) was significantly higher compared to those who used Evithrom (3%) using antibody development, which remains a major concern in bovine-derived thrombin products despite clear achievement in hemostasis. Clinically notable AHA side effects are undetermined immunological reactions.

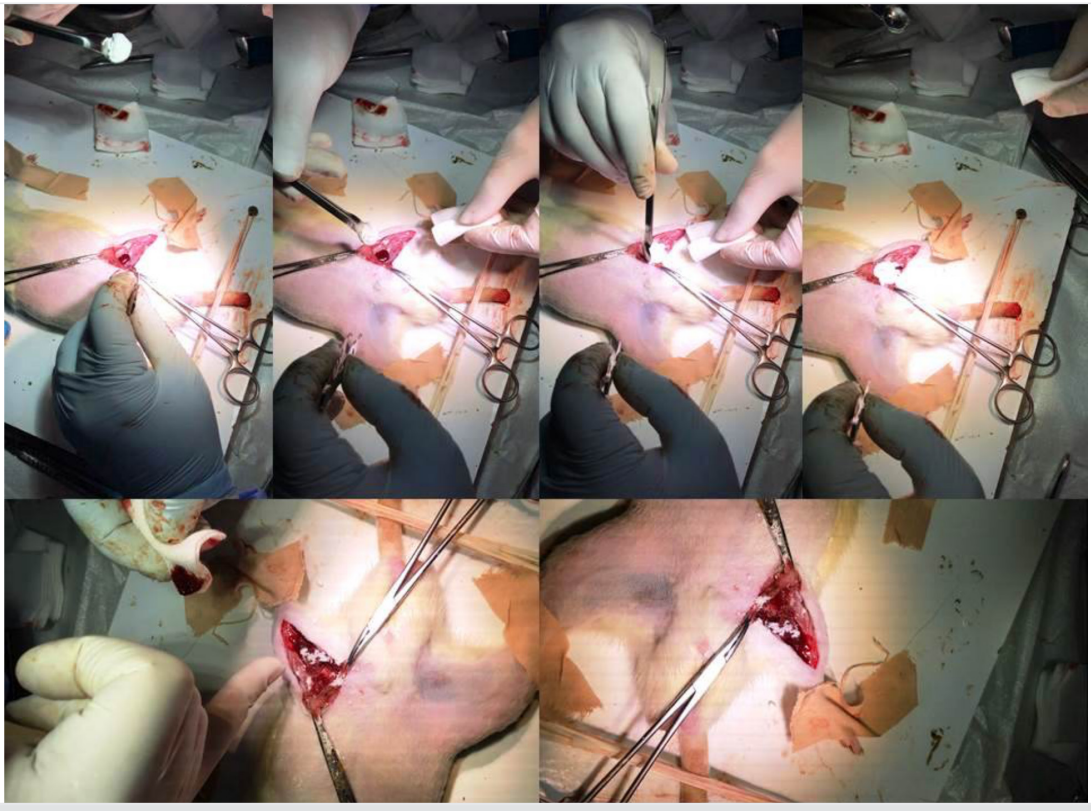

Figure 2. Femoral arterial hemorrhage in the bleeding area before AHA powder application. Controlled appearance of femoral arterial hemorrhage following AHA powder administration

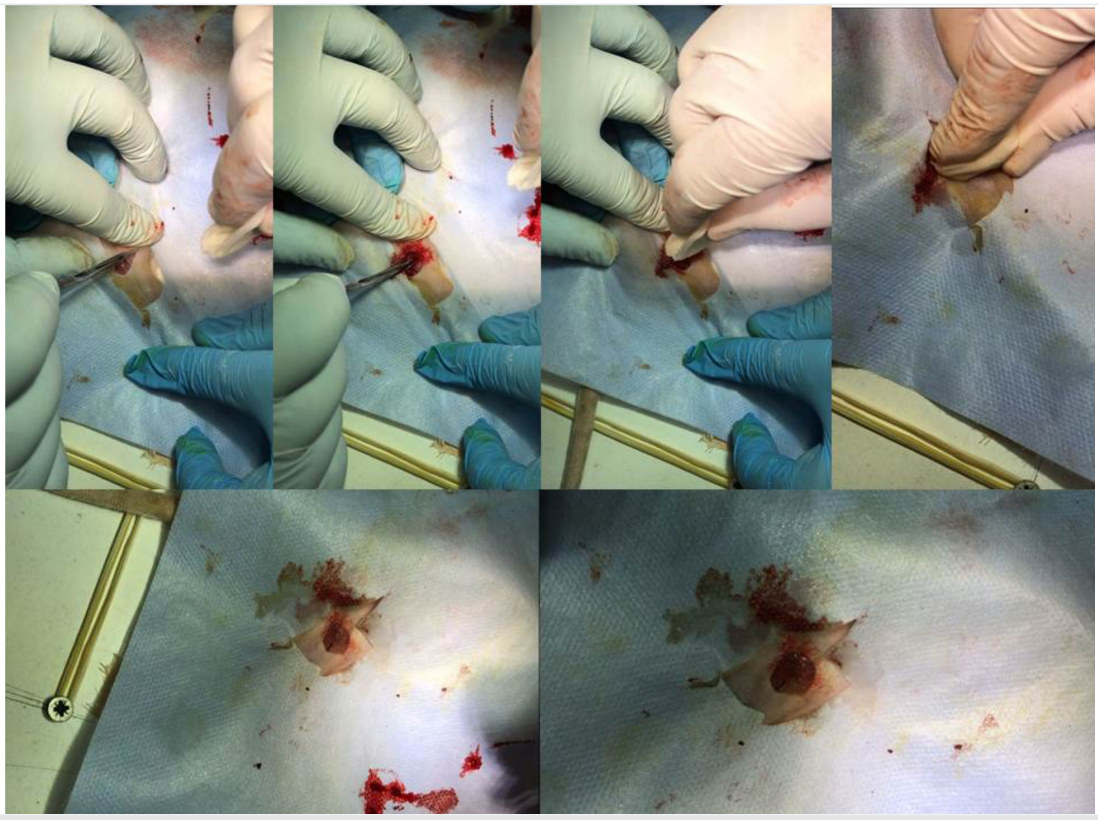

Figure 3. Femoral arterial hemorrhage in the bleeding area before AHA sponge application. Controlled appearance of femoral arterial hemorrhage following AHA sponge administration

Mechanical HA agents do not contain an active drug substance and form a physical barrier over the bleeding site. Several MHA, which is produced from various chemicals, including oxidized cellulose, gelatin, polysaccharide spheres, and collagen, are available in the market (11,12). The matrix barrier activates the extrinsic clotting pathway and facilitates the formation of additional settings for platelet aggregation, which in turn expedites clotting plug formation (13). Additionally, polysaccharide beads absorb free water that facilitates protein and platelet accumulation at the wound edges (13). MHAs should therefore be kept in place until clotting plug formation and gently removed to avoid clotting disorder and bleeding recurrence. Since mechanical HAs do not contain a specific active drug substance for blood coagulation, they are most effective as a first-line treatment option for minimal bleeding. Importantly, mechanical HAs are considered appropriate to use in patients with an adequately functioning coagulation system (12,16).

According to the hemostatic report, AHA primarily provides hemostasis by forming a mechanical barrier at the bleeding site as a hemostatic agent. Additionally, AHA activates both intrinsic and extrinsic clotting pathways to facilitate a strong hemostatic effect.

Among the types of hemostatic agents are synthetic sealants that are commonly used to prevent suture hole bleeding in cardiac and vascular surgeries. They form a watertight barrier at bleeding sites and are used as tissue adhesives (12).

This study used three different physical forms of AHA, which were in powder, liquid, and sponge. A significant statistical difference was found compared to the control group, thus all AHA forms were very effective. However, the powder form controlled the bleeding more quickly than AHA liquid and sponge forms. However, no compressions were made to the bleeding area in the liquid group. The bleeding duration in the control group was very long compared to the AHA experimental groups. In internal hemorrhages that cannot be compressed, the liquid form gave hope as an effective hemostat.

A limited number of studies were found in the literature that compared local hemostatic agents with similar femoral artery methods (2,18). Similar studies by Ankaferd and Chitosan were unable to control the bleeding in the first minute, but Ankaferd was able to provide 40% and Chitosan 30% hemostasis in the second minute. In the fourth minute, Ankaferd and Chitosan were able to provide 60% homeostasis. With Chitosan, bleeding was not controlled at 10% in the fourth minute (18). This study excised the femoral artery and vein. Our study damaged the femoral artery using the needle tip. In a study in the literature, similar to our study, the femoral artery has been damaged by the incision method (2). Our study used a 24-gage needle to puncture the femoral artery. Once the excessive bleeding had been observed, the HAs were poured directly onto the bleeding site, and a 200-g scale weight was placed on for 30 s. The bleeding was evaluated at 30 s intervals. Upon the scale weight removal, hemostasis was assessed. If hemostasis was not established, the

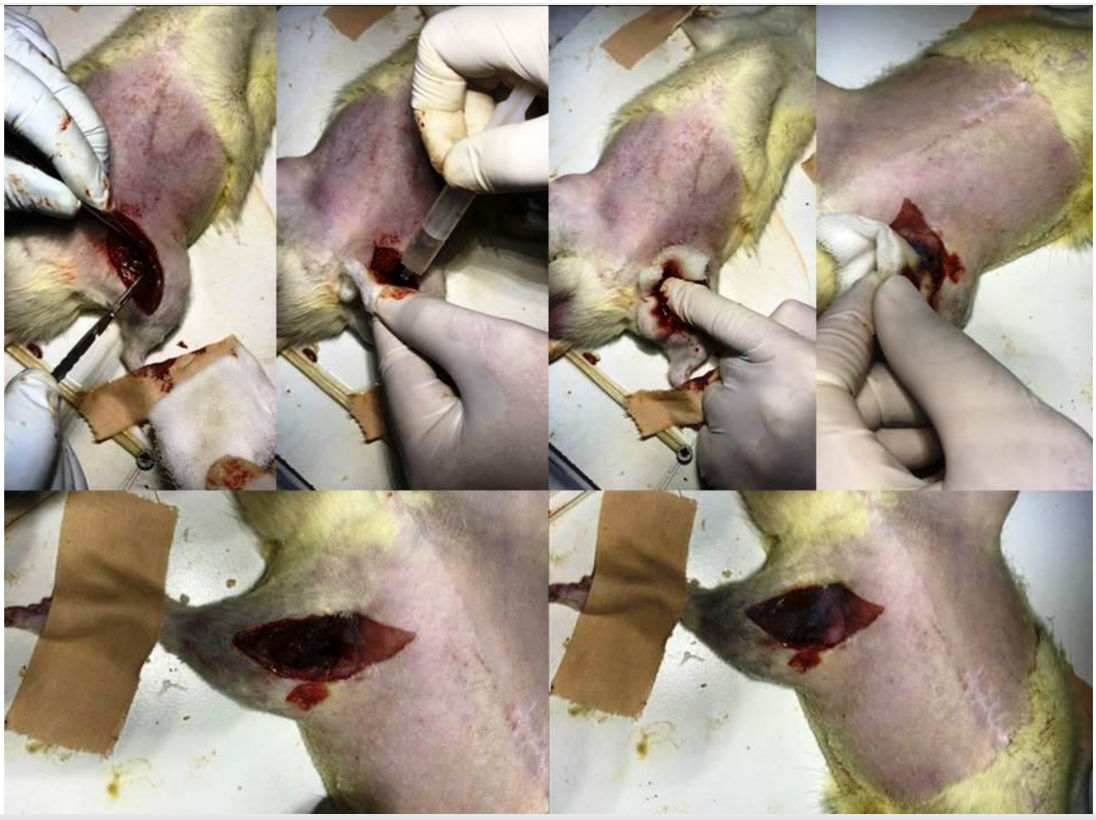

Figure 4. Femoral arterial hemorrhage model with no sponge applied to the bleeding area after AHA liquid application and the appearance of the bleeding under local control

weight was reapplied. If hemostasis did not occur after the third application, the test was scored as failed.

In our study, unlike in the use of the AHA powder and sponge forms, no pressure was applied to the bleeding site when the AHA liquid form is used that might have prolonged the bleeding period. However, one should not question the effectiveness of the AHA liquid, as there is no similar product in the literature. Compared to the AHA powder and sponge, the AHA liquid was the least effective hemostat in bleeding control; however, it seems to be more effective than many local hemostats available in the literature made by the same method (18).

A study by Karahaliloglu et al. (21) revealed that a standard sponge stopped the bleeding after 245 s. The hemostasis time of native and coagulative agents-doped hemostatic dressings ranged from 80 to 180 s. Compared with the standard sponge, hemostatic dressings had significantly better performance. According to this study, the native and active agents-doped hemostatic dressings quickly stopped the bleeding in a femoral artery bleeding rat model with low mortality, more platelet activation, reduced tissue reaction, and improved biological tissue compatibility compared to a standard sponge. Additionally, native or active agent-doped hemostatic dressings would provide impressive and safe hemostasis for the femoral artery bleeding model.

An additional important aspect is that the prepared hemostatic dressings can become a unique tool for surgeons with ease of handling and low cost as HAs (21). AHA products are easy to apply, inexpensive, and can be applied with or without compressions. AHA products do not need the removal of any kind of cleaning procedure because of biodegradability; however, they are easy to clean from the field of application.

Few guidelines are available for the use of HAs (16,19). AHA products are available in various forms, e.g., liquid, powder, and sponge that provide a wide range of indications in controlling various types of bleeding (22,23,24,25).

Our study applied the AHA liquid form to the area in the femoral artery bleeding model in the absence of compressions. Its hemostatic activity was almost similar to the sponge and powder forms. Liquid hemostats come into prominence to control internal bleeding, where the application of other forms, such as sponge, powder, and fiber and nonwoven type hemostats, is impossible. AHA liquid form immediately turns into gel after application, thus it can be effectively used in the military area, in cases where physical access to the bleeding area is difficult or impossible in gunshot wounds.

The literature reported various rates of mortality and exothermic reaction (26,27). For instance, the femoral artery injury had resulted in 75% mortality in the standard dressing group. However, active component coated dressings had dramatically decreased the mortality to 37.5% (approximately two-fold). The addition of kaolin to hemostatic dressing had increased the mortality rate compared with other fabricated experimental groups. Literature

reports that the mortality rate for commercial products, such as Celox Gauze and ChitoGauze, are 90% and 70%, respectively. Combat Gauze showed a mortality rate of 60% (26).

Letourneau et al. (27) studied the hemostatic potential of the active dressings group and revealed that the overall survival rate was 54%. Many studies in the literature with similar test methods have different results in control groups among effective local hemostatic agents (28,29). Compared to other products, further studies are required to evaluate the bleeding control of other bleeding arrestors due to many factors, such as animal weight, experience, technical differences, vessel variations, and laboratory conditions that affect this difference.

The results of this study should be supported with larger studies. Our study used healthy rats. Additional studies are needed to evaluate the results of already hypovolemic and hypotensive subjects due to major artery bleedings. The limitations of this study include the absence of data on the mean arterial pressure, blood gases analysis, and histological examinations.

Conclusion

The AHA effectively controlled the bleeding in a short period in a well-characterized animal model: the rat femoral artery bleeding. The AHA offers some advantages due to its availability in three different forms since it can be used in various types of bleeding.

Ethics

Ethics Committee Approval: This study was conducted following the Local Ethics Committee of Animal Experiments as specified in the literature (Kırıkkale University Animal Experiments Local Ethics Committee, protocol number: 2018/16).

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: H.E., A.K., A.M., E.Y, Design: H.E., A.K., A.C.O., H.D., A.M., M.S.B., E.Y., Data Collection or Processing: H.E., A.K., A.C.O., H.D., A.M., Analysis or Interpretation: H.E., A.K., A.C.O., H.D., A.M., Literature Search: H.E., A.C.O., H.D., A.M., M.S.B., Writing: H.E., S.S.D., A.C.O., H.D., A.M., E.Y.

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

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Original Article

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Evaluation of Patients' Awareness Levels Regarding Implant And Implant-Supported Prosthesis Who were Admitted to Bezmialem Vakıf University Faculty of Dentistry

Bezmialem Vakıf Üniversitesi Diş Hekimliği Fakültesine Başvuran Hastaların İmplant ve İmplant-Destekli Protezler ile İlgili Bilinç Seviyelerinin Değerlendirilmesi

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ABSTRACT

Objective: The aim of this study was to investigate the knowledge level of the totally or partially edentulous patients who were admitted to the Dentistry Faculty of Bezmialem Vakıf University and to investigate the factors affecting their ideas when choosing this treatment.

Methods: To measure the knowledge level of the patients who were admitted to Faculty of Dentistry and to determine the factors affecting the decision-making processes, a survey was planned. A total of 250 participants were included in the survey.

Results: While 57.3% of the participants knew that implant treatment was an alternative treatment, 13.3% of them stated that they had no idea, 29.3% had no opinion at all. When we asked the level of knowledge of the patients about the implant, 16% found it to be quite inadequate and 22% found it very adequate. Of the patients 40.6% stated that they acquired the information from the physician, when they were asked where the information about the implant was obtained. The other sources were friends and family in 24.6%, social media in 16%, internet in 14%, and other sources in 4.6%. While 49.3% of patients preferred implant treatment, they chose the option of being expensive as the biggest factor causing them to think negatively.

ÖZ

Amaç: Bu anket çalışmasında Bezmialem Vakıf Üniversitesi Diş Hekimliği Fakültesi'ne başvuran total ve parsiyel dişsiz hastaların implant hakkındaki bilgi düzeyleri ve bu tedaviyi tercih ederken fikirlerini etkileyen unsurların incelenmesi amaçlanmıştır.

Yöntemler: Diş hekimliği fakültesine başvuran hastaların implant ve implant tedavisi hakkındaki bilgi düzeylerini ölçmek ve karar verme süreçlerini etkileyen faktörleri belirlemek amacıyla anket yoluyla araştırma düzeni planlanmıştır. Ankete toplam 250 katılımcı eklenmiştir.

Bulgular: Katılımcıların %57,3'ü implant tedavisinin alternatif bir tedavi olduğu bilincine sahipken, %13,3'ü kısmen fikir sahibi, %29,3'ü hiç fikirlerinin olmadığını belirtmiştir. Hastaların implant ile ilgili bilgi düzeylerini sorduğumuzda %16'sı oldukça yetersiz bulurken, %22'si çok yeterli bulmuştur. Katılımcıların implant ile ilgili bilgiyi nereden edindikleri sorulduğunda hastaların %40,6'sı hekimden bilgiyi edindiğini belirtirken, %24,6'sı arkadaş ve aile, %16'sı sosyal medya, %14'ü internet, %4,6'sı diğer seçeneğini seçmiştir. Hastaların %49,3'ü implant tedavisini tercih ederken negatif düşünmelerine sebep olan en büyük etmen olarak pahalı olması seçeneğini seçmiştir.

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Conclusion: As a result of the questionnaire, it was concluded that the knowledge level of the patients about implant treatment and the physician were insufficient in the transfer of this information. Further studies should be increased in order to raise awareness among patients.

Keywords: Implant, implant-supported denture, dental treatment, total edentulous jaw, partial edentulous jaw, awareness level

Sonuç: Anket sonucunda hastaların implant tedavisi hakkındaki bilgi seviyesinin ve implant tedavisi aşamalarının aktarımında hekimin yetersiz kaldığı sonucu çıkmıştır. Hastaların bu konuda daha çok bilinçlenmesi için çalışmaların arttırılması gerekmektedir.

Anahtar Sözcükler: İmplant, implant-destekli protez, dental tedavi, total dişsiz çene, parsiyel dişsiz çene, bilinç düzeyi

Introductıon

Today, implant therapy, which has become rapidly popular among dentists and patients, has begun to replace many alternative treatment methods (bridges, removable prostheses, etc.) (1-6). The first known implants were made by the Egyptians with gold wire around 2,500 BC (7). With the developing technology and industry over time, significant developments have taken place especially in the last 100 years. Implant material, which has undergone various modifications over the years, has begun to be produced in many different types and sizes (8). In addition, implant-supported prosthetic restorations have been diversified and developed with the widespread use of implant treatment (9). This difference is determined by many factors depending on the physician and especially the patient.

When determining patient-related factors, it is necessary to evaluate from many aspects. One of these factors is the patient's physical condition. Patient's intra-oral status (condition of alveolar crests, number of missing teeth, condition of gingiva, etc.), extra-oral face circumference and tissue condition (such as facial symmetry, facial type), physiological health status (disorders such as cardiac, diabetic, blood pressure) and physical examination factors (age, gender) are important criteria to be evaluated when planning implant and implant supported prosthese prostheses (1). Other factors are psychological, environmental and socioeconomic status. Financial conditions, lifestyles, social environments (friends, family, work) and psychological conditions of the patients also play major roles in deciding the treatment option they want to have (10).

The explanations and directions made by the physician are also effective in the patient's decision. Physician-related factors such as the physician's knowledge, friendliness, ability to explain, and persuasion are effective in guiding the patient. Although the effect of these factors is known when the literature is examined, the number of scientific studies that evaluate these parameters and provide the opportunity to evaluate the level of awareness in patients is very few. Various studies have been conducted to show the of patients about dental implants in different countries (10-17).

In this study, it was aimed to examine the level of knowledge that patients had about implant and implant supported prosthese prostheses and the factors that affected them while making a decision. The study was carried out according to the results of the questionnaire presented to 250 patients who were admitted to Bezmialem Vakıf University (BVU) Dentistry Faculty Hospital to have implants.

The hypothesis of the research was that totally or partially edentulous patients did not have sufficient awareness about implant and implant treatment when they were admitted to BVU Faculty of Dentistry.

Method

This survey study was carried out in a period of 6 months (December 2018-May 2019) in accordance with the Principles of the Declaration of Helsinki. Permission for the study was obtained from the BVU Non-interventional Research Ethics Committee with the decision number 23/301 on 18.12.2018.

In order to measure the knowledge level of the patients who were admitted to BVU Faculty of Dentistry Hospital about the implant and to determine the factors affecting their decision-making processes, a questionnaire was planned (Figure 1, 2). A pilot test was applied to 25 patients to evaluate the effectiveness of the questionnaire. Then the questionnaire was applied to 250 patients. The data were evaluated as descriptive analysis items. Patient preferences were evaluated with Person Chi-square test. For a 5-point Likert-type question, it was calculated that at least 250 questionnaires should be filled in order to determine the theoretical frequency of 1/5=0.20 with 0.04 error and 95% confidence level.

The survey consisted of 15 questions:

1. Information of the patients about the stages of implant treatment and the materials used

2. Factors that affect patients when deciding on implant treatment

3. Information resources of patients about treatment

4. Patients' awareness of the negative or positive effects of the implant on the bone

5. Whether the patients had sufficient information during the decision-making process for implant treatment and after treatment

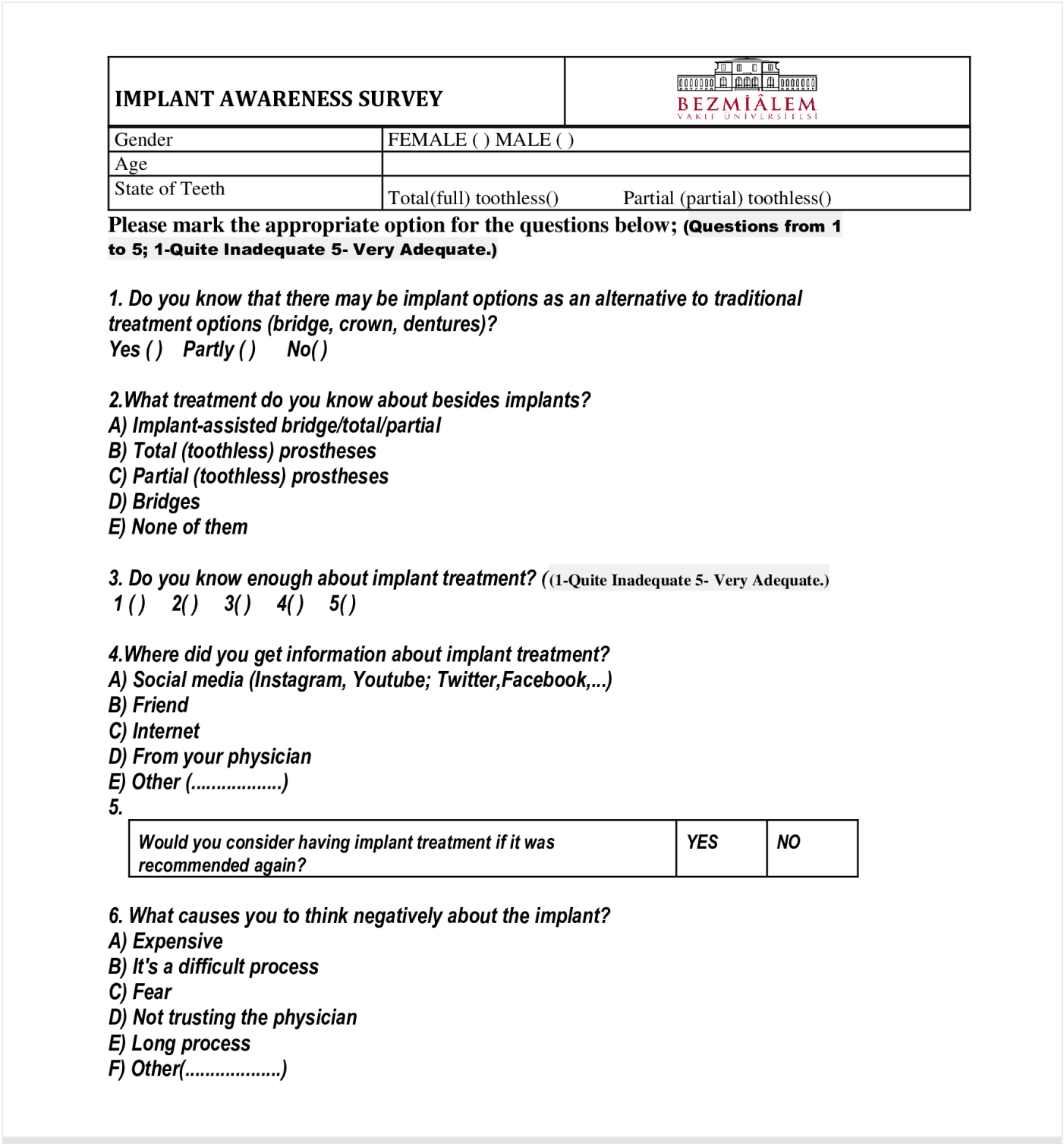
The questionnaires were presented to the patients in the Department of Prosthetic Dentistry. Questionnaires were applied to the patients who were in the implantation phase. Patients who did not agree to participate in the survey were excluded from the study.

Statistical Analysis

The obtained data were transferred to digital environment with Excel (Microsoft Corporation). Since the data obtained with Excel and SPSS (IBM Company, V22.0, Chicago, IL, USA) programs did not show homogeneous distribution according to the Kolmogorov-Smirnov test result, the Kruskal-Wallis test was used to determine the intergroup differences, and Dunn's test was used to determine the within-group differences. The numbers and percentages of the data were determined by descriptive statistics. P<0.05 was considered statistically significant.

Results

Of the participants 31.3% were between the ages of 20-39, 40% were between the ages of 40-54, and 28.6% were between the



IMPLANT AWARENESS SURVEY	BEZMİÂLEM VAKIF ÜNİVERSİTESİ
Gender	FEMALE ( ) MALE ( )
Age	
State of Teeth	Total(full) toothless() Partial (partial) toothless()

Please mark the appropriate option for the questions below; (Questions from 1 to 5; 1-Quite Inadequate 5- Very Adequate.)

1. Do you know that there may be implant options as an alternative to traditional treatment options (bridge, crown, dentures)?
Yes ( ) Partly ( ) No( )

2.What treatment do you know about besides implants?
A) Implant-assisted bridge/total/partial
B) Total (toothless) prostheses
C) Partial (toothless) prostheses
D) Bridges
E) None of them

3. Do you know enough about implant treatment? (**(1-Quite Inadequate 5- Very Adequate.)**
1 ( ) 2( ) 3( ) 4( ) 5( )

4.Where did you get information about implant treatment?
A) Social media (Instagram, Youtube; Twitter,Facebook,...)
B) Friend
C) Internet
D) From your physician
E) Other (.....)
5.

Would you consider having implant treatment if it was recommended again?	*YES*	*NO*

6. What causes you to think negatively about the implant?
A) Expensive
B) It's a difficult process
C) Fear
D) Not trusting the physician
E) Long process
F) Other(.....)

Figure 1. 1st page of the questionnaire

7. Why do you prefer the implant?
A) Social popularity
B) Reject to cut healthy teeth
C) More aesthetic
D) More robust and long-lasting
E) Other(.....))
8. Do you know what effect implant placement has on your bone, positive or negative?
Yes ( ) Partly ( ) No( )

9.What is the most important option when choosing implant material?
A) Price
B) Company Origin (Foreign-Turkish)
C) Physician's guidance
D) Impact of the environment (Friend-Neighbor-Relative)
E) Other(.....))
10. What do you pay the most attention to when choosing the material to be used on the implant?
A) Aesthetics
B) Price
C) Robustness
D) Physician's choice
E) Other(.....)
11.Do you know that implant and implant supported prosthesis treatment are performed in cooperation of two different departments as surgical and prosthetics?
Yes ( ) No( )
12.Do you know that surgical and prosthesis departments are paid separately in implant and implant supported prosthesis treatment?
Yes( ) No( )
13.What feature of the physician can be effective in your decision making?
A) Information
B) Friendliness
C) Ability to explain
D) Persistence
E) Other(.....)
14.Which department was most effective about your request to have implant treaatment?
A) Surgery
B) Prosthesis (Prosthetic Dental Treatment)
C) First examination (Radiology)
D) Periodontology
E) Other (.....)
15.Is there any difference in your implant knowledge between beginning and present?
Yes( ) Partially( ) No( )

Figure 2. 2nd page of the questionnaire

ages of 55-72. Of the participants 51.3% were female and 48.7% were male (Figure 3). In addition, 83.3% of the patients had partial edentulism, while 16.6% had total edentulism.

The first criterion we evaluated was whether patients knew that implant treatment was an alternative to traditional treatment options (bridge, crown, removable prosthesis). While 57.3% of the participants knew that implant treatment was an alternative treatment, 13.3% had a partial idea and 29.3% stated that they had no idea. No significant difference was found between male and female participants (p>0.05).

In our second question, the patients' knowledge of a treatment other than implant treatment was measured. While 52.0% of the participants knew about bridge treatment, 14% stated that they did not know about implant-supported removable prostheses, 13.3% stated that they did not know about total and partial dentures, and 20.7% stated that they did not know about any treatment. No significant difference was found between male and female participants (p>0.05).

When we asked about the knowledge level of the patients about the implant, 16% found it quite insufficient, while 22% found it very sufficient. No significant difference was found between male and female participants (p>0.05). When we divided the patients into 3 groups; 29.8% of patients aged 20-39 stated that they had a very sufficient level of knowledge, 26.7% of patients aged 40-54 stated that they had insufficient knowledge, and 34.9% of patients aged 55-72 stated that they had an average level of knowledge.

In the 4th question, when the participants were asked where they got the information about the implant, 40.6% of the patients stated that they got the information from the physician, while 24.6% from friends and family, 16% from social media, 14% from internet, and 4.6% from other sources. No significant difference was found between male and female participants (p>0.05). According to the question 4, the difference between the mean ages was checked and it was found to be p=0.019 in the Kruskal-Wallis test. As a result of Dunn's test, it was observed that there was a difference between groups 1-4 (1= social media, 4= physician) (p=0.0044). It was observed that the 1st group had lower mean age than the 4th group.

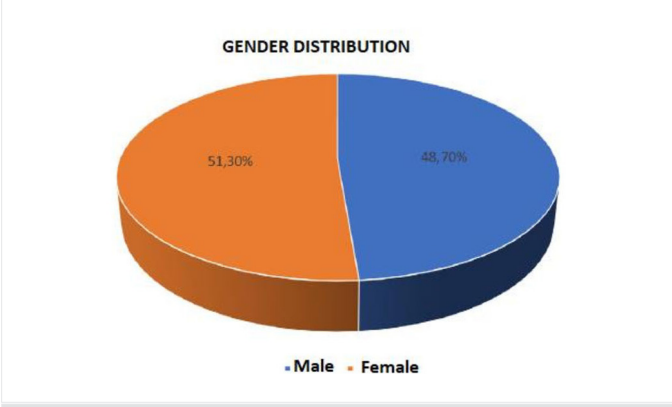


Figure 3. 2nd page of the questionnaire

The patients who participated in the survey were asked whether they would consider having implant treatment if they were offered again. According to the results, 93.3% of them considered having implant treatment if it was recommended and 6.6% of them did not consider. No significant difference was found between male and female participants (p>0.05).

According to question 6, in 49.3% of the patients who participated in the survey expensiveness caused them to think negatively, while in 14% long process caused them to think negatively. Other factors that caused them to think negatively were fear in 13.3%, difficulty of the process in 11.3%, not trusting the physician in 8%, and other factors in 4%. No significant difference was found between male and female participants (p>0.05).

According to Question 7, when the positive reasons affecting the patients' choice of implant treatment were examined; 56.7% of the patients said that implant treatment was more robust and long-lasting, 27.3% of them said that they did not want to have their healthy teeth cut, 8% said that implant was more aesthetic, 3.3% said that they would choose implant treatment because of social popularity, and 4.4% chose the other reasons. No significant difference was found between male and female participants (p>0.05).

The question "Do you have any information about the positive or negative effect of implant placement on your bone?" was posed. Of the patients 60% stated that they had no idea, 19.3% stated that they had partial knowledge, and 20.6% stated that they had no knowledge. No significant difference was found between male and female participants (p>0.05).

When the patients were asked about the most important factor when choosing the materials to be used in implant treatment; the most important factor was physician referral in 50% of the patients, price in 27.3%, company origin in 22.0%, and environmental impact in 0.7%. There was no significant difference between male and female participants (p>0.05).

When the patients were asked about the most important factor in the material selection of the restoration to be made in the implant treatment; 35.3% chose durability, 30% chose physician's choice, 17.3% chose price, 16% chose aesthetics, and 1.3% chose the others. No significant difference was found between male and female participants (p>0.05).

The question "Do you know that implant and implant supported prosthese treatment are performed jointly by two separate departments which are surgery and prosthesis departments?" was asked, and 62% answered "no" and 38% answered "yes". There was no significant difference between male and female participants (p>0.05).

The question "Do you know that in implant and implant supported prosthese treatment, you pay to surgery and prosthesis departments separately?" was asked, and 54% answered "no" and 46% answered "yes". There was no significant difference between male and female participants (p>0.05).

When the 13th question was asked to the patients, they chose which feature of the physician was important in the decision-making of the patients. While 62% chose knowledge, 18.6% chose ability to explain, 19.6% chose friendliness, 3.3% chose other options, and none of the patients chose persistence. There was no significant difference between male and female patients ($p>0.05$).

In the 14th question, "Which department was effective in your desire to have implant treatment", 45.3% chose surgery department, 18.6% chose prosthetic dental treatment department, 11.3% chose periodontology department, 10.6% chose oral diagnosis department, and 14% chose other options. No significant difference was found between male and female patients ($p>0.05$).

The patients were asked whether there was any difference in terms of their knowledge between the time they were admitted to the faculty of dentistry and the time until the time the questionnaire was conducted. According to the results, 45.3% stated that there was a significant difference, 24% stated that there was a small difference, and 30.6% stated that there was no difference. There was no significant difference between male and female patients ($p>0.05$).

Discussion

This research was a study examining the knowledge levels of patients, who were admitted to BVU Faculty of Dentistry Hospital in İstanbul, about implant treatment, the reasons for choosing this treatment, and the factors affecting this choice. The study group consisted of faculty members, specialist doctors and patients who were admitted to the Prosthetic Dentistry Clinic due to the ease of access. The age and gender distribution of the participants was randomly selected. According to the result of the research, it was observed that the patients did not have sufficient knowledge about the implant, implant treatment and the stages of this treatment. Hypothesis was accepted.

Implant treatment is an increasingly popular treatment option with a high success rate. Recently, it has become the focus of attention for patients, especially due to the widespread use of social media, television programs and the internet (6). In this study, it was shown that 57.3% of the patients knew dental implants among different options for rehabilitating missing teeth. It was found that more than half of the patients knew that the implant was a treatment applied to replace missing teeth. Tomruk et al. showed that 43.5% of the patients had sufficient knowledge about implant in the implant awareness survey conducted in the student clinic in Istanbul (1). The difference was thought to be due to the fact that the socio-cultural structure of the patients who came to the student clinic where the study was conducted was different from that of the patients who came to the clinic where there were specialists and academic staff. Zimmer et al. (10), Berge (13) and Tepper et al. (14) reported the implant awareness rates in their countries as 77%, 70.1% and 72%, respectively. The differences between these countries (America, Norway and Austria) and Turkey may be due to sample differences, because we can talk about a social and economic difference between the participants in our study and those in other countries (1). In addition, oral implant technology has been developed recently in Turkey, but this technology has been in use earlier in other countries (1).

As a result of the research, it was revealed that the treatment method that the patients had the most opinion about as a Prosthetic Dental Treatment option, apart from the implant, was the bridge treatment with 52%. The most important reason why patients chose this treatment was that it was done very often in the past to treat partial tooth loss, and because of this situation, they learned about this treatment (18).

When we looked at the implant awareness levels, it was concluded that the patients were not at a sufficient level in this regard. While the knowledge level of young patients about the implant was more sufficient, the awareness level of middle-aged and elderly patients was found to be insufficient. It can be thought that this result is due to the differences in obtaining information due to the more common use of social media and the internet in younger patients (23).

Of the patients 40.6% stated that they learned the information about the implant from their physicians, and 30% of the participants stated that they obtained the information from the internet and social media platforms (Instagram, Youtube, Twitter, Facebook, etc.). Suprakash et al. (19), Ozçakır Tomruk et al. (1), Kaurani and Kaurani (20) and Ünal Erzurumlu et al. (21) stated that the main source of information in their studies was the dentist. Zimmer et al. (10) and Berge (13) reported that the main source of information was the media, emphasizing that the role of dentists was less. The average age of the patients who chose the social media option was 38.5, and those who obtained information from the physician were 53. Despite the widespread use of the internet and social media, the fact that the age group of the patients who had implants was mostly from the elderly patient group might cause the source of information to be different. In our study, similar to the studies of Ozçakır Tomruk et al. (1) and Ünal Erzurumlu et al. (21), it was concluded that the patients obtained information about dental implants and procedures primarily from dentists. In this case, the duty of the physician should be to keep the level of knowledge about the implant high and to convey this information to the patient in a good way.

Of the patients 49.3% considered the expensiveness of the implant treatment as the most important negative aspect of this treatment. Similar results were obtained in similar survey studies (10,14,16,22). Patients should be told about the necessity of increasing their quality of life rather than complaining from the high cost, and the advantages of implant treatment over other treatments should be mentioned.

Of the patients 56.7% stated that the more robust and long-lasting implant treatment was the most important reason for them to prefer this treatment. When we looked at the literature on this subject, no study was found. According to this result, it

can be concluded that the patients think of the implant as their permanent teeth and may think that it should be long-lasting and robust. Other factors, such as aesthetics and not wanting to have healthy teeth cut, remain in the background. It can be concluded that the emphasis on the durability and longevity of this option while explaining the implant treatment to the patients significantly affects the preference of the patients.

Implant treatment has a positive effect on bone resorption compared to other restorative options (8). When the patients were asked whether they had knowledge about the positive and negative effects of implant placement on the bone, 60% stated that they had no idea and 20% stated that they had insufficient knowledge. This showed that patients were not informed about the effect of the implant on bone resorption, which was actually one of the most important advantages of the implant, or that they did not learn about it from sources other than the physician (TV, internet, social environment). More work needs to be done on this topic. Awareness of patients on this issue may make implant treatment more preferable.

Patients are presented with many options when choosing implant material. When the physician's referral and other factors were evaluated among these options, 50% of the patients stated that the doctor's referral was the most important factor. The cost lagged behind the physician's guidance in choosing the patient. This topic has not been explored before. According to the result, the effective speech and persuasion ability of the physician is more important than the cost in the patient's implant material preference. This result also shows that the ethical responsibility of the physician has increased even more.

There are many different options in the selection of the material to be used in the prosthesis over the implant when the prosthetic stage is passed after the surgical stage. According to our results, while the choice of the physician was of great importance when choosing the implant material, the durability and the choice of the physician were very close to each other when choosing the prosthesis material on the implant. When the prosthesis stage is passed, explaining the durability of the implant materials to the patients will make a positive contribution to convincing the patient.

We thought that detailed information about the stages and pricing of implant and implant supported prosthese prosthesis treatments were not given to patients in dental clinics such as university hospitals and large outpatient clinics where different treatments were performed in different departments. In our study, the majority of the patients stated that they did not know that implant treatment consisted of two parts as oral and dental surgery and prosthetic dental treatment and that they were not informed about it. Likewise, they stated that they did not know that separate fees were paid for the implant material and the prosthetic restoration on the implant. No research has been found on this topic. According to the result, it is thought that this deficiency is caused by insufficient informing during the oral diagnosis and surgical stage, which is the first stage. Patients complain about this situation and become victims. It is necessary to carry out studies on informing in oral diagnosis and surgery departments.

Patients coming to our hospital are admitted to many departments for various treatments. They are informed about implant treatment in different departments and they are directed to this treatment. When the patients were asked about the department that affected this situation the most, almost one out of every 2 patients stated that they were convinced of implant treatment by Oral and Maxillofacial Surgery. No research has been found on this topic. The effects of the other sections were very close to each other and there was no difference between them ($p>0.05$).

As can be seen from the results of our survey, the physician greatly influences the patient's decisions. When the patients were asked which feature of the physician was effective in their decision making, a large percentage of them (62%) emphasized that the physician's knowledge was very important in their decision making. The conclusion to be drawn from this is that the physician who seems knowledgeable is very effective in the decision making of the patients. Also, it was seen that none of the patients chose the persistence of the physician effecting their decision.

Finally, the patients were asked whether there was a difference in their knowledge about the implant from the time they were first admitted to our hospital to the time we conducted the survey. Of the participants 45% stated that they felt a significant difference in their knowledge.

Study Limitations

In our study, there was a population of patients from social and economic environments that were generally close to each other. For this reason, the answers given were more localized. In order to diversify this, conducting such tests in different countries or cities and in different socio-economic segments may ensure that the results are more accurate and clear. Such studies show that patients have difficulties in obtaining the right information about the treatment to be applied and obtaining this information from the right source. In order to increase awareness on this issue, it is necessary to increase the researches on the subject.

Conclusion

When the data of this research was examined, it was concluded that the patients were not sufficiently informed about the implant treatment and the process of this treatment and that they were not adequately informed by the physicians. As young patients are informed via the internet and social media, older patients cannot benefit from these channels. For middle-aged and older patients, it is very important to be informed by the physician. Physicians need to keep their knowledge fresh on this subject, improve themselves in effective informing, and inform patients accurately about this treatment.

Ethics

Ethics Committee Approval: Our study was approved by the ethics committee of our university (ethics committee file

number: 22/420), and the principles stated in the Declaration of Helsinki were complied with.

Informed Consent: Written and verbal consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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

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Original Image

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Cardiac Calcified Amorphous Tumor Presenting with Thromboembolism in a Patient Under Apixaban Treatment

Apiksaban Tedavisi Gören Bir Hastada Thromboemboli ile Birlikte Gelen Kardiyak Kalsifiye Amorf Tümör

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Keywords: Calcified amorphous tumor, thromboembolism, apixaban
Anahtar Sözcükler: Kalsifiye amorf tümör, tromboembolism, apiksaban

A 75-year-old male patient had his first acute ischemic stroke attack two years ago. After the Holter monitoring, the patient was diagnosed with paroxysmal atrial fibrillation. Simultaneously, transthoracic echocardiographic examination (TTE) was performed, which provided mitral annular calcification without any thrombus or tumor formation within the intra-cardiac cavity. Vitamin K antagonist and warfarin were offered; however, the patient refused to take them. Therefore, he was prescribed a new oral anticoagulant, i.e., apixaban at 5 mg twice a day. The patient was admitted to our neurology department due to the second ischemic stroke attack one week ago. Contrast computed tomography angiography showed non-significant atherosclerotic plaques in the right and left carotid arteries. Therefore, the patient was consulted by our department to exclude any sources of cardioembolism. TTE showed a hyper-echogenic mass located on the posterolateral mitral valve (Figure 1A). The 3D transesophageal echocardiography examination showed a hyper-echogenic mass with a diameter of 11x15 mm that was located on the left-ventricular side of the mitral valve (Figure 1B and 1C). Cardiac magnetic resonance imaging was performed to aid the diagnosis. It revealed a mass that was compatible with a cardiac calcified amorphous tumor (CAT) (Figure 1D). The patient underwent cardiac valve surgery, including tumor resection due to thromboembolism (Figure 1E and 1F). Pathological examination confirmed the diagnosis of cardiac CAT.

CAT is an extremely rare non-neoplastic cardiac tumor, which is pathologically characterized by calcification and amorphous fibrinous material (1). CAT is usually asymptomatic, and it is incidentally detected with cardiac imaging (2). However, as in our case, CAT should be considered in the differential diagnosis of patients who present with acute ischemic stroke due to thromboembolism. Additionally, our case demonstrates that when this tumor is present, apixaban treatment may be ineffective for preventing thromboembolism in such patients.

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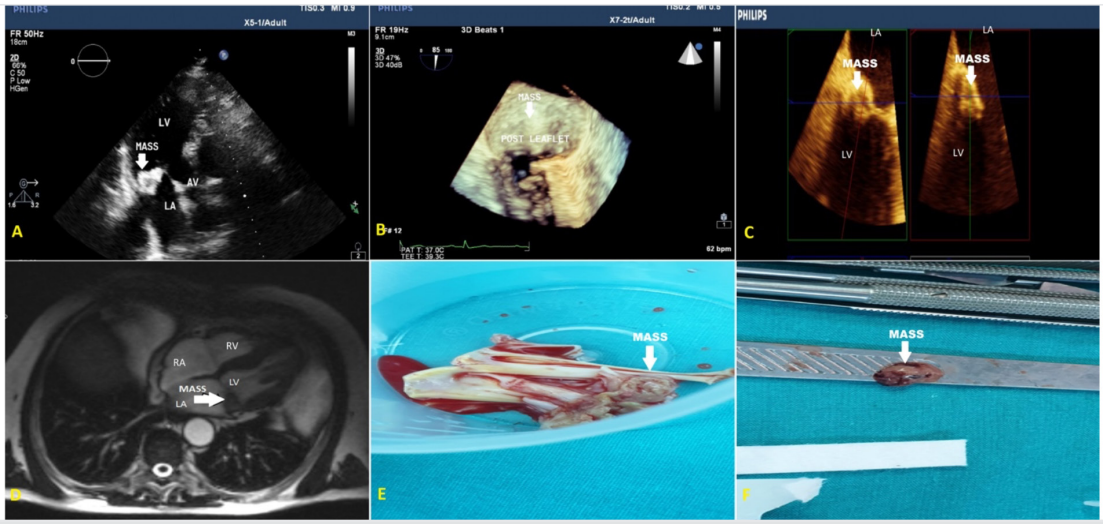

Figure 1. A-) Transthoracic echocardiography showing a hyperechogenic mass on the left ventricle side of the mitral valve, B and C-) 3-D Transosefageal echocardiography showing a hyperechogenic mass located on the posterolateral leaflet of the mitral valve, D-) Cardiac magnetic resonance imaging showing a mass which was compatible with calcified amorphous tumor, E-F) Pathological specimens showing a cardiac calcified amorphous tumor

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Case Report

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Multifocal, Non-Human Papillomavirus Inflammatory Papillary Hyperplasia: A Rare Case Report

Multifokal, HPV Olmayan Enflamatuvar Papiller Hiperplazi: Nadir Bir Olgu Sunumu

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ABSTRACT

Oral papillary lesions include a variety of reactive, developmental, and neoplastic conditions. Inflammatory papillary lesions almost involve the hard palate and are usually associated with the use of ill-fitting dentures and poor oral hygiene. Contrarily, perioral involvement of papillomatosis can also be found in neoplastic or syndromic conditions. This case report aimed to present a 44-year-old male patient with rarely encountered multifocal non-human papillomavirus (HPV) inflammatory papillary hyperplasia and evaluate the differential diagnosis that represents similar clinical and histopathological conditions. Multifocal papillary lesions on the lips, tongue, alveolar crest, and oral mucosa were surgically removed via scalpel and laser application. The histopathologic examination confirmed the diagnosis of non-HPV inflammatory papillary hyperplasia. Complete recovery was achieved and the patient was rehabilitated with a new removable prosthesis. Surgical removal of the papillary lesions seems to be a reliable treatment option. In addition to HPV-induced lesions and poor oral hygiene, other etiologic factors should be eliminated with clinicopathologic consultation and genetic investigations.

Keywords: Inflammatory papillary hyperplasia, human papillomavirus, multifocal, surgical removal, laser, the non-denture wearer

ÖZ

Oral papiller lezyonlar çeşitli reaktif, gelişimsel ve neoplastik durumlardan oluşur. Enflamatuvar papiller lezyonlar neredeyse tamamen sert damağı tutar ve genellikle uygun olmayan protezlerin kullanımı ve kötü ağız hijyeni ile ilişkilidir. Diğer tarafta, papillomatozun perioral tutulumu neoplastik veya sendromik durumlarda da bulunabilir. Olgu raporunun amacı, nadiren karşılaşılan multifokal non-human papillomavirüs (HPV) enflamatuvar papiller hiperplazili 44 yaşında bir hasta hastayı sunmak ve benzer klinik ve histopatolojik durumları temsil eden farklı tanıları değerlendirmektir. Ağız mukozası, dudak, dil ve alveol kretlerde tespit edilen multifokal papiller lezyonlar cerrahi olarak bistüri ve lazer uygulaması ile çıkarıldı. Histopatolojik inceleme HPV olmayan enflamatuvar papiller hiperplazi tanısını doğruladı. Tam iyileşme sağlandı ve hasta yeni bir hareketli protez ile rehabilite edildi. Papiller lezyonların cerrahi olarak çıkarılması güvenilir bir tedavi seçeneği gibi görünmektedir. HPV'ye bağlı lezyon ve kötü ağız hijyeninin yanı sıra diğer etiyolojik faktörler klinikopatolojik konsültasyon ve genetik araştırmalarla elimine edilmelidir.

Anahtar Sözcükler: Enflamatuvar papiller hiperplazi, human papilloma virüs, multifokal, cerrahi eksizyon, lazer, hareketli protez kullanımı

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Introduction

Oral papillary hyperplasia (OPH) is a benign lesion of the oral mucosa that is characterized by the presence of numerous wart-like, red nodular growths of the affected mucosa. Papillary lesions include a variety of reactive, developmental, and neoplastic conditions and are histopathologically described as papillary projections that are covered by stratified squamous epithelium with or without chronic inflammation. The clinical features of this lesion are well-established. The histologic samples of the lesion are currently believed to have a predominantly inflammatory nature, although fewer pathologists are familiar with its malignancy potential (1).

The etiopathogenesis is unclear; however, OPH is associated with the long-term use of removable dentures, poor oral hygiene, age, human papillomavirus (HPV), and systemic disorders but can also be found in patients with dentures without a history of removable prostheses (2). OPH is also associated with Candida colonization due to poor oral hygiene, but Candida is solely not a factor for the onset of symptoms. The lesion almost exclusively involves the hard palate, as well as the upper and lower lips, alveolar crest, gingiva, and tongue in rare circumstances. The lesion is generally asymptomatic (3).

This report aimed to present a case of a rarely encountered multifocal non-HPV inflammatory papillary hyperplasia and discuss other differential diagnoses, which represent similar clinical and histopathological conditions.

Case Report

A 44-year-old male patient was referred to the Department of Oral and Maxillofacial Surgery, at the faculty of dentistry, Bezmialem Vakıf University with a chief complaint of papillary lesions on the lips and tongue. The medical history of the patient revealed that wart-like lesions on the lips and hands were first diagnosed 15 years ago and were treated with cryotherapy. The patient had two heart attacks at intervals of 3 months in 2015 and underwent stent operations after the coronary angiography. The pre-prandial blood glucose level of the patient was recorded as 130 mg/dL. The patient receives metformin hydrochloride of 1,000 mg per day for diabetes mellitus treatment and acetylsalicylic acid of 100 mg per day for stent thrombosis prophylaxis.

The patient mainly complained about esthetic and function. Clinical examination revealed no history of wearing a removable prosthesis and multifocal papillary projections on the lips, tongue, and alveolar mucosa. Radiological examination revealed no bony involvement of nearby lesions. Multifocal lesions were asymptomatic. Clinical manifestations of the lesion are presented in Figure 1.

Histopathologic Examination

The biopsy specimen with the provisional diagnosis of HPV-induced OPH was obtained and sent for histopathologic examination. The microscopic features of the inflammatory papillary hyperplasia were verified. The lesion showed numerous papillary growths of the oral mucosa that were covered by parakeratotic stratified squamous epithelium. The connective tissue forms the cores of the papillary growths presented edema, vascular proliferation, and low-grade chronic inflammatory cell infiltration (Figure 2). Candida colonization was investigated using Grocott-Gomori's Methenamine Silver Staining (Figure 3), which identified no signs of Candida infection. The diagnosis of HPV-induced lesion was also eliminated by in situ hybridization (Figure 4).

The patient has undergone excisional biopsy and then, laser therapy was applied to the base of the lesion for stable and healthy mucosa for the prosthetic rehabilitation of the jaws. The hyperemic and papillary formations were resolved within a month (Figure 5). Removable prosthetic rehabilitation of the upper and lower jaw was achieved after a 2-month healing period.

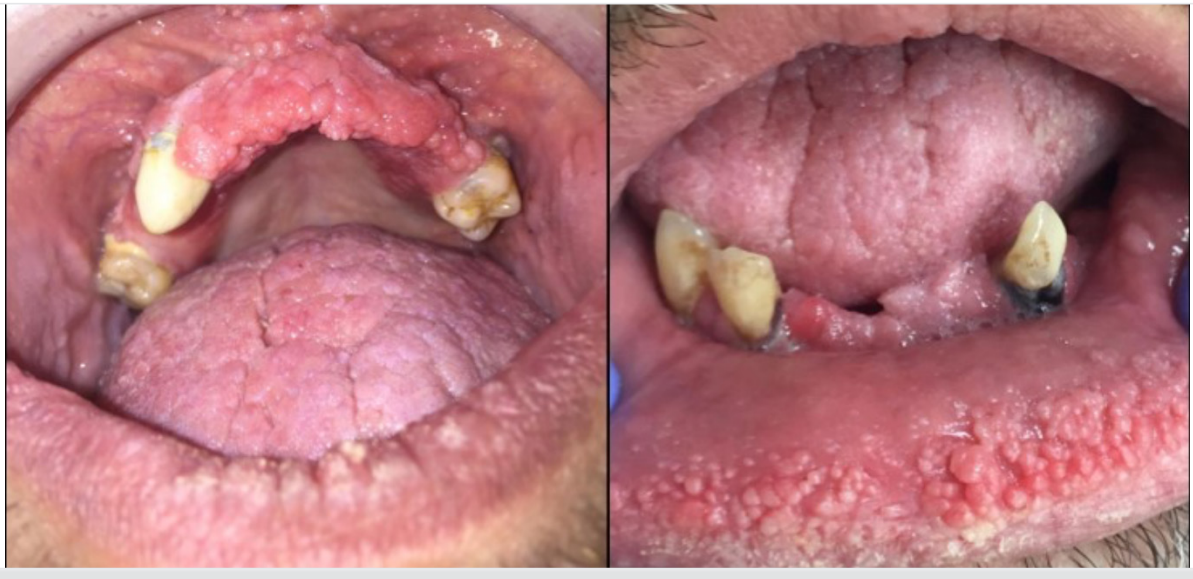

Figure 1. Clinical manifestations of the multifocal epithelial hyperplasia on the upper and lower jaws, lips, and tongue

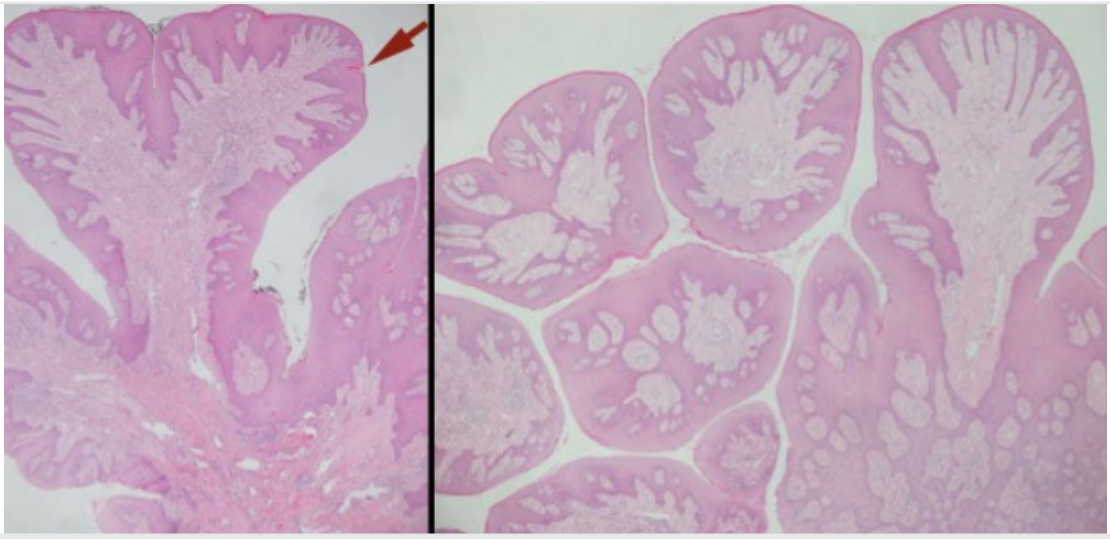

Figure 2. Numerous papillary growths (red arrow) of the oral mucosa that were covered by parakeratotic stratified squamous epithelium and edema, vascular proliferation, and low-grade chronic inflammatory cell infiltration in the connective tissue

Figure 3. Grocott-Gomori's Methenamine Silver Staining to identify Candida colonization

Discussion

The treatment type for OPH is associated with clinical manifestation and histopathological verification. A concern arises regarding the malignancy potential of OPH; however, the treatment modalities mostly include denture removal as conservative therapy, as well as electrocauterization, cryotherapy, surgical removal of the lesion, or complete excision. The denture removal can eliminate the edema and hyperemia; however, the connective tissue cannot be removed with conservative treatment (4). Non-invasive and superficial lesions can be treated with mouth rinse or denture removal. Clinicians have recommended that aggressive and extensive papillary lesions can be treated with excision, laser, electrosurgery, or cryotherapy (4,5).

The etiologic factors revealed several causes that are associated with OPH. Night-time use of ill-fitting dentures and poor oral hygiene has been reported as frequent causes, but OPH has also been found in patients with no history of wearing a removable denture (6). Some authors have reported HPV-driven infections of the oral mucosa, which represent a similar clinical appearance with OPH (7).

In addition to HPV-induced and removable denture-related lesions, oral papillary lesions also include a variety of developmental and neoplastic origins. Differential diagnoses are made with verruciform xanthoma, Costello syndrome, and paraneoplastic conditions as malignant acanthosis nigricans (8). The histological features of verruciform xanthoma are similar to OPH. A papillary proliferation of stratified squamous epithelium that is associated with hyperparakeratosis is usually encountered. The outstanding characteristic feature of these lesions includes the presence of xanthoma-like cells (foamy lipid-laden histiocytes) and the biopsy specimen shows cytoplasmic immunopositivity (CD69, CD63, and CD163) (9,10).

Hyperemic papillary growths usually begin on the palatal surface, and then extend to the entire hard palatal mucosa. However, perioral involvement of papillary lesions can be found in neoplastic or syndromic conditions. Acanthosis nigricans, which is a variety of paraneoplastic conditions associated with gastrointestinal malignancy, shows a characteristic of florid papillomatosis of the lips, labial commissures, or oral mucosa. Perioral papillomatosis was also reported in patients with Costello syndrome (8).

Multifocal inflammatory papillary hyperplasia is a rare condition and its pathogenesis remains unclear. Multifocal localization of papillary lesions in non-denture wearers can be a challenging issue

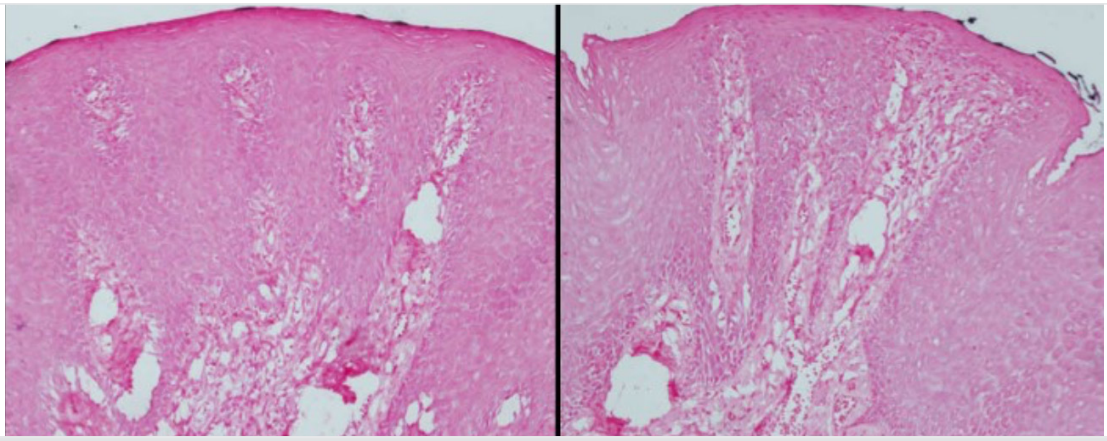

Figure 4. In situ hybridization to identify HPV

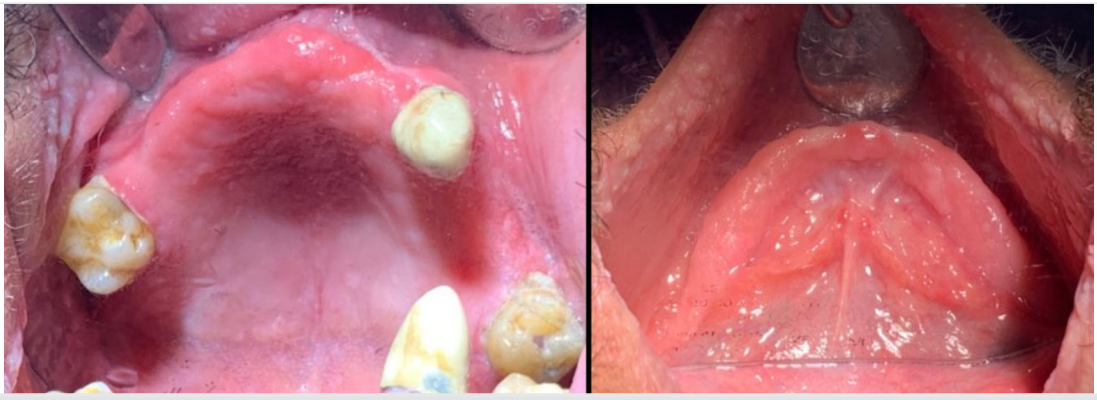

Figure 5. Clinical manifestations of a healthy oral mucosa after a 2-month healing period

in disease diagnosis and patient management. Clinicopathologic correlation and collaboration can prevent diagnostic pitfalls. Differential diagnosis should be rendered by the pathologist and clinicians based on the histopathologic and clinical presentations of the lesion. In this patient, malignant conditions and HPV-induced lesions were excluded via histopathologic and immunohistochemical analysis. The patient will undergo further genetic investigations.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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Case Report

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A Case of Gitelman Syndrome; Incidentally Diagnosed in Elderly

Tesadüfen Tanı Alan İleri Yaş Bir Gitelman Sendromu Olgusu

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ABSTRACT

Gitelman syndrome is an autosomal recessive renal tubular disease that is followed by symptoms, such as fatigue, muscle weakness, tetany, polydipsia, and nocturia. Additionally, hypokalemia, hypomagnesemia, and hypocalciuria are observed and it is usually diagnosed in adulthood but some cases are coincidentally diagnosed in the elderly. Herein, we had a 60-year-old female patient who was incidentally found to have hypokalemia and then diagnosed with Gitelman syndrome by furosemide loading test and SCL12A3 gene mutation detection.

Keywords: Bartter syndrome, Gitelman syndrome, elderly

ÖZ

Gitelman sendromu halsizlik, kas güçsüzlüğü, tetani, polidipsi ve noktüri gibi semptolarla seyredebilen otozomal resesif kalıtımlı renal tübüler bir hastalıktır. Hipokaleminin yanında hipomagnezemi ve hipokalsiüri ile seyreder ve genellikle erişkin yaşta teşhis edilir. Ancak bazı olgularda tesadüfen ileri yaşlarda da tanı alabilmektedir. Biz de tesadüfen izole hipokalemi tespit edilen sonrasında furosemid yükleme testi yapılarak ve *SCL12A3* gen mutasyonu saptanarak Gitelman sendromu tanısı konulan 60 yaşında bir kadın hastayı sunmayı amaçladık.

Anahtar Sözcükler: Bartter sendromu, Gitelman sendromu, ileri yaş

Introduction

Gitelman syndrome is an autosomal recessive inherited familial tubulopathy with hypokalemia, hypomagnesemia, and hypocalciuria that is accompanied by metabolic alkalosis (1). It occurs due to the *SCL12A3* gene mutation on the 16th chromosome encoding, the thiazide-sensitive sodium-chloride cotransporter that is expressed in the distal convoluted renal tubule (2-4). Unlike Bartter syndrome, which is a familial tubulopathy, Gitelman syndrome is mostly diagnosed in adulthood; however, some rare cases in the elderly are also observed (5,6). Herein, a 60-year-old female patient who was diagnosed with Gitelman syndrome by furosemide diuretic loading test and *SCL12A3* gene mutation detection after the incidental detection of hypokalemia in an outpatient clinic control is presented.

Case Report

A 60-year-old female patient with no past medical history and use of any drugs was admitted to our outpatient clinic with complaints of long-standing weakness, fatigue, and shortness of breath with mild to moderate exertion.

Physical examination revealed normal respiratory sounds and other system findings. No pathology was found in the posteroanterior chest radiography, electrocardiogram, transthoracic echocardiography, and renal ultrasonography. The blood biochemistry revealed a potassium level of 2.65 mmol/L, chloride of 98 mmol/L, the calcium of 9.6 mg/dL, magnesium of 1.2 mg/dL (normal range: 1.6-2.6 mg/dL), whereas sodium, blood urea nitrogen, and serum creatinine were within normal range. The arterial blood gas pH was 7.49, partial oxygen pressure was 83 mmHg, partial carbon dioxide pressure was 36 mmHg,

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bicarbonate (HCO_3) was 29 mmol/L, and oxygen saturation was 98.3. Complete urinalysis revealed specific gravity of 1.013 and pH of 7 without proteinuria or glycosuria. The 24-hour urine revealed a calcium level of 18 mg/day (normal range: 100-320 mg/day), whereas sodium, potassium, and chlorine were within the normal range. Further laboratory evaluation revealed the thyroid-stimulating hormone, free T4, and serum basal cortisol within the normal range. After an overnight supine position, plasma renin activity, and aldosterone level was found as 3.4 ng/mL/h (normal range: 0.51-2.61 ng/mL/h) and 6.04 ng/dL (normal range: 3-16 ng/dL), respectively (Table 1). The knee radiography did not reveal any abnormal findings.

According to these findings, the patient was believed to have Gitelman syndrome, thus intravenous (IV) replacement treatment started with 7.5% potassium chloride (7.5% 10 mL potassium chloride; Onfarma) and 15% magnesium sulfate (15% magnesium sulfate; Biofarma). After elevating the serum potassium value to the normal range (potassium: 4.36 mmol/L), the diuretic loading test was performed with 40 mg of IV furosemide (Furoson 40 mg/4 mL; Onfarma) due to insufficient thiazide preparation in our country after 12 h of fasting. Serum and spot urine electrolyte levels were measured before and after furosemide infusion in the patient who was closely monitored during the test (Table 2). Increased furosemide response in the urine (increased sodium, potassium, and chloride excretion) was interpreted in favor of Gitelman syndrome. The patient was followed-up in our clinic for another day after the test. Serum potassium and magnesium levels of the patient's sister were checked for family screening and were observed within the normal range. For genetic analysis, 2 mL of venous blood was taken to the EDTA tube and sent to the genetic laboratory. The diagnosis of Gitelman syndrome was confirmed by detecting homozygous mutations of the *SLC12A3* gene (c.2869A>T [p.Lys957Ter]) in the chromosomal analysis.

Table 1. Biochemical profile of the patient

	Patient ranges	Normal ranges
Serum electrolytes		
Na (mmol/L)	140	135-145
K (mmol/L)	2.65	3.5-5.5
Mg (mmol/L)	1.2	1.6-2.6
Ca (mmol/L)	9.6	8-12
Cl (mmol/L)	98	98-105
24-hour urine electrolytes		
Na(mmol/day)	210	40-220
K (mmol/day)	92	25-125
Ca (mmol/day)	18	100-320
Cl (mmol/day)	218	200-300
Blood gases		
pH	7.49	7.35-7.45
HCO3 (mmol/L)	29	22-24
PCO2 (mmHg)	83	35-45
Others		
Serum basal cortisol (µg/dL)	10.98	10-12
Plasma renin activity* (ng/mL/saat)	3.4	0.51-2.61
Serum aldosterone level* (ng/dL)	6.04	3-16

*After an overnight supine position

Upon the absence of any complaints during follow-up, the patient was discharged with the control of spironolactone (Aldactone 25 mg; Aris), magnesium citrate (Magnesium Diaspora at 610 mg Şase; Assos Pharma), and potassium citrate/potassium HCO_3 (Kalinor 8 mg; Abbot). In the outpatient follow-up, the complaints of the patient regressed and serum potassium and magnesium levels were within normal range.

Discussion

Gitelman syndrome is one of the causes of chronic and treatment-resistant hypokalemia (5) and is usually diagnosed in early adulthood with symptoms of muscle weakness, fatigue, and tetany. Normal blood pressure, hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria are prominent features (7,8). Patients with Gitelman syndrome are mostly clinically and biochemically diagnosed, and no further investigation is needed. However, Bartter syndrome should be considered in the differential diagnosis.

A 60-year-old female patient was admitted to our clinic with complaints of weakness, fatigue, and shortness of breath with mild to moderate exertion. She was normotensive with hypokalemic metabolic alkalosis along with hypomagnesemia and hypocalciuria. Chondrocalcinosis was not detected in the patient who had a slight pain in her knees while climbing the stairs. Her clinical and biochemical parameters were consistent with Gitelman syndrome, except for the patient's old age. Even though rare in the literature, some are cases of Gitelman syndrome are diagnosed in old age (6,9).

History, clinical, and biochemical parameters of the patient can be used to differentiate familial tubulopathies; however, some Bartter syndrome variants may exhibit similarities to Gitelman syndrome (5). Genetic analysis is an expensive, long time consuming, and exhausting process; however, it is the most specific method for tubulopathy differentiation (10). In our case, the diagnosis of Gitelman syndrome was confirmed by detecting homozygous mutations of the *SLC12A3* gene on the 16th chromosome [c.2869A>T (p.Lys957Ter)] in the chromosomal analysis. The serum electrolyte levels of the patient's sister were checked to demonstrate autosomal recessive inheritance but no pathology was found.

Another method for differential diagnosis is the diuretic loading test (11). However, the patient should not have an electrolyte

Table 2. Furosemide loading test results: fractionated electrolyte clearance (FEx) before/after furosemide and the number of changes (ΔFE

	Before furosemide	After furosemide	ΔFE
FENa (%)	0.24	16.44	16.2
FECl (%)	0.35	23.31	23.35
FEK (%)	10.78	61.22	50.44

imbalance and must be normotensive in this test (12). Only a furosemide diuretic loading test was performed in our case due to insufficient pure thiazide preparation in our country, wherein increased tubule response to furosemide was evaluated in favor of Gitelman syndrome.

The treatment of Gitelman syndrome recommended the patient to take a diet rich in potassium and magnesium and the patient is prescribed oral potassium and magnesium supplements. Potassium-sparing diuretics and prostaglandin analogs are also agents that can be used in the treatment (13).

The patient was discharged with oral potassium citrate/potassium HCO_3 (8 mg/day), magnesium citrate (610 mg/day), and spironolactone (25 mg/day), and in outpatient clinic control, her electrolyte levels were detected within the normal range and her complaints also declined.

In conclusion, Gitelman syndrome must be considered in elderly patients although frequently diagnosed in young/adult cases, and a furosemide loading test can be used for Gitelman syndrome diagnosis as an alternative to genetic testing because of its ease in application and is cheap and fast.

Ethics

Informed Consent:

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.V.C., Design: M.V.C., Data Collection or Processing: S.K., Analysis or Interpretation: S.K., Literature Search: M.V.C., Writing: M.V.C.

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

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Review

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The Effect of Type 2 Diabetes Mellitus on the Development of Alzheimer's Disease and Its Molecular Mechanism

Tip 2 Diabetes Mellitus'un Alzheimer Hastalığının Gelişimindeki Etkisi ve Moleküler Mekanizmaları

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ABSTRACT

Following increased epidemiological studies indicating the relationship between diabetes and Alzheimer's disease (AD), Type 2 diabetes has been reported to be a risk factor for the progress of AD pathology. Insulin resistance that develops in the brain, impairment in the insulin signal delivery system and glucose metabolism have been shown among the most likely pathophysiological causes of AD. It has been reported that the increase in AD markers such as phospho tau and Aβ in the type 2 diabetes model of rats is associated with the decrease in the insulin receptor (IR) signaling and insulin-like growth factor-1 receptors (IGF-1R) ratio. Furthermore, intracellular components such as phospho-AKT (protein kinase B) and phospho-glycogen synthase kinase-3β (GSK3β), which are members of IR pathway, have been proved to be reduced in AD. Due to the common molecular mechanisms underlying the pathological development of Type 2 Diabetes and AD, treatment protocols indicated in diabetes have been used in the treatment of AD.

Keywords: Diabetes, Alzheimer's, IR, IGF-1R, p-AKT, GSK3β, amyloid β, tau

ÖZ

Diyabet ve Alzheimer hastalığı (AH) arasındaki ilişkiyi işaret eden epidemiyolojik çalışmaların artmasının ardından, Tip 2 diyabetin AH patolojisinin oluşumunda bir risk faktörü olduğu bildirilmiştir. Beyinde gelişen insülin rezistansı, insülin sinyal iletim sisteminde ve glukoz metabolizmasında bozuklukların meydana gelmesi en olası patofizyolojik sebepler arasında gösterilmiştir. Tip 2 diyabet modeli sıçanlarda fosfo tau ve Aβ gibi AH belirteçlerinin arttığı bununla beraber insülin reseptör (IR) sinyalinin ve insülin benzeri büyüme faktörü-1 reseptörlerinin (IGF-1R) azaldığı bildirilmiştir. Ayrıca AH'de insülin reseptör yolağında yer alan fosfo-AKT (protein kinaz B) ve fosfo-glikojen sentaz kinaz-3β (GSK3β) gibi hücre içi bileşenlerinin azaldığı kanıtlanmıştır. Tip 2 diyabet ve AH'deki patolojik süreçlerin altında yatan ortak moleküler mekanizmalar nedeniyle, AH tedavisinde diyabette endike olan tedavi protokolleri kullanılmaya başlanmıştır.

Anahtar Sözcükler: Diyabet, Alzheimer, IR, IGF-1R, p-AKT, GSK3β, amiloid β, tau

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Introduction

The prolongation of life expectancy has led to an increase in the prevalence of dementia that develops with aging and the incidence of Alzheimer's disease (AD) as the predominant diagnosis. The incidence is low among individuals under the age of 70, but the risk of AD doubles in individuals over the age of 70 every 5 years (1). However, the inability to effectively treat AD constitutes one of the most important health and socioeconomic problems in the world (2).

Alzheimer's disease is a progressive, neurodegenerative CNS disease characterized by deterioration of memory and cognitive functions (3). Pathologically, senile plaques with extracellular amyloid-β (Aβ) accumulation, and neurofibrillary tangles (NFTs) formed by hyperphosphorylation of tau protein in the cell are seen. Neuroinflammation, active gliosis, synaptic disorders and neuronal loss in the brain cause significant cerebral atrophy (4).

AD is categorized in two forms as familial (inherited) and sporadic (late onset). Although there are no similarities in the etiology of familial and sporadic AD, the morphological endpoint in the brain and clinical picture occurring are the same (5). Of patients 5% have familial AD which is inherited by autosomal inheritance. Mutations in the *amyloid precursor protein* (APP) gene in the 21st chromosome, the *presenilin-1* gene in the 14th chromosome and the presenilin-2 gene in the 1st chromosome are held responsible for the development of familial AD. Sporadic AD, on the other hand, accounts for 90-95% of patients. Although the cause of the sporadic form is not known exactly, it is thought to occur as a result of interactions between environmental and genetic risk factors during the aging process (6).

Type 2 diabetes mellitus (T2DM) is the inability of body cells to fully respond to insulin, called "insulin resistance", and is a chronic metabolic disease characterized by hyperglycemia resulting from insufficient insulin secretion. Due to the decrease in the response of the cells to the hormone during insulin resistance, an increase in insulin production occurs over time. However, as a result of overworking pancreatic beta cells and the body's inability to keep up with the increasing insulin needs, insufficient amount of insulin is produced (7,8).

Patients with T2DM constitute approximately 90-95% of all diabetic patients (9). According to the information in the guide published by the International Diabetes Federation (IDF) in 2019, there were 351.7 million people with diabetes between the ages of 20-64 who were diagnosed or undiagnosed in 2019. This number is expected to increase to 417.3 million in 2030 and to 486.1 million in 2045. T2DM usually occurs after the age of 30, but it has been increasingly seen in children and young adults due to reasons such as increasing obesity, physical inactivity and not eating a healthy and balanced diet (7,8).

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Following the increasing interest in the effects of T2DM on the brain in recent years, the number of studies investigating the relationship between these two diseases has also increased (10). However, a growing body of epidemiological and molecular knowledge demonstrates the existence of common risk factors, pathophysiological mechanisms and consequent comorbidities, which significantly encompass T2DM and AD.

Neuroimaging studies have revealed differences in brain structure and function in individuals with long-standing T2DM compared to healthy individuals. It has been found that cerebral atrophy is more common in the brain, especially in areas related to cognition, in elderly individuals with insulin resistance and diabetes compared to elderly individuals without insulin resistance or diabetes (11). Increasing epidemiological studies show that patients with T2DM have a higher risk of developing AD (9,12,13). According to a cohort study with 9 years of longitudinal follow-up, diabetic patients had a 65% higher risk of developing AD than non-diabetic controls. Cognitive dysfunction is now recognized as a complication of chronic T2DM, and T2DM is seen as an important risk factor for decreased performance in various neuropsychological areas (10). Ongoing clinical and epidemiological studies show that impaired metabolic parameters such as hyperglycemia and hyperinsulinemia are associated with decreased cognitive functions and the development of late-onset AD pathology (14).

In this study, it is aimed to focus on T2DM and related mechanisms that contribute to the development of sporadic AD pathology and play an important role in the clinical course of AD.

Possible Mechanisms Associated with Alzheimer's Disease and Type 2 Diabetes Mellitus

Insulin and Insulin-Like Growth Factor 1 (IGF-1)

AD is referred to as "Type 3 diabetes" in some references due to the repeated link between insulin and the mechanisms involved in AD pathology (15). First of all, it is known that insulin, which is accepted as a hormone effective in the periphery, has strong effects on the brain as well.

In the brain, insulin receptor (IR) density is highest in the olfactory bulb, hypothalamus, hippocampus, cerebral cortex, striatum, and cerebellum. Insulin levels in the cerebrospinal fluid (CSF) are much lower than in plasma, but these levels correlate with serum insulin levels, suggesting that most of the insulin in the brain originates from circulating pancreatic insulin (16).

Insulin, a peptide secreted by pancreatic beta cells, is transported across the blood brain barrier (BBB) to the central nervous system (CNS) by receptor-mediated saturation sensitive transport. Transition from BBB can be affected by a number of factors

such as obesity, triglycerides, inflammation and hyperglycemia. Studies conducted on humans have reported that the CSF/serum ratio of insulin decreases with insulin resistance, AD, and increasing age (11,15).

The detection of insulin mRNA transcripts in certain regions of the brain, especially in the hippocampus and hypothalamus, as a result of studies conducted in human post-mortem brain tissue suggests that insulin may also be produced in certain regions of the brain (11,12). Studies on IR expression and receptor binding in humans compared patients with AD with age-matched controls and showed decreased expression of IR mRNA and protein in patients with AD. The decrease in IR binding in AD has been associated with pathological severity (11,12,17-19). However, in some studies, it has been reported that there is an unchanged level of IR protein (20,21).

Insulin activity in the brain occurs via the Phosphatidylinositol-3-kinase (PI3K)/Akt pathway and the Ras/Mitogen-Activated Protein Kinase (MAPK) pathway. In the PI3K pathway; binding of insulin to extracellular α-subunits of IR induces dimerization of β-subunits that activate intrinsic tyrosine kinases and cause receptor autophosphorylation. The tyrosine kinase activity of IR phosphorylates tyrosine residues on IR Substrate 1 (IRS1) or IR Substrate 2 (IRS2). IRS1 and IRS2 bind to the p85 regulatory subunit of the PI3K complex. It provides the expression of phosphatidylinositol 3,4,5-triphosphate (PIP3) by phosphorylation of phosphatidylinositol 4,5-diphosphate (PIP2) (11,22). PIP3 activates other enzymes in the cascade, including serine/threonine kinase Akt (protein kinase B) and protein kinase C, by stimulating the phosphorylation of phosphoinoside-dependent protein kinase 1 (PDK1) (23). AKT, which is associated with systemic glucose control, induces the translocation of Type 4 Glucose Transporter (GLUT-4) to the cell membrane, which is responsible for glucose uptake in muscle, fat and some neurons (11). GLUT-4, which moves to the cell surface, provides glucose entry into cells (24). It has been shown that this insulin signaling pathway is altered, and IRs are significantly reduced in the brain of individuals with AD (Figure 1) (25,26).

Although most of the glucose uptake in neurons occurs via GLUT-3, studies have shown that GLUT-4, which is regulated by insulin activity, is co-expressed with GLUT-3 in rodent brain regions associated with cognitive behavior. These regions include the basal forebrain, hippocampus, amygdala, and to a lesser degree the cerebral cortex and cerebellum. Insulin activation is thought to not only induce the translocation of GLUT-4 to the neuron cell membrane through an AKT-dependent mechanism, but also improve glucose flow to neurons during periods of high metabolic processes such as learning (11). However, it is known that insulin activity changes in both AD and T2DM (27).

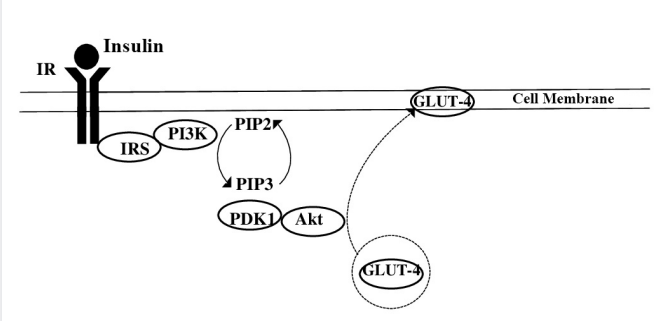

Figure 1. Insulin/PI3K/Akt pathway

Insulin binding to IRs can also initiate other intracellular signaling cascades. IR-mediated signal transduction is related to PI3K-dependent activation of protein kinase B, which triggers phosphorylation of glycogen synthase (GS) kinase 3 (GSK-3) and stimulates the enzyme GS. As detected in the studies, the disorder in the phosphorylation of GSK-3 is associated with a number of neurological disorders, including AD. Studies show that the reduction of phosphorylated GSK-3β facilitates the formation of NFT, as it may cause hyperphosphorylation of tau (10,26).

Insulin-like growth factor (IGF-1) has a critical importance for cell proliferation, coping with stress and survival in many cell types in the body. In the CNS, there is expression of IGF-1 receptor (IGF-1R) in neurons, glia cells and brain vessels, which indicates that they are critical effectors for IGF-1 signaling (28). Like insulin, IGF-1 is responsible for transmitting signals necessary for cellular survival and growth through IRS molecules. Decreased IRS expression levels are associated with resistance to GF in the CNS. Decreased IGF-1, IGF-1R and IRS gene expressions cause downregulation of the IRS-associated PI3 signaling pathway (with decreased levels of IRS-1 associated with p85), decreased levels of phospho-Akt (decreased Akt activity), and reduced levels of phospho-GSK3β (increased GSK-3β activity) (29). Results of a study on postmortem AD brains show that impaired IGF-1 mechanism leads to abnormalities in AD (17).

Various studies conducted to date have emphasized that insulin and IGF resistance in the brain cause inhibition of signaling pathways necessary for cell growth and survival mechanisms. Previous studies have shown that insulin improves neuronal survival by inhibiting apoptotic processes. This hormone may exert a neuroprotective effect by interfering with toxins and stress-mediated apoptosis, and possibly via the PI3K/Akt pathway or the mTOR-p70S6K pathway (10).

Soluble Aβ peptide oligomers are known to act synaptotoxicly. Since Aβ and insulin are both amyloidogenic peptides that share a common sequence recognition motif, it is possible that both molecules can bind to IR. It is known that Aβ binds to IRs in the hippocampus, inhibits the receptors, increases the neurodegenerative process in the region and causes significant cognitive losses. Given this assumption, Aβ can increase insulin resistance through its antagonistic effect, block the IR downstream pathway, and facilitate the phosphorylation of GSK3, a tau-related molecule. Therefore, the aging process associated with insulin resistance, Aβ production and tau hyperphosphorylation may lead to neuronal dysfunction (14). Despite all these findings, in a study on the relationship between T2DM and AD, amyloid accumulation was examined on 28 human brain samples with

T2DM and 19 without T2DM, and it was reported that T2DM did not increase the frequency of amyloid formed in the brain. However, in the same study, it was stated that the amyloid size formed in patients with T2DM increased with the progression of the diabetes process (30).

While IR and IGF-1R are abundant in healthy human brains, it has been shown that both IRs and IGF-1Rs are significantly reduced in the brains of patients with AD. In individuals with AD, there is a decrease in insulin and IGF-1 levels in their brains and the cellular sensitivity of the brain to these factors due to impaired transport throughout the BBB. The obtained data highlight a gradual decrease in hypothalamic IR sensitivity, downstream signaling molecules such as (IRS-1), insulin and IGF receptor expression in patients with AD. Neuropathological findings suggest that brain insulin resistance and decreased IR function may be associated with memory problems. Additionally, studies have linked decreased gene expressions and protein levels of IGF-1R and other downstream signaling molecules with impaired acetylcholine production and impaired cognitive performance. Desensitation of neuronal IRs and low insulin concentrations in the CNS lead to a decrease in acetylcholine secretion and a consequent decrease in cerebral blood flow. These events cause chronic abnormalities in oxidative brain metabolism (10,14,26,31).

In vitro experiments have shown that phosphorylation of tau, a marker of AD, is normally regulated by insulin and IGF-1. In a study, it was shown that serum IGF-1 levels in STZ-induced diabetes model rats were decreased compared to the control group. Impaired insulin signaling can result in tau hyperphosphorylation. Likewise, there are studies showing that impaired IGF-1 signal may be responsible for this effect. These degradation processes can also cause cell death mediated by apoptosis, mitochondrial dysfunction or necrosis. These disruptions may also promote oxidative stress, which contributes to the neurodegeneration cascade and leads to behavioral and cognitive deficits associated with dementia (10,27).

Impaired insulin function and IGF-1 signaling have been implicated as pathogenetic factors contributing to the onset of AD. When all these data are taken together, it is thought that there may be common causes and mechanical connections in the underlying mechanisms of T2DM and AD (31).

Insulin Degrading Enzyme (IDE)

Although insulin is known to be a neurotrophic factor at moderate concentrations, its increased presence in the brain suggests that it may be associated with decreased Aβ degradation. This effect may be related to their competition for binding to insulin degrading enzyme (IDE), which is the common excretion mechanism of Aβ and insulin.

The IDE is a Zn^{+2} metalloprotease that catabolizes both insulin and Aβ and can critically interfere with Aβ degradation.

When the insulin-PI3K-Akt signaling pathway is activated, besides promoting the brain's glucose uptake, this signaling pathway activation stimulates the production of IDE to lower the insulin level. If this mechanism is disrupted, IDE is downregulated.

Since insulin controls IDE expression and intracellular Aβformation, decreased insulin amount in the brain may increase intraneuronal Aβ accumulation. Aβ can compete directly with insulin for binding to IDE. Therefore, in the case of hyperinsulinemia, Aβ cannot be eliminated by IDE due to competitive binding of insulin and Aβ to IDE, and then Aβaccumulates. A study has shown that immunomodulatory agents (IL-6, C-reactive protein, tumor necrosis factor-α (TNF-α)) involved in inflammatory states are associated with decreased IDE levels. In conclusion, studies emphasize that there may be abnormal Aβ accumulation in diabetes due to impaired insulin signaling, which causes decreased IDE levels (9,10,32).

Despite all these data, the evidence for the relationship between T2DM and molecular or pathologically defined neurodegenerative diseases in humans is mostly negative. Only one study in the literature found that systemic insulin resistance was associated with Aβ positivity in the brain on PET imaging (33). However, other studies showed increased total tau and phospho-tau levels in patients with T2DM, but did not find a relationship between T2DM and Aβ PET findings or CSF Aβ levels (34).

Hyperglycemia, Inflammatory Response and Aβ

According to a 6-year cohort study, high blood glucose levels increase the risk of developing dementia in both people with and without diabetes (35). Constantly high blood glucose in diabetes causes an imbalance in the formation and destruction of reactive oxygen species (ROS), accumulation of excessive advanced glycation end products (AGEs), and disruption of intracellular messenger pathway signals (10).

The AGEs are formed from glucose by irreversible and non-enzymatic reactions. Production of AGEs is accelerated due to the increased formation of reactive oxygen species in diabetic patients (32). In an immunohistochemical postmortem study on brain samples from patients with diabetes, AD and both, it was reported that patients with AD with T2DM had higher levels of AGEs and microglial activation in the CNS compared to patients with AD without T2DM (36).

In addition, increased AGE formation causes excessive ROS formation. In vitro findings show that ROS production caused by AGEs stimulates APP-related signaling pathways, leading to Aβ formation and accumulation (10,37). In AD, AGE immunoreactivity is increased especially in Aβ plaques and hippocampal neurons. Therefore, it is thought that oxidative damage may have an early effect in the development of AD (32). The high level of AGE immunoreactivity found in senile plaques and NFTs confirms that AGEs cause amyloidosis (Aβ deposition) and NFT formation. Accumulated AGEs bind to their receptors (RAGE). RAGEs belong to the immunoglobulin superfamily, which can be located in various cell domains, and they can recognize and bind to various ligands. RAGEs found in brain

endothelium, microglia, and neurons may also act as receptors for Aβ and mediate Aβ-related microglia activation, resulting in the inflammatory response in AD. Furthermore, excessive RAGE expression in microglia was found to increase the production of interleukin-6 (IL-6) and TNF-α and accumulation of Aβ in AD-associated brain regions in mutant APP/RAGE rodents (Figure 2). AGEs binding to RAGEs induce sustained upregulation of the NFκB transcription factor. As a result, NFκB signal triggers the accumulation of Aβ in the brain in AD (9,10). In a study conducted on 92 brain samples, it was observed that dementia was associated with more Aβ accumulation and free radical damage in nondiabetic patients with dementia, while dementia in diabetic patients was reported to occur mostly with activation of neuroinflammation and microvascular infarcts (38). In conclusion, in the light of the above-mentioned data, it can be concluded that the persistently high blood glucose levels and inflammation in the diabetes process affect AD-related pathologies through various mechanisms.Amyloid Precursor Protein (APP) and Beta Secretase 1 Enzyme (BACE-1)

The Aβ peptide load and cerebral plaques in the neocortical terminal areas of the brain are important pathological features of AD (4). The Aβ peptide contains 36-43 amino acids and is formed as a result of sequential proteolysis of APP under normal physiological conditions (39).

The APP is an integral membrane glycoprotein of which physiological role has not been fully elucidated. However, APP is known to affect neurite outgrowth and synaptic plasticity.

The APP is degraded by the enzymes α-secretase, β-secretase (BACE-1) and γ-secretase, and a protein complex that includes presenilin 1 (PS1). While cleavage of APP by α secretase results in soluble peptides; its cleavage by β and γ secretases in neuropathological conditions leads to amyloidogenic metabolism and accumulation of Aβ. While Aβ degradation enzyme 1 (β-secretase) (BACE-1) cuts APP at its N-terminal end, γ-secretases cut it at its C-terminal end and fragments of 40 and 42 amino acids Aβ40 and Aβ42 are formed extracellularly (Figure 3).

BACE-1 is also known as the rate-limiting enzyme in the production of Aβ through degradation of APP in AD. Animal studies indicate that insulin deficiency can alter APP-related processes to promote β-amyloidogenesis via BACE-1 translational upregulation. Recent data from animal studies have demonstrated that neuronal expression of human BACE-1 induces systemic diabetes complications through stimulation of hypothalamic dysfunction, insulin resistance, and glucose changes. In an experiment using PLB4 mice, it was shown that the risk of diabetes increased when BACE-1 was overexpressed in neurons, and that there was a complex mechanical interaction between T2DM and AD (10,14).

Glycogen Synthase Kinase-3 (GSK-3) and Tau Hyperphosphorylation

The GSK-3β is a protein kinase that is phosphorylating GS and is inactivated by phosphorylation. Although its specific and precise mechanism is still unclear, recent studies suggest that the insulin signaling pathway-related GSK-3β may be a potential link between AD and T2DM (22).

The insulin-activated PI3K/Akt signaling pathway also plays a role in the physiological function of the hippocampus, which is severely affected in AD, apart from the direct modulation of glucose uptake (10). Studies have shown that insulin increases cell survival by stimulating cell proliferation and inhibiting the apoptosis process through the PI3K/Akt/GSK-3β signaling pathway. Studies show that dysfunction of the PI3K/Akt/GSK-3β signaling pathway leads to excessive phosphorylation of tau by increasing GSK-3β activity. High expression of GSK-3β has been associated with decreased insulin sensitivity, decreased blood sugar regulation and insulin deficiency.

The islet β-cells are endocrine cells in the body that secrete insulin and lower blood sugar levels. GSK-3β is also one of the key factors mediating β islet cell apoptosis. In diabetic mice, overactivation of GSK-3β has been shown to result in decreased β islet cell proliferation, and studies have closely linked GSK-3β with insulin deficiency. When there are insulin deficiency and IGF-1 signal dysfunction, GSK-3β inhibition is prevented by inhibition of PI3K/Akt activity, and therefore the regulation of blood sugar is impaired. Under diabetic conditions, the increase in oxidative stress leads to activation of the C-Jun-N terminal kinase (JNK) pathway, resulting in increased phosphorylation of GSK-3β. GSK-3β hyperactivity also has anti-proliferative and pro-apoptotic effects on the body. Studies have shown

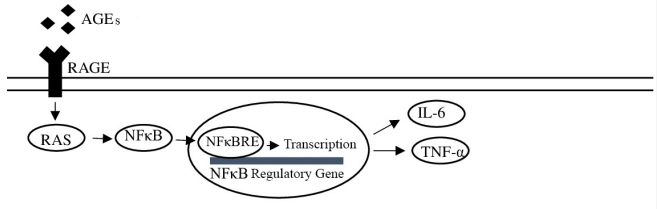

Figure 2. Schematic representation of the inflammatory response
AGE: Advanced glycation end products, RAGE: AGE receptors, NFκB : Nuclear Factor kappa B, NFκBRE: Nuclear Factor kappa B response element, IL-6: interleukin-6, TNF-α: tumor necrosis factor-α

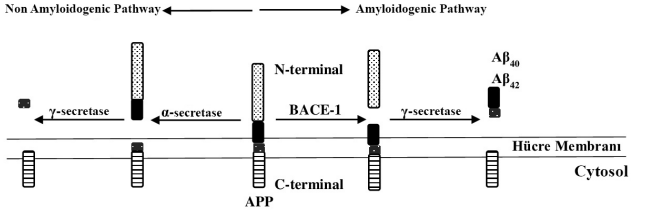

Figure 3. Schematic representation of metabolic pathways of amyloid precursor protein

that PI3K/Akt/GSK-3β pathway disorders result in tau hyperphosphorylation (9,22).

Again in diabetic animal models, AD-like pathoanatomical features such as decreased learning ability have been observed in animals as a result of down-regulation of Akt and GSK-3β phosphorylation. In addition, in vitro experiments have shown that activated GSK-3α in neurons triggers APP-related γ-secretase activity and thus increases Aβ production (10).

Apolipoprotein E (APOE)

It is known that the Apolipoprotein E (APOE) genotype affects peripheral glucose and insulin metabolism. The ε4 allele of the APOE gene has been associated as a risk factor for AD. Diabetic patients carrying the ε4 allele of the APOE gene have a higher risk of developing AD than non-diabetic volunteers who also carry the ε4 allele. This information is understood as a result of the understanding that patients with AD who do not carry the apolipoprotein ε4 alleles have a better response to intranasal insulin than those who do.

In addition, as in other diseases, gender has an effect on the tendency and incidence of pathology. APOE-positive carrier women are at higher risk than men in terms of developing sporadic AD and giving less favorable response to insulin-related treatments (14,25,40). However, studies paying attention to the APOE genotype in patients with T2DM have also reported that the extent of AD pathology is higher in patients with T2DM who carry the ε4 allele of the APOE gene compared to those who do not (41,42). Moreover, recent findings have reported that APOE4 causes worsening of impaired insulin signaling by interacting with IR and disrupting the exchange mechanisms between endosomes and plasma membranes (14).

Along with all these studies, Starks et al. (43) stated that they found a positive relationship with tau measurements in apolipoprotein E (APOE) ε4 positive individuals, but that they also did not find a direct relationship between systemic insulin resistance and CSF Aβ, total tau or phospho-tau levels (19).

Investigation of the Effects of Drugs Used in the Treatment of Diabetes on Alzheimer's Disease

Studies on intranasal insulin administration have reported that it has significant effects on cognition and neurophysiology (11).

Data from previous preclinical studies suggest that intranasal administration of insulin or insulin analogs provides some degree of improvement in memory or protection against cognitive impairment in AD mouse models. In a recent study, it was reported that intranasal insulin administration improved memory at a certain level in patients with mild cognitive impairment or AD (14,37).

Studies have shown that acute and chronic intranasal insulin administrations improve memory and other cognitive functions in adults with T2DM. Improvement in memory functions was observed with intranasal insulin administration in patients with AD, but this improvement was reported only for patients without APOE ε4 allele (11,40).

In addition to treatment with insulin, drugs that are commonly used in T2DM, acting by increasing insulin sensitivity, have recently attracted attention as potential treatments for brain insulin resistance in AD-like dementias. The use of GLP-1 agonists in AD mouse models reduced the levels of pathological markers of AD, including oligomeric Aβ and Aβ plaque burden, and the amount of microglial activation, and improved memory-related behaviors. The GLP-1 analogs can reverse tau hyperphosphorylation induced by AGEs, and the main mechanism here is thought to be downregulation of GSK-3β (32,37). Many *in vivo* and *in vitro* studies have reported that GLP-1 receptor agonists are neuroprotective in experimental models of AD (44). In an animal study, GLP-1 was shown to protect neurons from oxidative stress, reduce apoptosis, inflammatory response and plaque formation, and maintain synaptic plasticity in the brain. Sitagliptin (DPP4 inh) treatment in a mouse model of AD increased brain GLP-1 levels, reduced brain nitrosative stress and inflammation, and prevented memory impairment associated with Aβ accumulation (25).

The DPP-4 inhibitors have been shown to reduce GSK-3β activity by increasing GSK-3β Ser9 phosphorylation. In this way, it is possible to inhibit Aβ-induced neuronal cell apoptosis and subsequently the impairment in insulin signaling induced by Aβ ameliorates and tau hyperphosphorylation decreases. Researchers have shown that the use of Metformin, the most commonly prescribed drug for T2DM, in patients with mild cognitive impairment (MCI) or early dementia due to AD produces some signs of benefit. In addition, thiazolidinedione-based nuclear peroxisome proliferator activated receptor-γ (PPARγ) agonists, originally developed to increase insulin sensitivity in T2DM, have demonstrated numerous beneficial neuronal effects in animal models of neurodegenerative diseases. Drugs targeting glucagon-like peptide-1 (GLP 1) have shown promising results in AD in preclinical and early clinical studies (11,37). Impairment in spatial learning, tau hyperphosphorylation, and neuroinflammation were improved in 3xTg-AD mice treated with Pioglitazone for 4 months (14).

Systemic administration of Liraglutide for 8 weeks in AD transgenic mice was shown to prevent memory impairment, neuronal loss, and impaired synaptic plasticity in the hippocampus. The GLP-1 receptor agonists, Liraglutide and Exenatide, were found to antagonize processes associated with neurodegeneration and AD's progression, even in mouse models without diabetes. It was shown that litaglutide could reduce amyloid plaque accumulation by 40-50% and reduce the active microglial cell inflammatory response. Exenatide, another GLP-1 analogue, was also shown promising results in use for neurodegenerative diseases in preclinical studies (32).

In Table 1, clinical studies on the effects of some drugs used in diabetes on AD or mild cognitive disorders are summarized (45).

Table 1. Phase studies investigating the effects of drugs used in the treatment of diabetes on Alzheimer's disease.

Drug	Phase	CT number	Title of the study	Disease
Insulin detemir	Phase 2	NCT01547169	Study of Nasal Insulin to Fight Forgetfulness - Long-acting Insulin Detemir - 21 Days	Alzheimer's disease, mild cognitive impairment
Insulin glulisine	Phase 2	NCT02503501	Intranasal Glulisine in Amnestic Mild Cognitive Impairment and Probable Mild Alzheimer's Disease	Alzheimer's disease, mild cognitive impairment
Insulin glulisine	Phase 2	NCT01436045	Safety and Effectiveness Study of Intranasal Insulin Glulisine on Cognitive and Memory in Mild-Mod AD Patients	Alzheimer's disease
Insulin (Humulin® R U-100)	Phase 3	NCT01767909	The Study of Nasal Insulin in the Fight Against Forgetfulness (SNIFF)	Alzheimer's disease, amnestic mild cognitive impairment
Metformin	Phase 3	NCT04098666	Metformin in Alzheimer's Dementia Prevention (MAP)	Mild cognitive impairment
Metformin	Phase 2	NCT00620191	Metformin in Amnestic Mild Cognitive Impairment (MCI)	Amnestic mild cognitive impairment
Rosiglitazone	Phase 3	NCT00428090	Rosiglitazone (Extended Release Tablets) As Monotherapy In Subjects With Mild To Moderate Alzheimer's Disease	Alzheimer's disease
Rosiglitazone	Phase 3	NCT00348140	Rosiglitazone (Extended Release Tablets) As Adjunctive Therapy In Subjects With Mild To Moderate Alzheimer's Disease (REFLECT-3)	Alzheimer's disease
Rosiglitazone	Phase 2	NCT00334568	Effects Of Rosiglitazone (Extended Release Tablets) On Cerebral Glucose Utilisation And Cognition Alzheimers Disease	Alzheimer's disease
Rosiglitazone	Phase 3	NCT00550420	Study Of Rosiglitazone XR In Subjects With Mild-to-Moderate Alzheimers	Alzheimer's disease
Rosiglitazone	Phase 3	NCT00490568	Open-Label Extension Study Of Rosiglitazone XR As Adjunctive Therapy In Subjects With Mild-to-Moderate Alzheimers	Alzheimer's disease
Pioglitazone	Phase 3	NCT02284906	AD-4833/TOMM40_303 Extension Study of the Safety and Efficacy of Pioglitazone to Slow Cognitive Decline in Participants With Mild Cognitive Impairment Due to Alzheimer Disease	Mild Cognitive impairment due to alzheimer's disease
Pioglitazone	Phase 2	NCT00982202	Pioglitazone in Alzheimer Disease	Alzheimer's disease
Liraglutide	Phase 2	NCT01843075	Evaluating Liraglutide in Alzheimer's Disease (ELAD)	Alzheimer's disease
Liraglutide	Not applicable	NCT01469351	Identifying Potential Effects of Liraglutide on Degenerative Changes	Alzheimer's disease
Exendin-4	Phase 2	NCT01255163	A Pilot Clinical Trial of Exendin-4 in Alzheimer's Disease	Alzheimer's disease, amnestic mild cognitive impairment

Discussion

There appear to be studies highlighting convincing evidence that patients with diabetes have an increased risk of developing AD. However, it can be said that there are few detailed epidemiological data for risk factors. In addition, understanding which of the possible mechanisms are clinically significant with studies explaining the pathophysiological features of these two diseases will provide a better understanding of the relationship between these two diseases.

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Review

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The Place and Importance of Propolis in Cancer Immunotherapy

Propolisin Kanser İmmünoterapisindeki Yeri ve Önemi

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ABSTRACT

Nowadays, the increasing number of cancer patients is a major concern all over the world. Therefore, finding safe and effective treatments has become one of the main goals of researchers. Immunotherapy is a form of treatment that allows the individual to fight against many diseases including cancer by using the immune system. The aim is to enable cells of the immune system to target and destroy cancer cells. Immunotherapeutic strategies in cancer are spread to a wide range of research areas including monoclonal antibodies, cancer vaccines, adoptive immunotherapy, cytokines, and immune system enhancing drugs. Due to the specificity of the immune response in new treatment methods, it is aimed that the immunity against the tumor is to destroy the tumor selectively without harming the patient. In recent scientific studies, it has been revealed that propolis is one of the most promising immunomodulating agents. Propolis is a natural medicine that widely used since ancient times and contains several bioactive compounds. More than 300 components of propolis have been identified to date and *in vitro*, *in vivo* and clinical studies of these components are ongoing. The major anticancer components in propolis are Convective available potential energy, chrysin, nemorosone, artepilin C, galangin and cardanol. The in vitro, in vivo and human clinical researches report that the propolis shows positive effect against the several different cancer types. Propolis as a natural food with these properties may support the immune system and body function of cancer patients.

Keywords: Cancer, ımmunotherapy, cancer immunotherapy, propolis

ÖZ

Günümüzde gittikçe artan kanser olguları, tüm dünyada büyük bir endişe kaynağı olmaktadır. Bu nedenle; güvenli ve etkili tedaviler bulmak araştırmacıların ana hedeflerinden biri haline gelmiştir. İmmünoterapi; bireyin bağışıklık sistemini kullanarak kanser dahil çok sayıda hastalıkla mücadele etmesini sağlayan bir tedavi biçimidir. Amaç, immün sisteme ait hücrelerin kanser hücrelerini hedef almalarını ve yok etmelerini sağlamaktır. Kanserde immünoterapötik stratejiler; monoklonal antikorlar, kanser aşıları, adoptif immünoterapi, sitokinler, immün sistemi destekleyici ilaçlar da dahil olmak üzere geniş bir araştırma alanına yayılmaktadır. Yeni tedavi yöntemlerinde immün yanıtın özgül olması nedeniyle tümöre karşı bağışıklığın, hastaya zarar vermeden seçici olarak tümörü yok etmesi amaçlanmaktadır. Son yapılan bilimsel araştırmalarda propolisin güçlü bir şekilde en umut verici immünomodülasyon ajanlarından biri olduğu ortaya konmuştur. Propolis, antik çağlardan beri yaygın olarak kullanılan ve bünyesinde birçok biyoaktif bileşen barındıran doğal bir ilaçtır. Propolisin 300'den fazla bileşeni bugüne kadar tespit edilmiş olup bu bileşenlerle ilgili *in vitro*, *in vivo* ve klinik çalışmalar devam etmektedir. Propolisin içindeki başlıca antikanser bileşenler; Convective available potential energy, chrysin, nemoroson, artepilin C, galangin ve kardanoldür. Propolisin birçok farklı kanser türüne karşı olumlu etki gösterdiği *in vitro* ve *in vivo* olarak ve insan klinik çalışmalarıyla bildirilmiştir. Doğal bir besin olan propolisin tüm bu özellikleri ile kanser hastalarının vücut fonksiyonlarını ve hastaların vücut direncini destekleyebileceği düşünülmektedir.

Anahtar Sözcükler: Kanser, immünoterapi, kanser immünoterapisi, propolis

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Introduction

Millions of people are diagnosed as having cancer every year in the world and more than half of these patients die due to cancer. Despite all scientific advances, cancer is a process in which there are many difficulties for patients throughout the treatment that develops from its diagnosis (1). On the other hand; this situation causes great concern in societies. For all these reasons, safe and effective anticancer treatment researches are still continuing today. As a result of these researches; a method called immunotherapy, which aims to use the power of the body's own immune system against cancer, has also been introduced (2). In the last decade, the successful clinical use of immunotherapeutic agents in cancer treatment has increased the interest in tumor immunology and in the use of immunotherapy with high response rates in tumors including solid tumors. Cancer immunotherapy includes the processes of using and/or activating components of the immune system such as antibodies, dendritic cells and T-lymphocytes to treat cancer (3). Target in cancer treatment is the complete elimination of the disease or the prolongation of life expectancy (1). Immunotherapy is thought to be a more effective and durable form of treatment than conventional treatments for cancer by using the body's own immune system (4). Today, studies on the contribution of naturally occurring plant and/or animal origin products and foods to the treatment process of cancer are important (5). For example, it has been reported in studies that bee products may have the potential to be used in cancer immunotherapy thanks to their immunomodulatory effects, as well as their antiinvasive and antitumor effects. Propolis, which is an important bee product, contains important phenolic compounds such as gallic acid, catechin, caffeic acid, quercetin, cinnamic acid, naringenin, apigenin, galangin and caffeic acid phenyl ester (CAPE). Studies have proven the anticancer, antiproliferative and anti-inflammatory effects of propolis and new studies are continuing. In this review, the state of the immune system in cancer patients, the ways and mechanisms of cancer in suppressing the immune system, the effects and side effects of immunotherapeutic methods that are frequently used in cancer treatment, and the anticancer effects of propolis with immunotherapeutic mechanisms were presented with scientific data. In this context, *in vitro, in vivo* and clinical human studies were also considered.

Cancer

What is Cancer?

Cancer is the clonal spread of cells with impaired growth characteristics, which is known as the most common and the most complicated somatic genetic disease (6). All cancers, as a result of successive mutations in the DNA sequence, can cause the cell to grow and the formation of a cancer clone derived from this cell (7).

Cancer and the Genome

With exposure to mutagens and carcinogens, fractures occur in the genetic material of the cell (7). The genotoxic effect of mutagenic and carcinogenic compounds can be determined by detecting DNA breaks (damage). This genotoxic effect, which is also defined as DNA damage, is accepted as a cancer-initiating mechanism. Cancer differs depending on the cell of origin and the spectrum that promotes genomic changes, which also affect the therapeutic response (8). However, it is a known fact that all cancer types are basically a genomic disease (9).

Cancer Treatments and Ways of Prevention

At the end of the 20th century, animal cancer models were used to develop drugs necessary for the treatment of cancers (9). These studies have led to the development of adjuvant chemotherapy studies and the creation of cancer guidelines. It is known that environmental factors and positive dietary habits are also very important in the prevention of cancers (10).

Immune System

The immune system is a collection of organs, special cells and substances that protect the individual from infections and other diseases. It also helps to protect the person from cancer (11). The immune system, which consists of lymph vessels, lymph nodes, bone marrow, thymus, spleen, tonsils, organs, tissues and white blood cells of the lymph system, detects a large number of threats and prevents these threats from distrupting homeostasis (12). Immune system cells and the substances they produce show their effects by circulating the body. The immune system monitors all substances in the body. When it encounters any foreign substance, it receives an alarm that causes it to attack and responds to protect and defend the body (11,13). This foreign substance can be an infectious agent or a tumor cell.

The Immune System in Cancer

The detection and destruction of tumor cells formed in the body by the immune system is called immune surveillance. The existence of immune surveillance has been known since the early 1900's (13). However, despite the presence of immune surveillance, the ability of the immune system to fight cancer on its own is limited, and therefore cancer develops despite all mechanisms. The immune system does not always recognize cancer cells as foreign. The reason for this is that cancer cells undergo changes, are not sufficiently different from normal cells, and go out of control (11). Sometimes the immune system can recognize cancer cells, but immune responses often fail to prevent tumor growth (11,13). Cancer cells can also produce some substances that keep the immune system under control (11).

Immune Surveillance of Cancer

The functions of the immune system to prevent the growth of transformed cells or to destroy them before they become harmful are called "cancer immunosurveillance" (14). Immune surveillance is possible only when the tumor begins to carry cell surface antigens that can be defined as foreign by the immune system (13).

Immune Control of Cancer

Tumor cells go through three stages before they become clinically noticeable. The development of tumors in humans despite

immune surveillance is tried to be explained by the "3E" theory of immune editing (Figure 1). These three phases are "Elimination", "Equlibrium" and "Escape". Although the immune system tries to prevent the survival of cancer cells during these three stages, it is ineffective in the elimination of some cancer cells (13). The immune surveillance of the host is suppressed and malignant cells emerge in this way (14).

The efforts of the immune system to prevent the formation of cancer lead to various consequences such as the ability to completely prevent the formation of some tumors, to remain unprotected in some tumors, and the formation of immunological anergy or tolerance (14,15).

Elimination

The immune system first attacks tumor cells with polymorphic leukocytes, natural killer cells (NK), and monocytes/macrophages. Pro-inflammatory cytokines released and tumor-related peptide sequences prepared and presented by monocytes/macrophages and dendritic cells activate T- and B-cells of the cellular/adaptive immune system. The release of interferon-gamma (IFN-γ), which is very important among cytokines, increases the migration of immune system cells to the tumor site, and induces apoptosis by showing cytotoxic effects with its anti-proliferative and anti-angiogenic effects (13). With its apoptotic and antiproliferative effects, IFN-γ causes death of tumor cells to a limited extent and induces the release of chemokines from tumor cells and surrounding normal tissues. These chemokines, which have angiostatic effects, cause the elimination of more tumor cells by stopping the formation of new vessels around the tumor (14). DC and macrophages infiltrating the tumor provide NK activation with the release of interleukin 12 (IL-12) and IFN-γ, and perforin causes more tumor cells to die through tumor necrosis factor (TNF)-related apoptosis-inducing ligand and reactive oxygen formation mechanisms. With the cytokines they secrete, CD4+ T-cells help B-lymphocytes to turn into plasma cells and secrete antibodies, NK and CD8+ T-lymphocytes to become more activated and thus to eliminate tumor cells (13). NK and CD8+ T-lymphocytes undertake the final task in tumor immunity, and if successful, tumor cells are destroyed (13-15).

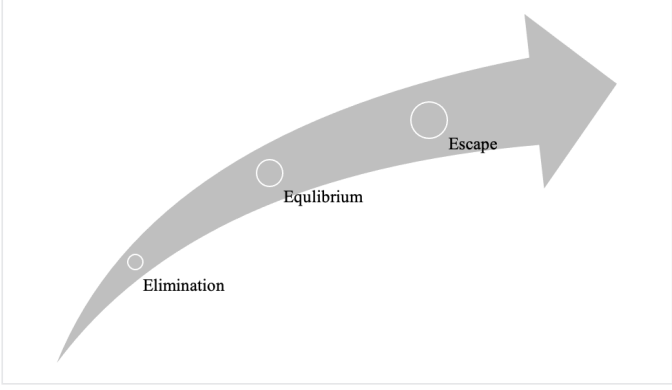

Figure 1. The "3E" theory of immunoediting

Equlibrium

Despite all these eradication efforts against the tumor, genetic/environmental or unknown microbial factors that are effective in tumor formation may cause genetic instability to continue and new methods to be produced against immune system defense mechanisms (13). Lymphocytes and IFN-γ exert a potent selection pressure on tumor cells that genetically mutate rapidly. In the meantime, many tumor cells that have undergone variation are destroyed, but there are also variants that show new mutations that are much more resistant to immune attacks. It is thought that this phase is the longest among the three phases and it takes years (14).

Escape

The escape phase indicates the formation of immunological tolerance, which means immunologically non-recognition and/or non-response. Genetic or epigenetic changes in the tumor cause the tumor to resemble normal body cells and escape from the immune system. In order to escape from CD4+ T-lymphocytes, tumor cells reduce the formation of tumor antigens or their surface expression, which is responsible for antigen presentation. Another method used by tumors is to secrete factors that bind pro-inflammatory cytokines and prevent them from functioning (13). All these mechanisms cause the body to be completely defenseless (13-15). Tumor variants become insensitive to immunological detection and proliferate uncontrollably. As a result, clinically observable malignant disease occurs and if untreated, it causes death of the host. To overcome these, ways such as immunotherapy have been found to help the immune system recognize cancer cells and strengthen its response (11).

Cancer Immunotherapy

Immunotherapy is a form of treatment in which parts of the individual's immune system are used to fight a certain group of diseases, including cancer. The aim is to enable cells of the immune system to target and destroy cancer cells (16). When the innate immune system is stimulated, tumor antigens released from the tumor are recognized and some T-cells stimulated by the immune system capture and destroy the tumor cells. Other T-cells, on the other hand, stimulate B-cells, which are other cells of the immune system, and these cells turn into antibody-producing plasma cells (17). The main strategy aims to provide patients with antitumor effectors (antibodies and T-cells), stimulating the patient's own antitumor response. Tumors develop mechanisms that enhance their survival (eg, Bcl-2 expression) and immunoregulatory molecules (eg, programmed cell death-1 (PD-1), PD-1 ligand (PD-L1), cytotoxic T-lymphocyte-associated protein- 4 (CTLA-4) inhibitors of immune checkpoints) can evade the immune response (18). The presence of identifiable tumor antigens in most of the tumor cells and the inability of the immune system to prevent tumor growth led to the formation of immunotherapy. The use of methods such as the production of antigen-specific T-lymphocytes and antibodies targeting tumor antigens, identification and purification of tumor antigens with the latest developments in technology has revealed the idea

that tumors can be destroyed by immunotherapy. In addition, lymphocyte isolation and increasing the efficiency of the immune system with cytokines also supported immunotherapy (14). Tumors can evade the immune response by developing mechanisms that enhance their survival (eg, Bcl-2 expression), and by expressing immunoregulatory molecules [eg, immune checkpoints inhibitors such as programmed cell death-1 (PD-1), PD-1 ligand (PD-L1) and CTLA-4] (18).

Various side effects are seen depending on the treatment method used in cancer treatment, the chemotherapeutic agent used, and the dose of chemotherapy and/or radiotherapy (17). Because new treatment modalities affect the immune response, it is aimed that tumor-specific immunity will selectively destroy the tumor without harming the patient. It is possible to interfere with the immune system with immunotherapy in order to regulate the immune response and to achieve tumor eradication despite the escape of tumors from the immune system (14).

Treatment Methods Used in Cancer Immunotherapy

Monoclonal Antibodies

It is a treatment method that ensures that cancer cells circulating in the body and carrying antigens are destroyed by other parts of the immune system until monoclonal antibodies find and neutralize the foreign protein (17).

Cancer Vaccines

Cancer vaccines have been produced to induce tumor-specific immune responses, particularly cytotoxic CD8-positive T-cells specific for tumor antigens. These vaccines help in cancer treatment or prevent the recurrence of cancer after other treatments (19). The patient can be vaccinated with his own tumor cells or tumor antigens. Vaccines can be given as recombinant proteins with adjuvants to increase the immune response (14). Cancer vaccines enable the immune system to attack tumor cells containing one or more specific antigens. Since memory cells are effective in the immune system, it is hoped that the vaccine will continue to work long after it is given (19).

Adaptive Immunotherapy

In this treatment, tumor-specific cytotoxic T-cells are given to cancer patients for the purpose of recognizing, targeting and destroying tumor cells. T-cells are harvested from a patient's blood or tumor site, then stimulated to grow and expand in an in vitro culture system. After sufficient in vitro growth, these cells are re-injected into the host, thereby causing tumor destruction (20).

Cytokines

With the use of cytokines, it is aimed to optimize the response after the patient creates an immune response (14).

Nutritional Supplements with Immunodilator and Anticancer Effects

Apart from the reported immunotherapy treatments; components of nutrients such as black cumin, turmeric, soy products, cinnamon and garlic (thymoquinone, curcumin, genistein, p-coumaric acid and allicin, respectively) can reduce the effectiveness of cancer cells and increase the effectiveness of some cancer drugs (21, 22). Ginseng (Panax ginseng, Korean ginseng) prevents drug resistance and increases the recognition of tumor cells (21). Polysaccharopeptides (edible mushrooms) help prevent the vascularization of cancer cells and regulate the immune system (21). Also; some betaglucans such as lentinan with polysaccharide structure found in fungi have been shown to stimulate macrophages, NK cells, T-cells and cytokines. Researches continue in this area. Agaricus subrufescens, Lentinula odedes, Grifola frundosa and Hericium erinaceus are known to have these properties (23). Adequate selenium intake (200-400 μg/day), beta carotene, zinc and fungal polysaccharides can stimulate NK cells (21).

Side Effects of Cancer Immunotherapy

The side effects of immunotherapies are caused by immune-mediated damage to normal tissues. These damages are due to the changes in the interactions between cancer cells and the immune system due to the treatments. The skin and mucosa, luminal gastrointestinal system, liver and endocrine system are the most frequently affected organs and systems. Skin rashes are usually the earliest side effect. There may be erythematous, reticular or maculopapular skin rashes. Mucositis may occur with dry mouth (18).

Propolis

What is Propolis?

Propolis is a resinous substance collected by honey bees from leaf buds and cracks (24). Honey bees form propolis by mixing the β-glucosidase enzyme found in their salivary secretions and partially digested wax into the resin they collect. Apis Mellifera honey bees living around Europe, the Ural Mountains, Africa and Asia play a role in the production of propolis (25). Propolis is a natural medicine that has been widely used since ancient times (26). The use of propolis in folk medicine is dated to 300 BC. Positive anticancer, antioxidant, anti-inflammatory, antibiotic, antifungal and antihepatotoxic effects have been demonstrated in studies. Propolis is a substance widely used in foods to promote health and prevent health problems such as inflammation, diabetes, cancer and cardiovascular diseases (27). Research against the composition and biological activities of propolis is still ongoing. More than 300 components of propolis have been identified to date (28). Propolis has anti-bacterial, anti-fungal, anti-viral, anti-tumor, hepatoprotective, anti-inflammatory effects. In addition to these features, it has been used as a part of traditional medicine since ancient times, as it naturally increases the body's resistance to infections and treats gastroduodenal ulcers (26).

Chemical Structure of Propolis

Many studies have been done on the structure and chemical properties of propolis, and hundreds of chemical compounds have been identified in propolis. However, there is no chemical standardization of propolis based on active principles (29). The

positive effects of propolis on health have been demonstrated in many *in vivo* and *in vitro* experimental studies. In particular, the polyphenols in its content prevent many specific diseases and prevent the progression of diseases.

It acts through various mechanisms (22). Phenolic and aromatic compounds such as flavonoids show the most important pharmaceutical and biological activity in propolis. The flavonoid and phenolic compounds of propolis are known as the most active substances with anticancer effect. Propolis inhibits the growth of tumor cells. Its cytotoxic effect is associated with different activities of different propolis types (30).

Uses of Propolis

Propolis collected from the hive is obtained as raw and must be used after being purified. Especially; since some allergic reactions may occur due to its composition in its medicinal use, propolis should be produced under the necessary controls, presented and used after processing (31). There are great differences in the compositions of propolis samples taken from different geographical regions. However; it is observed that all samples have antibacterial, antiviral and antifungal activity in common. These activities of propolis are related to the use of propolis by bees as a defense against infections (32). Propolis is a versatile substance used in apitherapy centers, in the food industry, in the pharmaceutical and cosmetic industry due to its antibacterial and antioxidant effects and the chemicals it contains (33).

Thanks to the rich vegetation of our country, Turkish propolis contains a wide variety of compounds (5). Turkish propolis is especially rich in polyphenolic compounds such as pinocembrin, isalpine, pinotropin, naringenin, quercetin, chrysin, galangin, pinobanksin, apigenin, 3,40, 7-trimethoxy flavanone and caffeic acid (34). In a study examining the *in vitro* effects of Turkish propolis on lung cancer; it was found that the ethanolic extract of propolis had a pro-apoptotic effect by reducing the mitochondrial membrane potential of A549 cells and inducing caspase activity (35). The bioactivity of propolis develops depending on the variety and concentrations of the compounds contained in propolis.

Immunological Effects of Propolis

In recent scientific research, propolis is thought to be one of the substances with a strong immunomodulating effect. This aspect of propolis needs to be supported by exploratory studies including more clinical trials. Propolis can be considered as a complementary therapy due to its immunomodulatory effects and can be seen as an alternative therapy in immune disorders (36). The antitumor effect of propolis and its components has been found to be associated with regulating the immune system through macrophage activation (37).

Immunotherapeutic Effects of Propolis in Cancer

Propolis is used in medicine as a treatment for cancer and immune diseases (38). Propolis has biological activities such as antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, cytotoxic, immunomodulatory, local anesthetic, antiulcer, antitumor and immunostimulatory effects (39). Flavonoids, aromatic acids and their esters are thought to be the compounds responsible for the biological activity of propolis (33). Effective antitumor components in propolis are known as CAPE, chrysin, nemoroson, artepilin C, galangin and cardanol (40). The anticancer effect of propolis is the result of its antioxidant, anti-inflammatory, immunomodulatory, cytostatic, antineoplastic features, suppression of proliferation in cancer cells, reduction of cancer stem cells and populations, inhibition of specific oncogene signaling pathways, providing anti-angiogenesis, modulating the tumor microenvironment and increasing chemotherapeutic activity (40,41). Also, propolis seems to alleviate the side effects caused by drugs (41). Stimulating effects of propolis on antibody production and lytic activity of NK cells against tumors have been demonstrated (42). Propolis creates resistance against various pathogens and tumor cells by affecting macrophage functions, lymphocyte proliferation and plaque-forming cells in the spleen (43).

It has been observed that water-soluble derivatives of propolis increase the immunomodulatory capacity. Propolis provides stimulation and induction of lymphocytes and some cytokines and affects IL-1 and TNF. Propolis injection in mice showed complementary activity in humoral immunity (44). It was observed that in vivo application of water-soluble propolis extract (WSP) increased the sensitivity of tumor cells to hyperthermal intraperitoneal chemotherapy (HIPEC) and reduces the toxic and genotoxic effect of cisplatin (CIS) on normal cells without affecting its cytotoxicity on tumor cells (45). Adding WSP to chemotherapy increased the survival rate of mice by 160.3%.

While propolis helps cancer treatments such as chemotherapy and radiotherapy, it also prevents the damage these treatments can cause to healthy cells (46). In an *in vitro* experiment with WSP, it was seen that WSP changed the tumoricidal activity of macrophages, increased the production of lymphocyte-activating factors, inhibited the human cervical carcinoma cell line and mouse lung fibroblast (V79) (47). In the study investigating the antitumor, genotoxic, chemopreventive and immunostimulatory effects of HIPEC with local chemoimmunotherapy in mice with Ehrlich acid tumor (EAT); mice were injected with 50 mg/kg WSP 3 and 7 days before implantation of EAT cells, and 5 mg/kg CIS 3 days after. The combination of WSP + CIS provided inhibition of tumor growth. WSP application increased the cytotoxic effects of macrophages on tumor cells (45).

Propolis and its components such as chrysin, quercetin and CAPE increase the levels of cell cycle progression inhibitors such as p21, p27 and cyclins *in vitro*, and enables stopping of the cell cycle at different stages. In a study examining the *in vitro* antitumor activity of propolis ethanolic extract in human colon carcinoma HCT15 cells, dose- and time-dependent cytotoxic effects were observed (48). Its mechanism of action was explained as a decrease in glucose consumption and lactate production and modulation of glycolytic metabolism.

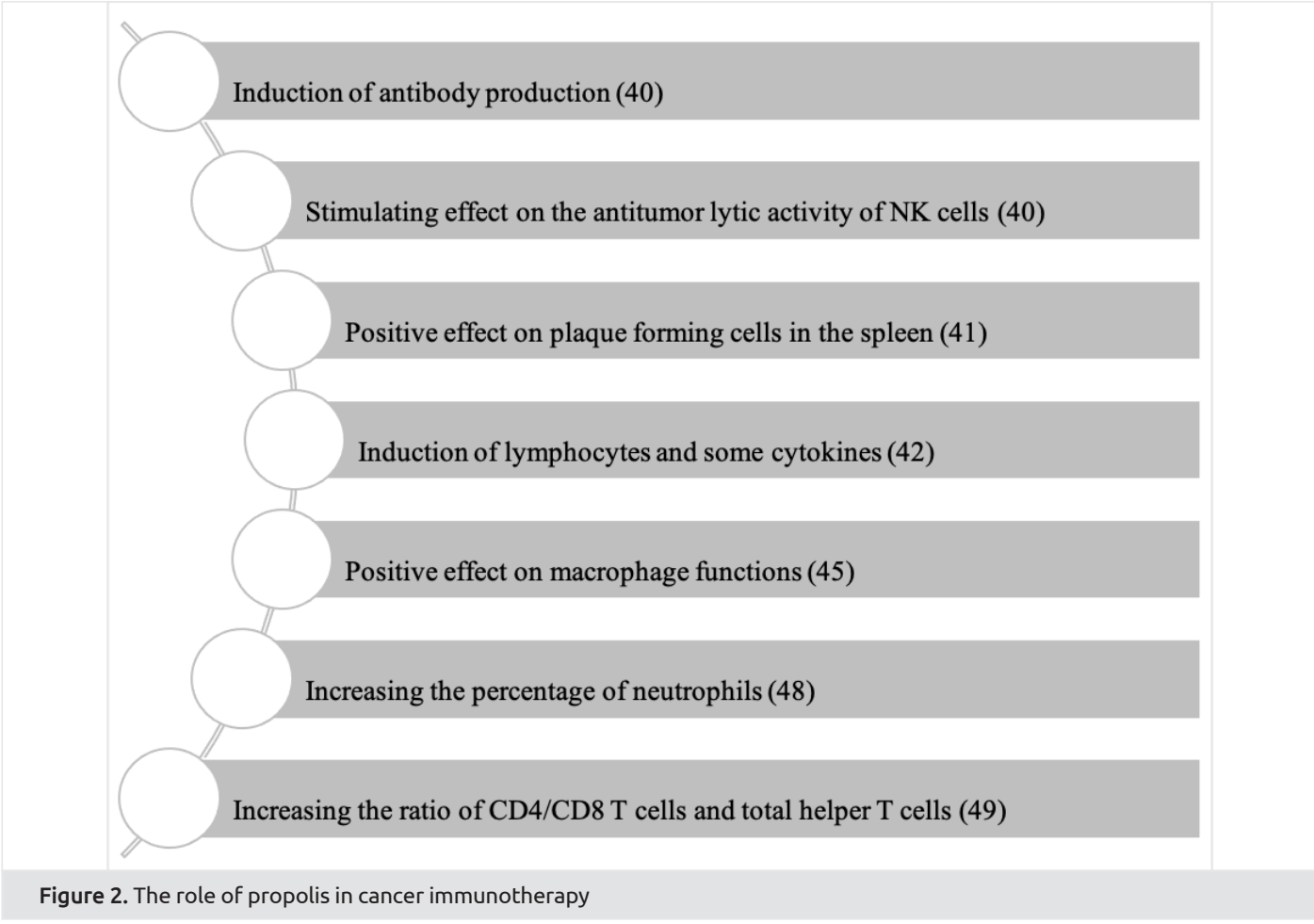

Figure 2. The role of propolis in cancer immunotherapy

Adding propolis to the anticancer drug irinotecan (IRI) treatment increases the antitumor activity of IRI (49). Compared to mice injected with EAT cells in the control group, the percentage of tumor cells in the peritoneal cavity was significantly reduced and the percentage of neutrophils was significantly higher in the experimental group treated with combined WSP and EEP. In a study in which 500 μg artepilin C (3,5-diprenyl-4-hydroxycinnamic acid) obtained from Brazilian propolis was applied to human and murine malignant tumor cells three times a week. It was found that artepilin C showed cytotoxic effects and inhibited the growth of tumor cells *in vitro* and *in vivo* (50). The cytotoxic effects of artepilin C are most pronounced in carcinoma and malignant melanoma. In addition to the suppression of tumor growth, artepilin C also increased the ratio of CD4/CD8 T cells and total helper T-cells. These findings show that artepilin C has antitumor activity and activates the immune system.

All these studies have shown that propolis has a direct regulatory effect on the basic functional properties of immune cells (Figure 2). Therefore; propolis, a bee product, is a potent and natural anti-inflammatory agent that affects different types of immune response via immunoregulatory T-cells.

Conclusion

Propolis shows its important effects on the immune system with tumor-specific immunity. Propolis can increase the expression of immune system cells as well as increase the effects of these cells on the tumor. At the same time, it can direct immune system cells to tumor cells that can escape recognition by the immune system with certain mechanisms. According to the findings obtained from *in vitro*, *in vivo* and clinical studies; Propolis shows its immunotherapeutic effects on cancer cases as well as preventing the formation of cancer. Therefore; More clinical studies are needed on propolis indications and usage doses.

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