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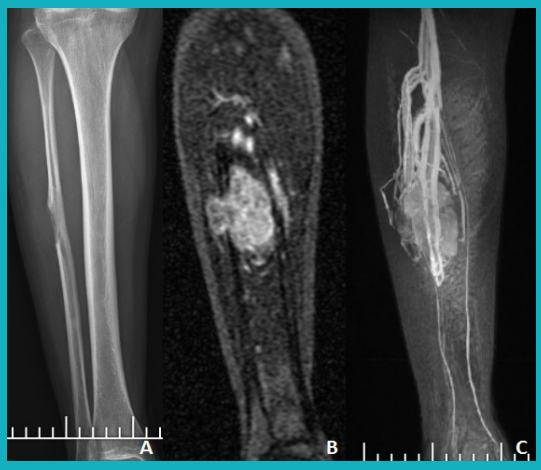

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EDITORIAL

Dear Readers,

The year 2020 has come off with a challenging start for the world and our country. We're with you with our second issue in these days we're dealing with COVID-19, which started in China and spread all over the world. We have encountered many sad events in the world and in our country, and we are still in a crisis where we do not know when it will end. Hail to the doctors, nurses and all the health workers who have worked selflessly in this field. In the meantime, I offer my deepest condolences for the doctors and scientists we have lost all over the world. They are values we have lost in this war and we will not forget them. I would like to thank our editorial board and our publishing house for their efforts to publish our journal even in these difficult days.

In this issue we are with you with new topics. We have chosen the cover picture of this issue from the original article by ÖZTÜRK et al., entitled "Surgical Treatment of alveolar Soft part Sarcoma of the extreme: Results of at Least 5 years of Follow-up".

In this issue; the article entitled "Comparison of Intravenous, Intra-articular, and Combined Tranexamic Acid Use in Primary Total Knee Arthroplasty without a Tourniquet and a Drain" by UZER et al., the article entitled "A Rabbit Model of Avascular Necrosis of Femoral Head Using Surgical Trauma and Systemic Steroids'' by OZBEN et al., and the article entitled ''Comparison of the Role of Endocan With Other Laboratory Tests in Diagnosis of Acute and Perforated Appendicitis in Children'' CEVIZCI et al. are the articles that are prominent.

We have set the subject of our next supplement as COVID. If you have studies or reviews about COVID, we expect you to share them with us.

I hope that we will have good days with health and peace in our country and the world.

Kindest regards

Prof. Dr. Adem AKCAKAYA

Editor-in-Chief

Original Article

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Bezmialem Science 2020;8(2):106-12

Retrospective Analysis of AMATEM Patients Treated in Psychiatry Inpatient Unit of Adiyaman Training and Research Hospital: Data for 2018

Adıyaman Eğitim ve Araştırma Hastanesi Psikiyatri Servisinde Tedavi Gören AMATEM Hastalarının Geriye Dönük Olarak İncelenmesi: 2018 Yılı Verileri

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ABSTRACT

Objective: The prevalence of substance use disorder (SUD) is increasing in the world and in our country. The most important centres in the treatment of SUD in Turkey are Alcohol and Drug Addiction Treatment and Research Centres (AMATEM). In this study, we aimed to investigate the substance use characteristics of the patients who were hospitalized in our hospital.

Method: The study was conducted as a retrospective study of AMATEM admissions between January 1, 2018 and December 31, 2018. Data such as gender, age and substance use characteristics were obtained from the patient recording system.

Results: Forty-two male patients (91.3%) and 4 (8.7%) female patients were included in the study. The mean age of the patients was 28.43±10.64 years. There were 10 patients (21.7%) with opiate use disorder (OUD), 14 patients (30.4%) with cannabis use disorder (CUD), 12 (26.1%) patients with alcohol use disorder (AUD), 3 (6.5%) patients with stimulant use disorder (SIUD), and 7 (15.2%) patients with inhalant use disorder (IUD). The mean age of AUD was significantly higher than the other groups (p=0.010). The mean duration of hospitalization was 7.63±7.01 days (p=0.073). The mean number of hospitalizations was 2.78±2.61 (p=0.874). The mean

ÖZ

Amaç: Madde kullanım bozukluğunun (MKB) yaygınlığı, dünyada ve ülkemizde giderek artmaktadır. Ülkemizde MKB tedavisinde en önemli merkezler Alkol ve Uyuşturucu Madde Bağımlıları Tedavi ve Araştırma Merkezleri'dir (AMATEM). Biz bu çalışmada hastanemizde yatarak tedavi gören MKB tanılı hastaların madde kullanım karakteristiklerini incelemeyi amaçladık.

Yöntem: Çalışma, 1 Ocak 2018-31 Aralık 2018 tarihleri arasındaki AMATEM başvurularının retrospektif olarak incelenmesi şeklinde gerçekleştirildi. Başvurulara ait cinsiyet, yaş ve madde kullanım özellikleri gibi bilgilere hasta kayıt sisteminden ulaşıldı.

Bulgular: Çalışmaya 42 (%91,3) erkek, 4 (%8,7) kadın olmak üzere 46 hasta dahil edildi. Hastaların yaş ortalaması 28,43±10,64 yıldı. On (%21,7) hastanın opiat kullanım bozukluğu (OPKB) tanısı, 14 (%30,4) hastanın esrar kullanım bozukluğu (EKB) tanısı, 12 (%26,1) hastanın alkol kullanım bozukluğu (AKB) tanısı, 3 (%6,5) hastanın stimülan kullanım bozukluğu (SKB) tanısı, 7 (%15,2) hastanın inhalan kullanım bozukluğu (İKB) tanısı vardı. AKB grubunun yaş ortalaması anlamlı olarak diğer gruplardan yüksekti (p=0,010). Tüm hastaların ortalama yatış süresi 7,63±7,01 gündü (p=0,073). Tüm hastaların ortalama yatış sayısı 2,78±2,61 idi. Tüm

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duration of substance use was 9.67±8.73 years. The duration of substance use was significantly higher in the AUD group (p=0.001). Thirty-six (78.3%) of all patients had a forensic history. Twenty-one (45.7%) of the patients needed hibernation. Ten (21.7%) of the patients had suicide attempt history. Twenty-eight (60.9%) of the patients had homicidal behaviour. Psychotic symptoms were present in 15 (32.6%) patients. Homicidal behaviour was significantly higher in patients with forensic history (p=0.024). The forensic history was significantly lower in the AUD group than in the other diagnoses (p=0.009).

Conclusion: SUD was accompanied by additional psychiatric symptoms. SUD was clearly related with crime. Further studies are needed to develop more robust strategies.

Keywords: Substance use disorder, AMATEM, suicide attempt, forensic history, hibernation

grupların ortalama yatış süreleri benzerdi (p=0,874). Tüm grubun ortalama madde kullanım süresi 9,67±8,73 yıldı. Madde kullanım süresi AKB grubunda anlamlı olarak daha yüksekti (p=0,001). Hastaların 36'sının (%78,3) adli bir öyküsü vardı. Hastaların 21'inde (%45,7) hibernasyona ihtiyaç duyulmuştu. Hastaların 10'unun (%21,7) özkıyım girişimi öyküsü mevcuttu. Hastaların 28'i (%60,9) homisidal davranış sergiliyordu. Hastaların 15'inde (%32,6) psikotik semptom vardı. Adli öyküsü olanlarda homisidal davranış belirgin olarak yüksekti (p=0.024). Adli öykü AKB grubunda diğer gruplara göre anlamlı olarak düşüktü (p=0.009).

Sonuç: MKB, ek psikiyatrik semptomların eşlik ettiği; suç ilişkisi belirgin olarak bulunan bir durumdur. Daha sağlam stratejilerin geliştirilebilmesi için gelecek çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Madde kullanım bozukluğu, AMATEM, özkıyım girişimi, adli öykü, hibernasyon

Introduction

Substance use is as old as human history. Substance use disorder (SUD) and problems have become more important in the last few decades in psychiatry. Substance use causes people to experience social, economic and personal problems. Patients use an increasing amount of substance due to the growing tolerance. This causes them to live more physical and mental problems than others (1-4). Dependency affects the brain and therefore behaviour. The person who starts to experience more problems with his/her environment is in a vicious circle (5-7). In addition to the genetic characteristics in the emergence of addiction, environmental characteristics play an important role in the maintenance of drug addiction. On the other hand, biological processes contribute to continuity (8,9). Considering that many different substances are addictive, treatment modalities for substances are also different. Treatment also varies depending on the characteristics of the person and on the problems associated with substance use (10-12). In addition, the presence of mental, occupational, general medical and social problems in many patients makes the treatment of addiction difficult. Drug addiction treatment consists of behavioural therapy (counselling, cognitive therapy and other psychotherapies), drug therapy, and a combination of these treatments (13,14).

The leading centres in the treatment of SUD in Turkey are Alcohol-Drug Addiction Research, Treatment and Training Centers (AMATEM) and they have been in service since the 1980s and the number of centers has increased. It is possible to say that these centers, where outpatient or inpatient services can be provided, have made some significant progress in our country, although it is early to say that they are in a certain standard. These clinics serve for termination of substance addiction and re-functioning of individuals. Treatment strategies are determined according to the individual because of the change in the risk factors of SUD (13). Inspection services in these centers are voluntary. As a result of the examination, the treatment plan is explained to the person and to his/her relatives and the treatment process is started. If necessary, hospitalization is made. The combination of buprenorphine+naloxone could be started with a specific protocol and the treatment process continued to be followed up, frequently. The studies about the patients who are being treated in AMATEM clinics are reached through the literature (13,14).

In AMATEM units, it is possible to determine the disease-related profiles of the patients who are being treated, to determine the treatment efficiencies and to make new plans. Savaşan et al. (15) stated that the average age of the patients was 45.42 (year) and the male percentage was 96.9% based on the data of an inpatient AMATEM unit in Izmir province between 2011 and 2012. In this study, 78% of the patients were diagnosed as having AUD, 6% as having illicit substance use disorder, and 16% as having AUD plus illicit substance use disorder. Savaşan et al. (15) emphasized that individual or group psychotherapy programs to be organized within the first six months or one year might be beneficial for relapse prevention. Karaağaç et al. (16) retrospectively examined the patients who were followed-up in an AMATEM hospital in Kayseri province between 2007 and 2015 and found that the percentage of males were 94.8% and the mean age of patients was 33.6 years. In addition, the mean age of the patients with AUD was higher than the drug users and the most common cause of admission was AUD (37.2%) and cannabis use disorder (CUD) (34.1%). Bulut et al. (17) evaluated AMATEM data of 2001-2005 in Gaziantep province and found that the percentage of men was 96.8%, the mean age was 36.02 years, the rate of patients with AUD diagnosis was 46.8%, the rate of patients with opiate use disorder (OUD) was 42.1% and the rate of patients with CUD was 7.1%. The data of the AMATEM clinics changed according to the years of the studies. Eğilmez et al. (13) reported that 97.8% of the 401 patients were male and the mean age was 25.75 years in Adiyaman province. According to their study, mean age of patients with AUD was significantly higher than patients with other diagnoses; 89.6% of the patients were in the age range of 20-29 years; 84.8% of the patients were diagnosed as having OUD; recurrent admissions were significantly higher in patients with OUD than patients with other disorders. Eğilmez et al. (13) emphasized that the use of opiates in Adiyaman province

was a serious problem. According to our literature review, a study on AMATEM inpatient data in Adiyaman province was not performed before. Considering that AMATEM data shows regional changes, interventions based on regional differences will be beneficial (14). In addition, it is thought that the data of Adiyaman province will provide comparison with AMATEM studies in different regions with similar characteristics. In this study, we aimed to retrospectively examine the patients who were admitted in our AMATEM inpatient clinic within one-year period.

Method

Study Design

Our study was planned retrospectively. The patients who met the DSM-5 (18) diagnostic criteria in the psychiatry department of Adiyaman University Training and Research Hospital and the patients withat least one substance in their urine toxic screenings were found through the patient registry system and were included in the study. The diagnostic category was determined according to the verbal declarations of the type of substance they preferred frequently and the declarations were consistent with the results of the toxic screening in the urine and patients with OUD, CUD, AUD, inhalant use disorder (IUD), stimulant use disorder (SIUD), hallucinogenic use disorder (HUD) were determined. All these steps were performed by an experienced psychiatrist (OBE). Sociodemographic data such as age, gender, and disease diagnoses were obtained from the patients registry system. A total of 55 records of hospitalized AMATEM patients were obtained. Nine of them were excluded from the study, whose diagnosis was not known and could not be confirmed due to toxic screening in urine. Forty-six hospitalizations were included in the study. In this study, the number of admissions was taken into consideration. So, there might be more than one application belonging to the same person. Ethics committee approval was obtained from Adıyaman University Non-Invasive Clinical Research Ethics Committee for this study (2019/3-6).

Biochemical Analysis

Biochemical analysis was performed in the laboratory of our hospital by means of "Instant-View Multi-Drug Abuse Urine Test Kit". All analyses were performed between 09:00 a.m. and 15:00 a.m. The urine toxic scans of the patients who were hospitalized in the AMATEM service were requested after a short examination and performed with the detailed examination test results. In our laboratory, biochemical analysis of drug was performed by immunochromatographic methods.

Statistical Analysis

Statistical analysis was performed using the Windows SPSS 22.0 program. Descriptive statistics and continuous variables were given as mean ± standard deviation and categorical variables were given as frequency and percentage. Independent sample t-test was used to evaluate the differences in means between the two groups. Chi-square test was used to analyse categorical data. ANOVA was used for multiple comparisons. A p value <0.05 was accepted as statistically significant.

Results

Forty-two male patients (91.3%) and 4 (8.7%) female patients were included in the study. The mean age of the patients was 28.43±10.64 years. The mean age of the males was 28.67±10.94 years and the mean age of the females was 26.00±7.34 years (p=0.543).

There were 10 patients (21.7%) with OUD, 14 patients (30.4%) with CUD, 12 (26.1%) patients with AUD, 3 (6.5%) patients with SIUD, 7 (15.2%) patients with IUD. The mean age of OUD was 24±5.56 years, the mean age of CUD was 26.57±9.26 years, the mean age of AUD was 37.25±14.24 years, the mean age of SIUD was 20.67±4.61 years, and the mean age of IUD was 26.57±2.99 years. The mean age of AUD was significantly higher than other groups (p=0.010). The mean duration of hospitalization was 7.63±7.01 days in all patients. The mean duration of hospitalization in patients with OUD was 5.00±3.97 days, with CUD was 11.29±9.83 days, with AUD was 8.50±5.46 days, with SIUD was 2.00±1.73, and with IUD was 5.00±3.41 days. The mean duration of hospitalization was similar (p=0.073). The mean number of hospitalization in whole group was 2.78±2.61, in OUD group was 2.70±1.49, in CUD group was 2.36±2.00, in AUD group was 3.25±4.33, in SIUD group was 2.00±1.00, and in IUD group was 3.29±1.60. The mean duration of hospitalization was similar (p=0.874). The mean substance use duration in total was 9.67±8.73 years, in OUD group was 5.40±2.45 years, in CUD group was 7.21±4.54 years, in AUD group was 18.08±12.95 years, in SIUD group was 4.67±0.57 years, and in IUD group was 8.43±3.25 years. The duration of substance use was significantly higher in the AUD group (p=0.001) (Table 1). Thirty-six (78.3%) of all patients had a forensic history.

Eighteen (39.1%) patients received anxiolytic treatment during hospitalization, 42 (91.3%) antipsychotics, 25 (54.3%) antidepressants and 3 (6.5%) mood stabilizers. Twenty-one (45.7%) patients needed hibernation (it is the creation of a state of inactivity with psychotropic drugs, preferably with 10 mg haloperidol intramuscularly plus 5 mg biperiden intramuscularly). Ten (21.7%) patients had suicide attempt history. Two (4.3%) patients had suicidal thoughts at admission. Twenty-eight (60.9%) patients had homicidal behaviour. Thirty (65.2%) patients were discharged after the treatment was completed and 16 (34.8%) were discharged upon their own request. Psychotic symptoms were present in 15 (32.6%) patients.

The forensic history was significantly lower in the AUD group compared with other diagnoses (p=0.009). There was no significant difference between the groups in terms of anxiolytic, antipsychotic, antidepressant and mood stabilizers use (p=0.114, p=0.254, p=0.059 and p=0.431, respectively). The need for hibernation was significantly higher in the CUD group (p=0.044). There was no significant difference between the diagnostic groups in terms of suicide attempt history (p=0.545). There was no significant difference between the diagnostic groups in terms of active suicide thoughts (p=0.311). Homicidal behaviour was significantly higher in CUD and IUD groups (p=0.000). There

was no significant difference between groups in terms of type of discharge (p=0.064). The psychotic symptoms were significantly higher in the CUD group (p=0.003).

There was no difference in the type of discharge in the OUD group (p=0.720). There was no difference in the need for hibernation when patients with OUD were accepted as first group and the others were accepted as second group (p=0.066). When patients with AUD were evaluated as one group and the remaining patients as a second group, the use of anxiolytic drugs was significantly higher in AUD group (p=0.023). When AUD patients were evaluated as one group and the remaining patients as a second group, forensic history was significantly lower in AUD group (p=0.000). When AUD patients were evaluated as one group and the remaining patients as a second group, there were no significant differences between groups in terms of the need for hibernation, suicide attempt history, active suicide thoughts, homicidal behaviour, type of discharge, and psychotic symptoms (p=0.725, p=0.190, p=0.390, p=0.113, p=0.408 and p=0.171, respectively). There was no relationship between forensic history and need for hibernation, suicide attempt history, suicidal thoughts, and type of discharge (p=0.261, p=0.880, p=0.322 and p=0.267, respectively). Homicidal behaviour was significantly higher in patients with forensic history (p=0.024).

Table 1. Socio-demographic variables

	Diagnosis	Mean ± SD	p
Age (year)	OUD (n=10)	24.10±5.56	0.010*
	CUD (n=14)	26.57±9.26	
	AUD (n=12)	**37.25±14.25**	
	SIUD (n=3)	20.67±4.61	
	IUD (n=7)	26.57±2.99	
	Total (n=46)	28.43±10.64	
Duration of Hospitalization (day)	OUD	5.00±3.97	0.073
	CUD	11.29±9.83	
	AUD	8.50±5.46	
	SIUD	2.00±1.73	
	IUD	5.00±3.41	
	Total	7.63±7.01	
Number of Hospitalization	OUD	2.70±1.49	0.874
	CUD	2.36±2.06	
	AUD	3.25±4.33	
	SIUD	2.00±1.00	
	IUD	3.29±1.60	
	Total	2.78±2.61	
Duration of Substance Use (year)	OUD	5.40±2.45	0.001*
	CUD	7.21±4.54	
	AUD	**18.08±12.95**	
	SIUD	4.67±0.57	
	IUD	8.43±3.25	
	Total	9.67±8.73	

*p<0.05, **Independent sample t-test, chi-square test
OUD: Opiate use disorder, CUD: Cannabis use disorder, AUD: Alcohol use disorder, SIUD: Stimulant use disorder, IUD: Inhalant use disorder, SD: Standard deviation

Discussion

Our study was based on one-year period in a province and showed the substance use characteristics of patients admitted in AMATEM inpatient clinic. The majority of the patient group consisted of men. The mean age was similar between males and females and was between 20 and 30 years of age. These findings were consistent with the literature. Savaşan et al. (15) found that the mean age of AMATEM patients was 45.42 years and the male percentage was 96.9%. Again in that study, 78% of the patients had AUD, 6% had SUD and 16% had AUD and SUD. In that study, the mean age was higher in patients with AUD than the others. In our study, the mean age of the AUD group was significantly higher than the other diagnostic groups. Karaağaç et al. (16) found that 94.8% of the AMATEM patients were male and that the mean age was 33.6 years. They also reported that the mean age of alcohol users was higher than the drug users and that the most common reason for admission was AUD (37.2%). Egilmez et al. (13) reported that 97.8% of the 401 patients were male and the mean age was 25.75 years. According to that study, mean age was significantly higher in patients with AUD than patients with other diagnoses.

Alcohol use disorders in elderly people are associated with widespread impairments in physical, psychological, social, and cognitive health. Among elderly people, sociodemographic factors associated with alcohol use disorders include being male, socially isolated, single, and separated or divorced (19). Serious medical disorders among elderly people who misuse alcohol are much more common than the overall population of similar age. Heavy drinker elderly people have more major illnesses, poorer self-perceived health status, more visits from the physicians, more depressive symptoms, less satisfaction with life, and smaller social networks than younger drinkers, non-heavy drinkers and people who have never drunk (19-21).

Almost all patients did not continue to be hospitalized for the time required for SUD treatment. The possible causes may be somatic symptoms, side effects, vegetative symptoms due to deprivation and withdrawal. The majority of patients had more than one hospitalization. It is known that relapses are common after SUD treatment in the world and in our country. Ramo et al. (22) reported that relapses were more frequent among users of alcohol and non-cannabis substances. Patients in whom the relapse occurred earlier were those who did not see substance use as a problem. Patients with early relapses were more introverted. Again, Ramo et al. (22) stated that life stress, conflicts, negative emotional states were associated with relapse. Decker et al. (23) stated that comorbid psychiatric conditions and failure to complete residential substance use treatment were associated with higher relapse. Domino et al. (24) reported that the risk of relapse with substance use was increased in patients who had a family history of substance use disorder. Brecht and Herbeck (25) suggested that significant protective factors predicting longer time to relapse included having experienced serious drug-related

behavioral problems, longer duration of the index treatment episode, and participating in self-help or other treatment during the post-treatment abstinence period; and that risk factors for shorter time to relapse included having a parent with alcohol and/or drug use problems.

Substance use causes individuals to behave in a manner that does not recognize rules, acts as a harm to themselves and the environment, and leads to crime. Sometimes the substance is used to undermine the control mechanism of consciousness during the crime. Deposits, theft, murder, prostitution and other crimes are also committed in order to obtain the money needed to buy the substance (26,27). One of the leading sources of violent behaviour is drug abuse. Alcohol and substance use, aggression and violent acts have been found to escalate each other. Amphetamines, cocaine and hallucinogens play a direct role in the emergence of aggressive and violent acts by their chemical effects. As a result of the weakening of the control mechanisms on the human brain or the emergence of an intense energy state, individuals can be more aggressive and uncontrolled (28). Many researches have been conducted to investigate the relationship between substance use and crime and it has been demonstrated that there is a relationship between drug use and crime (29). In our study, the majority of patients (78.3%) had a history of forensic events. The forensic history was significantly lower in the AUD group than in the other groups. Homicidal behaviour was significantly higher in patients with forensic history. The forensic history was lower in the AUD group. Chen and Wu (30) suggested that there was a positive association between the frequency of substance use and the odds of engaging in gun-related behaviours. Walters (31) suggested that illicit drug use at year two predicted an increase in arrests between the first and third years of the analysis and arrests at year two predicted an increase in illicit drug use over this same time period. Walters (31) stated that alcohol use failed to predict a change in arrests and arrests failed to predict a change in alcohol use. Lee and Lee (32) reported that participants' rates of alcohol and drug use were higher among those who experienced violence victimization than those who did not.

There are two critical points in the treatment of substance dependence. The first is to control the withdrawal crisis, and the second is to prevent the relapse in the recovered patient. The deprivation crisis is a critical factor in maintaining substance dependence. Tolerance develops in a short time to the effects of abused substances. The growing tolerance contributes to the rapid establishment of physical dependence with more substance intake. The substance-seeking behaviour at the beginning is intended to avoid the complete deprivation of crisis. Control of the deprivation crisis is extremely important in terms of eliminating the need for substances (33,34). Considering the effects of addictive substances in terms of brain neurochemistry, the fact that almost all known neurotransmitters from GABA, serotonin, noradrenaline to glutamate are related to substance dependence and that many genetic, social, cultural and behavioural factors make substance dependence very complicated. It is too optimistic to think that such a complex brain problem can be treated with a single miracle drug in a radical way (35). Antidepressants and some antipsychotics, which are not addictive over time, can be used as preventive or adjuvant therapy at various stages of drug addiction (36). In our study, the majority of patients were treated with antipsychotics. Because of the homicidal behaviour of the patients, antipsychotic use was needed. Some patients were treated for agitation (hibernation). Some patients also had psychotic symptoms. The use of anxiolytic and antipsychotic drugs was needed for the treatment of psychotic symptoms.

Cannabis is a toxic substance for the central nervous system. Cannabis use has been associated with decreased intelligence and brain function. It has been reported that there is a complex relationship between cannabis use and schizophrenia, and this is only partially clarified (37). Murray et al. (38) found that cannabis use was associated with increased psychotic symptoms and increased risk of psychosis, such as schizophrenia. It has been proven that long-term cannabis use causes neurocognitive impairment in healthy individuals and increases the risk of psychosis. In our study, the need for hibernation was significantly higher in the CUD group. Homicidal behaviour was significantly higher in the CUD and IUD groups. Psychotic symptoms were significantly higher in the CUD group.

The prevalence of substance-related disorders is increasing in the world and in our country.

Conclusion

This study addressed the characteristics of patients with substance use treated in an AMATEM service in our province. Physicians interested in the treatment process of substance use disorders should question the psychiatric comorbidities. In order to obtain more detailed information on this subject, studies with large patient groups are needed.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Adıyaman University Non-Invasive Clinical Research Ethics Committee for this study (2019/3-6).

Informed Consent: Informed consent form has been signed.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.H.Ö., Design: O.B.E., M.H.Ö., M.Z.K., Data Collection or Processing: O.B.E., M.H.Ö., M.Z.K., Analysis or Interpretation: O.B.E., M.Z.K., Literature Search: O.B.E., M.H.Ö., M.Z.K., Writing: M.H.Ö.

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

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References

1. Johannessen DA, Nordfjærn T, Geirdal AØ. Change in psychosocial factors connected to coping after inpatient treatment for substance use disorder: a systematic review. Subst Abuse Treat Prev Policy 2019;14:16.
2. Ozen ME, Kalenderoglu A, Orum MH, Egilmez OB. Topiramate add-on for treatment of migraine-type headache cures alcohol dependence: A case report. Journal of Mood Disorders (JMOOD) 2017;7:241-2.
3. Orum MH, Kustepe A, Kara MZ, Dumlupinar E, Egilmez OB, Ozen ME, et al. Addiction profiles of patients with substance dependency living in Adiyaman province. Med Science 2018;7:369-72.
4. Orum MH, Kara MZ, Egilmez OB, Kalenderoglu A. Complete blood count alterations due to the opioid use: what about the lymphocyte-related ratios, especially in monocyte to lymphocyte ratio and platelet to lymphocyte ratio? J Immunoassay Immunochem 2018;14:1-12.
5. Madeo G, Bonci A. Rewiring the addicted brain: Circuits-based treatment for addiction. Cold Spring Hasb Symp Quant Biol 2019. pii: 038158.
6. Orum MH, Kara MZ, Egilmez OB. Relationship between immune cells and alcohol dependents and controls: what about the lymphocyte-related ratios? J Immunoassay Immunochem 2018;39:348-50.
7. Orum MH, Kara MZ, Egilmez OB, Ozen ME, Kalenderoglu A. Evaluation of probation implementations of drug users in Adiyaman university training and research hospital: A one-year retrospective study. Med Science 2018;7:754-8.
8. Ozen ME, Orum MH, Kalenderoglu A, Atmaca M. Attention-deficit/hyperactivity disorder in patients attending remedial treatment due to substance use disorder in Adiyaman University Training and Research Hospital. Psychiatry and Behavioral Sciences 2018;8:57-62.
9. Özen ME, Örüm MH, Kalenderoğlu A. Hot shower therapy in cannabinoid hyperemesis syndrome: A case report. FNG & Bilim Tıp Dergisi 2018;4:142-4.
10. Kustepe A, Kalenderoglu A, Celik M, Kaya-Bozkurt E, Orum MH, Uguz S. Evaluation of impulsivity and complex attention functions of subjects with substance use: Sample from Adiyaman province. Med Science 2019;8:67-71.
11. Örüm MH, Kara MZ, Örüm G, Eğilmez OB. Biperiden bağımlılığı ve nöroleptik malign sendrom ile ayırıcı tanısı: Olgu sunumu. FNG & Bilim Tıp Dergisi 2018;4:194-6.
12. Örüm MH, Kara MZ, Kuştepe A, Kalenderoğlu A. Bilişsel hatalar ve dikkat-eksikliği hiperaktivite bozukluğu belirtilerinin madde kullanım özellikleri ile ilişkisi. Bağımlılık Dergisi–Journal of Dependence 2019;20:47-60.
13. Egilmez OB, Örüm MH, Kara MZ. Adıyaman ili AMATEM verilerinin geriye dönük olarak incelenmesi: 2018 yılı verileri. Bağımlılık Dergisi – Journal of Dependence 2019;20:88-96.
14. Egilmez OB, Örüm MH, Dumlupınar E, Egeli A. Denetimli serbestlik uygulaması kapsamında yapılan başvuruların geriye dönük olarak değerlendirilmesi: 2018 yılı verileri. Bağımlılık Dergisi – Journal of Dependence 2019;20:80-7.
15. Savaşan A, Engin E, Ayakdası D. Bir amatem kliniğinden taburcu olan bağımlı hastaların yaşam tarsi değişiklikleri ve nüks durumları. Psikiyatri Hemşireliği Dergisi 2013;4:75-9.
16. Karaagac H, Esenkaya-Usta Z, Usta A, Gümüş-Yarmalı M, Godekmerdan A. Retrospective analysis of sociodemographic characteristics of inpatients at Kayseri Research and Training Hospital AMATEM Clinic. Dusunen Adam 2017;30:251-7.
17. Bulut M, Savaş HA, Cansel N, et al. Gaziantep Üniversitesi alkol ve madde kullanım bozuklukları birimine başvuran hastaların sosyodemografik özellikleri. Bağımlılık Dergisi 2006;7:65-70.
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). Washington, DC, American Psychiatric Association, 2013.
19. O'Connell H, Chin AV, Cunningham C, Lawlor B. Alcohol use disorders in elderly people—redefining an age old problem in old age. BMJ 2003;327(7416):664-7.
20. Goldstein MZ, Pataki A, Webb MT. Alcoholism among elderly persons. Psychiatr Serv 1996;47:941-3.
21. Saunders PA, Copeland JR, Dewey ME, Davidson IA, McWilliam C, Sharma V, et al. Heavy drinking as a risk factor for depression and dementia in elderly men. Findings from the Liverpool longitudinal community study. Br J Psychiatry 1991;159:213-6
22. Ramo DE, Anderson KG, Tate SR, Brown SA. Characteristics of relapse to substance use in comorbid adolescents. Addict Behav 2005;30:1811-23.
23. Decker KP, Peglow SL, Samples CR, Cunningham TD. Long-term outcomes after residential substance use treatment: Relapse, morbidity, and mortality. Mil Med 2017;1821589-95.
24. Domino KB, Hornbein TF, Polissar NL, Renner G, Johnson J, Alberti S, et al. Risk factors for relapse in health care professionals with substance use disorders. JAMA 2005;293:1453-60.
25. Brecht ML, Herbeck D. Time to relapse following treatment for methamphetamine use: a long-term perspective on patterns and predictors. Drug Alcohol Depend 2014;139:18-25.
26. Choenni V, Hammink A, van de Mheen D. Association between substance use and the perpetration of family violence in industrialized countries: A systematic review. Trauma Violence Abuse 2017;18:37-50.
27. Ozen ME, Orum MH, Kalenderoglu A. Difficult patient in psychiatry practice: A case-control study. Adıyaman Üni Sağlık Bilimleri Derg 2018;4:1064-73.
28. Stoddard SA, Epstein-Ngo Q, Walton MA, Zimmerman MA, Chermack ST, Blow FC, et al. Substance use and violence among youth: a daily calendar analysis. Subst Use Misuse 2015;50:328-39.
29. Löfving-Gupta S, Willebrand M, Koposov R, Blatný M, Hrdlička M, Schwab-Stone M, et al. Community violence exposure and substance use: cross-cultural and gender perspectives. Eur Child Adolesc Psychiatry 2018;27:493-500.
30. Chen D, Wu LT. Association between substance use and gun-related behaviors. Epidemiol Rev 2016;38:46-61.
31. Walters GD. Does drug use inhibit crime deceleration or does crime inhibit drug use deceleration? A test of the reciprocal risk postulate of the worst of both worlds hypothesis. Subst Use Misuse 2018;53:1681-7.
32. Lee Y, Lee KS. Associations between history of hospitalization for violence victimization and substance-use patterns among adolescents:

A 2017 Korean National Representative Survey. Int J Environ Res Public Health 2018;15. pii: E1543.

33. Soyka M, Mutschler J. Treatment-refractory substance use disorder: Focus on alcohol, opioids, and cocaine. Prog Neuropsychopharmacol Biol Psychiatry 2016;70:148-61.
34. Klein JW. Pharmacotherapy for substance use disorders. Med Clin North Am 2016;100:891-910.
35. Gardner EL. Addiction and brain reward and antireward pathways. Adv Psychosom Med 2011;30:22-60.
36. Bernstein SL, D'Onofrio G. Screening, treatment initiation, and referral for substance use disorders. Addict Sci Clin Pract 2017;12:18.
37. Hosseini S, Oremus M. The effect of age of initiation of cannabis use on psychosis, depression, and anxiety among youth under 25 years. Can J Psychiatry 2019;64:304-12.
38. Murray RM, Englund A, Abi-Dargham A, Lewis DA, Di Forti M, Davies C, et al. Cannabis-associated psychosis: Neural substrate and clinical impact. Neuropharmacology 2017;124:89-104.

Original Article

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Evaluation of Awareness of Cervical Cancer and Pap Spear Test of Working Women by Health Belief Model

Çalışan Kadınların Rahim Ağzı Kanseri ve Pap Smear Testi Farkındalıklarının Sağlık İnanç Modeli Ölçeği ile Değerlendirilmesi

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ABSTRACT

Objective: The aim of the study was to identify awareness and beliefs of working women regarding cervical cancer and Pap smear test.

Methods: The data of the study designed in sectional and descriptive style were collected between June-August, 2017. The study was conducted on a total of 120 married women with no cervical cancer history, who were working in the Provincial Tax Directorate and volunteered to participate in the research. Forms containing identifying information about women and Health Belief Model scale for Cervical Cancer and Pap smear test were used.

Results: The mean age of the women was 39.5±9.02 years and 59.2% of them had undergone a Pap smear test. Sub-dimensional score averages of the working women were at medium level. While cervical cancer sensitivity score was found to be higher in women with familial history of cervical cancer and in those with higher levels of income, Pap smear benefit and motivation score was found to be higher in women who had sufficient knowledge about early diagnosis methods ($p<0.05$). While women's knowledge on gynecologic cancer and gynecological examinations increased Pap smear behavior by three times on average, women's age increased pap smear behavior by about one fold.

Conclusion: Women with a high level of education did not have sufficient knowledge about cervical cancer. Pap smear test benefit, sensitivity, seriousness and health motivation score averages of these women should be elevated and their barrier perception score average should be decreased. Training of working women at workplace should be supported.

Keywords: Cervical cancer, Pap smear, health belief model, women cancer

ÖZ

Amaç: Çalışmanın amacı, çalışan kadınların rahim ağzı kanseri ve Pap smear test ile ilgili inançlarını ve farkındalıklarını belirlemektir.

Yöntemler: Kesitsel ve tanımlayıcı tipteki bu çalışmanın verileri Haziran-Ağustos 2017 tarihleri arasında toplanmıştır. İl merkezindeki Vergi Dairesi Başkanlığı'nda çalışan, evli, rahim ağzı kanseri öyküsü olmayan, araştırmaya katılmayı gönüllü kabul eden toplam 120 kadın ile çalışma tamamlanmıştır. Verilerin toplanmasında, kadınları tanıtıcı bilgi formu ve Rahim Ağzı Kanseri ve Pap Smear Testi Sağlık İnanç Modeli ölçeği kullanılmıştır.

Bulgular: Kadınların yaş ortalaması 39,5±9,02 yıldır ve %59,2'si Pap smear testi yaptırmıştır. Çalışan kadınların ölçeğe ait alt boyut puan ortalamaları orta düzeyde belirlenmiştir. Rahim ağzı kanseri duyarlılık puanı, ailesinde rahim ağzı kanseri öyküsü olan ve gelir durumu fazla olanlarda yüksek iken, Pap smear yarar ve motivasyon puanı, erken tanı yöntemleri bilgisi yeterli olanlarda daha yüksektir ($p<0,05$). Kadınların Pap smear yaptırma durumunu, erken tanı bilgileri ve jinekolojik muayene yaptırmaları ortalama üç kat, yaşları ise yaklaşık bir kat etkilemiştir.

Sonuç: Eğitim düzeyi yüksek kadınların rahim ağzı kanser bilgileri yeterli değildir. Bu kadınların Pap smear testi yararlılık, duyarlılık, ciddiyet ve sağlık motivasyonu puan ortalamaları yükseltilmeli, engel algısı puan ortalamaları ise düşürülmelidir. Çalışan kadınların iş ortamlarında eğitim almaları desteklenmelidir.

Anahtar Sözcükler: Serviks kanseri, Pap smear, sağlık inanç modeli, kadın kanseri

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Introduction

Cervical cancer is a cancer that has a screening program within gynecologic cancers and is therefore preventable. However, it is an important cause of death in developing and underdeveloped countries (1,2). Cervical cancer is the second most common cancer among women in the world, and is the fourth most common cancer among all cancers. It accounts for 7.5% of deaths due to cancer in females, with a total of 528,000 new cases in 2012 (3). In Turkey, it is ranked fourth among women's cancers and tenth among all cancers seen in women. The incidence of cervical cancer in the 25-49 age group is higher than in other age groups (3.6%) (4).

Human papillomavirus (HPV) is a very common virus group in the world and is the most obvious cause of cervical cancer. There are more than 100 types of HPV. In particular, type 16 and 18 HPV causes 70% of cervical cancer and precancerous cervical lesions. The Pap smear test has been the standard method in cervical cancer screening. It reduces incidence by 60-90% and mortality by 90% (2). Our country has changed national screening standards since 2013 (5). National screening standards recommend screening with cytology or HPV DNA testing once every 5 years between the ages of 30-65 (6). With cervical cancer screening, precancerous lesions can be easily detected and treated. In developed countries, 80% of cervical cancers are prevented by early diagnosis and treatment. In developing countries, this situation is reversed (2). In recent studies in our country, it is stated that the frequency of screening with Pap smear test is still not sufficient and that these rates vary between 21.9% and 50% (7-10).

The Health Belief Model (HBM) is often used in explaining preventive health behaviors. The Model argues that an individual's health behaviors will be influenced by their beliefs, values and attitudes, and is often used to explain early diagnosis and screening behaviors of breast and cervical cancer. Socio-demographic variables, psychological characteristics and structural factors are important in behavior change (11). A study found a strong relationship between cervical cancer screening practices and healthy lifestyle behaviors. In addition, women who were working were found to have lower Pap smear barrier scores on cervical cancer and Pap Smear test of Health Belief Model scale compared to women who were not working (8). Moore et al. (12) found that information about cervical cancer was not sufficient in women with high levels of education. In another study, women with a history of Pap testing had higher sensitivity, utility, severity, and perceived barriers scores than women without a history of Pap testing (12). In the literature, there were studies in which the characteristics of women's education and work status were not separated and they were compared. The aim of this study was to evaluate working women who had high educational level and to determine the health beliefs and practices of these women for cervical cancer and screening and to determine the factors that affected them.

Methods

This descriptive and cross-sectional study was conducted in a Presidency of Tax Office located in a provincial center. The universe of the research was made up of 132 married women working in the Tax Office. The study was completed with a total of 120 women. The data were collected between June and August 2017. Inclusion criteria were: Working in the presidency of Tax Office, being 18 years old or over, being married, not diagnosed as having gynecologic cancer and volunteering to participate in the study.

Data Collection Tools

The data was collected using a "Descriptive Data Form" and a "Cervical Cancer and Pap Smear Test Health Belief Model scale".

Descriptive information form; this form was created by researchers scanning the literature (8-10). The form consisted of 20 questions. These questions included women's socio-demographic characteristics (age, education, income, smoking), cervical cancer risk factors, cervical cancer and Pap smear test information, application questions and family history of cervical cancer.

The Cervical Cancer and Pap Smear Test Health Belief Model scale was developed by Güvenç et al. (13) based on Champion's HBM. The scale determines women's beliefs about cervical cancer and Pap smear testing. The likert-type scale with 5 options consists of 35 items and five sub-dimensions. The sub-dimensions are; Pap smear benefit and motivation [minimum-maximum (min-max)=8-40], Pap smear barriers (min-max=14-70), cervical cancer (CC) seriousness (min-max=7-35), CC sensitivity (min-max=3-15), and CC health motivation (min-max=3-15). In this likert-type scale, each part is scored from 1 to 5 as; "strongly disagree" (1), "disagree" (2), "neutral" (3), "agree" (4), "totally agree" (5). Each dimension is evaluated separately. There is no total scale score. As scores increase, sensitivity, caring and health motivation increase; benefits for benefit perception, barriers for obstacle perception are perceived high. Sub-dimensions other than the barrier perception sub-dimension are positively correlated with Pap smear screening behavior. Cronbach's Alpha coefficients range from 0.62 to 0.86 for five sub-dimensions (13). In this study, Cronbach's Alpha coefficients were between 0.79 and 0.94.

Data Collection

The data were collected by researchers using a face-to-face interview technique. Between July and August 2017, women were reached during working hours. Women with reports (5 people) and those who did not want to participate (9 people) were not included in the study. The answering time of the questionnaire took about 10-15 minutes.

Ethics Approval

Approval was obtained from the Non-interventional Clinical Research Ethics Committee of a University (Board meeting date 04.07.2017 and number 09) and from the institution where the study was conducted. The purpose of the study was explained to

the women who participated in the study and their oral consent was obtained.

Statistical Analysis

All data were analyzed with the Statistical Package for the Social Sciences program (version 24.0). The data were evaluated with number, percentage, t-test and variance analysis tests. Logistic regression analysis was performed with variables affecting women's Pap smear test status. Statistical significance level was considered as $p<0.05$.

Results

The average age of women was 39.5±9.02 years and 50.0% were ≥40 years old. Of the participants, 59.2% stated that they had a Pap smear test. Of them, 60.8% were undergraduate or postgraduate. Of women, 11.7% had sufficient knowledge about early detection methods of cervical cancer and 42.5% had regular gynecological examinations (Table 1). The mean scores of the sub-dimensions were 7.1±2.9 for CC sensitivity, 19.9±7.04 for CC/seriousness, 31.9±7.2 for Pap smear benefit and motivation, 8.9±3.2 for CC health motivation and 30.1±10.1 for Pap smear barriers (Table 2).

Women with a family history of cervical cancer and high income status had a higher CC sensitivity sub-dimension score without a statistically significant difference ($p<0.05$). Women with adequate knowledge of early diagnosis methods had higher Pap smear benefit and motivation sub-dimension scores with a statistically significant difference ($p<0.001$). Benefit and sensitivity sub-dimension scores were significantly lower ($p<0.01$), while Pap smear barrier scores were significantly higher ($p<0.05$) in high school and associate degree graduates than in undergraduates and postgraduates. The mean score of CC health motivation sub-dimension of the scale was found to be significantly higher in women who were undergraduate or postgraduate and who had adequate knowledge of early diagnosis. Pap smear barriers sub-dimension scores were significantly higher in women with high school and associate degree education and who did not have regular gynecological examinations ($p<0.001$) (Table 2).

In Table 3, the factors that are effective in the behavior of Pap smear testing and the degree of effect are shown by the logistic regression model. It was determined that no sub-dimensions of the scale affected the behavior of Pap smear testing ($p>0.05$). While women's knowledge on gynecologic cancer and gynecological examinations increased Pap smear behavior by three times on average, women's age increased Pap smear behavior by about one fold.

Discussion

In this study, women's Cervical Cancer and Pap Test Health Belief Model scale lower size score averages were determined at moderate levels. The average scores of women with higher education levels in studies conducted in different educational groups are consistent with our study (8,9,14-17). A study in educated women in West Africa (2014) highlighted the necessity of education about cervical cancer even if women were knowledgeable and educated (12). Health protective behaviors for cervical cancer in women with high levels of education were lower than expected. Regardless of women's educational status, positive health behaviors for cervical cancer and Pap smear testing should be increased.

In this study, women's perception of CC sensitivity was influenced by their good income status. These variables were thought to be effective in accessing information. Income status was not found to be effective in other sub-dimensions which only affected sensitivity perception in our study. Women with good income may have easier access to health care. Ersin et al. (9) stated that no variables affected sensitivity perception in female health care personnel. Another variable that affects women's perception of CC sensitivity is the presence of a history of CC in the family.

Table 1. Distribution of women by their characteristics

Characteristics	Number	%
Age group		
20-29 years	19	15.8
30-39 years	41	34.2
40 years or above	60	50.0
Mean age	**39.5±9.02**	
Education level		
High school and associate degree	47	39.2
Graduate	73	60.8
Income		
Income=expense	57	47.5
Income<expense	45	37.5
Income>expense	18	15.0
Cigarette smoking		
Yes	31	25.8
No	89	74.2
Knowledge of early diagnosis methods		
Sufficient	14	11.7
Low	73	60.8
None	33	27.5
Having a history of cervical cancer in family		
Yes	4	3.3
No	116	96.7
Status of Pap smear testing		
Yes	49	40.8
No	71	59.2
Regular gynecological examination		
Yes	51	42.5
No	69	57.5
Total	120	100.0

Table 2. Comparison of women's health belief model scale scores with different variables

	Scale sub-dimentions									
Variables	**CC sensitivity**		**CC seriousness**		**Pap smear benefit and motivation**		**CC health motivation**		**Pap smear barriers**	
	Mean ± SD	p	Mean ± SD	p	Mean ± SD	p	Mean ± SD	p	Mean ± SD	p
Education status*										
High school and associate degree	7.4±3.4		18.7±7.2		30.6±8.8		7.9±3.2		33.0±11.3	
Graduate	6.9±2.3	0.36	20.7±6.7	0.15	32.8±5.8	0.13	9.2±3.2	0.018	28.3±8.3	0.001
Age**										
20-29 years	6.9±2.6		20.2±5.6		34.2±5.8		8.3±3.3		31.3±8.3	
30-39 years	7.4±2.7	0.26	19.2±7.4	0.75	31.0±7.8	0.26	8.6±3.0	0.46	30.9±12.0	0.62
40 years or over	7.0±3.0		20.3±7.2		31.9±7.1		9.2±3.4		29.3±9.2	
Income**										
Income=expense	7.5±2.8		20.8±6.5		33.3±5.1		8.9±3.1		30.5±9.5	
Income<expense	6.2±2.9	0.03	18.0±6.8	0.06	31.0±8.3	0.11	9.0±3.7	0.85	29.3±10.3	0.70
Income>expense	7.8±2.5		21.9±8.5		29.9±9.1		8.5±2.7		31.5±11.7	
Knowledge of early diagnosis methods **										
Sufficient	7.8±3.8		20.3±7.5		35.3±3.5		10.6±2.9		25.4±12.3	
Low	7.3±2.6	0.28	20.2±6.6	0.70	32.7±6.1	0.00	9.0±2.9	0.01	30.0±8.9	0.09
None	6.5±2.9		19.0±7.9		28.8±9.3		7.7±3.7		32.4±11.0	
Having a history of cervical cancer in family *										
Yes	10.5±2.4		24.0±4.5		36.0±3.1		8.2±1.7		23.5±9.8	
No	7.0±2.8	0.01	18.8±7.0	0.16	31.8±7.3	0.06	8.9±3.2	0.69	30.4±10.0	0.18
Regular gynecological examination *										
Yes	6.6±2.9		19.1±6.7		32.4±7.3		9.3±3.3		26.6±8.2	
No	7.5±2.8	0.08	20.5±1.3	0.29	31.6±7.1	0.51	8.6±3.2	0.24	32.8±10.5	0.000
Total	**7.12±2.9**		**19.9±7.0**		**31.9±7.2**		**8.9±3.2**		**30.1±10.1**	

SD = Standard deviation, *t= Student t-testi, **F= One-way ANOVA test

Jia et al. (18) found that women with a family history of cancer had higher levels of knowledge about CC. Although having a history of cancer in the family has a positive impact on women's susceptibility to CC and it affects knowledge levels positively; education and monitoring of these women who are in the high risk group should be carried out more carefully. Perceptions of women of not being at risk for cervical cancer may hamper their approach to early diagnosis practices. Increasing CC sensitivity can positively affect Pap smear behavior. Therefore, effective training should be considered. Kissal and Baser (10) stated that the training given by nurses based on HBM was effective in raising the sensitivity and perception of benefits of CC.

In our study, it was determined that the variables that were examined did not affect the CC seriousness sub-dimension. Contrary to our study, Koç et al. (17) stated that education increased the severity of CC. Interestingly, in this study, although all women had a high level of education, they did not take the disease seriously and ignored it. Women will also not find it meaningful to participate in cancer screening studies if they do not take the disease seriously.

In this study, the score of women who only had knowledge about early diagnosis was higher in the area of pap smear benefit and motivation. Although women had a high level of education, the fact that only those who had knowledge had different perceptions of benefits suggested that all women needed to increase their level of knowledge. If the individual has information about the disease, his/her perception is affected accordingly (19). Studies highlight that women's high benefit perception is effective in getting a Pap smear test (20,21). The high perceived benefit indicates the importance of the screening method and the perception of a program (21). Jia et al. (18) showed that cervical cancer knowledge was associated with women's participation in cervical cancer screening. The benefit and motivation of Pap smears were determined higher in women who graduated from

Table 3. Regression analysis of factors associated with pap test

Variables	β (SE)	Wald statistic	Df	p	95% CI for odds ratio		
					Odds ratio	Lower	Upper
Age	-.099 (.028)	12.695	1	.000	.906	.858	.957
Regular gynecological examination	1.118 (.504)	4.912	1	.027	3.059	1.138	8.221
Knowledge of early diagnosis methods	1.103 (.472)	5.465	1	.019	3.015	1.195	7.603
Pap smear benefit and motivation	-.043 (.035)	1.512	1	.219	.958	.894	1.026
Pap smear barriers	.007 (.025)	.070	1	.792	1.007	.958	1.058
Seriousness	.010 (.037)	.071	1	.791	1.010	.940	1.085
Sensitivity	.007 (.091)	.005	1	.941	1.007	.843	1.202
Health motivation	-.060 (.077)	.604	1	.437	.942	.810	1.095
Constant	3.874 (1.797)	4.644	1	.031			

Hosmer and Lomeshow Test, x^2=2.47; p>0.05
Nagelkerke R2 = 0.412Model x^2 = 43.763; p<0.000, CI: Confidence interval

college, had an occupation and worked, had knowledge of Pap testing, and had a history of gynecologic cancer in the family in the study by Egelioglu Cetisli et al. (8). Increasing perceptions and knowledge of cervical cancer benefit will be effective in increasing women's likelihood of taking preventive action. At-home monitoring and training by medical staff affects women's level of knowledge about cervical cancer (22).

Women's willingness to have cervical cancer screenings reveals their health motivations. In our study, only high level of education and knowledge of early diagnosis affected the perception of health motivation. In addition to their results supporting the findings of our study, Egelioglu Cetisli et al. (8) showed that the working condition of women was also effective. Koç et al. (17) showed that education given raised women's perception of health motivation and increased their tendency to perform screening behavior. Women should be empowered by effective training in increasing women's health motivations and ensuring their willing participation in screening behaviors. According to the Health Belief Model, as women's positive perception of the usefulness of the Pap smear test increases, sensitivity, seriousness and health motivation increase in parallel (23).

In this study, the barrier perception score of educated women was moderate. Studies in Turkey found that among the barriers to screening cervical cancer were ignorance, neglect, shame, fear of cancer and death, lack of Social Security, thinking that they were not a risky group, presence of transportation difficulties, inability to go to the doctor without permission from their spouses and inability to be examined by a male doctor (17,24,25). In other studies in the literature, reasons similar to the perceptions of barriers in our country were expressed (18,21,26,27). Gokgoz et al. (16), showed that women with educational attainment of high school and university had lower perceptions of barrier than other educational groups. In this study, women who did not have regular gynecological examinations and who had lower educational levels had significantly higher perception of barrier. Women who do not have regular gynecological examinations may be the result of the perception of Pap test barrier in the literature. Medical staff should therefore question the causes that hinder women's screening behaviour and provide approaches to eradicating it. Screening behaviors for CC can be increased when the perception of disability is reduced or eliminated. Studies of CC and HPV prevalence and educational efforts highlighting the medical importance of screening can reduce stigma and barriers to Pap testing for CC and screening (28).

In our country, national based cervical cancer screening has been conducted more systematically and free of charge in recent years (6). In our study, more than half of women had Pap tests, but cervical cancer and Pap test beliefs were not sufficient. Women who participated in our study may also have had Pap testing under the screening program. One study highlighted that women had little awareness of CC and had negative judgments and beliefs about screening methods (9). In order to gain knowledge of CC

and Pap smear test behaviors, education of women with high levels of education should also be considered.

In this study, age variable increased women's Pap smear test behavior approximately by one fold, while early diagnosis information and gynecological examination increased it by 3 folds. Similar to our study results, Jeihooni et al. (21) determined that age and knowledge were effective variables in performing Pap smear test by women. Ma et al. (29) showed that age and education were effective variables in pap smear screening behaviors. Our study and other studies showed that Pap test-performing behaviors increased as age increased (29). The emergence of gynecological problems in women with age can lead to increased fear and anxiety and to screening behaviors. Lack of information is an important factor affecting Pap smear test behavior. Gokgoz et al. (16) determined that women's knowledge of why a Pap smear test was performed affected their behavior by having a Pap smear test. In this study, it was also determined that the attitudes of women regarding gynecological examination influenced the behavior of having a Pap smear test (16). The socio-demographic characteristics of women are important in the behavior of having Pap smear tests. However, adoption of preventative behaviors depends not only on external factors, but also subjective factors towards women (30). All these features should be taken into account in increasing the rates of women having Pap smear tests.

In regression analysis, none of the sub-dimensions of the scale affected women's Pap testing. Similarly, in the study of female health personnel; sensitivity, seriousness and benefit perceptions were not found to be effective in Pap smear testing (9). Unlike our work, Jeihooni et al. (21) showed positive association between SIM structures and Pap test performance. Ma et al. (29) showed that, in terms of the perceived benefits of pap smear test, approximately 50% of women believed that Pap testing was the best way to detect CC and that it was important, and that women who believed them were two to four times more likely to have a Pap test than those who did not believe. Tanner-Smith and Brown (23) found that perceived benefits and barriers were the strongest determinants of participation in screening behaviors. Increasing women's health beliefs about CC and Pap testing will also affect their participation in screening behaviors. Studies in the literature highlight that trainings based on the Health Belief Model increase participation in CC screening programs (10,17,22,26,27,31). Health personnel should carry out planned training activities in all areas where health services are provided in an orderly manner. However, considering that working women cannot come to receive education and do not have the time, planned training activities can be carried out in their fields of study.

Conclusion

As a result, awareness of CC and Pap smear test were not enough in working women with high level of education. In our study, the score averages of the sub-dimensions of the HBM scale were moderate. These women's perceptions of CC usefulness, sensitivity, seriousness, and the Pap smear test health motivation average scores should be increased and the Pap test barrier perception average scores should be lowered. It is thought that improving awareness of cancer prevention will be effective in ensuring the effectiveness of screening programmes, no matter what level of education women are at. All health workers play an important role in preventing CC, providing effective and accurate information. In particular, nurses are effective in providing health education that will affect women's screening behavior and in increasing women's motivations. Planned training programs should be conducted continuously for women in work environments and wherever they come to receive health care. Training educated women is suggested by the idea that they may be role models in society.

Ethics

Ethics Committee Approval: Approval was obtained from the Non-interventional Clinical Research Ethics Committee of a University (Board meeting date 04.07.2017 and number 09) and from the institution where the study was conducted.

Informed Consent: The purpose of the study was explained to the women who participated in the study and their oral consent was obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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References

1. Kanbur A, Çapık C. Servikal Kanserden Korunma, Erken Tanı-Tarama Yöntemleri ve Ebe/Hemşirenin Rolü. Sağlık Bilimleri Fakültesi Hemşirelik Dergisi 2011:61-72.
2. World Health Organization. Human papillomavirus (HPV) and cervical cancer. http://www.who.int/mediacentre/factsheets/fs380/en/. Erişim Tarihi: 18Mart 2018.
3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers CI, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:359-86.
4. Türkiye Halk Sağlığı Kurumu, Kanser Daire Başkanlığı 2014 Yılı Türkiye kanser ıstatistikleri [Internet] Ankara: Türkiye Halk Sağlığı Kurumu; 2016. [cited 2017 Apr 11]. url:http://kanser.gov.tr/daire-faaliyetleri/kanser-istatistikleri/2106-2014-yılı-türkiye-kanser istatistikleri.html
5. Gültekin M, Akgül B. HPV screening in Islamic countries. Lancet Infect Dis 2017;17:368.
6. Gültekin M, Dundar S, Kucukyildiz I, Karaca Zayifoğlu M, Boztaş G, Turan SH, et al. Survival of gyne1cological cancers in Turkey: where are we at? J Gynecol Oncol 2017;28:85.

7. Taşcı Duran E, Koc S, Korkmaz M. Turkish Social Attitudes towards to Cancer Prevention: a Health Belief Model Study. Asian Pac J Cancer Prev 2014;15:7935-40.
8. Egelioğlu Çetişli N, Top ED, Işık G. Cervical Cancer and Pap Smear Test Health Beliefs and Health Promoting Lifestyle of Women in Turkey. IJCS 2016;9:630-9.
9. Ersin F, Kıssal A, Polat P, Koca BD, Erdoğan M. Perception Of Female Medical Personnel Toward Cervical Cancer And The Affecting Factors, HEMAR-G 2016;18:31-43.
10. Kıssal A, Beşer A. Results of breast and cervical cancer Health Promotion Model for older Turkish women. Journal of Human Sciences 2017;14:2374-85.
11. Bebiş H. Sağlığın Geliştirilmesi ile ilgili Modeller. İçinde: Alkaya AS. editör. Sağlığın Geliştirilmesi. Ankara: Hedef Yayıncılık Matsa Basımevi, I. Baskı; 2017:47-61.
12. Moore AR, Driver N. Knowledge of Cervical Cancer Risk Factors Among Educated Women in Lomé, Togo: Half-Truths and Misconceptions. SAGE Open 2014:1-8.
13. Güvenc G, Akyuz A, Açikel CH. Health belief model scale for cervical cancer and Pap Smear test: psychometric testing. J Adv Nurs 2011;67:428-37.
14. Demirtas B, Acikgoz I. Promoting attendance at cervical cancer screening: understanding the relationship with Turkish women"s health beliefs. Asian Pac J Cancer Prev 2013;14:333-40.
15. Bal MD. Evaluation of Women Having Pap Smear Test by Health Belief Model Scale. MÜSBED 2014;4:133-8.
16. Gökgöz N, Aktaş D. Determination of women awareness level of cervical cancer & conducting Pap-smear test. Yıldırım Beyazıt University Faculty of Health Sciences Nursing E-Journal 2015;3:11-23.
17. Koç Z, Özdeş EK, Topatan S, Çinarli T, Şener A, Danaci E, Palazoğlu CA. The Impact of Education About Cervical Cancer and Human Papillomavirus on Women's Healthy Lifestyle Behaviors and Beliefs: Using the PRECEDE Educational Model. Cancer Nurs 2019;42:106-18.
18. Jia Y, Li S, Yang R, Zhou H, Xiang Q, Hu T, et al. Knowledge about cervical cancer and barriers of screening program among women in wufeng county, a high-incidence region of cervical cancer in China. PLoS One 2013;8:e67005.
19. Erci B. Halk Sağlığı Hemşireliği Kitabı. İkinci baskı. Ankara: Nobel Tıp Kitapevi; 2016.
20. Lee EE, Fogg L, Menon U. Knowledge and Beliefs Related to Cervical Cancer and Screening Among Korean-American Women. West J Nurs Res 2008;30:960-74.
21. Jeihooni AK, Kashfi SM, Bahmandost M, Kashfi SH. The Survey of Factors Affecting Pap Smears Based on Health Belief Model in Health Centers in Fas'a, Fars Province, Iran. Women's Health Bull 2015;2:e25565.
22. Kolutek R, Aydın Avcı İ. The Effect of Training and Monitoring at Home on the Knowledge Level and Practices of Married Women Regarding Breast and Cervical Cancer. J Breast Health 2015;11:155-62.
23. Tanner Smith EE, Brown TN. Evaluating the Health Belief Model: A critical review of studies that predict mammography and pap screening. Social Theory & Health 2010;8: 95-125.
24. Ersin F, Bahar Z. Effects of health promotion models on breast cancer early detection behaviors: A literature review. DEUHYO ED 2012;5:28-38.
25. Aydoğdu NG, Bahar Z. The Effects of Using Health Belief and Health Promotion Models in Low-Income Women with Regard to Breast and Cervical Cancer Early Detection Behaviour. DEUHYO ED 2011;4:34-40.
26. Parsa P, Sharifi F, Shobeiri F, Karami M. Effects of Group Counseling Based on Health Belief Model on Cervical Cancer Screening Beliefs and Performance of Rural Women in Kaboudrahang, Iran. Asian Pac J Cancer Prev 2017;18:1525-30.
27. Coronado Interis E, Anakwenze CP, Aung M, Jolly PE. Increasing Cervical Cancer Awareness and Screening in Jamaica: Effectiveness of a Theory-Based Educational Intervention. Int J Environ Res Public Health 2016:13.
28. Rees HD, Lombardo AR, Tangoren CG, Meyers SJ, Muppala VR, Niccolai LM. Knowledge and beliefs regarding cervical cancer screening and HPV vaccination among urban and rural women in León, Nicaragua. Peer J 2017;5:3871.
29. Ma GX, Gao W, Fang CY, Tan Y. Feng Z, Ge S, et al. Health Beliefs Associated with Cervical Cancer Screening Among Vietnamese Americans. J Womens Health (Larchmt) 2013;22:276-88.
30. Evangelista Rodrigues D, Alves Moreira KF, Souza de Oliveira T. Barriers to prevention of cervical cancer in the city of Porto Velho, Rondônia, Brazil. Invest Educ Enferm 2016;34;58-66.
31. Shobeiri F, Javad MT, Parsa P, Roshanaei G. Efficacy of Group Training Based on the Health Belief Model for Pap Smear Testing in Iranian Women: a Quasi-Experimental Study. Asian Pac J Cancer Prev 2016;17:2871-6.

Original Article

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Comparison of Intravenous, Intra-articular, and Combined Tranexamic Acid Use in Primary Total Knee Arthroplasty without a Tourniquet and a Drain

Turnike ve Dren Olmadan Primer Total Diz Artroplastisinde İntravenöz, İntra-artiküler ve Kombine Traneksamik Asit Kullanımının Karşılaştırılması

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ABSTRACT

Objective: We assessed the effect of tranexamic acid (TXA) route of administration on the estimated blood loss (EBL) in patients undergoing primary total knee arthroplasty (TKA) without tourniquet and drain use.

Methods: One hundred fifty three patients who underwent primary TKA with use of TXA, between December 2012 and February 2016 were evaluated retrospectively. The patients were divided into three groups according to the route of TXA use: group I, 2 g of intravenous (IV; n=50); group II, 2 g of intraarticular (IA, n=50); and group III, 1 g of IV and 1 g IA combined use (n=53). We recorded the body mass indexes, the platelet counts, haemoglobin, haematocrit levels, prothrombin time, partial thromboplastin time, and international normalised ratio, preoperatively and at 1st and 7th days, postoperatively. EBL was calculated using Meunier's formula.

Results: On the first day, the mean EBLs for groups I to III were 286.3±128.8 mL, 342.7±176.0 mL, and 379.7±228.9 mL, respectively (p=0.029 for group I vs. group III). On 7th day postoperatively, they were calculated as 823±619.3 mL, 1175.1±970.5 mL, and 1092.2±766.7 mL (p=0.073) During the first 90 days postoperatively, we did not see any symptomatic thromboembolic complications, delayed haemorrhage, or surgical site or periprosthetic infections.

ÖZ

Amaç: Turnike ve dren kullanmadan primer total diz artroplastisi (TDA) geçiren hastalarda traneksamik asit (TXA) uygulama yolunun tahmini kan kaybı (EBL) üzerindeki etkisini değerlendirdik.

Yöntemler: Aralık 2012-Şubat 2016 tarihleri arasında TXA kullanılarak primer TDA uygulanan 103 hasta retrospektif olarak incelendi. Hastalar TXA kullanım yoluna göre üç gruba ayrıldı: grup I, 2 g intravenöz (IV; n=25); grup II, 2 g intraartiküler (IA, n=25); ve grup III, 1 g IV ve 1 g IA kombine kullanım (n=53). Vücut kitle endeksleri, platelet sayımı, hemoglobin, hematokrit seviyeleri, protrombin zamanı (PT), parsiyel tromboplastin zamanı (PTT) ve internationel normalized ratio (INR) preop, postop 1. ve 7. günde değerlendirdik. EBL, meunier formülü kullanılarak hesaplandı.

Bulgular: İlk gün I ila III. grupların ortalama EBL'leri sırasıyla 286,3±130,15 mL, 342,7±177,87 mL ve 379,7±228,85 mL idi ve istatistiksel olarak farklı değildi (p=0,152). Ameliyat sonrası 7. günde 823±625,75 mL, 1175,1±980,6 mL ve 1092,2-766,7 mL (p=0,250) ameliyattan sonraki ilk 90 gün boyunca herhangi bir semptomatik tromboembolik komplikasyon, gecikmiş kanama veya cerrahi bölge veya periprostetik enfeksiyon görülmedi.

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Conclusion: IV, IA or combined uses of TXA are effective and safe for reducing blood loss and transfusion requirements in primary TKA without a tourniquet and drain.

Keywords: Tranexamic acid, total knee arthroplasty, blood loss

Sonuç: IV, IA veya TXA'nın kombine kullanımları, turnike ve drenaj olmadan primer TDA'da kan kaybını ve transfüzyon gereksinimlerini azaltmak için etkili ve güvenlidir.

Anahtar Sözcükler: Traneksamik asit, total diz artroplastisi, kan kaybı

Introduction

Total knee arthroplasty (TKA) is the surgical option used most frequently in the treatment of symptomatic knee osteoarthritis and it usually results in patient satisfaction. However, it is prone to several complications related to the 800-1500 mL blood loss involved and the requirement for intraoperative and early postoperative allogeneic blood transfusions in 10-30% of patients (1-8). Decreasing the rate of blood loss and the need for allogeneic blood transfusion is very important in TKA for improving functional recovery and decreasing transfusion-related risks and costs (9). Tranexamic acid (TXA) is a potent antifibrinolytic agent that decreases bleeding in TKA by preventing fibrinolytic activity. It acts by binding to the lysine-binding area of plasminogen, consequently blocking the attachment of plasminogen to fibrin. The half-life of TXA, which has been used safely since 1964, is 1.9-2.7 h and a large amount of TXA is excreted in urine without being metabolised when used intravenously (10,11). Recent meta-analyses have revealed that antifibrinolytics are safe and cost-effective, and they decrease the need for blood transfusion and shorten the hospital stay (1,12).

The literature contains no reports on adverse thromboembolic events related to the intravenous (IV) administration of 1-3 g TXA in TKA, but there are potential advantages in terms of tolerability and decreased costs (13). Topical TXA use decreases the plasma TXA concentration ten-fold compared with an IV dose and has 70% less systemic absorption, which decreases the likelihood of adverse effects (14). In addition, to maintain microvascular haemostasis, it is important to reach maximum concentrations at the surgical site (15). The effectiveness of intra-articular (IA) TXA compared to IV administration has not been proven. In some studies, IA TXA reduced postoperative swelling around the knee compared with placebo (16,17). However, there is still no clear evidence whether IA administration has similar effects with IV application.

The literature on the combined IV and IA use of TXA is limited; almost all of the available studies involved tourniquet use, which stimulated fibrinolysis and consequently bleeding (18-20). Therefore, this comparative retrospective study assessed the effect of TXA route of administration (IV, IA, or combined) on the estimated blood loss in patients undergoing primary TKA without tourniquet and drain use.

Methods

This retrospective study included 103 patients with tricompartmental osteoarthritis who underwent primary TKA between December 2012 and February 2016. Patients using anticoagulant or anti-aggregant medications (such as enoxaparin, fondaparinux, clopidogrel, Factor Xa, or thrombin inhibitors) and oral contraceptives, having thrombophilia, oncological disease, hepatic or renal dysfunction, a history of myocardial infarction, deep venous thrombosis (DVT), and alcohol abuse were excluded. The patients were divided into three groups according to the route of TXA use: Group I, 2 g IV [n=50; 46 females, 4 males; mean age, 65.9 (range=46-77) years]; group II, 2 g IA [n=50; 40 females, 10 males; mean age, 70 (range=59-80) years]; and group III, g IV and 1 g IA together [n=53; 46 females, 7 males; mean age, 66.3 (range=54-87) years].

All of the surgeries were performed by three arthroplasty surgeons under spinal anaesthesia and without use of a tourniquet and Hemovac drains. We administered 2 g of IV cefazolin for infection prophylaxis, 30 min before the incision. All patients underwent cemented, cruciate-retaining, tricompartmental TKA using a medial parapatellar approach. Group I was given 2 g TXA in 100 mL of saline, intravenously. Group II was given 2 g of TXA in 30 mL of saline injected intra-articularly after closing the joint capsule. Group III was given 1 g of TXA in 100 mL saline intravenously and 1 g in 15 mL of saline intra-articularly. During the postoperative period, we administered 1 g IV cefazolin for infection prophylaxis for 24 h and 0.4 mL of enoxaparin for DVT prophylaxis for 2 days. On the third day, the patients were discharged and advised to take 100 mg oral aspirin daily and to use anti-embolic socks for the next 6 weeks.

We recorded the body mass index (BMI) preoperatively, and the platelet count, haemoglobin level (Hb), haematocrit (Hct) and international normalised ratio (INR), preoperatively and on 1st and 7th days, postoperatively. The blood loss was estimated using the Meunier's formula: (21)

Estimated blood loss volume (EBV)=BV × $(Hb_i-Hb_f)/Hb_i$, where BV is the estimated blood volume [=weight × average blood volume (75 mL/kg for males, 65 mL/kg for females], Hb_i is the initial preoperative Hb, and Hb_f is the Hb on a given day postoperatively.

The estimated blood losses of the three groups were compared. Patients were investigated for thromboembolic complications, delayed haemorrhage, and periprosthetic infection for 3 months postoperatively.

Statistical Analyses

The data were analysed using one-way analysis of variance (ANOVA) with post hoc tests, using the program SPSS. A p value <0.05 was defined as statistically significant with 95% confidence interval.

Results

The mean BMI and its range in groups I to III were 34.4 (23-47), 33.2 (26-43), and 33.7 (23-50) kg/m^2, respectively (p=0.537). The demographic information for the three groups and preoperative Hb, Hct, and EBV values are shown in Table 1. On the first day, the mean EBV and its standard deviation in groups I to III were 286.3 (128.8), 342.7 (176.0), and 379.7 (228.9) mL, respectively, and did not differ statistically among the groups. The mean EBV was significantly lower in the group I than the group III (p=0.029). There was no significant difference between group I and II (p=0.277) and between group II and III (p=0.564). On the 7th postoperative day, the EBV values were 823 (619.3), 1175.1 (970.5), and 1092.2 (766.7) mL, respectively (p=0.073) (Table 2).

During the first 90 days postoperatively, we did not see any symptomatic thromboembolic complications, delayed haemorrhage, or surgical site or periprosthetic infections.

Discussion

There is still no consensus on the dosage and route of administration of TXA in orthopaedic surgery. Adequate blockage of fibrinolysis in the tissues requires an approximately 80% decrease in plasminogen activity. For this reason, the plasma TXA concentration should be 10 ng/mL and this plasma concentration can be obtained with a 10 mg/kg dose of IV TXA in 3 h (22). In the literature, TXA decreased the need for blood transfusion by up to 38% in orthopaedic, cardiovascular, cranial, and general surgeries (23). The estimated blood loss in groups I and III showed that both dosages were sufficient for reaching the effective plasma concentration.

Topical TXA has less systemic absorption and higher local concentrations compared with IV administration, which means it has fewer systemic side effects. It also decreases the need for transfusion 13-fold compared with placebo (10,15,24). Wang et al. (15) reported that IV TXA was not superior to IA administration in reducing blood loss or the need for transfusion. Maniar et al. (22) showed that a single 3 g IA TXA dose is as effective as single 10 mg/kg IV TXA dose. A review by Pantelli et al. (25) compared topical TXA application of less than 2 g and more than 2 g with placebo and found that both dosages decreased the rate of transfusion need, although the decrease was not significant in the group who received less

Table 1. Demographic data and preoperative blood counts

	IV group	IA group	Combined group	P value
No. of patients (M/F)	50 (4/46)	50 (10/40)	53 (7/46)	
Age (SD)	65.9 (8.3)	70.1 (6.7)	66.3 (8)	0.101
BMI (kg/m^2) (SD)	34.4 (6.5)	33.2 (4.5)	33.7 (5.3)	0.537
Preop. Hb (g/dL)	12.6 (1.6)	12.7 (1.4)	12.8 (1.4)	0.741
Preop. HcT (%)	37.6 (4.3)	38.8 (3.5)	39.4 (3.7)	0.061
Preop platelet count X1000	267.7 (73.6)	254.7 (62.5)	271.4 (98)	0.541
Preop INR	1.05 (0.10)	1.14 (0.21)	1.05 (0.21)	0.131
Estimated blood volume (mL) (SD)	5666.7 (1019)	5727.8 (779.7)	5648.1 (1046.4)	0.908

SD: Standard deviation, HcT: Haematocrit, Hb: Haemoglobin , INR: International normalised ratio

Table 2. Summary of the data on the first and seventh postoperative days

	Intravenous group (SD)	Intra articular group (SD)	Combined group (SD)	p value
Hb (g/dL) (first day)	11 (1.6)	10.9 (1.3)	10.7 (1.3)	0.541
HTC (%) (first day)	32.4 (4.5)	32.2 (3.8)	32.6 (3.6)	0.879
Hb (g/dL) (7th day)	11 (1.2)	10.7 (1.6)	10.8 (1.3)	0.576
HTC (%) (7th day)	32.4 (3.4)	32.8 (4.9)	34.1(4.7)	0.296
Estimated blood loss (first day)	286.3 (128.8)	342.7 (176)	379.7 (228.9)	0.037 (group I vs III)
Estimated blood loss (7th day)	823 (619.3)	1175.1 (970.5)	1092.2 (766.7)	0.073

SD: Standard deviation, Hb: Haemoglobin, HTC: Hematocrit

than 2 g topical TXA. In their topical TXA group, the decrease in the postoperative Hb level was around 1 g/dL. In our study, the means of decrease in the Hb level on the first postoperative day in groups I to III were 1.6±0.6, 1.9±0.9, and 2.1±1.0 g/dL, respectively (p=0.009). On day 7, the differences between the pre- and postoperative Hb levels in groups I to III were 1.6±1.1, 2.0±1.4, and 2.0±1.2 g/dL, respectively (p=0.133). Although there was a statistically significant difference in terms of the mean Hb loss in the first postoperative day between groups I and III, which might not have a clinical importance, no statistical difference was seen in the 7th postoperative day. Postoperatively, no symptomatic anaemia or need for blood transfusion was seen in any patient.

Although TXA is expected to increase the rates of DVT and pulmonary embolism due to its antifibrinolytic activity, Astedt et al. (26) reported that TXA did not exert its antifibrinolytic activity on the walls of veins and it protected against thrombosis. Moreover, several studies have proven that TXA decreases blood loss without increasing the incidence of DVT or thromboembolic events (10,27,28). We did not see a symptomatic DVT or pulmonary embolism in any patient and in parallel with the literature, we think that this is a consequence of using TXA and not using a tourniquet in our study.

This study had some limitations. First, it was a retrospective study with a limited number of patients. It would have been better if we had groups with tourniquet or drain use or combined use of them. Lastly, we could not compare the results of different dosages of TXA.

Conclusion

Intravenous, intra-articular, or combined use of TXA is effective and safe for reducing blood loss and transfusion requirements in primary TKA without using tourniquet and drains.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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References

1. Jain NP, Nisthane PP, Shah NA. Combined Administration of Systemic and Topical Tranexamic Acid for Total Knee Arthroplasty: Can It Be a Better Regimen and Yet Safe? A Randomized Controlled Trial. J Arthroplasty 2019;31:542-7.
2. Callaghan JJ, O'Rourke MR, Liu SS. Blood management: issues and options. J Arthroplasty 2005;20(4 Suppl 2):51.
3. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, Syed KA, Muhammad Ovais Hasan S, De Silva Y, Chung F. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010;92:2503.
4. Charoencholvanich K, Siriwattanasakul P. Tranexamic acid reduces blood loss and blood transfusion after TKA: a prospective randomized controlled trial. Clin Orthop Relat Res 2011;469:2874.
5. Hiippala ST, Strid LJ, Wennerstrand MI, Arvela JV, Niemela HM, Mantyla SK, Kuisma RP, Ylinen JE. Tranexamic acid radically decreases blood loss and transfusions associated with total knee arthroplasty. Anesth Analg 1997;84:839.
6. Goodnough LT, Verbrugge D, Marcus RE. The relationship between hematocrit, blood lost, and blood transfused in total knee replacement. Implications for postoperative blood salvage and reinfusion. Am J Knee Surg 1995;8:83
7. Bong MR, Patel V, Chang E, Issack PS, Hebert R, Di Cesare PE. Risks associated with blood transfusion after total knee arthroplasty. J Arthroplasty 2004;19:281.
8. Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Br J Anaesth 2003;90:596.
9. Husted H. Fast-track hip and knee arthroplasty: clinical and organizational aspects. . Acta Orthop 2012;Suppl 83:1.
10. Alshryda S, Mason J, Vaghela M, Sarda P, Nargol A, Maheswaran S, Tulloch C, Anand S, Logishetty R, Stothart B, Hungin AP. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial (TRANX-K). J Bone Joint Surg Am 2013;95:1961.
11. Kim C, Park SS, Davey JR. Tranexamic acid for the prevention and management of orthopedic surgical hemorrhage: current evidence. J Blood Med 2015;6:239.
12. Chen TT, Jiandong L, Wang G, Jiang SL, Li LB, Gao CQ. Combined treatment of ulinastatin and tranexamic acid provides beneficial effects by inhibiting inflammatory and fibrinolytic response in patients undergoing heart valve replacement surgery. Heart Surg Forum 2013;16:E38.
13. Smit KM, Naudie DD, Ralley FE, Berta DM, Howard JL. One dose of tranexamic acid is safe and effective in revision knee arthroplasty. J Arthroplasty 2013;28(8Suppl):112.
14. Ng W, Jerath A, Wasowicz M. Tranexamic acid: a clinical review. Anaesthesiol Intensive Ther 2015;47:339.
15. Wang H, Shen B, Zeng Y. Comparison of topical versus intravenous tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled and prospective cohort trials. Knee 2014;21:987.
16. Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Opperer M, Boettner F, Memtsoudis SG. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the

United States: retrospective analysis of effectiveness and safety. BMJ 2014;349:4829.

17. Ishida K, Tsumura N, Kitagawa A, Hamamura S, Fukuda K, Dogaki Y, Kubo S, Matsumoto T, Matsushita T, Chin T, Iguchi T, Kurosaka M, Kuroda R. Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. Int Orthop 2011;35:1639.
18. Roy SP, Tanki UF, Dutta A, Jain SK, Nagi ON. Efficacy of intra-articular tranexamic acid in blood loss reduction following primary unilateral total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2012;20:2494.
19. Karaaslan F, Karaoglu S, Mermerkaya MU, Baktir A. Reducing blood loss in simultaneous bilateral total knee arthroplasty: combined intravenous-intra-articular tranexamic acid administration. A prospective randomized controlled trial. Knee 2015;22:131.
20. Fahmy NR, Patel DG. Hemostatic changes and postoperative deep-vein thrombosis associated with use of a pneumatic tourniquet. J Bone Joint Surg Am 1981;63:461.
21. Meunier A, Petersson A, Good L, Berlin G. Validation of a haemoglobin dilution method for estimation of blood loss. Vox Sang 2008;95:120.
22. Maniar RN, Kumar G, Singhi T, Nayak RM, Maniar PR. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. Clin Orthop Relat Res 2012;470:2605.
23. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. BMJ 2012;344:e3054.
24. Damji KF, Noel LP, Peterson RG, Ma PE, Clarke WN, Gilberg S, Crouch ER, Jr., Williams PB. Topical versus intravenous administration of tranexamic acid: a comparison of intraocular and serum concentrations in the rabbit. Can J Ophthalmol 1998;33:308.
25. Panteli M, Papakostidis C, Dahabreh Z, Giannoudis PV. Topical tranexamic acid in total knee replacement: a systematic review and meta-analysis. Knee 2013;20:300.
26. Astedt B, Liedholm P, Wingerup L. The effect of tranexamic acid on the fibrinolytic activity of vein walls. Ann Chir Gynaecol 1978;67:203.
27. Zhang F, Wang K, Li FN, Huang X, Li Q, Chen Z, Tang YB, Shen HX, Song QX. Effectiveness of tranexamic acid in reducing blood loss in spinal surgery: a meta-analysis. BMC Musculoskelet Disord 2014;15:448.
28. Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. J Bone Joint Surg Br 2001;83:702.

Original Article

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Socio-demographic and Clinical Characteristics of 113 Adolescents with Bipolar Disorder: An Inpatient Sample from Turkey

Bipolar Bozukluk Tanısı ile İzlenen 113 Ergen Hastada Sosyo-demografik ve Klinik Özellikler: Bir Yataklı Klinik Örneklemi

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ABSTRACT

Objective: Pediatric bipolar disorder (BD) is a highly morbid disorder which is associated with impairments in social, academic, and family functioning. Despite its great impact on public health, the literature is scarce regarding the studies examining the clinical phenomenology of BD in children and adolescents.

Methods: A retrospective chart review of 113 children and adolescents' files (ages 13-18 years) who were consecutively admitted to our inpatient clinic between March 2012 and November 2014 and diagnosed as having BD type I or BD type II was made. The diagnoses were based on DSM-IV-TR criteria. A sociodemographic and clinical data form was created by the authors and was filled out for each patient by the authors themselves.

Results: Totally 113 adolescents (71 male, 42 female) were included in the study. Mean age of the sample was 16.054±1.23 (range=13-18) years. Mean age of onset of BD was 15.04±1.74 (range=9-17) years. The first mood episode was manic in 60% of patients, depressive in 27.3%, mixed in 10.9% and hypomanic in 1.8% of patients. Of the patients, 23.4% had a suicide attempt history, 48.2% had a previous referral to a psychiatry clinic before the onset of BD. History of

ÖZ

Amaç: Pediyatrik bipolar bozukluk (BB) sosyal, akademik ve aile içi işlevsellikte bozulma ile seyreden bir ruh sağlığı bozukluğudur. Toplum sağlığı açısından taşıdığı öneme karşın, literatürde çocuk ve ergenlerde BB klinik görünümlerine ilişkin araştırma sayısı göreceli olarak azdır.

Yöntemler: Bir yataklı tedavi ünitesinde BB-1 ve BB-2 tanısı ile izlenen 113 çocuk ve ergen olgunun tedavilerine ilişkin kayıtlar geriye dönük olarak taranmıştır. BB-1 ve BB-2 tanıları DSM-IV-TR kriterleri temel alınarak konulmuştur. Araştırmacılar tarafından oluşturulan sosyo-demografik ve klinik veri formu, her bir olguya ait kayıtların, araştırmacılarca incelenmesi sonucunda elde edilen bilgiler doğrultusunda doldurulmuştur.

Bulgular: Çalışmaya toplamda 113 hasta (71 erkek, 42 kız) dahil edilmiştir. Örneklemin ortalama yaşı 16,054±1.23 (13-18) olarak saptanmıştır. BB ortalama başlangıç yaşı 15,04±1,74 (9-17) idi. Olguların %60'ında ilk duygudurum epizodu manik, %27,3'ünde depresif, %10,9'unda karma, ve %1,8'inde hipomanikti. Olguların %23,4'ünün öyküsünde geçmişte intihar girişimi mevcuttu. Olguların % 48,2'si BB başlangıcından önce bir psikiyatri kliniğine başvuruda bulunmuştu. Olguların %27,4'ünde madde/alkol

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substance/alcohol use was present in 27.4% of the patients. Of the patients, 84.9% were using combination treatments.

Conclusion: High rates of suicide attempt, substance use and significant functional impairment found in our study sample indicate that early recognition and intervention of BD, specialized educational programs and occupational support for these children and adolescents seem indispensable.

Keywords: Bipolar disorder, adolescent, inpatient, clinical characteristics

kullanımı mevcuttu. Olguların %84,9'unda çoklu ilaç tedavisi kullanılmıştı.

Sonuç: İntihar girişimi, madde kullanımı ve işlevsellikte önemli ölçüde bozulma sıklığı BB'de erken tanı ve tedavinin, özel eğitim programlarının ve mesleki desteğin, bu tanıyı alan çocuk ve ergenler için öneminin büyüklüğünün altını çizmektedir.

Anahtar Sözcükler: Bipolar bozukluk, ergen, yataklı tedavi, klinik özellikler

Introduction

Bipolar disorder (BD) is a highly morbid disorder increasingly recognized in adolescents (1). The overall rate of BD was reported to be 1.8% in a meta-analysis of epidemiologic studies of pediatric BD including participants between the ages of 7 and 21 years (2). Several studies have supported a strong genetic component in pediatric patients and early onset BD; and family studies have found a high rate of BD particularly among the relatives of individuals with pediatric BD (3-7). Age at onset has been defined as a clinical marker that may indicate more homogenous, neurobiologically distinctive subgroups (8). Pediatric BD is associated with high rates of repeated hospitalizations and suicide attempts and impairments in social, academic, and family functioning (5,9-13). Furthermore, significant associations were found between pediatric BD and substance use disorders (SUDs) in several studies (8,10,14-19). In a study including 502 outpatients with BD, Holtzman et al. reported that 328 of those with childhood or adolescent-onset BD had significantly higher rates of unfavorable illness characteristics, lifetime alcohol use disorder, and prior suicide attempt, than those with adult-onset BD (8).

Despite the high rate of the disorder and its public health significance, there are relatively few published studies examining the clinical phenomenology of BD in children and adolescents in Turkey. To our knowledge, there are only two epidemiologic studies of BD in Turkish children. Both studies were conducted in prepubertal community samples. Diler et al. (20) screened 2468 (1.176 girls; 1.292 boys) randomly selected elementary school students aged between 7 and 11 years by using the Parent-Young Mania Rating scale (P-YMRS). In the study, 19 (59.4%) boys and 13 (40.6%) girls had mania (mean age=9.31±1.47). In the mania group, being talkative/pressured speech, increased motor activity (high energy), elevated mood, sleep problems, rapid thoughts / flight of ideas, and irritability were the symptoms with the highest mean P-YMRS scores. In a recent epidemiologic study, Karacetin et al. screened affective disorders in 5842 (51.5% male; mean age 8.7±1.2), elementary school students between second and fourth grades by using the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children- Present and Lifetime Version (K-SADS-PL) as a part of the "The Epidemiology of Childhood Psychopathology in Turkey" (EPICPAT-T) study (21). In this study, the reported prevalence rate of affective disorders was 2.5% without taking into account impairment and 1.6% when impairment was considered. However, unlike the study by Diler et al. (20), none of the participants in this research diagnosed with BD.

In a study from Turkey, Erkıran et al. (22) aimed to determine the relationship between age at onset and phenomenology of BD. Socio-demographic and clinical features, type of episode, number and duration of hospitalizations were compared between the groups consisted of adolescent-onset adolescents (n=60), adolescent-onset adults (n=60) and adult-onset adults (n=60). The authors concluded that adolescent-onset BD was associated with higher probability of mixed episodes, psychotic features including mood congruent or incongruent hallucinations and delusions. A case series of children and adolescents with BD aged between 7 and 15 years was reported by Inal Emiroğlu (23). In this case series, 7 (3 girls, 4 boys) children and adolescents with BD were assessed by Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia, Lifetime and Present Episode Version, DSM-IV (WASH-U-KSADS). The authors reported that grandiosity, distractibility and abnormal energy were the most frequently detected symptoms. In this case series, 4 patients had mixed cycling features, 5 had ultradian cycling and 1 had rapid cycling (23).

In another study, Diler et al. (24) aimed to differentiate Turkish children with attention deficit hyperactivity disorder (ADHD) from those with comorbid ADHD and BD and compare the clinical features of the groups. In their study, they evaluated 147 treatment- and drug-naive children (123 boys, 24 girls), aged between 7 and 13 years, who had been consecutively admitted to the ADHD clinic. In the group studied, 12 children (8.2%; 12 boys) had comorbid bipolar disorder (ADHD + BD). In comparison with the ADHD group, the ADHD + BD group had increased rates of depressive disorders, oppositional defiant disorder (ODD), panic disorder and a family history of BD. The onset of manic episodes in the ADHD+ BD group was 9.24±0.68 years of age. Seven cases (58.3%) in the ADHD + BD group had bipolar disorder not otherwise specified (BD-NOS). Of the patients with BD-NOS, 57.1% had rapid-cycling episodes. Four patients (33.3%) had BD type I with mixed episodes (75% of them were rapid-cycling), 1 (8.3%) patient with BD type I had manic episodes. Seven patients (58.3%) in both groups had rapid cycling episodes. None of the patients with ADHD + BD had psychotic symptoms (24). In a similar study, Lus and Motavalli Mukaddes (25) evaluated the comorbidity of BD in 121 individuals, aged 6-16 years (23 girls; 98 boys), with a diagnosis of ADHD. A comorbid diagnosis of BD (ADHD + BD) was

identified in 10 children (8.3%; 8 boys, 2 girls). The age of onset of BD in ADHD + BD group ranged between 7 and 12 years (mean age=8.9±2.2 years). Two patients (20%) in the ADHD + BD group had BD type II and 8 patients (80%) had BPD type I, of whom 2 had rapid cycling episodes and 1 of them had rapid cycling episodes with psychotic features (25).

In a naturalistic and prospective study, Inal Emiroğlu et al. (26) aimed to describe the clinical manifestation and predictors of response to treatment in Turkish children and adolescents with BD. The study included 27 consecutive referrals to a child and adolescent psychiatry clinic. The mean age of the study group was 12.95±3.8 years. The results of the study showed that mood stabilizers and atypical antipsychotic combinations were required in many cases (73.7%). Most of the patients responded to mood stabilizers and antipsychotic agents (89.5%). In this study, episodic patients mostly consisted of adolescent cases were more likely to have psychotic features and to have a later age of onset compared to the non-episodic group (26). Ertan and Cetinkaya (27) conducted a retrospective chart review of 47 patients (mean age=19.2±1.7; 31 female, 16 male) consecutively admitted to an adolescent outpatient clinic and diagnosed as having BD (27). Of the patients, 38.3% (18) were admitted with mania/hypomania symptoms first, and 23.4% (11) of the patients were admitted with depressive symptoms. The mean duration between the first occurrence of the symptoms and the diagnosis was 1±1.6 years. Of the participants, 25.5% (12) committed suicide and 12.8% had self-injurious behavior. Of the patients, 59.6% had at least one comorbid disorder. The most detected comorbid disorders were ADHD (21.3%), intellectual disability (14.9%), and obsessive compulsive disorder (10.6%) respectively. Of the cases, 87.2% were using mood stabilizers, 93.6% were using antipsychotic agents and 19.1% were using antidepressants. Lithium (38.2%, n=18) was the most frequently prescribed mood stabilizer in the study group which was followed by valproic acid (29.7%, n=14) and lamotrigine (23.4%, n=11) respectively. The most frequently prescribed antipsychotics were olanzapine (27.6%, n=13), risperidone (27.6%, n=13) and aripiprazole (21.2%, n=10). Sertraline (4.2%, n=2), fluoxetine (4.2%, n=2) and venlafaxine (4.2%, n=2) were the most frequently used antidepressants. Of the patients, 6,4% used psychostimulants; and atomoxetine was used in 2 patients (4.2%). Of the patients, 19.2% (n=9) were treated with monotherapy; 44.7% (n=21) with 2; and 36.1% (n=17) with 3 or more psychotropic agents (27). Although main aim of the researchers was to define the clinical and neuropsychological characteristics of BD in adolescents and to evaluate the clinical and neuropsychological variables in adolescents with a higher familial risk of BD, and to identify probable early markers of the disorder; Karakurt et al. (28) reported clinical features of 25 patients with BD (aged 12-18 years). Of those, 12 (48%) had BD type I, 10 (40%) BD type II and 3 (12%) BD-NOS. In their study group, the mean age of onset was 12±2.7 years; mean age at diagnosis was 13.7±2.0 years; mean number of depressive episodes and mania/hypomania episodes was 1.3±0.9 and 1.4±0.9, respectively. Of the patients, 22 (88%) were using mood stabilizers, 4 (16%) were using antidepressants and 3 (12%) were using stimulants. The number of the cases using multiple psychotropic agents was 22 (88%). The most detected comorbid disorder were ADHD (56%, n=14), anxiety disorders (28%, n=7) and conduct disorders (24%, n=6) (28).

As summarized above, there are a few studies from Turkey presenting sociodemographic data, clinical presentation and treatment regimens of child and adolescent patients with BD and the total number of the child and adolescent patients reported in these studies is still limited. In this study, we aimed to examine the clinical characteristics and family history of children and adolescents with BD having treatment in an inpatient unit. We hypothesized that the family history of BD, history of suicide attempts and substance use; and functional impairment would be high in this sample.

Methods

A retrospective chart review of 113 children and adolescents' files (ages 13-18 years) who were consecutively admitted to our inpatient clinic between March 2012 and November 2014 and diagnosed as having BD type I or BD type II was made. The diagnoses were based on the DSM-IV-TR (29) criteria and made by the child and adolescent psychiatrists who were experienced in the field at least for ten years.

A sociodemographic and clinical data form was created by the authors and filled out for each patient by the authors themselves. Data were obtained from the patients' files. The data form covered the current age and education status of the patient, employment status, age at onset of BD, type of the first and the current episode, history of suicide attempt, history of substance/alcohol use, previous referral to a psychiatry clinic before the onset of BD, family history for BD or any psychiatric disorder and treatment regimens during the inpatient stay.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences), version 16.0 (SPSS, Inc., Chicago, IL) was used for analyzing the data obtained in this study. Descriptive analyses were utilized for sample description: frequencies and percentages for discrete variables and means and standard errors for continuous variables. Categorical variables were compared with two tailed X^2 test (Fisher's test). Statistical significance was defined by a probability level of $p<0.05$.

Results

Totally 113 (71 male, 42 female) adolescents were included in the study. Mean age of the study group was 16.054±1.23 (range=13-18) years. There was no statistically significant difference between male and female subjects regarding onset age of BD (females: mean age at onset 14.94±1.9; males: mean age at onset 15.1±1.6, $p>0.05$), regarding substance use history and history of BD in the family ($p>0.05$). However, suicide attempt rates were higher in female subjects (58%) compared to male subjects (32%) ($p=0.02$). During the time of assessment, 39 adolescents (34.5%) were attending a high school, 12 (10.6%) had a regular job, 62 (54.9%) were not attending any school

or did not have a regular job. Mean education year for the whole group was 8.2 years. There was no difference between the subjects not attending any school or not having a regular job and the rest of the study group with regards to the age at onset of BD, history of BD in the family and substance use history (p>0.05).

Mean age at onset of BD was 15.04±1.74 (range=9-17) years. In 50% of the study group the age at onset of BD was less then age of 15 years and in 15.4%, it was less than age of 13 years. There was no statistically significant difference between childhood onset (≤ 13 years) and adolescent onset (>13 years) cases regarding occupational functioning (attending school or having a regular job), suicide attempt history, substance use history, and history of BD in the family (p>0.05).

Of the patients, 92.5% had a diagnosis of BD type I, and 7.5% had BD type II. The first mood episode was manic in 60% of patients, depressive in 27.3%, mixed in 10.9% and hypomanic in 1.8% of the patients. Of the patients, 32.1% had a positive family history for BD. In 56.6%, a history of any psychiatric disorder was reported in the first-degree relatives. Of the patients, 23.4% had a suicide attempt history, 48.2% had a previous referral to a psychiatry clinic before the onset of BD. History of substance/alcohol use was detected in 27.4% of the patients. Types of the first and the current mood episodes of the patients are shown in Table 1.

Eighty nine (78.7%) patients were using "atypical antipsychotic + mood stabilizer" combination (55 patients: Atypical antipsychotic + valproate; 30 patients: Atypical antipsychotic + lithium; 4 patients: Atypical antipsychotic + carbamazepine), 16 (14.1%) patients were using only atypical antipsychotics; 2 (1.7%) patients were using "atypical antipsychotic + typical antipsychotic" combination (haloperidol), 4 (3.5%) patients were using "mood stabilizer + mood stabilizer" combination (1 patient, valproate + lithium; 2 patients, lithium + carbamazepine, 1 patient, lithium + topiramate), 1 patient was using only valproate and 1 patient was using "lithium + antidepressant" combination.

Discussion

In this study, we found high rates of family history of BD, suicide attempt history and substance use history in an adolescent inpatient sample with BD. Functional impairment was striking given that more than half of the patients were not attending any school or did not have a regular job. This was compatible with the literature strongly suggesting that pediatric BD was associated with chronic functional impairment (30-32). According to DelBello and colleagues' study, 85% of adolescents with BD had syndromic recovery during the first year after initial inward treatment, whereas 39% had symptomatic recovery and 39% had functional recovery (32). Only 20% experienced all three types of recovery. Goldstein et al. (33) also reported mild to moderate psychosocial functional impairment in work (including academics) and interpersonal domains in children and adolescents with BD. When patients with greater occupational impairment (not having a regular job or not attending any school) were compared with the rest of the study group, we found no difference with regards to onset age or family history of BD. In line with our finding, the literature suggests that childhood or adolescent onset BD both cause significant functional impairment, although inconsistencies exist (26,31,33). To the best of our knowledge, this was the first study to examine the link between familiality and the severity of functional impairment in pediatric BD. However, in line with our findings, Sanchez-Moreno et al. (34) reported no significant relationship between a history of affective disorders in the family and low functioning in adults with BD.

Table 1. Types of the first and the current mood episodes

	First mood episode		Current mood episode	
	N	%	n	%
Manic	66	60	82	73.2
Depressive	30	27.3	6	5.4
Mixed	12	10.9	22	19.6
Hypomanic	2	1.8	2	1.8

The number of male patients was higher than the female patients in our study. Although bipolar disorder affects both males and females equally, patients with early-onset disorder, particularly cases with an onset before 13 years of age are reported to be predominantly male (35). In this study, female and male subjects did not show any difference with regards to onset age of BD, substance use history and family history of bipolar disorder. However, suicide attempt rates were higher in female subjects. Previous researches indicated that pediatric BD showed similarities regarding most clinical features between the sexes (36-38) with exception that there was a later age at onset in female subjects (37,38). Subject ascertainment differences and older mean age in our study sample might be responsible for this discrepancy. Along with our results, one of two comprehensive reviews on suicidality in BD suggested that female genderwas a possible risk factor for suicide attempts in youth with BD, however, this finding was not consistent (39,40).

Most of our patients had BD-1 diagnosis and the current mood episode was manic in most of the group which was an expected finding considering that our study sample consisted of patients having treatment in an inpatient clinic. These two findings might be the result of referral bias, that is, patients with disruptive behaviors are identified easily and probably more referred for treatment in an inpatient unit.

In this study, the first mood episode was manic in more than half of the patients. This finding seemed to be in contradiction with the study including 1081 patients diagnosed as having BD, which reported that the majority of first episodes (58.9%) were depressive (41). But the estimated onset age was reported as 28.5±12.4 years in that study which was older than our sample's onset age. Our study sample consisted of individuals from lower socioeconomic level, therefore a depressive episode may have been easily overlooked by the parents who had many challenges

in life. However, in a study including 82 juveniles with BD, most of whom were prepubertal at illness-onset, the first episode was reported as manic in 52.4%, mixed in 30.5%, and depressive in 17.1% of cases (42). In a study from Turkey, similarly, the most frequent first episode was reported to be manic in an inpatient sample of adolescents with BD although the rates (38.3%) were smaller than those found in our study (27).

Nearly half of the cases had a history of previous psychiatric referral before the onset of BD. This finding may be consistent with the data that BD is a highly comorbid disorder (12,43) or this may be the result of the developmental differences in the expression of manic symptoms of this disorder in children. In addition, premorbid mental problems have been reported to be frequent in early-onset BD, particularly disruptive behavior disorders, irritability, and behavioral dyscontrol (35,44-46). Moreover, Ertan and Çetinkaya (27) reported a comorbidity rate of 59.6% in their adolescent inpatient sample which was also compatible with our study. Karakurt et al. (28) also reported increased rates of ADHD and generalized anxiety disorder in their study group of adolescents with BD compared to adolescents with BD in a first-degree relative.

Suicide is a serious problem for patients with BD. Suicide attempt rates range from 25% to 56%, and completed suicides range from 10% to 15% (47). Significant relations were reported especially between early-onset BD and lifetime suicide attempts in many studies (5,10-12). Nearly a quarter of our patients had a history of suicide attempt. This finding was compatible with a comprehensive review of BD, which reported that 31.1% of the individuals with BD attempted suicide at least once (48). In addition, Ertan and Çetinkaya (27) also reported similar rates (25.5%) of suicide attempts in another Turkish adolescent inpatient sample with BD. In line with the previous literature (49), we also found that the suicide attempt ranges were significantly higher in the patients with a family history of BD (37%) compared with the ones who did not have a family history of BD (17%) (p=0.03).

Nearly one-third of our patients had used alcohol or illicit drugs at a point in their lives. There is a substantial body of evidence demonstrating a greater risk of substance use in youth with BD, with a prevalence rate ranging between 16% and 39% (50,51). The nature of the relationship between BD and SUD seems bidirectional. Besides genetic vulnerabilities, adolescents with BD may be inclined to self-medicate themselves due to the associated features of pediatric BD such as affective instability, behavioral disinhibition, high impulsivity, sensation seeking, cognitive impairment, and deficient self-regulation (52). Substance use in adolescents with BD is associated with higher rates of legal problems, suicidality, psychiatric comorbidity and physical or sexual abuse (50-54). Thus, one might hypothesize that substance use might contribute to the poorer academic and occupational functioning in adolescents with BD. Conversely, in our analysis, the patients without a regular job and who did not attend school did not differ from the others with regards to substance use history.

In more than half of the patients there was a psychiatric disorder history in the first-degree relatives, and in more than one-third there was BD history including all relatives. In the literature on adults with BD; twin, adoption, and family history studies supported a significant genetic vulnerability, with a four to six-fold raised risk for BD in first degree relatives of affected individuals (55). The degree of familiality seemed to be greater in early-onset cases (6). Since psychopathology in parents may be regarded as an early-life stressor as well as a marker of a genetic vulnerability to mental health problems, the raised risk of bipolar disorder in the offspring is not surprising, given that psychiatric symptoms in parents might impact family functioning and lead to a less cohesive environment, which renders offspring liable to the development of psychopathology (7).

In 50% of the participants in our study, the onset age of BD was less than age of 15 years and in 15.4% it was less than age of 13 years. Suicide attempt history, substance use history and history of BD in the family did not differ between childhood and adolescent onset subjects. A comprehensive review of suicidality in pediatric BD implied that adolescent onset BD might be related with a greater risk of suicide attempts, however this was not a consistent finding (40,56). Considering that our study group consisted of inpatient cases with a possibility of greater severity, that might be related to a lack of difference in suicide attempt risk across onset age groups. Propper et al. (56) reported that very early onset subjects were more likely to have a first-degree relative with an affective disorder and they showed lower global functioning compared with early onset subjects. However, in the study by Propper et al. (56), the age cut off between very early and early onset subjects were older (age cut off=15 years) and their study sample consisted of only adult subjects. Literature provided controversial results on whether the prevalence rate of substance use differed between childhood or adolescent onset BD. Wilens et al. reported higher risk for substance use in adolescent onset BD in an ongoing, controlled, family-based study (54,57), whereas Goldstein et al. (53) presented similar results with our study. Retrospective data from adults with BD also indicated that early onset BD was associated with greater risk for substance use, but childhood onset and adolescent onset BD appeared to confer similar vulnerability to substance use (58).

In our study, most of the patients were using atypical antipsychotic + mood stabilizer combination. Sodium valproate was the most frequently prescribed mood stabilizer in this combination. To date, lithium, risperidone, olanzapine, aripiprazole and quetiapine were approved by the Food and Drug Administration (FDA) for the treatment of acute mixed and manic episodes in pediatric BD. Second generation antipsychotics are reported to be more effective than mood stabilizers for the treatment of manic episodes in pediatric bipolar disorder. There is some evidence in the literature suggesting that divalproex might be effective in the treatment of acute manic episodes in pediatric BD, however current data on divalproex use in pediatric BD are quite limited (59,60). The only medication that is currently approved for the treatment of depressive episodes in pediatric BD is olanzapine/fluoxetine combination (60). Although current data on whether

combination therapy is more effective than monotherapy in pediatric bipolar disorder remain scarce, antipsychotic + mood stabilizer combination might be an alternative treatment for the patients resistant to mood stabilizer monotherapy (60). Our sample was collected from an inpatient unit which might be related with a more severe course of illness, thus led to a greater likelihood for the use of combination treatment. Similarly, studies with inpatient adolescent samples from Turkey also reported higher rates of combination therapies (80.8% and 88%, respectively) (26,28).

Our study had some limitations which should be taken into account. Since our clinic served sometimes as a tertiary clinic, and most of our patients had a low socio-economic background, our sample may have represented a more severely impaired group. This may have contributed to our findings of high rate of family history of psychiatric disorders, substance and alcohol use and combination therapies, and low rate of school attendance or having regular job. Secondly, age at onset of BD was retrospectively determined, therefore inaccuracies in recall could not be precluded. Third, the sample consisted of inpatients who probably had more severe illness, so it was difficult to generalize these results for all children and adolescents with BD in Turkey. However, a considerable number of patients were included in this study and there were few studies in the literature from Turkey including inpatient youths with BD.

Conclusion

Our results are generally consistent with the literature that early-onset BD cases have high rates of family history of BD, suicide attempts and substance use and exhibit chronic impairments in functioning. The similarity of our results with the results of those from Western countries can be interpreted as there seems no significant cultural differences regarding clinical characteristics of BD. High rates of suicide attempt, substance use and significant functional impairment found in our study sample indicate that early recognition and intervention of BD, specialized educational programs and occupational support for these children and adolescents seem indispensable.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: H.G., C.T., H.D., Ö.Ş.Ü., Design: H.G., C.T., H.D., Ö.Ş.Ü., Data Collection or Processing: H.G., C.T., H.D., A.G.K., Analysis or Interpretation: H.G., C.T., Writing: H.G., C.T., H.D., A.G.K., Ö.Ş.Ü.

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References

1. Wilens TE, Biederman J, Martelon M, Zulauf C, Anderson JP, Carrellas NW, et al. Further Evidence for Smoking and Substance Use Disorders in Youth with Bipolar Disorder and Comorbid Conduct Disorder. J Clin Psychiatry 2016;77:1420-27.
2. Van Meter AR, Moreira AL, Youngstrom EA. Meta-analysis of epidemiologic studies of pediatric bipolar disorder. J Clin Psychiatry 2011;72:1250-56.
3. Baldessarini RJ, Tondo L, Vazquez GH, Undurraga J, Bolzani L, Yildiz A, et al. Age at onset versus family history and clinical outcomes in 1,665 international bipolar-I disorder patients. World Psychiatry 2012;11:40-6.
4. Benazzi F. Classifying mood disorders by age-at-onset instead of polarity. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:86-93.
5. Ortiz A, Bradler K, Slaney C, Garnham J, Ruzickova M, O'Donovan C, et al. An admixture analysis of the age at index episodes in bipolar disorder. Psychiatry Res 2011;188:34-9.
6. Faraone SV, Glatt SJ, Tsuang MT. The genetics of pediatric-onset bipolar disorder. Biol Psychiatry 2003;53:970-77.
7. Bergink V, Larsen JT, Hillegers MH, Dahl SK, Stevens H, Mortensen PB, et al. Childhood adverse life events and parental psychopathology as risk factors for bipolar disorder. Transl Psychiatry 2016;6:e929.
8. Holtzman JN, Miller S, Hooshmand F, Wang PW, Chang KD, Hill SJ, et al. Childhood-compared to adolescent onset bipolar disorder has more statistically significant clinical correlates. J Affect Disord 2015;179:114-20.
9. Weinstein SM, West AE, Pavuluri M Psychosocial intervention for pediatric bipolar disorder: current and future directions. Expert Rev Neurother. 2013;13:843-50.
10. Azorin JM, Bellivier F, Kaladjian A, Adida M, Belzeaux R, Fakra E, et al. Characteristics and profiles of bipolar I patients according to age-at-onset: findings from an admixture analysis J Affect Disord. 2013;150:993-1000.
11. Coryell W, Fiedorowicz J, Leon AC, Endicott J, Keller MB. Age of onset and the prospectively observed course of illness in bipolar disorder. J Affect Disord 2013;146:34-8.
12. Moor S, Crowe M, Luty S, Carter J, Joyce PR. Effects of comorbidity and early age of onset in young people with Bipolar Disorder on self-harming behavior and suicide attempts. J Affect Disord 2012;136:1212-15.
13. Goldstein TR, Birmaher B, Axelson D, Goldstein BI, Gill MK, Esposito-Smythers C, et al. Psychosocial functioning among bipolar youth. J Affect Disord 2009;114:174-83.
14. Carter TD, Mundo E, Parikh SV, Kennedy JL. Early age at onset as a risk factor for poor outcome of bipolar disorder. J Psychiatr Res 2003;37:297-303.
15. Ernst CL, Goldberg JF. Clinical features related to age at onset in bipolar disorder. J Affect Disord 2004;82:21-7.
16. Etain B, Lajnef M, Bellivier F, Mathieu F, Raust A, Cochet B, et al. Clinical expression of bipolar disorder type I as a function of age and polarity at onset: convergent findings in samples from France and the United States. J Clin Psychiatry 2012;73:e561-566.

17. Javaid N, Kennedy JL, De Luca V. Ethnicity and age at onset in bipolar spectrum disorders. CNS Spectr 2011;16:127-34.
18. Lin PI, McInnis MG, Potash JB, Willour V, MacKinnon DF, DePaulo JR, Zandi PP. Clinical correlates and familial aggregation of age at onset in bipolar disorder. Am J Psychiatry 2006;163:240-46.
19. Rende R, Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, et al. Childhood-onset bipolar disorder: Evidence for increased familial loading of psychiatric illness. J Am Acad Child Adolesc Psychiatry 2007;46:197-204.
20. Diler RS, Uguz S, Seydaoglu G, Avci A. Mania profile in a community sample of prepubertal children in Turkey. Bipolar Disord 2008;10:546-53.
21. Karacetin G, Arman AR, Fis NP, Demirci E, Ozmen S, Hesapcioglu ST, et al. Prevalence of Childhood Affective disorders in Turkey: An epidemiological study. J Affect Disord 2018;238:513-21.
22. Erkiran M, Karamustafalioğlu N, Tomruk N, Kahraman E, Alpay N. Phenomenological differences between adolescent and adult onset mania: a comparative study. Turk Psikiyatri Derg 2003;14:21-30.
23. Inal Emiroğlu FN. Case series with childhood bipolar disorder phenotype features. Turk Psikiyatri Derg 2004;15:148-54.
24. Diler RS, Uguz S, Seydaoglu G, Erol N, Avci A. Differentiating bipolar disorder in Turkish prepubertal children with attention-deficit hyperactivity disorder. Bipolar Disord 2007;9:243-51.
25. Lus G, Motavalli Mukaddes N. Co-morbidity of bipolar disorder in children and adolescents with attention deficit/hyperactivity disorder (ADHD) in an outpatient Turkish sample. World J Biol Psychiatry 2009;10:488-94.
26. Inal Emiroglu FN, Baykara B, Miral S. A case series of Turkish children and adolescents with bipolar spectrum disorder: a naturalistic clinical phenomenological follow-up. Minerva Pediatr 2008;60:51-7.
27. Ertan EA, Çetinkaya BÖ. Bipolar Disorder in Adolescents: Treatment Strategies and Comorbidities. Kriz Dergisi 2018;26.
28. Karakurt MN, Karabekiroğllu MZ, Yüce M, Baykal S, Şenses A. Neuropsychological profiles of adolescents with bipolar disorder and adolescents with a high risk of bipolar disorder. Turk Psikiyatri Derg 2013;24:221-30.
29. American Psychiatric Association. DSM-IV. Diagnostic and Statistical Manual of Mental Disorders 4th edition, TR. Washington, DC: American Psychiatric Association; 2000.
30. Wilens TE, Biederman J, Forkner P, Ditterline J, Morris M, Moore H, et al. Patterns of comorbidity and dysfunction in clinically referred preschool and school-age children with bipolar disorder. J Child Adolesc Psychopharmacol 2003;13:495-505.
31. Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Cayton GA, et al. Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. J Psychiatr Res 2005;39:611-22.
32. DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. Am J Psychiatry 2007;164:582-90.
33. Goldstein TR1, Birmaher B, Axelson D, Goldstein BI, Gill MK, Esposito-Smythers C, et al. Psychosocial functioning among bipolar youth. J Affect Disord 2009;114:174-83.
34. Sanchez-Moreno J, Bonnin CM, González-Pinto A, Amann BL, Solé B, Balanzá-Martinez V, et al. Factors associated with poor functional outcome in bipolar disorder: sociodemographic, clinical, and neurocognitive variables. Acta Psychiatr Scand 2018;138:145-54.
35. McClellan J, Kowatch R, Findling RL; Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2007;46:107-25.
36. Geller B, Zimerman B, Williams M, Bolhofner K, Craney JL, Delbello MP, et al. Diagnostic characteristics of 93 cases of a prepubertal and early adolescent bipolar disorder phenotype by gender, puberty and comorbid attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 2000;10:157-64.
37. Biederman J, Kwon A, Wozniak J, Mick E, Markowitz S, Fazio V, et al. Absence of gender differences in pediatric bipolar disorder: findings from a large sample of referred youth. J Affect Disord 2004;83:207-14.
38. Wozniak J, Biederman J, Martelon MK, Hernandez M, Woodworth KY, Faraone SV. Does sex moderate the clinical correlates of pediatric bipolar-I disorder? Results from a large controlled family-genetic study. J Affect Disord 2013;149:269-76.
39. Schaffer A, Isometsä ET, Azorin JM, Cassidy F, Goldstein T, Rihmer Z, et al. A review of factors associated with greater likelihood of suicide attempts and suicide deaths in bipolar disorder: Part II of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder. Aust N Z J Psychiatry 2015;49:1006-20.
40. Halfon N, Labelle R, Cohen D, Guilé JM, Breton JJ. Juvenile bipolar disorder and suicidality: a review of the last 10 years of literature. Eur Child Adolesc Psychiatry 2013;22:139-51.
41. Baldessarini RJ, Tondo L, Visioli C. First-episode types in bipolar disorder: predictive associations with later illness. Acta Psychiatr Scand 2014;129:383-92.
42. Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB. Pediatric bipolar disorder: phenomenology and course of illness. Bipolar Disord 2004;6:305-13.
43. Leverich GS, Post RM, Keck PE Jr, Altshuler LL, Frye MA, Kupka RW, et al. The poor prognosis of childhood-onset bipolar disorder. J Pediatr 2007;150:485-90.
44. Geller B, Zimerman B, Williams M, Delbello MP, Bolhofner K, Craney JL, et al. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2002;12:11-25.
45. Fergus EL, Miller RB, Luckenbaugh DA, Leverich GS, Findling RL, Speer AM, et al. Is there progression from irritability/dyscontrol to major depressive and manic symptoms? A retrospective community survey of parents of bipolar children. J Affect Disord 2003;77:71-8.
46. McClellan J, Breiger D, McCurry C, Hlastala SA. Premorbid functioning in early-onset psychotic disorders. J Am Acad Child Adolesc Psychiatry 2003;42:666-72.
47. Carrà G, Bartoli F, Crocamo C, Brady KT, Clerici M. Attempted suicide in people with co-occurring bipolar and substance use

disorders: systematic review and meta-analysis. J Affect Disord 2014;167:125-35.

48. Tondo L, Pompili M, Forte A, Baldessarini RJ. Suicide attempts in bipolar disorders: comprehensive review of 101 reports. Acta Psychiatr Scand 2016;133:174-86.
49. Berutti M, Nery FG, Sato R, Scippa A, Kapczinski F, Lafer B. Association between family history of mood disorders and clinical characteristics of bipolar disorder: results from the Brazilian bipolar research network. J Affect Disord 2014;161:104-8.
50. Goldstein BI, Bukstein OG. Comorbid substance use disorders among youth with bipolar disorder: opportunities for early identification and prevention. J Clin Psychiatry 2010;71:348-58.
51. Scavone A, Timmins V, Collins J, Swampillai B, Fonseka TM, Newton D, et al. Dimensional and Categorical Correlates of Substance Use Disorders among Canadian Adolescents with Bipolar Disorder. J Can Acad Child Adolesc Psychiatry 2018;27: 159-66.
52. Lorberg B, Wilens TE, Martelon M, Wong P, Parcell T. Reasons for substance use among adolescents with bipolar disorder. Am J Addict 2010;19:474-80.
53. Goldstein BI, Strober MA, Birmaher B, Axelson DA, Esposito-Smythers C, Goldstein TR, et al. Substance use disorders among adolescents with bipolar spectrum disorders. Bipolar Disord 2008;10:469-78.
54. Wilens TE, Biederman J, Adamson JJ, Henin A, Sgambati S, Gignac M, et al. Further evidence of an association between adolescent bipolar disorder with smoking and substance use disorders: a controlled study. Drug Alcohol Depend 2008;95(3):188-98.
55. Nurnberger JI Jr, Foroud T. Genetics of bipolar affective disorder. Curr Psychiatry Rep 2000;2:147-57.
56. Propper L, Ortiz A, Slaney C, Garnham J, Ruzickova M, Calkin CV, et al. Early-onset and very-early-onset bipolar disorder: distinct or similar clinical conditions? Bipolar Disord 2015;17:814-20.
57. Wilens TE, Biederman J, Kwon A, Ditterline J, Forkner P, Moore H, et al. Risk of substance use disorders in adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2004;43:1380-6.
58. Perlis RH, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, et al. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2004;55:875-81.
59. Stepanova E, Findling RL. Psychopharmacology of Bipolar Disorders in Children and Adolescents. Pediatr Clin North Am 2017;64(6):1209-22.
60. Goldstein BI, Birmaher B, Carlson GA, DelBello MP, Findling RL, Fristad M, CU, et al. The International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder: Knowledge to date and directions for future research. Bipolar Disord 2017;19:524-43.

Original Article

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A Rabbit Model of Avascular Necrosis of Femoral Head Using Surgical Trauma and Systemic Steroids

Cerrahi Travma ve Sistemik Steroid Uygulaması ile Tavşanlarda Femur Başı Avasküler Nekroz Modeli

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ABSTRACT

Objective: Avascular necrosis of the femoral head (ANFH) is a disease caused by the diminished circulation of the femoral head. The incidence of the disease is increasing and it has heavy socioeconomical burden. Animal models are indispensable for the development of new treatments for bone avascular necrosis. There is not any reliable animal model for simulating the early stages of femoral head osteonecrosis. The aim of this study is to present an animal model of femoral head osteonecrosis induced by systemic steroid use combined with surgery.

Methods: Six New Zealand White rabbits were divided into 3 groups. Each group contained 4 femoral heads. For the induction of osteonecrosis, every hip underwent surgical dislocation followed by cauterization of extraperiosteal vessels around the femoral head and ligamentum teres resection. A single dose intramuscular steroid was administered to each rabbit. Rabbits were sacrificed at 2nd, 4th and 6th weeks and femoral heads were sent to histological evaluation.

Results: The femoral heads showed typical signs of avascular necrosis at the end of 2nd week. In addition to osteocyte loss and marrow necrosis, there was also new osteoblast formation at the end of 4th week. At the end of 6th week, epiphyseal new bone formation next to large necrotic areas were visible.

Conclusion: These results suggest that the single steroid administration combined with hip luxation and cauterization of neck vessels may create femoral head osteonecrosis in rabbits in a repeatable and reliable manner. This model can be presented as an alternative model for the new studies on the treatment of femoral head avascular necrosis in the early stage.

Keywords: Avascular necrosis, femoral head, rabbit

ÖZ

Amaç: Femur başı avasküler nekrozu (FBAN), femur başının kanlanmasındaki azalmadan kaynaklanan, görülme sıklığı giderek artan ve ağır sosyo-ekonomik etkileri olan bir hastalıktır. Hayvan modelleri, kemiklerdeki avasküler nekrozlar için yeni tedavi yöntemlerinin oluşturulmasında vazgeçilmezdir. Halen, erken dönem FBAN'yi simüle edebilen güvenilir bir hayvan modeli yoktur. Bu çalışmanın amacı, cerrahi ve sistemik steroid kombinasyonu ile tavşanda FBAN modeli oluşturmaktır.

Yöntemler: Altı Yeni Zelanda beyaz tavşanı 3 gruba ayrıldı. Her grup 4 femur başı içermekteydi. FBAN oluşturmak için her kalçaya cerrahi olarak dislokasyon, femur boynu periosteal damarların koterizasyonu ve ligamentum teres eksizyonu yapıldı. Sonrasında her tavşana tek doz intramusküler steroid uygulandı. Gruplardaki hayvanlar sırasıyla 2., 4. ve 6. haftalarda sakrifiye edildi ve tüm femur başları rezeke edildi. Femur başları histolojik olarak avasküler nekroz bulguları açısından değerlendirildi.

Bulgular: İkinci haftanın sonunda incelenen femur başlarında tipik histolojik avasküler nekroz bulguları mevcut idi. Dördüncü hafta sonunda alınan örneklerin yapılan histolojik değerlendirmelerinde osteosit kaybı ve kemik iliği nekrozuna ek olarak osteoblast oluşumları görüldü. Altıncı hafta sonunda yapılan incelemelerde epifizyel alanlarda geniş kemik iliği nekrozlarına ek olarak yeni kemik oluşumları görüldü.

Sonuç: Bu sonuçlar, femur başı luksasyonu ve koterizasyonu ile tek doz steroid uygulamasının tavşanlarda güvenilir ve tekrarlanabilir şekilde femur başı nekrozu oluşturduğunu göstermektedir. Bu model, femur başı osteonekrozlarının erken dönem tedavisi araştırmalarında kullanılabilecek bir seçenek olarak sunulabilir.

Anahtar Sözcükler: Avasküler nekroz, femur başı, tavşan

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Introduction

Avascular necrosis of the femoral head (ANFH) is a progressive and functionally restrictive disease. Its etiologic factors include systemic steroid use, alcoholism, blood diseases, radiotherapy, trauma and disbaric diseases (1). Bleeding of the femoral head decreases due to either direct trauma (fractures of the femoral neck) or increased intraosseous pressure (2). ANFH most commonly affects the population aged between 20 and 50 years (3). If left untreated, femoral heads may deform and collapse leading to permanent functional constraints. In this sense, ANFH can lead to severe social and economic problems.

Histologically, the first signs of ischemia in the bone can be seen in the bone marrow from the second day at the earliest. Marrow cell nuclei begin to not hold the stain histologically, and large round cavities filled with adipose tissue form (4). After the 15th day, osteocyte lacunae are empty and cells on trabecular surfaces disappear (Figure 1). The new capillaries, fibroblasts, histiocytes and osteoclasts that break down the necrotic marrow and trabeculae appear at the border of the necrotic areas. In the ongoing process, new spongy bone is formed on the dead trabeculae (5).

Animal models are needed to assess the efficacy of new treatments developed for ANFH. None of these animal models are fully reliable. Since the etiopathogenesis of ANFH is not well known, it is also quite difficult to determine the criteria of a valid animal model. The most commonly used method in animal models is systemic steroid administration (6-8). Ethanol injection to femur head, heating of the femur head with microwave, freezing of the femur head with liquid nitrogen and then burning the femur neck with cerclage are the other methods present (2,9,10,11).

The aim of this study is to present a technique in which surgical trauma and systemic steroid administration are combined as the ANFH model in rabbits. The hypothesis of the study is that with this model, the histological changes of ANFH in its early stages can be simulated.

Method

Six female New Zealand rabbits weighing 3 kilograms (Harlan Laboratories Srl, San Pietro al Natisone, Italy) were operated in the Inter-Departmental Animal Laboratory of Modena and Reggio Emilia University (Modena, Italy). The study was carried out following the approval of the Institutional Animal Experiments Ethics Committee of Modena and Reggio Emilia University (2012/07/16-57). ANFH induction was performed on every 2 hips of each animal. The rabbits were then divided into 3 groups; each group contained 4 femoral heads. The animals in the groups were sacrified in the CO_2 chamber at the end of the 2nd week, 4th week and 6th week respectively, and histological examination of the femoral heads was performed.

AVFH Induction Model: Each rabbit was given general anesthesia with 3% Sevorane following sedation with 1 mg/kg midazolam. Following proper surgery site cleaning and skin disinfection, the incision was made which centralised the trochanter major. The Tensor Fascia Lata was cut longitudinally. Gluteus Medius muscle was removed from trochanteric adhesion site. The hip joint capsule was opened and the femoral head was luxated with lateral traction. The Ligamentum Teres was resected totally. The femoral neck was cauterized with bipolar cautery from the trochanteric area to the epiphyseal area (Figure 2). Cartilage in the femoral head was preserved. Then the hip was reduced. The joint capsule and subcutaneous tissue was closed with absorbant sutures, while skin was closed with non-absorbant sutures. The same procedure was applied to the other hip. A single dose of methylprednisolone was administered intramuscularly at a dose of 20 mg/kg. Then the anesthesia was terminated. Each animal was given 2.5 mg/kg of enrofloxacin intramuscularly every day for 5 days as antibiotic prophylaxis.

Histological Examination: Animals in groups were sacrified in the CO_2 chamber at the end of 2nd, 4th and 6th weeks. Femoral heads were osteotomized from their intertrochanteric regions. Femoral heads were stored in 10% formalin solution for 2 days and decalcified for 21 days in rapid decalcification solution (BDH Laboratories, Pool, UK) containing 5% acid formalin and

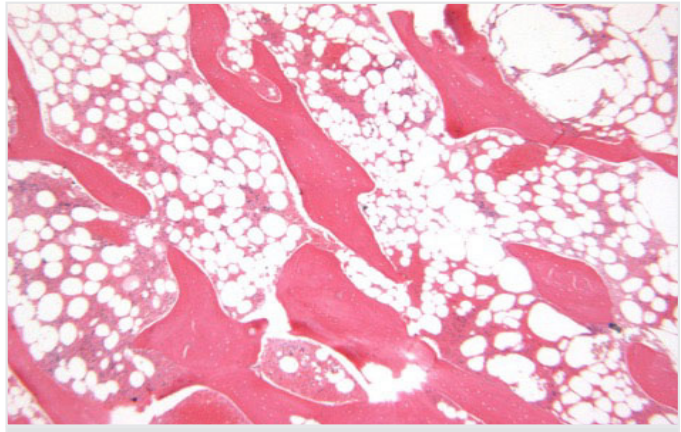

Figure 1. Classic histological findings in avascular osteonecrosis are coagulative necrosis of marrow cells and empty osteecyte lacunae in trabeculae (haematoxylene-eosin, 10X)

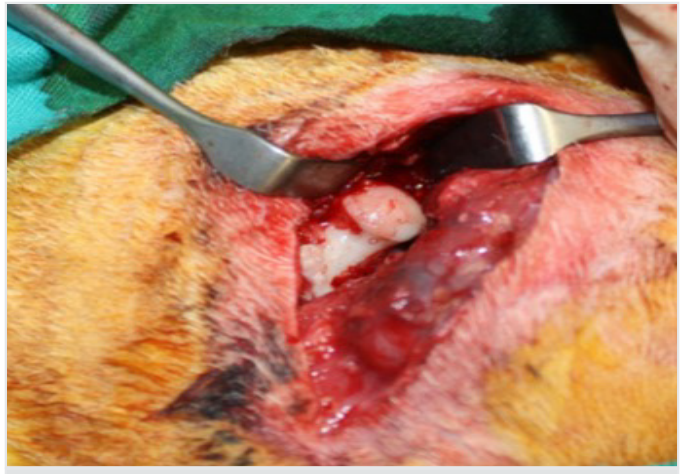

Figure 2. After the hip is dislocated, the femoral neck is cauterized with bipolar cautery, circumferentially

5% trisodium citrate. The femoral heads were then inserted into the paraffin. Three μm-thick sections were deparaffinized and stained with Haematoxylene-eosin. All samples were examined under 10 and 40 magnification with Zeiss axioscope (Carl Zeiss, Germany). Signs of osteonecrosis such as the presence of empty lacunae, osteocytes with picnotic nuclei in bone trabeculae, bone marrow necrosis, bone marrow fat degeneration, thrombosis, and cartilage damage were noted. New trabecular bone formation, which indicated repair process, surrounding necrotic areas was also evaluated.

Statistical Analysis

In this experimental study, the images under the microscope were compared and the differences were stated as interpretations. Therefore, no statistical analysis was performed. Therefore, a headline such as "statistical analysis " will not be appropriate. Another experimental study published in your journal; "The effects Of Lucilia sericata Larval Secretions on The Expression of MicroRNAs that are Suggested to be Related with Wound Healing in Experimental Diabetic Rat Wound Model" also does not contain a headline such as statistical analysis.

Results

At the end of the second week, all 4 femur heads examined showed histologically typical signs of osteonecrosis, fatty degeneration of bone marrow and empty bone lacunae. The boundaries of the dead bone trabeculae were evident. Mesenchymal tissue and bone debris materials were visible at marrow distances. Of bone lacunae, 22% were empty. New bone formation was not observed (Figure 3).

The findings of osteonecrosis were more pronounced in the femoral heads collected at the end of the fourth week. The rate of empty bone lacunae without osteocytes reached 80% in some areas. Bone marrow necrosis and adipocyte hypertrophy and increase in the number of macrophages were noted. In addition, osteoblasts that began to appear around the necrotic bone sites were indicative of new bone formation (Figure 4).

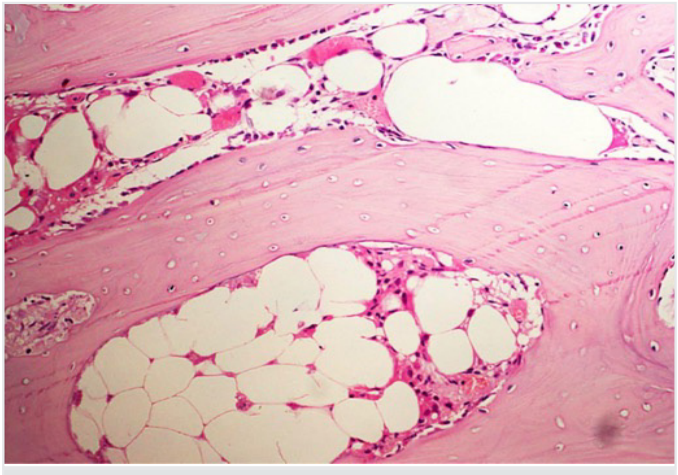

Figure 3. At the end of the second week, the number of cells in the femur heads decreases and necrotic debris and empty osteocyte lacunae are observed

Areas covered with widespread necrosis and irregular granulation tissue, as well as spontaneous bone regenerations were also evident in the femur heads examined at the end of the sixth week. The necrotic bone was covered with living bone tissue. Dead osteocytes and irregular fibrous tissue were still seen at the Centers of the old necrosis sites. The necrotic marrow areas in the pineal areas showed the extent of the damage (Figure 5).

All of the animals lived for the duration of the prescribed experiment. There were no complications, such as wound detachment or infection. Wound detachment caused by an animal biting the suture area was sutured again.

Discussion

Femoral head osteonecrosis is a common disease, affecting the relatively young population (2). Although its pathomechanism has not been definitively elucidated, it is assumed that there is an ischemic factor and blood loss problem in both traumatic and non-traumatic femoral head osteonecrosis (2). Pathologies caused by different etiologies are similar. Appropriate experimental animal models are needed to establish treatment and prevention facilities for ANFH.

In our study, surgical femoral head luxation, cauterization of extraperiosteal vessels of femoral neck and systemic steroids were used to create ANFH model in rabbits. Our histological results showed that this method was able to replicate early avascular necrosis in the head of the rabbit femur. In addition, we believe that this method we apply is more reliable and effective than other previously published models and creates a mechanism closer to pathomechanism of ANFH in human beings.

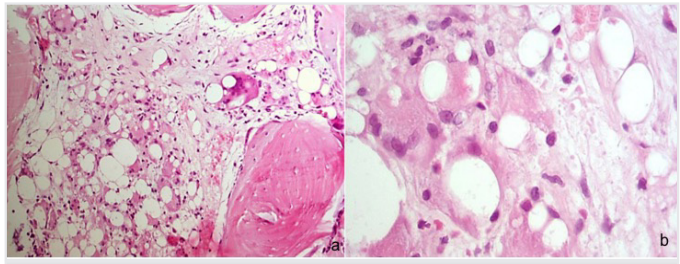

Figure 4. At the end of the fourth week, the bone marrow contains adipocytes and fibrotic tissue (a). Osteoblasts seen around their necrotic sites are a sign that the process of autoregeneration has begun (b)

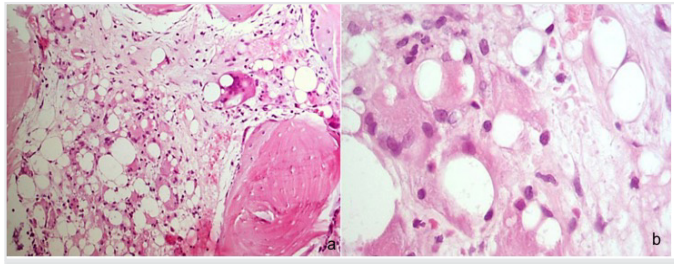

Figure 5. At the end of the sixth week the medullary canal is covered with irregular granulation tissue and necrosis (a). Osteoblasts initiate the formation of new bone tissue around necrotic trabeculae (b)

Systemic steroid administration has been shown in previous publications to create osteonecrosis in rabbits (7,10,12,13). However, almost all of these studies showed that osteonecrosis developed histologically in almost every part of the long bones, but osteonecrosis remained at a relatively low rate of 29%, especially in the proximal epiphysis of the femoral head (10). Osteonecrosis state in metaphyses may not lead to joint destructions, such as subcondral osteonecrosses. Therefore, the animal model to be developed should create osteonecrosis, especially in the proximal femoral epiphysis. In our model, avascular necrosis developed in all of 12 femurs taken from every 6 rabbits. In addition, mortality rates ranging from 2% to 44% were reported in rabbits after high dose steroid administration (7,13). The 6 rabbits used in our study did not have complications such as mortality, local or systemic infection which indicated that our model was reliable.

Different methods have been tried to create osteonecrosis only in the subchondral area of the head of the femur. Li et al. created heat damage with a microwave antenna sent from the subcapital area to the center of the femoral head after surgically exposing the femoral heads, and histologically verified the development of osteonecrosis (11). Zhang-hua et al. and Song applied liquid nitrogen to the cartilage in the load-bearing region of the femoral head after surgically exposing the femoral head to create ANFH in rabbits (14,15). Manggold et al. injected pure ethanol into the thin tunnel they opened in the femoral head in their study on sheep (9). Although the findings of osteonecrosis could be seen histologically in these studies, bone damage was caused by thermal and chemical factors. In addition, cartilage damage developing in the middle and late stages of patients with ANFH was one of the first findings seen in studies using these thermal methods. Our study aimed to create disturbance in vascularization of the femoral head epiphysis, which was the main factor in etiology of avascular osteonecrosis, and as a result to create ANFH.

Another method to disturb vascularization of the femoral head has also been suggested by Hwang et al. (2). In that study, after the proximal femur was exposed to create traumatic ANFH, a tight cerclage wire was wrapped around the femur necks of one group of rabbits, while a cerclage wire was wrapped around the femur necks of another group and electric current was given to this wire by monopolar cautery. As a result, osteonecrosis was detected more in both 2 groups compared with the group who underwent systemic steroid administration alone (2). In our study, extraperiosteal circulation was blocked by burning the femoral neck vessels in a similar way. In addition, the endosteal circulation was disrupted by systemic steroid administration. In this way, it was predicted that the autoregeneration that would begin after ANFH was formed in the rabbit could be delayed.

As with all trials in rabbits, the weakness of our study was that 4 weeks after ANFH formation, autoregeneration-induced recovery began in rabbits. This situation causes completion of recovery of the femoral head before cartilage damage begins and makes it difficult to perform studies about experimental treatments aimed to prevent the arthrotic changes that will be seen in the late period.

Conclusion

ANFH models in animals are invaluable in the research of pathomechanism, prophylactic measures and treatment of the disease. As far as is known today, there is no method to one-to-one replicate the formation of this disease in rabbits. Early findings of ANFH can be established in rabbits effectively and reliably with low complication rate with surgical hip dislocation, peripheral cauterization of femoral neck and single dose systemic administration of methylprednisolone. In order to investigate the treatment of late-stage complications of ANFH, autoregenerative processes in animals need to be delayed.

Ethics

Ethics Committee Approval: The study was carried out following the approval of the Institutional Animal Experiments Ethics Committee of Modena and Reggio Emilia University (2012/07/16-57).

Peer-review: Externally peer reviewed.

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References

1. Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head. J Bone Joint Surg Am 1995;77:459-74.
2. Hwang Y, Park J, Choi SH, Kim G. Traumatic and non-traumatic osteonecrosis in the femoral head of a rabbit model. Lab Animal Res 2011;27:127-31.
3. Wen Q, Ma L, Chen YP, Yang L, Luo W, Wang XN. A rabbit model of hormone-induced early avascular necrosis of the femoral head. Biomed Environ Sci 2008;21:398-408
4. Frost HM. In vivo osteocyte death. J Bone Joint Surg Am 1960;42-A:138-43.
5. Phemister DB. The classic: repair of bone in the presence of aseptic necrosis resulting from fractures, transplantations, and vascular obstruction. Clin Orthop Relat Res 2008;466:1021-33.
6. Kawai K, Tamaki A, Hirohata K. Steroid-induced accumulation of lipid in the osteocytes of the rabbit femoral head. A histochemical and electron microscopic study. J Bone Joint Surg Am 1985;67:755-63.
7. Motomura G, Yamamoto T, Irisa T, Miyanishi K, Nishida K, Iwamoto Y. Dose effects of corticosteroids on the development of osteonecrosis in rabbits. J Rheumatol 2008;35:2395-99.
8. Yamamoto T, Irisa T, Sugioka Y, Sueishi K. Effects of pulse methylprednisolone on bone and marrow tissues: corticosteroid-induced osteonecrosis in rabbits. Arthritis Rheum 1997;40:2055-64.

9. Manggold J, Sergi C, Becker K, Lukoschek M, Simank HG. A new animal model of femoral head necrosis induced by intraosseous injection of ethanol. Lab Anim 2002;36:173-80.

10. Qin L, Zhang G, Sheng H, Yeung KW, Yeung HY, Chan CW, Cheung WH, Griffith J, Chiu KH, Leung KS. Multiple bioimaging modalities in evaluation of an experimental osteonecrosis induced by a combination of lipopolysaccharide and methylprednisolone. Bone 2006;39:863-71.

11. Li Y, Han R, Geng C, Wang Y, Wei L. A new osteonecrosis animal model of the femoral head induced by microwave heating and repaired with tissue engineered bone. Int Orthop 2009;33:573-80.

12. Miyanishi K, Yamamoto T, Irisa T, Motomura G, Jingushi S, Sueishi K, Iwamoto Y. Effects of different corticosteroids on the development of osteonecrosis in rabbits. Rheumatology (Oxford) 2005;44:332-6.

13. Wang GJ, Sweet DE, Reger SI, Thompson RC. Fat-cell changes as a mechanism of avascular necrosis of the femoral head in cortisone-treated rabbits. J Bone Joint Surg Am 1977;59:729-35.

14. Zhang-hua L, Wen L, Xi-long C, You-hao C, Tian-shu L, Ming L, Yi Y. Effects of Cbfa1 on osteoanagenesis during avascular necrosis of femoral head. Sci Res Essays 2010;5:2721-2730

15. Song Hj. Peripheral blood Stem cell transplantation for ischemic femoral head necrosis. Transplant Proc 2010;42:1862-1864

Original Article

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Investigation of Ghrelin Levels in Antimuscarinic Induced Convulsions in Fasted Animals After Food Intake

Aç Hayvanlara Antimuskarinik Uygulanması ve Yem Verilmesi ile Oluşan Konvulsiyonlarda Ghrelin Seviyelerinin Araştırılması

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ABSTRACT

Objective: Atropine reduces ghrelin secretion and ghrelin inhibits epileptic seizures. It is interesting that atropine treated fasting animals develop clonic convulsions soon after food intake. Present study was designed to investigate relationship between these antimuscarinic induced convulsions and ghrelin levels.

Methods: Balb/C mice were fasted for 24 hours, then treated with saline or scopolamine (3 mg/kg, i.p.) and then given food 20 minutes later. All animals were observed for 30 minutes for the incidence and development of convulsions. Then ghrelin levels were measured in blood and brain tissue.

Results: Scopolamine treatment caused convulsions in fasted animals after food intake. In saline treated fasted animals, plasma ghrelin concentration was significantly higher than saline treated fed animals. Plasma and tissue ghrelin concentrations were found significantly lower in animals with convulsion than in fasted animals which were given food after saline injection.

Conclusion: It was shown that ghrelin levels were reduced in the group with convulsions due to scopolamine administration and food intake. Therefore, it is suggested that ghrelin may have possible role on these convulsions.

Keywords: Ghrelin, scopolamine, convulsion, mouse, fasting

ÖZ

Amaç: Atropin ghrelin salınımını azaltmakta, ghrelin ise epileptik nöbetleri baskılamaktadır. Aç hayvanlara atropin uygulanması ve ardından yem verilmesi ile klonik konvülsiyonlar oluştuğunu bildiğimizden bu bilgi dikkat çekicidir. Bu nedenle çalışmamızda, antimuskarinikle indüklenen bu konvülsiyonlar ile ghrelin seviyelerinin ilişkisinin araştırılması amaçlanmıştır.

Yöntemler: Balb/C fareler 24 saat aç bırakıldı, bu süre sonunda serum fizyolojik veya skopolamin (3 mg/kg, i.p.) uygulandı ve 20 dakika sonra yem verildi. Konvülsiyon oluşumu ve sıklığını belirleyebilmek için tüm hayvanlar 30 dakika süreyle izlendi. Alınan plazma ve beyin dokularında ghrelin seviyeleri ölçüldü.

Bulgular: Skopolamin uygulanan aç farelerde yem yedikten sonra konvulsiyon oluştuğu izlendi. Serum fizyolojik uygulanan aç hayvanlardaki plazma ghrelin seviyesinin, toklara kıyasla anlamlı derecede yüksek olduğu saptandı. Konvülsiyon geçiren hayvanlardaki plazma ve doku ghrelin seviyelerinin, açlık sonrasında serum fizyolojik uygulanan ve ardından yem verilen hayvanlara göre anlamlı derecede düşük olduğu belirlendi.

Sonuç: Konvülsiyon geçiren farelerdeki ghrelin düzeylerinin, skopolamin uygulanması ve yem verilmesi sonucunda azaldığı görülmektedir. Çalışmamızdaki bulgular, ghrelinin bu konvülsiyonların oluşumunda rolü olabileceğini düşündürmektedir.

Anahtar Sözcükler: Ghrelin, skopolamin, konvülsiyon, fare, açlık

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Introduction

In previous studies, it was shown that fasted animals treated with antimuscarinic drugs (atropine, scopolamine or biperiden) developed convulsions soon after eating (1-3). It was observed that animals developed convulsions after food deprivation for 2, 3, 12, 18 and 24 h. and it was suggested that stress due to food deprivation, rather than its duration might contribute to the underlying mechanisms of convulsions (4). Prevention of hypoglycemia by glucose intake during fasting had no preventive effect on convulsion development. So, it is suggested that food deprivation itself, but not its hypoglycemic consequence, may have critical role in the development of convulsions (2). Also, it could be argued that convulsions were triggered by oral movements, because convulsions did not occur with fluid or slurry food (5).

[^{3}H]glutamate binding kinetics significantly changed after fasting for 48 h and this change was partly antagonized by scopolamine treatment and eating (6). Typical epileptiform discharges were shown in cortical electroencephalography recordings in animals with convulsion (7). Tizanidine, clonidine, chlorpromazine, haloperidol and MK-801 (noncompetitive N-methyl-D-aspartate antagonist) provided effective treatments in these convulsions (1,3,6). However, most of the major antiepileptics drugs (AEDs) and new AEDs were ineffective to suppress convulsions (2,8).

The manifestations of the seizures and the triggering factors of convulsions in antimuscarinic treated fasted animals beared some similarities with patients who had eating-evoked epilepsy (9). So, these convulsions in fasting animals may help to explain the mechanisms of this rare form of reflex epilepsy.

Ghrelin, an orexigenic peptide, regulates appetite and meal initiation. While its level increased during hunger and it sent signals to brain to eat (10), exogenous ghrelin administration caused body weight gain and induced food intake (11-13). Ghrelin secretion was under cholinergic control and a muscarinic receptor antagonist, atropine abolished its secretion (14).

It was shown that serum ghrelin levels were increased in epileptic patients (15). Exogeneous ghrelin administration inhibited development of seizures, reduced severity of seizures, and neuronal cell loss in hippocampus (16-18). Antiepileptic effects of ghrelin were shown in animals with pentylenetetrazole-(PTZ)-induced epilepsy (16). In another study, it was determined that ghrelin concentration was reduced in animals with PTZ-induced seizures (19).

Seizure development, fasting and cholinergic system all interact with each other in scopolamine induced convulsions in fasting mice after food intake. Also, based on recent data, ghrelin secretion was under cholinergic control and it was associated with convulsions and fasting state. There was no study in the literature that investigated the relationship between these mechanisms. So, we aimed to investigate the ghrelin levels in plasma and brain tissue for understanding relationship between mechanisms in these convulsions.

Methods

The present study was approved by the Istanbul University Local Ethics Committee on Animal Experiments (63/29.04.2010). All studies were in accordance with EU Directive 2010/63/EU on the protection of animals used for scientific purposes.

Drugs

Scopolamine hydrobromide (Sigma, St Louis, MO) 3 mg/kg (1-4) was dissolved in saline and injected intraperitoneally (i.p.).

Procedure

In this study, male Balb/C mice, weighing between 25-30 g were used. Animals were housed under standard laboratory conditions until experimentation. After weighing, mice were divided into two main groups as fed and fasted mice. Fasted animals were deprived of food for 24 hours. During the fasting period, animals could access to water.

Half of fed animals were injected 4 mL/kg saline (fed+sal group) and the other half 3 mg/kg scopolamine i.p. (fed+scop group).

Fasted mice were reweighed and injected saline or scopolamine i.p. and placed in wire mesh cages individually. Twenty minutes later, half of fasted animals were given 2 grams of food pellets and allowed to eat (fasted + sal + food group and fasted + scop + food group). The other half of fasted animals were not given food (fasted + sal group and fasted + scop group). All mice were observed for determining the incidence and onset of convulsions for 30 minutes after feeding. At the end of observing period, all animals were decapitated and tissue and blood samples were collected.

Stages of seizure activity were scaled as; no difference (stage 0); freezing and gustatory movements (stage 1); forelimb clonus (stage 2); forelimb clonus with rearing (stage 3); forelimb clonus with rearing and/or falling down (stage 4); generalized convulsions with rearing, falling down and jumping (stage 5).

Stage 3, 4 and 5 were assessed as a convulsive response. Onset of convulsions was defined as the time between re-feeding and the stage 3 activity. The incidence of convulsions was expressed as the percentage of animals displaying either stage 3, 4 or 5 activity.

Experiments were carried out in a temperature-controlled (21±2 ºC) room, between 08:00 and 22:00. Observers were blind to the groups.

Plasma and Tissue Ghrelin Levels

Blood samples of animals were collected in plastic ethylenediaminetetraacetic acid (EDTA) tubes soon after decapitation and for tissue processing, all brains were removed on ice.

Tissues were homogenized and supernatants were collected for procedure. Total ghrelin levels were determined in supernatants and plasma, by an enzyme immunoassay kit (Phoenix Pharmaceuticals, Inc. EK-031-31, Burlingame, USA) according to manufacturer's guidelines. Absorbance

data were collected by using a microplate reader (ELX-800 spectrophotometer, Vertmont, USA).

Statistical Analysis

Body weight loss was evaluated by using paired samples t-test. The data of time to onset of convulsions were evaluated using one-way analysis of variance (ANOVA) followed by Tukey's test. For the evaluation of the convulsion incidence, we used Fisher's exact test. Ghrelin levels in tissue and in plasma were investigated with One-way ANOVA followed by Tukey's test. Spearman correlation analyze was applied to investigate relationship between convulsion stages and ghrelin levels. A p-value less than 0.05 was considered statistically significant. All values were presented as mean ± SEM.

Results

Convulsions

The body weights of the animals fell to 91.3% of their initial body weights after food deprivation for 24 h. Only scopolamine treated fasted mice showed convulsions after food intake with an incidence of 83.3%. When compared with the saline-treated control group, the difference was statistically significant ($p<0.05$). The time to onset of convulsions was found 6.3±1.7 min.

Plasma Ghrelin Levels

Total plasma ghrelin levels are shown in Figure 1.

Total plasma ghrelin level was significantly higher in 24-hour fasted+sal group (5.6±0.5 nmol/mL) than fed+sal (2.9±0.3 nmol/mL) group ($p<0.05$). Ghrelin level in fasted+sal+food group (7.0±0.9 nmol/mL) was significantly higher than fed+sal group ($p<0.01$), and fasted+scop+food (3.8±0.9 nmol/mL) group ($p<0.05$).

Tissue Ghrelin Levels

Total tissue ghrelin levels are shown in Figure 2.

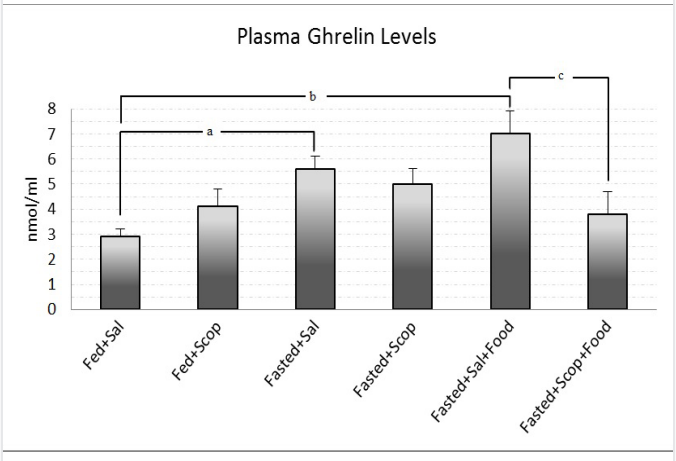

Figure 1. Total plasma ghrelin levels in all groups. Bars are presented as mean ± SEM

[a]$p<0.05$, [b]$p<0.01$ when compared to fed+saline group.
[c]$p<0.05$, when compared to fasted+scopolamine+food group.

Total ghrelin level in brain tissue was higher in fed + scop (1.5±0.6 nmol/mL) group than fed + sal (1.4±0.3 nmol/mL) group. Ghrelin level in fasted+scop (0.8±0.1 nmol/mL) group was lower than fasted + sal (1.8±0.4 nmol/mL) group. Animals in fasted + sal + food (3.8±0.6 nmol/mL) group had significantly increased tissue ghrelin levels when compared to fasted + sal group ($p<0.05$) and fed + sal, fasted + scop + food (0.9±0.1 nmol/mL) groups ($p<0.01$).

Convulsion Stage and Ghrelin Levels

Fasted mice developed convulsions after scopolamine treatment and food intake. Stage and time to onset of convulsions and ghrelin levels are shown in Table 1.

When we investigated the relationship between stage of convulsions and plasma and tissue ghrelin levels; weak positive correlation was found (Spearman's rho=0.29, $p<0.58$).

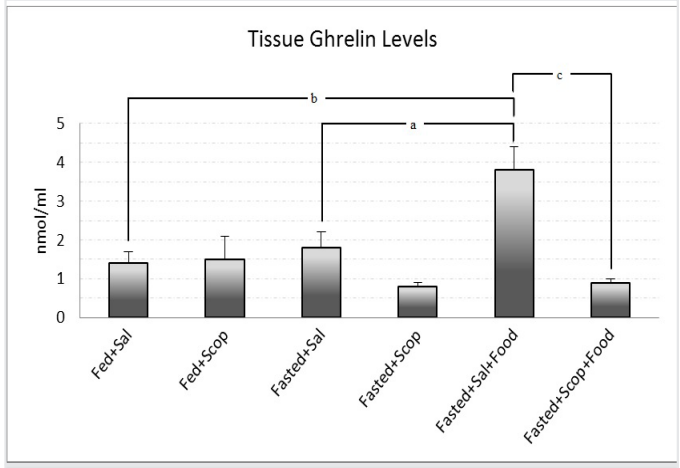

Figure 2. Total tissue ghrelin levels in all groups. Bars are presented as mean ± SEM

[a]$p<0.05$ when compared to fasted+saline group.
[b]$p<0.01$ when compared to fed+saline group.
[c]$p<0.01$ when compared to fasted+scopolamine+food group.

Table 1. Stage and onset of convulsions in each animal in fasted + scopolamine + food group. Also, the plasma and tissue ghrelin levels of each mouse are presented below

Animals	Plasma ghrelin levels (nmol/mL)	Tissue ghrelin levels (nmol/mL)	Stage of convulsion	Time to onset of convulsion (minute)
1	3.4	0.8	5	11
2	4.1	0.7	3	3
3	6.9	0.7	2	4
4	1.3	1.5	2.5	5
5	2.1	0.8	4	4
6	5.7	0.8	4	12

Discussion

In this study, we investigated the relationship between ghrelin levels and scopolamine-induced convulsions for the first time. In accordance with previous studies (1-3), scopolamine induced convulsions in 24-hour fasted mice (83.3%) after food intake. Recent studies showed that, animals had convulsions (50%) after fasting for 2 hours. So, it can be assumed that development of convulsions are not related to duration of fasting and thus, ghrelin concentration. However, the stress due to food deprivation and eating solid food can be related to ghrelin levels. Because, mRNA expression of plasma ghrelin increased significantly following acute tail pinch stress (20). Plasma ghrelin concentrations also increase in cases of calorie restriction, prolonged energy deficit and reduced feed intake (such as anorexia). Then, higher ghrelin levels in fasted groups due to stress of food deprivation may be expected . Considering that ghrelin concentration falls significantly after atropine administration to fasted animals, scopolamine as another antimuscarinic drug, may be expected to reduce ghrelin concentration in fasted animals. As we expected, ghrelin levels in plasma and tissue were higher in saline treated fasted animals, whereas they were lower in scopolamine treated fasted animals. But, this difference was not statistically significant.

Elevation of ghrelin levels with exogenous ghrelin administration, shortened time to onset of seizures and increased the incidence of seizures (16,18). It could be argued that, ghrelin did not show its protective effect against convulsions in fasted + scop + food group, because of low ghrelin levels in this group. In another study, it was shown that plasma ghrelin levels were decreased in rats with pentylenetetrazol induced seizures (21). Similar to this finding, plasma ghrelin levels of animals with convulsion reduced in our study.

Ghrelin plasma concentration elevated in fasting, and decreased to normal levels after meals (11,22). In our study, ghrelin levels in 24-hour fasted animals significantly elevated when compared to controls. Interestingly, plasma ghrelin levels in scopolamine-treated fed animals elevated too. It was known that, ghrelin secretion was modulated by cholinergic, dopaminergic and adrenergic systems (14,23). Previous studies showed that, ghrelin secretion increased with erythromycin, which was a cholinergic prokinetic agent (23) and decreased acutely after vagotomy (14). Also, there were studies showing changes in both muscarinic (24), glutamatergic (1) and GABAergic receptors (25) in different brain regions, after 24-hour or longer fasting.

It was known that dopamine secretion increased after re-feeding (26), dopamine inhibited acetylcholine secretion presynaptically (27) and acetylcholine increased ghrelin secretion (23). Also, it was shown that atropine, an antimuscarinic drug as scopolamine, reduced the plasma ghrelin levels in fasted animals (14). We found similar results in our study: Scopolamine-treated fasted animals had lower ghrelin levels than saline-treated fasted animals. It could be speculated that ghrelin secretion reduced in scopolamine-treated fasted animals after food intake for two reasons; firstly, increased dopamine suppressed acetylcholine and secondly, an antimuscarinic drug was administered. It is known that the convulsions in scopolamine-treated re-fed animals are not affected by the administration of physostigmine (1), but suppressed by administration of clonidine and tizanidine. In light of these findings, the effects of fasting, re-feeding and cholinergic system interactions on ghrelin secretion and convulsion development should be elucidated.

The ghrelin concentration declines to normal values, after 1 hour of eating (11,21). When we compared the fasted + sal group and fasted + sal + food group, we observed that ghrelin level increased after feeding. This finding was interesting, because ghrelin level after meal was expected to decrease. When 24-hour fasted animals were allowed to eat, they did not start to eat immediately and ate little amount of pellets. Considering this finding, it could be argued that there was no satiety in animals and therefore ghrelin concentration did not decrease. Also we could argue that, blood and tissue samples were taken 30 minutes after eating and ghrelin levels had not returned to normal values yet. These suggestions could explain why ghrelin level was found high in fasted + sal + food group.

Ghrelin suppressed apoptosis in hypothalamic neurons in the absence of oxygen and glucose, and reduced toxicity caused by kainic acid (28). In ischemic conditions, ghrelin was found to protect cortical neurons against cell death (29); while in other tissues it also had protective effect by reducing ischemia/reperfusion injury (30). Also, it was recently shown that oxidative stress markers were reduced by ghrelin administration in PTZ-induced seizures in rats, and seizures were reduced in accordance with high ghrelin levels (31). Considering all these findings, it may be thought that ghrelin suppresses the seizures by reducing degeneration. In a different study, it was shown that the plasma level of ghrelin decreased soon after PTZ-induced seizures in rats (19). Similar to this finding, fasted + scop + food group, in which all mice had convulsions, had significantly decreased tissue and plasma ghrelin levels compared with the fasted + sal + food group.

According to the findings of our unpublished studies, c-fos expression was suppressed in scopolamine-treated fasted animals. When evaluating this finding together with plasma and tissue ghrelin levels in this study, it seemed that decrease in ghrelin levels might be parallel with suppressed c-fos expression. The increase in ghrelin levels may be thought to contribute to the convulsions by increasing neuronal activity.

In this study, the relationship between ghrelin levels and antimuscarinic induced convulsions in fasted mice after food intake was investigated for the first time. As expected, plasma concentration of ghrelin was found elevated in fasted animals compared to fed animals. Tissue and plasma ghrelin concentrations were found to be low because scopolamine administration suppressed ghrelin secretion. Since ghrelin was shown to be protective in development of seizures; it could be argued that the protective effect of ghrelin was not observed in this study due to the low ghrelin level in animals with convulsion.

Conclusion

Present study suggested for the first time that ghrelin could have a possible role in antimuscarinic induced convulsions. Since there are many mechanisms effective on development of convulsions and regulation of fasting, further studies are needed to fully explain the mechanism of antimuscarinic induced convulsions in fasted mice after food intake.

Ethics

Ethics Committee Approval: The present study was approved by the Istanbul University Local Ethics Committee on Animal Experiments (63/29.04.2010).

Informed Consent: Is animal work.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: A.Z.T., A.N., Design: A.Z.T., A.N., Data Collection or Processing: A.Z.T., A.N., Analysis or Interpretation: A.Z.T., A.N., Literature Search: A.Z.T., A.N., Writing: A.Z.T., A.N.

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

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References

1. Enginar N, Nurten A, Yamanturk P, Koyuncuoglu H. Scopolamine-induced convulsions in food given fasted mice: Effects of physostigmine and MK-801. Epilepsy Res 1997;28:137-42.
2. Enginar N, Nurten A, Yamanturk-Celik P, Acikmese B. Scopolamine-induced convulsions in fasted mice after food intake: Effects of glucose intake, antimuscarinic activity and anticonvulsant drugs. Neuropharmacology 2005;49:293-9.
3. Enginar N, Yamanturk P, Nurten A, Koyuncuoglu H. Scopolamine-induced convulsions in food given to fasted mice: Effects of clonidine and tizanidine. Epilepsy Res 1999;35:155-60.
4. Enginar N, Nurten A, Ozunal ZG, Zengin A.Scopolamine-induced convulsions in fasted mice after food intake: the effect of duration of food deprivation. Epilepsia 2009;50:143-6.
5. Nurten A, Ozerman B, Ozen I, Kara I. The role of solid food intake in antimuscarinic-induced convulsions in fasted mice. Epilepsy Behav 2009;15:142-5.
6. Enginar N, Yamanturk P, Nurten A, Nurten R, Koyuncuoglu H. Scopolamine-induced convulsions in fasted mice after food intake: Determination of blood glucose levels, [3H] glutamate binding kinetics and antidopaminergic drug effects. Neuropharmacology 2003;44:199-205.
7. Nurten A, Ozen I, Karamursel S, Kara I. Electroencephalographic characterization of scopolamine-induced convulsions in fasted mice after food intake. Seizure 2006;15:509-19.
8. Büget B, Enginar N, Zengin Türkmen A, Allahverdiyev O. Antimuscarinic-induced convulsions in fasted animals after food intake: Evaluation of the effects of levetiracetam, topiramate and different doses of atropine. Naunyn-Schmiedeberg's Arch Pharmacol 2016;389:57-62.
9. Italiano D, Ferlazzo E, Gasparini S, Spina E, Mondello S, Labate A, et al. Generalized versus partial reflex seizures: a review. Seizure 2014;23:512-20. https://doi.org/10.1016/j.seizure.2014.03.014.
10. Sato T, Nakamura Y, Shiimura Y, Ohgusu H, Kangawa K, Kojima MJ. Structure, regulation and function of ghrelin. Biochem 2012;151:119-28.
11. Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001;50:1714-9.
12. Reimer RA, Maurer AD, Lau, DCW, Auer RN. Long-term dietary restriction influences plasma ghrelin and GOAT mRNA level in rats. Physiol Behav 2010;99:605-10.
13. Toshinai K, Yamaguchi H, Sun Y, Smith RG, Yamanaka A, Sakurai T, et al. Des-acyl ghrelin induces food intake by a mechanism independent of the growth hormone secretagogue receptor. Endocrinol 2006;147:2306-14.
14. Hosoda H, Kangawa K. The autonomic nervous system regulates gastric ghrelin secretion in rats. Reg Peptides 2008;146:12-8.
15. Berilgen MS, Mungen B, Ustundag B, Demir C. Serum ghrelin levels are enhanced in patients with epilepsy. Seizure 2006;15:106-11.
16. Obay BD, Tasdemir E, Tümer C, Bilgin HM, Sermet A. Antiepileptic effects of ghrelin on pentylenetetrazole-induced seizures in rats. Peptides 2007;28:1214-9.
17. Portelli J, Michotte Y, Smolders I. Ghrelin: An emerging new anticonvulsant neuropeptide. Epilepsia 2012;53:585-95.
18. Xu J, Wang S, Lin Y, Cao L, Wang R, Chi Z. Ghrelin protects against cell death of hippocampal neurons in pilocarpine-induced seizures in rats. Neurosci Letters 2009;453:58-61.
19. Ataie Z, Golzar MG, Babri S, Ebrahimi H, Mohaddes G. Does ghrelin level change after epileptic seizure in rats? Seizure 2011;20:34-9.
20. Diz-Chaves Y. Ghrelin, appetite regulation, and food reward: Interaction with chronic stres. Int J Peptides, 2011;1-11. https://doi.org/10.1155/2011/898450.
21. Aydın S, Özkan Y, Caylak E, Aydin S. Ghrelin ve biyokimyasal fonksiyonları. J Med Sci 2006;26:272-83.
22. Cummings DE, Frayo RS, Marmonier C, Aubert R, Chapelot D. Plasma ghrelin levels and hunger scores in humans initiating meals voluntarily without time- and food-related cues. Am J Physiol Endocrinol Metab 2004;287:297-304.
23. Sagkan-Ozturk A, Demir EA, Ozturk A. Prokinetics stimulate the increase of ghrelin in mice. Bratisl Lek Listy. 2016;117(12):726-729. doi: 10.4149/BLL_2016_139.
24. Saygı Bacanak M, Aydın B, Cabadak H, Nurten A, Gören MZ, Enginar N. Contribution of M(1) and M(2) muscarinic receptor subtypes to convulsions in fasted mice treated with scopolamine and given food. Behav Brain Res 2019;364:423-30.
25. Weizman A, Bidder M, Fares F, Gavish M. Food deprivation modulates gamma-aminobutyric acid receptors and peripheral benzodiazepine binding sites in rats. Brain Res 1990;535:96-100.
26. Taber MT, Fibiger HC. Feeding-evoked dopamine release in the nucleus accumbens: regulation by glutamatergic mechanisms. Neuroscience 1997;76:1105-12.

27. Benarroch EE. Enteric nervous system: functional organization and neurologic implications. Neurology 2007;13;69:1953-7.

28. Frago LM, Baquedano E, Argente J, Chowen JA. Neuroprotective actions of ghrelin and growth hormone secretagogues. Frontiers in Mol Neurosci 2011;4:1-11.

29. Chung H, Chung HY, Bae CW, Kim CJ, Park S. Ghrelin suppresses tunicamycin- or thapsigargin-triggered endoplasmic reticulum stress-mediated apoptosis in primary cultured rat cortical neuronal cells. J Endocrinol 2011;58:409-20.

30. Rajan D, Wu R, Shah KG, Jacob A, Coppa GF, Wang P. Human ghrelin protects animals from renal ischemia-reperfusion injury through the vagus nevre. Surgery 2012;151:37-47.

31. Obay BD, Tasdemir E, Tumer C, Bilgin HM, Atmaca M. Dose dependent effects of ghrelin on pentylenetetrazole induced oxidative stress in a rat seizure model. Peptides 2008;29:448-55.

Original Article

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Evaluation of the Opinions of the First, Second and Third Term Medical Students About Problem Based Learning Sessions in Bezmialem Vakıf University

Bezmialem Vakıf Üniversitesi Tıp Fakültesi 1. 2. ve 3. Sınıf Öğrencilerinin Probleme Dayalı Öğrenim Oturumları Hakkındaki Görüşlerinin Değerlendirilmesi

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ABSTRACT

Objective: Problem-based learning (PBL) is a student-centered small group study and active learning method. It aims to provide students with the skills of self-learning, learning to learn, and solving real-world problems and is used as a learning method in many medical faculties. In this study, it was aimed to examine and evaluate the perceptions and opinions of Bezmialem Vakif University Faculty of Medicine students about PBL applications and all processes.

Methods: For this purpose, a questionnaire consisting of 16 questions was prepared and applied to first, second and third term students in Bezmialem Vakıf University Faculty of Medicine. In this questionnaire, students' perceptions and opinions were evaluated with a five-point Likert scale and an open-ended question.

Results: According to the results, overall satisfaction was found to be 3.67 on average. These ratios were; 3.85 in the first term students, 3.54 in the second term students, and 3.66 in third term students. As a result, the highest satisfaction was achieved in the proposition "PBL participants are always respectful to the group" with a score of 4.19. The proposition "PBL trainers help to discuss problems in every way" was found to get the lowest score (3.57). The other lowest score (3.59) was achieved in the prosposition "Everyone comes prepared for the second session in PBL sessions".

ÖZ

Amaç: Probleme dayalı öğrenme (PDÖ), bir yönlendirici eşliğinde 6-8 öğrenciyle yapılan, öğrenci merkezli küçük grup çalışması ve aktif öğrenme yöntemidir. Öğrencilere kendi kendine öğrenme, öğrenmeyi öğrenme, gerçek dünyada yaşanabilecek problemleri çözme becerilerini kazandırmayı hedefler ve birçok tıp fakültesinde öğrenme yöntemi olarak kullanılmaktadır. Fakültemizde, her dönemde en az bir kez, PDÖ oturumları uygulanmakta ve oturumlarla ilgili düzenli geribildirimler alınmaktadır. Bu çalışmada ise, Bezmialem Vakıf Üniversitesi Tıp Fakültesi öğrencilerinin PDÖ uygulamaları ve süreçleri ile ilgili algı ve görüşlerinin incelenmesi ve değerlendirilmesi amaçlanmıştır.

Yöntemler: Bu amaçla Bezmialem Vakıf Üniversitesi Tıp Fakültesi Dönem I, II ve III öğrencileri için literatürden faydalanılarak, 16 sorudan oluşan bir anket hazırlanmış ve öğrencilere uygulanmıştır. Bu ankette öğrencilerin algı ve görüşleri beş puanlık likert ölçeği ve açık uçlu bir soru ile değerlendirilmiştir.

Bulgular: Anket sonuçlarına göre genel memnuniyet ortalama 3,67 olarak bulunmuştur. Bu oranlar; Dönem I'de 3,85, Dönem II'de 3,54, Dönem III'te 3,66 olarak belirlenmiştir. Anket sonucunda, en yüksek memnuniyet "PDÖ katılımcıları her zaman gruba saygılıdır" maddesi 4,19 puan ile en yüksek puanı almıştır. "PDÖ eğitmenleri sorunları her yönden tartışmaya yardımcı oluyor" maddesi ise 3,57

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Conclusion: With these data, accurate decisions can be made about which steps should be considered in our practices and the aspects that need to be improved. Our goal is to organize PBL sessions in each committee in the preclinical term.

Keywords: Problem-based learning, PBL, medical education, likert scale

puan ile en düşük puanı almıştır. Diğer 3,59 memnuniyet puanıyla en düşük olan madde ise "PDÖ oturumlarında 2. oturuma herkes hazırlıklı gelmektedir" maddesidir.

Sonuç: Bu verilerle, uygulamalarımızda hangi aşamalara dikkat edilmesi gerektiği ve iyileştirilmesi gereken yönler hakkında isabetli kararlar verilebilir. PDÖ oturumlarının öğrencilerin öğrenmesine katkıda bulunduğu açıktır. Henüz PDÖ oturumlarını kısıtlı sayıda uygulayabilmekteyiz. Ancak hedefimiz preklinik dönemde her kurulda PDÖ oturumları düzenlemektir.

Anahtar Sözcükler: Probleme dayalı öğrenme, PDÖ, tıp eğitimi, likert ölçeği

Introduction

Problem-based learning (PBL) approaches have a long history based on John Dewey's work explaining the relationship between learning by trying and doing and education. PBL is therefore part of the educational tradition where the importance of meaningful and experienced learning is emphasized. PBL has inspired from different theoretical approaches about learning. Although these approaches have different theoretical roots, all emphasize that learning is an active process and that gaining experience is an important part of the learning process. PBL also facilitates learning as a student-centered and interactive activity (1,2).

A problem in PBL scenarios needs to be based on reality, adapted to the student's preliminary knowledge level, able to involve students in discussions, provide identification of appropriate learning topics, encourage self-learning, and be interesting and relevant (1).

As an alternative approach to teaching and learning, PBL has become an increasingly popular practice and is now frequently used in almost all levels and areas of Education. There are some common goals in the problem-based curriculum. According to Hmelo-Silver, these goals for students can be listed as: Building a comprehensive and flexible knowledge base, developing effective problem solving and upper cognitive skills, self-management, developing lifelong learning skills, becoming effective collaborators and motivating oneself to learn (3). Basically, the goal of all learning curricula is to enable students to build a comprehensive and flexible knowledge base.

In PBL, the development of relevant competencies includes the ability to implement appropriate metacognitive and reasoning strategies. Metacognitive skills are often conceptualized as an interrelated set of competencies for learning and thinking, and include many of the skills needed for critical thinking, problem-solving, and decision-making. The development of metacognitive skills is a process by which students learn to learn (3).

Another important goal in PBL is taking responsibility by students for their own learning processes. It is stated that this responsibility taken by students can be used to improve content knowledge, problem solving, communication and critical thinking skills. In addition, there are studies showing that students who study with PBL are generally more successful at producing solutions than groups trained with other methods (1,3).

Being an effective collaborator means knowing how to work as part of a team. In PBL, students collaborate in small groups. The benefits of small group cooperation have been widely discussed in the PBL literature (1). According to researches, small group study creates a platform for the development of friendships between students, establishes closer contact and communication between the instructors and students, allows students to be diligent in their studies and complies with the deadline agreed by the group for the work and based on collaboration, it encourages students in small groups to establish a knowledge base (1). The aim of PBL is to genuinely motivate students and make them work on a task motivated by their interest in learning rather than exam and external motivations (3).

In the pre-clinical term from 2012 to the present day, PBL sessions are held at least once a year in each class in BVU Medical Faculty. The sessions take place in the training program, which will be in the committees recommended by the PBL Commission. It is implemented in three sessions in a one-week term immediately at the beginning of the committees. PBL routers take courses organized by the Department of Medical Education and Informatics, participate as monitors and then are assigned as routers. It is ensured that the scenarios are integrated with the subjects of the committees in which they are located, that they are interesting, curious in line with the learning goals and that they are also in the structure that addresses the biopsychosocial environment of the patient. Scenarios that have received the PBL Commission's approval are being implemented. Informative meeting is held with Term I students before the start of the PBL sessions, and the objectives, method of implementation, measurement and evaluation issues are explained to students. Students are divided into groups of 8-10 people, small group study rooms are prepared for the sessions, and PBL sessions are implemented in accordance with scenarios set out with a problem and the accompanying questions. Interactive methods such as brainstorming and discussions are implemented in the sessions, and the participation of all individuals in the group in the discussions is encouraged by the routers. There are structured assessment forms that evaluate student's participation and contributions during the sessions. Students are evaluated

by router lecturers through these forms. In addition, the grades taken from the multiple choice exam at the end of the sessions are evaluated and their impact value is 10% of the committee. At the end of the sessions, feedback is received from both lecturers and students and they are asked to express their views on the issues such as the session and scenario. Changes to be made for the next applications in line with the recommendations will be decided by the commission. Our training program does not consist entirely of PBL sessions. The integrated system is applied in the preclinical term. Although there are application targets in every committee, PBL can be applied in some committees.

Many valuable studies of educational science agree that PBL is an important learning method with many positive aspects. The aim of this study is to evaluate this method in our faculty with the eyes of the students and to obtain their opinions.

Methods

A 16-question questionna was prepared for the term I, II and III students to obtain their views on the PBL practices included in their curriculum in the 2017-2018 academic year. Prior to the study, an application was made to Bezmialem Foundation University Non-Interventional Ethics Committee and the approval was obtained with the decision number 10/146 on 16.05.2017. A total of 354 students filled out the survey and the data were collected. The survey questions were prepared using the process in our faculty, situations and similar literature. The survey questions mainly contained three key elements: 1. Awareness before PBL sessions, 2.Process during sessions and 3. Questions about the situation after the sessions and about activities and practices performed. Proposition 1 contains the situation and thoughts before the sessions, propositions 2-11 during the sessions, and propositions 12-16 after the sessions. The first question in the survey was answered as "Yes" or "No". The answers given to the other 14 questions were classified according to the quintuple rating system (5: absolutely agree, 4: agree, 3: uncertain, 2: disagree, 1: strongly disagree). The last (16^{th}) question was asked to students to make a general evaluation and a score between 1-5 was given. Prior to the study, approval was obtained from the BVU Non-Interventional Clinical Studies Ethics Committee. The population of term I students was 133 and 34 (25.6%) of them participated in the survey. The population of term II students was 94 and 37 (39.4%) of them participated in the survey. The population of term III students was 127 and 89 (70.1%) of them participated in the survey. A total of 354 students were given survey forms, but 160 (45.19%) answered the survey.

Statistical Analysis

All statistical analyses were conducted with IBM SPSS Statistics 21.0 program at α=0.05 significance level and 85% confidence range.

Results

A total of 160 students answered the survey by agreeing to participate in the study. Of these, 34 were term I students, 37 were term II students, and 89 were term III students. Of those who filled out the survey, 94 were female and 65 were male; while one did not answer by leaving it blank or skipping without marking. Looking at the age distribution; 54 students did not answer, while others stated that they were in the 18-26 age range. Responses to the survey and their rates are presented in Table 1. Twenty four of 160 students (15.0%) answered "No", while 119 (74.4%) answered "Yes" to the question "Did you know about the PBL sessions in advance?".

There was no age-related comparison in terms of overall satisfaction as the students were in similar age groups. However, gender comparison was made and no significant differences were found ($p \geq 0.05$) (Table 1).

According to the survey results, the overall satisfaction rate of the 16^{th} question was 3.67 on average. These rates were determined as 3.85 in term I, 3.54 in term II and 3.66 in term III students. Four (2.4%) of the students answered as "Not satisfied at all", 7 (4.4%) as "Not Satisfied", 48 (30.4%) as "Uncertain", 77 (48.7%) as "Satisfied" and 22 (13.9%) as "Very satisfied".

There was also no significant difference between term I, II and III in terms of PBL satisfaction rates ($P \geq 0.05$) (Table 2).

In the evaluation of the findings, the ratio of the students who chose the "Agree" and "Absolutely agree" categories to the study group was calculated and accepted as the student level with positive opinion, in addition to the average scores calculated for each item. "Disagree" and "Strongly disagree" answers were also rated as negative views. The "Uncertain" answer was not taken as a positive or negative opinion.

In this case, as the highest average, 134 students (83.7%) expressed a positive opinion on the proposition "Participants in PBL sessions always treat the group with respect", while 9 students (5.7%) expressed a negative opinion and the average $\bar{x}$ was determined as 4.19 with the "Uncertain" responses. As the lowest average, 94 students (59.5%) expressed a positive opinion on the proposition "PBL session routers help to discuss

Table 1. Views on general dissatisfaction about PBL by gender

Gender	n	Med (min-max)	Mean ± SD
F	94	4 (2-5)	3.67±0.890
M	65	4 (2-5)	3.66±0.834

min: Minimum, max: Maximum, SD: Standard deviation, PBL: Problem-based learning

Table 2. Views on general dissatisfaction about PBL by term

Term	n	Med (min - max)	Mean ± SD
1	33	4 (2-5)	3.85±0.795
2	37	4 (2-5)	3.54±0.988
3	88	4 (2-5)	3.66±0.828

SD: Standar deviation, min: Minimum, max: Maximum, PBL: Problem-based learning

all aspects of the issues", while 26 students (16.5%) expressed a negative opinion, and the average $\bar{x}$ was determined as 3.57 with the "Uncertain" responses. The answers to all questions and their rates are given in the Table (Table 3).

Some of the students wrote answer and expressed their views for the open-ended question "Is there anything else you want to add?". Some of these were: "The efficiency I got from PBL sessions varies according to the session router and the students involved", "The knowledge gained through the PBL sessions has had a positive impact on my learning life", "While some of the session routers were willing, some were unwilling and not motivating", and "The evaluations of the routers were not objective".

Discussion

It is suggested that PBL is much more motivating in solving theoretical or practical problems than a traditional flexible learning process. However, problems should be applied in a motivating and productive way that suits the students' existing knowledge. In other words, the character of the problem should

Table 3. Student views on before, during and after Problem-based Learning sessions

Proposition	Strongly disagree		Disagree		Uncertain		Agree		Strongly agree		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
1. Sufficient information about PBL is given before PBL sessions are held (N=159; $\bar{x}$=3.60)	6	3.8	14	8.8	51	32.1	54	34.0	34	21.3	159	100.0
2. Everyone is prepared for the second session in the PBL sessions (N=160; $\bar{x}$=3.59)	3	1.9	15	9.4	51	31.9	66	41.2	25	15.6	160	100.0
3. The classes where PBL sessions are held meet our needs (N=157; $\bar{x}$=3.79)	1	0.6	28	17.8	21	13.4	60	38.3	47	29.9	157	100.0
4. PBL sessions are held with an ideal number of students (N=160; $\bar{x}$=4.03)	3	1.9	11	6.9	25	15.6	60	37.5	61	38.1	160	100.0
5. PBL session routers help to discuss all aspects of issues (N=158; $\bar{x}$=3.57)	6	3.8	20	12.7	38	24.1	66	41.7	28	17.7	158	100.0
6. In PBL sessions, participants always treat the group with respect (N=160; $\bar{x}$=4.19)	3	1.9	6	3.8	17	10.6	65	40.6	69	43.1	160	100.0
7. I express myself adequately in PBL environments and/or group works (N=158; $\bar{x}$=3.83)	7	4.4	11	7.0	24	15.2	76	48.1	40	25.3	158	100.0
8. Discussions in PBL sessions have a positive impact on my knowledge (N=159; $\bar{x}$=3.91)	5	3.1	7	4.4	31	19.6	70	44.0	46	28.9	159	100.0
9. I contribute to the group in achieving the learning goals (N=160; $\bar{x}$=4.00)	4	2.5	5	3.1	29	18.1	71	44.4	51	31.9	160	100.0
10. I can easily convey what I have learned after independent study (N=158, $\bar{x}$=3.88)	4	2.5	9	5.7	29	18.4	76	48.1	40	25.3	158	100.0
11. Session routers are prepared and willing (N=160, $\bar{x}$=3.68)	4	2.5	14	8.8	42	26.2	69	43.1	31	19.4	160	100.0
12. PBL sessions have had a positive impact on my communication skills (N=157; $\bar{x}$=3.61)	7	4.5	10	6.4	42	26.7	76	48.4	22	14.0	157	100.0
13. I am happy to achieve the learning goals determined in the sessions by investigating rather than getting them as preset information (N=159, $\bar{x}$=3.72)	6	3.7	13	8.2	40	25.2	61	38.4	39	24.5	159	100.0
14. I am satisfied with the attitude of the faculty members who lead the session (N=160; $\bar{x}$=3.90)	4	2.5	5	3.1	36	22.5	73	45.6	42	26.3	160	100.0

PBL: Problem-based learning

be able to positively influence the motivation of students to learn in PBL curricula (1).

As there are medical faculties in our country that carry out all education with PBL method, there are also models that are applied with a scenario within the committees as applied in our faculty. In a 2008 study, it was reported that PBL sessions were held in nearly half of the medical schools providing education in our country(4). However, it is a fact that there may be differences in this proportion with new medical schools, which are rapidly increasing in time today. Some new faculties have such applications due to the importance of interactive education and the appropriateness of student numbers, while some have canceled PBL due to high number of students. In the study conducted by Musal et al. at Dokuz Eylül University Faculty of Medicine (5), student opinions on the effectiveness of PBL were taken and the average scores were reported to be between 3.69-4.27 (maximum 5). Our average value of 3.67 was slightly lower than the value of that faculty, which applied PBL throughout its education, but it showed conformity.

Musal et al. contributed much to implementation of PBL in our country with their publications about processes of PBL programs and the role of router lecturers (6-8). They detailed how all phases of implementation should be planned, implemented and evaluated and they provided ease of application for other faculties. PBL applications in BVU Medical Faculty are also carried out in three sessions in one week term, in groups of 10 students, by the trained lecturers and students. In the survey we applied in the study, the proposition "PBL session routers help to discuss all aspects of the issues" was evaluated with average score of 3.57, the proposition "Session routers are prepared and willing" with average score of 3.68, and the proposition "I am satisfied with the attitude and attitude of the session lecturers" with average score of 3.90. In a PBL session, the router is inherently important. However, students who are used to classroom lessons want to get more information from the router and may feel that they are not being adequately supported. The fact that the majority of the answers to the open-ended question were related to routers also underlined the importance of routing in PBL.

Velipaşaoğlu and Musal completed scale development studies related to PBL process, functioning and achievements. By using this detailed scale, the studies will be more comprehensive and useful in measuring the efficiency of PBL (9).

In the study where student opinions were taken about PBL sessions at On Dokuz Mayıs University, it was reported that the overall average of scores given in feedback for PBL was 8.06 ± 1.0 (6-10) out of 10 and the overall average of scores given for communication and discussion was 4.59 ± 0.6 out of 5 (10). In the survey we applied, 116 students (73.4%) gave positive views to the proposition "I express myself adequately in PBL environments and/or group studies" and $\bar{x}$ was determined as 3.83; while 116 students (72.9%) gave positive views to the proposition "Discussions in PBL sessions affect my knowledge positively" and the average $\bar{x}$ was 3.91. One hundred twenty one students (76.3%) gave positive views to the proposition "I contribute to the group in achieving the learning goals" and $\bar{x}$ was determined as 4.0. One hundred and sixteen students (73.4%) gave positive views to the proposition "I can easily convey what I have learned after independent study" and $\bar{x}$ was determined as 3.88. Ninety eight students (62.4%) gave positive views to the proposition "PBL sessions affected my communication skills positively", while 17 (10.9%) students gave negative views and $\bar{x}$ was determined as 3.61 with "uncertain" answers. Compared with the findings of that study, we found lower rates of positive opinions.

Alimoğlu et al. investigated the satisfaction of term I students in Akdeniz University Medical Faculty on PBL applications. It was stated that PBL contributed to students in self-learning, establishing connections between basic sciences and clinical sciences, and lifelong learning. In addition, the number of those who thought that it contributed to the development of basic skills such as communication with the patient, being able to approach the patient as a biopsychosocial whole, reasoning in the face of the problem, problem solving and decision making were found to be high. In their study, they found that 44.4% of the students were satisfied with PBL, 27.8% were dissatisfied and 27.8% were uncertain about it (11). In our survey, 99 BVU students gave positive view and 11 BVU students (6.9%) gave negative view to the question "What is your overall satisfaction with PBL sessions?", while 48 BVU students (30.4%) were uncertain about it. The average $\bar{x}$ value was determined as 3.67. It was observed that the rates of positive responses of BVU medical faculty students were slightly higher.

Demirören and Demirel (12) investigated the views of term II students in Ankara University Medical Faculty on the advantages and limitations of PBL. As a result, the students found PBL superior to traditional method and they found PBL environment motivating and enhancing universal competencies (problem solving, analysis and synthesis, communication skills). Integration of basic and clinical sciences, development of a biopsychosocial approach to human beings, and effective and motivating learning in small groups were mentioned as the most supported features of PBL. However, it was noted that students had difficulty in adapting to PBL, that they remained concerned about becoming independent learners, and that there were negative issues arising from PBL orientation processes (12).

In the survey we applied, 100 students (62.9%) expressed a positive opinion on the proposition "I am happy to achieve the learning goals determined in the sessions by investigating rather than getting them as preset information", while 19 students (12.0%) expressed a negative opinion and the average $\bar{x}$ was determined as 3.72 with the uncertain responses. High ratio and average values of positive responses suggested that the students were not forced into the PBL integration process and that their concerns about becoming independent learners were not high.

Gürpınar et al. included the views of router lecturers on the PBL program in their study. Of the lecturers, 70.2% stated that PBL applications were generally beneficial for the student and 56.5% answered "Yes" to the question "Are you satisfied with

PBL" (13). In their study in 2016, Musal (14) found that the scores given by router lecturers to the gains of the PBL method ranged from 3.3 to 4.7 out of 5. The highest scores were given to the improvement of communication skills (14). In our study, the lack of any questionnaire applied to router lecturers constituted the limitation of this study.

In a study that examined the change in the performance of students in PBL sessions over the years, the increase in performance scores obtained from term I to term III was evaluated as a positive finding. When the average score for each parameter was evaluated, it was determined that the scores of term III students were higher than term I students (15). In our study, performance evaluation was not performed between terms, but there was no significant difference in the satisfaction rates of PBL sessions.

Conclusion

As a result, the PBL has been formed with quite different pedagogical approaches. Unlike traditional learning, it actively centers the student. PBL imparts self-directed learning, finding learning goals, accessing and finding information, time management, question-asking behavior, critical thinking, and comprehensive self-monitoring and evaluation skills (16). These positive aspects bring PBL practices to the fore in medical education. It has been determined that the PBL sessions that we have implemented in some committees during the pre-clinical process, which consists of system-based committees, constitute an efficient training process in our faculty where integrated system is applied. We aim to apply this interactive method to every committee.

Ethics

Ethics Committee Approval: Prior to the study, an application was made to Bezmialem Foundation University Non-Interventional Ethics Committee and the approval was obtained with the decision number 10/146 on 16.05.2017.

Informed Consent: Survey study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: N.S.K., S.Ö., Design: N.S.K., S.Ö., Data Collection or Processing: N.S.K., S.Ö., Analysis or Interpretation: N.S.K., S.Ö., Literature Search: N.S.K., S.Ö., Writing: N.S.K., S.Ö.

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References

1. Schmidt GH, Rotgans JI, Yew EHJ. The process of problem-based learning: what works and why, Medical Education 2011;45:792-806.
2. Scott, B. Principles of Problem and Project Based Learning. Aalborg University.2000.
3. Hmelo-Silver CE. Problem-Based Learning: what and how do students learn? Educational Psychology Review 2004;16:235-66.
4. Musal B, Taşkıran HC, Özan S. Türkiye'de tıp fakültelerinde Probleme Dayalı Öğrenim yöntemi kullanımı. Tıp Eğitimi Dünyası 2008;28:1-7.
5. Musal B, Taşkıran C, Kelson A. Opinions of tutors and students about effectiveness of PBL in Dokuz Eylül Üniversitesi School of Medicine. Med Educ 2003;8:16.
6. Musal B, Akalın E, Kılıç O, Esen A, Alıcı E. Dokuz Eylül Üniversitesi Tıp Fakültesi Probleme Dayalı Öğretim programı, süreçleri ve eğitim yönlendiricilerinin rolü. Tıp Eğitimi Dünyası 2002;9:39-49.
7. Berna Musal, Yucel Gursel, H Cahit Taskiran, Sema Ozan, Arif Tuna. Perceptions of first and third year medical students on self-study and reporting processes of problem-based learning BMC Med Educ 2004;4:16.
8. Erol Gurpinar, Berna Musal, Gazanfer Aksakoglu, Reyhan Ucku. Comparison of knowledge scores of medical students in problem-based learning and traditional curriculum on public health topics. BMC Med Educ. 2005;5:7.
9. Velipaşaoğlu S, Musal B. Probleme Dayalı Öğrenim süreci, işleyişi ve kazanımlarına ilişkin ölçek geliştirme çalışmaları. Tıp Eğitimi Dünyası 2017;48:5-28.
10. Dikici M, Yalçın M, Büyükakkuş A, Özbenli T, Yarış F. Ondokuz Mayıs Üniversitesi Tıp Fakültesi öğrencilerinin mesleki beceri laboratuarı, Probleme Dayalı Öğrenme oturumları ve sunumlar hakkındaki görüşleri. Tıp Eğitimi Dünyası 2004;16:21-4.
11. Alimoğlu MK, Gürpınar E, Şenol Y, Çubukçu S, Aktekin M. Akdeniz Üniversitesi Tıp Fakültesi Dönem I öğrencilerinin Probleme Dayalı Öğrenim uygulamaları konusundaki memnuniyetleri. Tıp Eğitimi Dünyası 2004;14:8-14.
12. Demirören M, Demirel M. Ankara Üniversitesi Tıp Fakültesi Dönem 2 öğrencilerinin PDÖ uygulamalarının üstünlük ve sınırlılıklarına ilişkin görüşleri. Tıp Eğitimi Dünyası 2006;23:33-40.
13. Gürpınar E, Akyıldız F, Özbudak Ö, Şenol Y. Akdeniz Üniversitesi Tıp Fakültesinde uygulanan Probleme Dayalı Öğrenimin eğitim yönlendiricileri tarafından değerlendirilmesi. Tıp Eğitimi Dünyası 2005;20:46-52.
14. Musal B. Dokuz Eylül Üniversitesi Tıp Fakültesi program değerlendirme çalışmaları kapsaminda eğitim yönlendiricilerinin PDÖ programı konusundaki görüşleri. Tıp Eğitimi Dünyası. 2016;46:28-34.
15. Karademir S, Özan S, Gürsel Y, Musal B. Dokuz Eylül Üniversitesi Tıp Fakültesi öğrencilerinin Probleme Dayalı Öğrenim oturumlarındaki performanslarının yıllar içerisindeki değişimi. Tıp Eğitimi Dünyası 2005;19:29-33.
16. Musal B. Tıp eğitiminde program modelleri. Sayek İ, editor. Tıp Eğiticisi El Kitabı. 1. baskı, Ankara Güneş Tıp Kitabevleri, 2015. p.43-54.

Original Article

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Anxiety, Depression and Health Profile in Mothers with Children in the Pediatric Intensive Care Unit

Pediatrik Yoğun Bakım Ünitesindeki Annelerde Anksiyete, Depresyon ve Sağlık Profili

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ABSTRACT

Objective: The aim of this study was to investigate, anxiety, depression and health profile among mothers of patients at pediatric intensive care unit (PICU) and pediatric inpatient service (PIS).

Methods: The sample consisted of a total of 40 mothers, including mothers with children in a PICU (group I) and PIS (group II). The mothers' quality of life was measured with the Nottingham Health Profile (NHP), anxiety was measured with the State- Trait Anxiety Inventory (STAI), and depression levels were measured with the Beck Depression Inventory (Beck-D) for the all mothers.

Results: The mean age of the mothers was 31.5 years for group I and 31.25 years for group II. The mean total NHP score of the mothers was 279.0 for group I and 113.33 for group II. The mean total STAI-S score of mothers was 37.1 for group I and 36.65 for group II. The mean total of STAI-T score of mothers was 46.9 for group I and 47.75 for group II. The mean total Beck-D score was 39.7 for group I and 18.5 for group II. There was a statistically significant differences in the levels of anxiety, depression and health profile between the mothers with children in the PICU and those with children in the PIS ($p<0.001$).

Conclusion: This study showed that having a critically ill child at a PICU unit has negative 17 effect on mothers' depression levels, state anxiety levels and health profile.

Keywords: Critical illness, health profile, intensive care, parents, stress

ÖZ

Amaç: Bu çalışmanın amacı, pediatrik yoğun bakım ünitesinde (PYBÜ) ve pediyatrik yatılı servisteki (PYS) hastaların anneleri arasında anksiyete, depresyon ve sağlık profilini araştırmaktır.

Yöntemler: Örneklem, PYBÜ (grup I) ve PYS'de (grup II) çocuğu olan anneler dahil olmak üzere toplam 40 anneden oluşmuştur. Annelerin yaşam kalitesi Nottingham Sağlık Profili (NHP) ile, anksiyete Durum-Sürekli Kaygı Envanteri (STAI) ile, depresyon düzeyleri ise tüm anneler için Beck Depresyon Envanteri (Beck-D) ile ölçülmüştür.

Bulgular: Annelerin yaş ortalaması grup I için 31,5, grup II için 31,25 idi. Annelerinortalama toplam NHP skoru grup I için 279,0, grup II için 113,33 idi. Annelerin ortalama

toplam STAI-S skoru grup I için 37,1 ve grup II için 36,65 idi. Ortalama STAI-T puanortalaması, grup I için 46,9, grup II için 47,75 idi. Ortalama Beck-D skoru grup I için 39,7, grup II için 18,5 idi. PICU'lu çocukları olan anneler ile PIS'li çocukları olan anksiyete, depresyon ve sağlık profili düzeyleri arasında istatistiksel olarak anlamlı bir fark vardı ($p<0,001$).

Sonuç: Bu çalışma, PYBÜ'de kritik hasta bir çocuğa sahip olmanın annelerin depresyon düzeyleri, durumluk kaygı düzeyleri ve sağlık profili üzerinde olumsuz etkisi olduğunu göstermiştir.

Anahtar Sözcükler: Kritik hastalık, sağlık profili, yoğun bakım, ebeveyn, stres

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Introduction

Acceptance of the child to the pediatric intensive care unit (PICU) is among one of the most stressful parenting experiences. Families of children with chronic or severe illnesses sometimes face difficulties that have never been considered before. The result for the child is unknown, procedures and treatments may be invasive and uncomfortable for the patient, and the environment may include tensions that may affect the level of stress of the parents (1).Intensive care units are a complex and stressful environment for patients. It may also haveimportant physical, cognitive, psychological and functional consequences for patient relatives. Various treatment and care methods are applied by multidisciplinary staff for the patients that have an acute-chronic disease or disease predicted to develop (2). Hospitalization of a family member in critical care units causes overwhelming stress and distress (3).

PICU support children who are admitted with life-threatening medical conditions, as well as being intended for treating children with traumatic, surgical, internal, acute and chronic pediatric diseases with mostly complex approaches. Innovations in pediatric surgery, hematology/oncology and state-of-the-art advanced life support techniques have expandedtreatment options for critically ill infants and children. Mortality rates in childhood critical illness and injury have plummeted, and death rates in PICUs are uniformly low even fortertiary units at 1.5% to 8% (4). Additionally, since the technological environment, equipment and operation at the PICU are different from the other departments of hospitals, being treated at the PICU is a very troubling and stressful experience for both patients and their parents (5). Dramatic oscillations in the orbit of the disease may vary both to deterioration and recovery. This is a source of distress not only for the child in PICU but for the whole family (6).

A disease of the child causes important changes in the life of a family. Accordingly, everything will become different in comparison to before the child's disease, the life of the family will change completely, material costs will increase, and spiritual losses will be experienced. The sick child, the parents, siblings, even close relatives will be affected negatively because of stress created by illness and treatment.

Mothers get under stress for their children due to the uncertain results of short- or long-term conditions and possibilities like disability and death. Having a sick child increases the anxietyof mothers whether children are at the PICU or the inpatient hospital service.

Moreover, desperation of not being able to intervene in case of need increases anxiety and stress (7). Images that come from monitors, alarms of machines and different types of equipment, thesound of the staff, bright lights, smells, insomnia, witnessing the invasive interventions ontheir own children or other children constitute sources of stress for people who fall under the responsibility of looking after patients (8). It is shown in studies that lack of daylight, usingtechnologically complex machines, visiting at fixed times or being completely forbidden fromvisiting at certain hours cause stress and anxiety for patients and their families at these units (9). Depression is among the many psychological disorders that occur in all societies, and it may depend on many reasons. It is clear that a child's health status will affect the psychological well-being and quality of life of the family. Family members want to support,comfort, get close to and have the feeling of touching the patient as in normal times. Similarly, the patients that are at ICU need to be supported by their family members (10).

The purpose of our study was to evaluate the anxiety, depression and health profile among mothers at PICUs and PIS.

Methods

Study Design and Setting

This cross-sectional, single-center study was conducted with mothers of children who were hospitalized at Children's Health and Diseases Departments.

Subjects

The sample consisted of 40 children and their mothers. The children were recruited consecutively from amongst the patients who were hospitalized at the pediatric intensive care unit or the pediatric inpatient service at first time within the 6-month period from July 2016 to October 2016.

The inclusion criteria for mothers were as follows: hospitalized a child at PICU or PIS (Children's Health and Diseases Department); staying in PICU and PIS minimum 24 hours-3 months at first time; smaller than 12 years old for the children; absence of a severe or chronic medical condition (i.e., diabetes mellitus, musculoskeletal disorders); absence of a patient or a disabled person for whom the mother is responsible; absence of an application to an patient and/or outpatient clinic for kind of medical support within the last 3-months period prior to the study, being an adult and volunteering to participate in the study. Mothers of children who had cognitive or mental impairment as reported in their medical history and chronic psychobiological disorders were excluded. Group I (n=20) was defined as the mothers of children at the PICU, and the mothers of children at the pediatric inpatient service was in group II (n=20). The characteristics of the mothers and their children are listed in Table 1.

Approval of the local Ethics Committee was obtained for this study. Clinical Research Ethics committee decision no:1/15-24.06.2016. Written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

Data including age, sex, gestation week, birth type, birth weight, height and weight, diagnosis and time of diagnosis, frequency of hospitalization, cost of treatment, accompanying diseases, presence of intubation, surgeries, medication and doses, analgesics use, time of hospitalization, nutrition type of the

children were collected and recorded in the Child Clinical Data Form. Data including age, number of live and dead births, the age of becoming a mother for the first time, duration of education, working situation, previous psychiatric treatments and previous traumatic events, presence of disease of the mothers, financial situation of the families, the parents' expectation for the future of the child and daily hours of care were also collected and recorded in the Parent Clinical Data Form.

The risk of depression and depressive symptoms were assessed in the subject using the BeckDepression Inventory (Beck-D). It is a very reliable and well-validated scale that is easy to apply (11,12). This self-assessment scale that was developed by Beck as a 4-point Likert-type to measure pessimism, sense of failure, lack of satisfaction, feelings of guilt, restlessness,depressive symptoms such as fatigue, appetite, indecision, sleep disturbance, social withdrawal is made of 21 items. Each item has a 4-point scale self-assessment scoring whichidentifies depressive symptoms. The total score is between 0 points and 63 points.

The State-Trait Anxiety Inventory (STAI) is a 40-item inventory that is used to measurelevels of state and trait anxiety (13,14). The questionnaire has two parts: the SATI-S (20 questions) score, which provides the level of state anxiety at the time of completing theinventory, and the STAI-T (20 questions) score, which measures the inherent trait anxiety level of the subjects. There are four options for each expression in the STAI. These are; Not at all (1), Somewhat (2), Moderately so (3) and Very much so (4). In the inventory, the items 1, 2, 5, 8, 10, 11, 15, 16, 19 and 20 are the items that are inversely scored. In the assessment, the state anxiety point is calculated by extracting the result from the total point of direct assessments to opposite expressions and adding 50 points. There are responses as Never (1), Seldom (2), Often (3), Always (4) in the Trait Anxiety Scale. In this section, the inverselyscored expressions are the 21, 26, 27, 30, 33, 36 and 39th items. The trait anxiety point is calculated extracting the result from total point of direct assessments and adding 35 points. Both levels of anxiety are intended to be determined because state anxiety level rises in people who have a high level of anxiety. In general, if the scores of state and trait anxiety levels are high, the general anxiety level is high, and a person who has 60 points or more, they should receive professional help.

Table 1. Participant characteristics (n=40) participants 373

	Group I (n=20)	Mean ± SD or n (%) Group II (n=20)
Maternal characteristics		
Age at delivery (years)	31.5±3.76	31.25±4.86
Educational level		
Primary school	5 (25)	14 (70)
High school	14 (70)	4 (20)
University	1 (5)	2 (10)
Employed	5 (25)	2 (10)
Housewife	15 (75)	18 (90)
Infant characteristics		
Gender		
Boys	8 (40)	10 (50)
Girls	12 (60)	10 (50)
Birthweight (g)	3002.7±405.3	3113.67±259.1
Diagnosis		
Neurologic disorders	5 (25)	5 (25)
Surgery	6 (30)	5 (25)
Respiratory failure	9 (45)	10 (50)

SD: Standard deviation

The Nottingham Health Profile (NHP) that was developed by Hunt and McEwen is used to determine the relationship between health problems and common daily activities (15). The validity and reliability of the Turkish version of NHP have been well established through scientific adaptation procedures (16). This survey includes 38 items and assesses 6 dimensions about life status like energy (3 items), pain (8 items), emotional reactions (9 items), sleep (5 items), social isolation (5 items) and physical activities (8 items). The questions are answered by Yes/ No statements. Each section is scored between 0 and 100. Ascore of 0 is the best possible health status, and a score of 100 is the worst possible health status. In this study, the sub-scores and total scores of NHP were assessed. The total score was obtained by combining the sub-scores of NHP.

Questionnaires, which took approximately 30 minutes to complete, were given to the participants by the same researcher, in a private room at the hospital in face-to-faceinterviews.

Statistical Analysis

Statistical analysis was carried out by using the SPSS software (version 21; the Statistical Package for the Social Sciences, Chicago, IL, USA). Descriptive characteristics are presented as mean ± standard deviation or n (%). Student's t-test and Kruskal-Wallis test were used to test thedifferences in the BECK-D, STAI and NHP scores between the two groups. The anxiety, depression and health profile measurements of the mothers of children in different disease groups were compared with one-way analysis of variance (ANOVA) in independent groups.The level of statistical significance was accepted as $p<0.05$.

Results

The mean age of mothers in the sample (n=40) was 31.37±4.31 years. The proportions ofprimary school, high school and university graduates were 47.5%, 45% and 7.5%, respectively. The mean age of the mothers in group I (n=20) was 31.5±3.76 years (Table 1). Among the mothers in this group, 25% were employed, and 75% were housewives. Theproportions of primary school, high school and university graduates were 25%, 70% and 5%, respectively. The mean age of the mothers in group II (n=20) was 31.25±4.86 years. Among mothers in this group, 10% were employed, and 90% were housewives. The proportions of primary school, high school and university

graduates were 70%, 20% and 10%, respectively. There was a significant difference in the educational statuses between the groups (p=0.01), but there was no significant difference between the groups regarding the mothers' age (p=0.84) or occupational status (p=0.21). There was no statistically significant difference in the demographic characteristics of the mothers in the two groups (p>0.05). The children at the PICU were diagnosed with 5 (25%) neurological diseases, 6 (30%) postoperative surgeries and 9 (45%) respiratory failures, and they all received mechanical ventilator support. Children who were hospitalized included 5 (25%) with neurological diseases, 5 (25%) with postoperative surgery and 10 (50%) with respiratory failure. 1

Among the Beck-D Total Scores the mothers in group I, the minimum score was 18, the maximum score was 56, and the mean score was 39.7±9.71. The minimum score in the mothers of group II was 5, maximum score was 31 and the mean was 18.5±7.94 (Table 2). There was a statistically significant difference between the groups (p<0.001).

The mothers' state/trait anxiety scores are shown in Table 2. The mothers in Group I had significantly higher STAI-S scores than those in group II (36.5 *v* 31.3; p=0.001). Their mean STAI-T scores were 47.75 and 46.9, respectively. There were no significant differences between the groups in terms of their STAI-T anxiety scores (p=0.461).

Table 2. The Mean Values For Beck Depression Inventory and STAI Form Scores in Group I 398 and Group II (n=40 participants)

	Group I (n=20)	Group II (n=20)	p
	Mean ± SD	Mean ± SD	
BECK-D	39.7±9.71	18.5±7.94	0.001
STAI-S	36.5±3.48	31.3±4.6	0.001
STAI-T	47.75±4.07	46.9±6.01	0.461

BECK-D: Beck Depression Inventory Total score, STAI-S: The Anxiety Inventory-State, STAI-T: The State-Trait Anxiety Inventory-Trait, SD: Standard deviation

Table 3. The Mean Values For Nottingham Health Profile Subscale Scores in Group I and 415 Group II

	Group I (n=20)	Group II (n=20)	p
	Mean ± SD	**Mean ± SD**	
Nottingham health profile			
Nel	74.12±29.8	27.5±34.88	0.001
Np	21.65±24.9	9.99±22.5	0.30
Ner	75.2±23.8	36.16±28.39	0.001
Ns	34.7±26.9	15.6±22.9	0.008
Nsi	58.5±24.9	19.14±21.9	0.001
Npa	14.7±15.8	4.8±9.12	0.076
Nottingham total	279.0±83.1	113.33±76.97	0.001

Nel: Energy level, Np: Pain, Ner: Emotional reaction, Ns: Sleep, Nsi: Social isolation, Npa: Physical activity, SD: Standard deviation

The NHP scores of mothers are shown in Table 3. There were highly significant differences in the energy level, emotional reactions, sleep, social isolation and total scores of NHP between the groups (p<0.001). Group I had worse health profile. PICU group of children were divided into three subgroups as neurological (n=5), surgical (n=6) and respiratory failure (n=9) patients. When the anxiety, depression and quality of life levels of the mothers of children in different disease groups were compared, there was no statistically significant differenceamong the disease groups in terms of anxiety, depression or health profile levels (p>0.05).The children at the PIS were divided into three subgroups as neurological (n=5), surgical (n=5) and respiratory failure (n=10) groups for reasons of hospitalization. When the anxiety, depression and health profile measurements of the mothers of children in different disease groups were compared in independent groups, no statistically significant difference was found among the disease groups in terms of anxiety, depression or health profile (p>0.05).

Discussion

The results of this study showed that having a critically ill child at PICU has negative effect on mothers' depression levels, state anxiety levels and health profile status.

In particular, parents at PICU experience traumatic and negative emotions in a wide range. This is because they usually must make complex decisions about the critical illness of their children. These decisions could include some big and important operations and surgical procedures like brain operations, tracheostomy and gastrostomy intubation. Although these invasive operations are life-saving for children, they may cause depression, anxiety, social isolation and anger in their lives (3). Parents experience the stress of having a sick or injured child at the PICU, and they must be provided with continuous information so that they can absorb and process information (17). Carlson et al. (18) stated that frequent visits of the family members to the intensive care unit could provide more information about the medical condition of the patient, the families are more comfortable in dealing with the stress of their situation, and the communication with the medical team is easier. In this study, the primary caregivers were mothers, and although the anxiety and depression levels of the mothers were affected, the fact that they accompanied their children for 16 hours to participate in the nursing process and that medical information was accessed more frequently increased the adaptation of the mothers to the process. It facilitated their acceptance of the disease. Thus, they might need support and encouragement.

In addition to the severity of the status and disease variables, parental anxiety increased, and quality of life was reduced. A worried parent is more likely to perceive a higher risk for his child and misinterpret information about his child's condition. In a study with parents of children admitted to PICU, parents had a high level of anxiety within the first 24 hours (19). The authors hypothesized that higher parental anxiety would affect medical information 2adversely. The initial concern after being admitted to the PICU is usually reduced over time, which makes

it easier for parents to be informed (20). Mothers' anxiety levels, family dynamics and hospitalizations of the child may be affected by factors other than children's

illnesses. In our study, the reason that the mothers had more trait anxiety scores at the PICU than those who were at the PIS may be the anxiety that their children may change momentarily at the intensive care unit.

In our study, the reason why mothers at the PICU had higher state anxiety scores than thechildren at the PIS might be that the mothers of these children were concerned that their children's condition may change fast at the intensive care unit. Actually, the mothers were staying with their children for about 16 hours. Medical staff provided information continuously. We believe that this anxiety depends on the condition of the child and their dependence on the mechanical ventilator.

Parents may need to apply for support by others like physicians, other children's healthcareteams or other family members. Emotional overload and reactions could be reasons for this guidance. Parents who are worried about their children have to be informed in an appropriate and clear manner, to provide them with support and specific advice (21). Similarly, in ourstudy, the Nsi (social isolation) NHP score was higher than in Group I than Group II.Moreover, Group I had significantly higher scores of NSP than those in Group II (emotional reactions). We believe that this is due to the fact that these children's situation is more critical like the environment they are in.

Studies on children at PICUs usually focused on diseases and patient care, and the parent side has been relatively neglected. Our literature review revealed a limited number of studies that examined the quality of life mothers of children at PICUs.

According to the report published by WHO in 2004 on prevention of mental problems, stressful life events, physical discomfort and disruption of family order affect mental health risk factors. If these conditions persist for a long time, problems such as risk of cardiovascular disease and cancer increase (22). In our study, we believe that Group I had higher NHP Nel (energy) and Np (pain) scores than Group II, and these mothers felt more tired, which may cause some physical disturbances in the long-run. Although the N (p) scores were high in bothgroups, there was no significant difference between the groups. We believe that the physical conditions and care load of the mothers should be reviewed. Accompanying times may beshared with other family members. Recommendations may be made to attendants aboutprotection of their posture and musculoskeletal systems while putting the child on their lap, breastfeeding and sitting.

There are many studies in the literature that measured the quality of life of parents in negative situations. In 2010, Yılmaz et al. (23) carried out a study with 40 children with diagnoses of neuromuscular diseases. The health related quality of life levels of the mothers were assessed with the Turkish version of the NHP and Beck-D, while the Wee-Functional Independence Measure (Wee-FIM) was used to determine of functional independence levels of the children. They found that the functional levels of children affect the quality life of mothers. There was a moderate correlation between the total NHP scores of the mothers and the total FIM score and sphincter control of the child, while it was weakly correlated with the locomotion of the child ($p<0.001$). In any case of illness of children, including neuromuscular diseases, cancer and cerebral palsy, the illness was found to negatively impact maternal health related quality of life. In 2015, Erdogan et al. (24) applied Beck-D to the parents of 25 children in at a PICU to assess the depression levels of parents, compare these levels based on whether there is a difference between mothers and fathers. The depression rates were significantly higher in both the mother and father of the children at the PICU than those in the normal population. The study revealed the necessity of providing psychological counseling and psychiatric support to the parents of children. Adanir et al. (25) investigated the psychopathology in pediatric BMT (bone marrow transplantation) survivors and their mothers in comparison to healthy controls in 2017. The researchers used the Symptom Checklist-90-Revised (SCL-90-R) tool to assess psychopathology in mothers. Accordingly, clinicians should be aware of psychiatric symptoms or disease of the mothers whose children were operated or have experienced life- threatening conditions. Moreover, psychosocial support with medical treatment is very important.

Limitations of this study include its small sample size and assessment of only mothers. Additionally, the single-center methodology is another limitation of this study. Despite limitations, these findings suggest that mothers who have a child at PICU may have more stress, anxiety, depression, and so, low health profile.

Conclusion

The PICU should include managing not only a sick or injured child, but also the problems of the rest of the family members. In addition to the technical aspects of care, emotional support is also needed. Future research should not only focus on critically ill children at PICUs but also psychological support for their mothers. Healthcare professionals should consider and be aware of the psychological status and the health profile of the mothers.

Ethics

Ethics Committee Approval: Approval of the local Ethics Committee was obtained for this study. Clinical Research Ethics committee decision no:1/15-24.06.2016.

Informed Consent: Written informed consent was obtained from each participant.

Peer-review: Internally peer reviewed.

Authorship Contributions

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

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References

1. Lisanti AJ, Allen LR, Kelly L, Medoff-Cooper B. Maternal stress and anxiety in the pediatric cardiac intensive care unit. Am J Crit Care 2017;26:118-25.
2. Azoulay E, Pochard F, Kentish-Barnes N, Chevret S, Aboab J, Adrie C, et al. FAMIREA Study Group: Risk of post-traumatic stress symptoms in family members of intensive care unit patients. Am J Respir Crit Care Med 2005;171:987-94.
3. Pochard F, Azoulay E, Chevret S, Lemaire F, Hubert P, Canoui P, et al. Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. Crit Care Med 2001;29:1893-7.
4. Nicholson CE. Pediatric critical care for children with congenital neurodevelopmental 316 diagnoses. Pediatr Crit Care Med 2004;5:407-8.
5. Williams CM. The identification of family members' contribution to patients' care in the intensive care unit: a naturalistic inquiry. Nurs Crit Care 2005;10:6-14.
6. Fuhrman BP, Zimmerman J, eds. Pediatric Critical Care. 3rd ed. Philadelphia, PA: Mosby Elsevier; 2006;35-40.
7. Govier L. Spiritual Care In Nursing: A Systematic Approach. Nurs Stand 2000;14:32-6.
8. Rennick JE, Dougherty G, Chambers C, Stremler R, Childerhose JE, Stack DM, et al. Children's psychological and behavioral responses following pediatric intensive care unit hospitalization: the caring intensively study. BMC Pediatrics 2014;14:276.
9. Colville G, Darkins J, Hesketh J, Bennett V, Alcock J, Noyes J. The impact on parents of a child's admission to intensive care: integration of qualitative findings from a cross-sectional study. Intensive Crit Care Nurs 2009;25:72-9.
10. Ratliffe CE, Harrigan RC, Haley J, Tse A, Olson T. Stress in families with medically fragile children. Issues Compr. Pediatr Nurs 2002;25:167-88.
11. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561-71.
12. Hisli N. Beck A study on the validity of Beck Depression Inventory. Psikoloji Dergisi 1988;6:118-22.
13. Spielberger CD, Sydeman SJ, Owen AE, Marsh BJ. Measuring anxiety and anger with the State-Trait Anxiety Inventory (STAI) and the State-Trait Anger Expression Inventory (STAXI). In M. E. Maruish (eds.), The use of psychological testing for treatment planning and outcomes assessment 1999;p.993-1021.
14. Öner N, LeCompte WA. Durumluk Sürekli Kaygı Envanteri El Kitabı. İstanbul Boğaziçi Üniversitesi Yayınları 1985;333.
15. Hunt SM, McKenna SP, McEwen J, Williams J, Papp E. The Nottingham Health Profile: subjective health status and medical consultations. Soc. Sci. & Med. Vol. Part A: Medical Psychology & Medical Sociology 1981;15:221-9.
16. Küçükdeveci AA, McKenna SP, Kutlay S, Gürsel Y, Whalley D, Arasil T. The development and psychometric assessment of the Turkish version of the Nottingham Health Profile. Int J Rehabil Res 2000;23:31-8.
17. Sweet L, Mannix T. Identification of parental stressors in an Australian neonatal 348 intensive care unit. Neonatal Pediat Chil 2012;15:8-16.
18. Carlson EB, Spain D, Muhtadie L, McDade-Montez L, Macia KS. Care and Caring in the ICU: Family Members' Distress and Perceptions about Staff Skills, Communication, and Emotional Support. J Crit Care 2015;3:557- 61.
19. Needle JS, O'riordan M, Smith PG. Parental anxiety and medical comprehension within 24 hrs of a child's admission to the pediatric intensive care unit. Pediatr Crit Care Med 2009;10:668-74.
20. Huckabay LM, Tilem-Kessler D. Patterns of parental stress in PICU emergency admission. Dimens Crit Care Nurs 1999;18:36.
21. Madrigal VN, Carroll KW, Faerber JA, Walter JK, Morrison WE, Feudtner C. Parental sources of support and guidance when making difficult decisions in the pediatric intensive care unit. J Pediatr 2016;169:221-6.
22. Group TW. The World Health Organization Quality of Life assessment (WHOQOL): Development and general psychometric properties. Soc Sci Med 1998;46:1569-85.
23. Yılmaz O, Yıldırım SA, Öksüz C, Atay S, Turan E. Mothers' depression and health related quality of life in neuromuscular diseases: Role of functional independence level of the children. Pediatr Int 2010;52:648-52.
24. Erdoğan S, Oto A, Boşnak M. Depression Status in Children's Parents During Hospitalization in the in the Pediatric Intensive Care Unit. ACU Sağlık Bil Derg 2016; 367 2:79-82.
25. Sürer Adanir A, Taşkiran G, Küpesiz OA, Özatalay E. Psychopathology in pediatric bone marrow transplantation survivors and their mothers. Pediatr Int 2017;979-85.

Original Article

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Surgical Treatment of Alveolar Soft Part Sarcoma of the Extremity: Results of at Least 5 Years of Follow-up

Ekstremite Yerleşimli Alveolar Soft Part Sarkomların Cerrahi Tedavisi: En Az 5 Yıllık Takip Sonuçları

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ABSTRACT

Objective: Alveolar soft part sarcoma (ASPS) is a rare soft tissue tumor that usually affects young patients. Because of the rarity of the disease, most reports relating to ASPS are in the form of case reports or small series.

Methods: We performed a retrospective study to evaluate the clinic features, treatment and outcome in a consecutive series of patients with localized or metastatic ASPS between 2004 and 2014. Demographics, tumor sizes, sites of tumor and extent of disease, treatments provided, progression, and overall survival were evaluated.

Results: Total of 8 patients were identified. The clinical assumptive diagnosis of the doctor making first medical examination was benign soft tissue tumor like hemangioma in 3 cases (37.5%), delaying treatment. The most common loca¬tion of primary tumor was the thigh. The median diameter of the mass was 136.8±76.0 mm (range=4-572 mm). Median overall follow-up was 64 months.

Conclusion: It was found that age greater than 28 years at the time of diagnosis, and the non-thigh placement of the tumor on the limb were found to increase the risk of lung metastasis. It was found that 37.5% of the patients underwent inadequate operation with the pre-diagnosis of vascular-related benign tumors. So, a comprehensive preoperative evaluation for the differential diagnosis of ASPS is needed when interfering with hemangioma-like vascular associated tumors.

Keywords: Alveolar soft part sarcoma, extremity, thigh, prognostic factors, haemangioma

ÖZ

Amaç: Alveoler soft part sarkom (ASPS) genellikle genç hastaları etkileyen nadir görülen bir yumuşak doku tümörüdür. Hastalığın nadir olması nedeniyle, ASPS ile ilgili çoğu çalışma vaka raporları veya küçük seriler şeklindedir.

Yöntemler: Biz 2004 ve 2014 yılları arasında lokalize veya metastatik ASPS hastalarının klinik özelliklerini, tedavilerini ve tedavi sonuçlarını değerlendirmek için retrospektif bir çalışma yaptık. Demografik özellikler, tümör boyutları, hastalığın yerleri ve kapsamı, verilen tedaviler, prognoz ve genel sağkalım değerlendirildi.

Bulgular: Toplam 8 hasta tespit edildi. İlk tıbbi muayene doktorunun klinik ön tanısı, 3 olguda (%37,5) hemanjiyom gibi benign yumuşak doku tümörleri idi ve tedaviyi geciktirdi. Primer tümörün en sık yerleşim yeri uyluktu. Kitlenin ortanca çapı 136,8±76,0 mm (aralık=4-572 mm) idi. Ortalama genel takip süresi 64 aydı.

Sonuç: Hastanın yaşının tanı anında 28 yaşından büyük olması ve tümörün uyluk dışı ekstremite yerleşiminin akciğer metastazı riskini artırdığı tespit edildi. Hastaların %37,5'inin damar ilişkili benign tümör ön tanıları ile yetersiz operasyona tabi tutulduğu tespit edildi. Bu nedenle, hemanjiyom benzeri damar ilişkili tümörler ile ilgili ön tanılar düşünüldüğünde, ASPS'nin ayırıcı tanısı için iyi bir preoperatif değerlendirme gereklidir.

Anahtar Sözcükler: Alveoler sort part sarkom, ekstremite, uyluk, prognostik faktörler, hemanjiyom

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Introduction

Alveolar soft part sarcoma (ASPS) is a very rare type of soft tissue sarcoma (STS). It was first described in 1952 by Christopherson et al. (1).

The incidence of ASPS is 0.5-1% among all soft tissue sarcomas with a very young peak age, and unusual features such as frequent metastasis to the brain (2,3).

ASPS is mostly seen on the trunk and extremities, although it can also occur all over the body such as tongue, uterus, stomach and vagina (4). Tumor progression is painless and slow, as a result of this, distant metastasis is often detected at the time of first medical examination of the patients (5). It mostly metastasizes to the lung, brain, bone and lymph nodes (6).

This tumor is highly-vascularized; therefore, and its murmur can sometimes be misinterpreted as arteriovenous malformations (7,8).

Surgical treatment in non-metastatic tumors is the basis of treatment. Adjuvant radiotherapy and chemotherapy are the options used to provide local control of the tumor and in case of the presence of metastasis (8,9).

In this article, we reported 8 cases of ASPS who were detected among the patients treated due to soft tissue sarcoma in our clinic between January 2004 and January 2014.

Methods

In this article, we performed a retrospective analysis in order to evaluate the demographic characteristics of the patients and the characteristics of the tumor.

Between January 2004 and January 2014, the medical records of 8 patients who were diagnosed as having ASPS pathologically and underwent surgery in the orthopedics and traumatology clinic of our hospital were examined. Demographic data of the patients are summarized in the Table 1. Written informed consent was obtained from the patient's legal custodian or first-degree relatives to use the individual medical records.

All patients underwent wide resection. The mean age of the patients was 33.5± 17 years (19-74 years). The mean follow-up period was 64.0 months (range=21 to 145 months). Every living patient had a follow-up period of at least 5 years.

We noted the anatomical location of the tumor and the depth of the tumor in all patients. If the tumor invasion of the deep fascia was shown in magnetic resonance imaging (MRI) before the operation, the lesion was considered to be deeply localized.

The preoperative MRI scans and the excisional biopsy reports of some patients who underwent surgery at other hospitalswere used and the length, width and depth of the tumor were recorded and the tumor volume (V) was calculated using the cylinder formula.

In order to identify pulmonary or other distant metastasis and local tumor recurrence in two years after surgery, MRI scan of the extremity was performed every three months, and lung computed tomography (CT) and a full-body bone scintigraphy were performed every six months. MRI scan of the extremity was performed every six months, chest CT and bone scan were performed once a year for up to 5 years in the following period. After 5 years, patients were called up for screening once a year. The presence and absence of pulmonary or other organ metastasis or local recurrence in all patients were examined and recorded.

An excisional biopsy was performed in 3 out of 8 patients with a diagnosis of benign tumor. When the pathology reports were examined, no residue was left in any patient but the microscopic surgical margins were all positive. After the transfer to our hospital, 3 patients underwent extensive tumor resection. The other 5 patients were diagnosed as having ASPS preoperatively, and extensive tumor resection was performed.

Table 1. Baseline demographics

Characteristic	Total n=8
Age, year	
Mean ± SD	33.5±17.8
Median (min-max)	27.5 (19.0-74.0)
Age, n (%)	
<28	4 (50)
≥28	4 (50)
Sex, n (%)*	
Female	3 (37.5)
Male	5 (62.5)
Location, n (%)	
Thigh	4 (50)
Non- thigh	4 (50)
Tumor volume, mL	
Mean ± SD	136.8±76.0
Median (min-max)	187.8 (4.0-572.0)
Tumor volume	
<30	3 (37.5)
≥30	5 (62.5)
Pulmonary metastasis, n (%)	
Yes	5 (62.5)
No	3 (37.5)
Exitus, n (%)	
Yes	5 (62.5)
No	3 (37.5)

*Column percentage, SD: Standard deviation

The excision limit was assessed by microscopic examination as positive (tumor located within 1 mm from the edge of the excision) or negative (no tumor located within 1 mm from the edge of the excision).

Statistical Analysis

Statistical analysis was performed with SPSS 22.0 (Chicago IL) package program. In statistical analysis, categorical variables were given as numbers and percentages, and continuous variables as mean ± standard deviation (SD) and median [minimum-maximum (min-max value)] for descriptive analyses. Fisher's chi-square test was used for comparison of categorical variables between groups. Mann-Whitney U test was used for comparison of datasets which were not normally distributed for the variables. Receiver operating curve (ROC) analysis was used to determine cut-off values of age and tumor volume in distinguishing patients with pulmonary metastasis (Figure 1, Table 2). Survival analyses were performed with Kaplan-Meier methods and Log-rank test. $P<0.05$ was considered to be statistically significant.

Results

Demographic Data and Tumor Characteristics of Patients

The mean age of 5 male (62.5%) and 3 female (37.5%) patients was 33.5±17 years (19-74 years). The mean tumor volume was 129±201 mL (4-572 mL). The most common primary tumor localization was thigh (n=4, 50%) (Figure 2a-c), other localizations were hip (n=1, 12.5%), proximal humerus (n=1, 12.5%), fibula (n: 1, 12.5%) (Figure 3a-e) and forearm (n=1, 12.5%).

Metastases

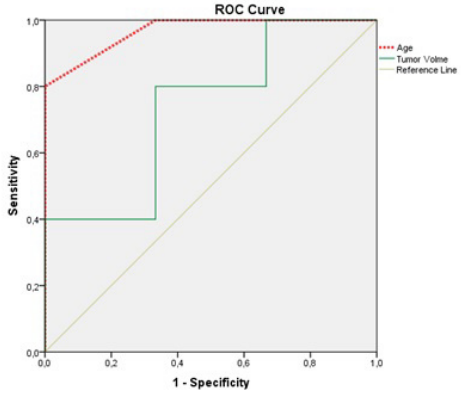

Figure 1. ROC curve of age and tumor volume for distinguishing patients with pulmonary metastasis

Five patients (62.5%) had pulmonary metastasis. Two of these 5 patients had metastasis in vertebrae in addition to lungs; one had liver, and one had liver and brain metastasis at the same time. Of these 5 patients, 3 were male and 2 were female. The mean age of these 5 patients was 40.6 years (range=24-74 years).

Development Time of Metastasis

Only 1 of the 3 patients who had no metastasis at the time of diagnosis developed lung metastasis at 53rd month after the operation.

Chemotherapy And Thoracotomy

IMA (ifosfamide, mesna, adriamycin) was given to 5 patients, and doxorubicin was given to 1 patient. Two patients were not given chemotherapy. No patient underwent thoracotomy because the patients did not accept or the lesion in the lung was inoperable.

Radiotherapy

In 3 patients (cases 5, 7 and 8) , radiotherapy was performed to the operation area, post-operatively. Two patients received radiotherapy because of vertebral metastases and 1 patient because of brain metastasis.

Local Recurrence

No local recurrence was detected in any of the patients.

Overall Survival Rate

The median overall survival time was 61.0 [95% confidence interval (CI)=1.9-120.1] months (Table 3). The 5-year overall survival rate of 8 patients was 62.5% (Figure 4a). The 5-year survival rate in patients without pulmonary metastasis

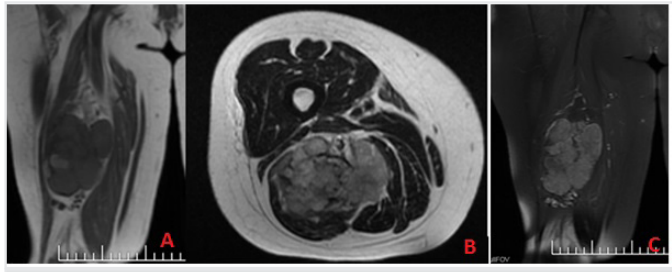

Figure 2. A) MRI images of posterior muscle plans of right lower thigh. The lesion seemed mildly hyperintense on T1-weighted sequences **B)** hypointense on t2-weighted sequences and showed **C)** no prominent contrast enhancement after intravenous contrast-material was injected to a lesion with lobulated contour with a size of approximately 74x39 mm

Table 2. The ability of age and tumor volume to distinguish pulmonary metastasis

	AUC (95% CI)	p	Cut-off	Sensitivity	Specificity
Age	0.967 (0.845-1.000)	0.037	≥28	80%	100%
Tumor volume	0.733 (0.352-1.000)	0.297	≥30	80%	67%

AUC: Area under curve, CL: Confidence interval

Table 3. Median survival times according to factors

	Median OS months (95% CI)
All patients	61.0 (1.9-120.1)
Patients with pulmonary metastases	16.4 (6.8-71.2)
Age ≥28 years	24.0 (0-63.2)
Tumor volüme ≥30 mL	16.4 (6.7-71.2)
Tumor volüme ≥50 mL	24.0 (0-63.2)

CI: Confidence interval, OS: Overall survival

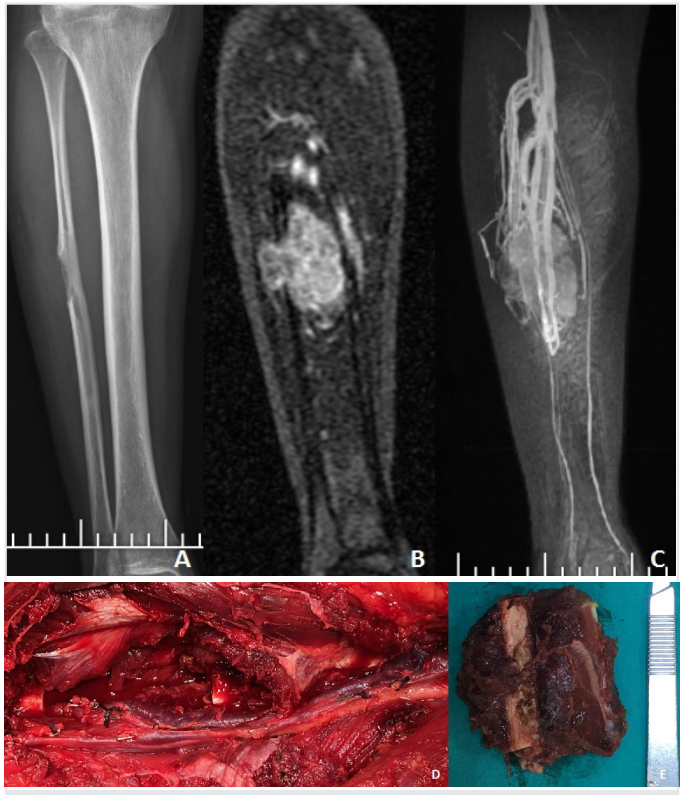

Figure 3. A, B, C) Right cruris direct X-ray and MRI angiography cross sections, a mass lesion was observed between the tibia and the fibula, filling and expanding the soft tissue at the middle part of the cruris. The integrity of the fibular cortex at the mass level could not be clearly selected in some regions. Therefore, it was thought that the mass could have a vascular origin. Fibular artery, tibialis anterior and posterior artery branches could not be clearly distinguished from the current mass. **D, E)** Medical surgery was performed first, intraoperative evaluation revealed that only fibular artery was associated with the tumor. This artery was ligated proximally and sacrificed. The tibial arteries were preserved, then the lateral fibula was osteotomized from the proximal and distal of the tumor and the tumor was removed with wide surgical margins.

was 100% and was only 40% in patients with pulmonary metastasis. However, the difference was not statistically significant (log-rank test; p=0.053; Figure 4b) (Table 4).

The 5-year survival rate for those under 28 years of age was 75% while it was 50% for those over 28 years of age. There was no significant difference in survival rates according to age groups (log-rank test; p=0.171; Figure 4c).

Table 4. Evaluation of baseline demographics according to pulmonary metastasis

	Patients without pulmonary metastases (n=3)	Patients with pulmonary metastases (n=5)	p
Age year			
Mean ± SD	21.7±2.5	40.6±19.5	0.036[1]
Median (min-max)	22.0 (19.0-24.0)	34.0 (24.0-74.0)	
Age n(%)			
<28	3 (100.0)	1 (20.0)	0.143[2]
≥28	0	4 (80.0)	
Sex n (%)*			
Female	1 (33.3)	3 (60.0)	1.000[2]
Male	2 (66.7)	2 (40.0)	
Location n (%)			
Thigh	3(100.0)	1 (20.0)	0.143[2]
Non- thigh	0	4 (80.0)	
Tumor volume mL			
Mean ± SD	55.7±73.7	185.4±226.1	0.297[1]
Median (min-max)	23.0 (4.0-140.0)	115.0 (18.0-572.0)	
Tumor volume			
<30 mL	2 (66.7)	1 (20.0)	0.464[2]
≥30 mL	1 (33.3)	4 (80.0)	
Exitus N (%)			
Yes	2 (66.7)	1 (20.0)	0.464[2]
No	1 (33.3)	4 (80.0)	

*Column percentage, [1]Mann-Whitney U test, [2]Fisher chi-square test, SD: Standard deviation

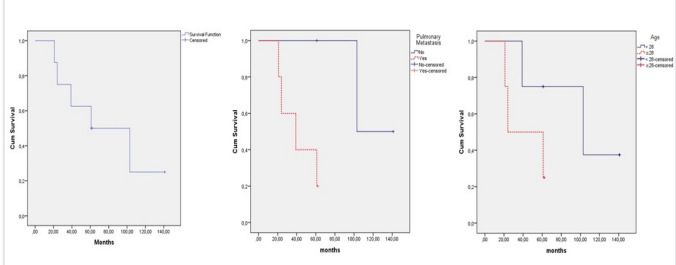

Figure 4. a) Kaplan-Meier curve for overall survival **b)** Kaplan-Meier curves for overall survival according to pulmonary metastasis **c)** Kaplan-Meier curves for overall survival according to age groups

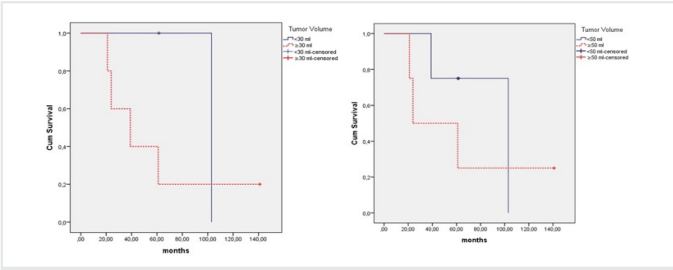

Figure 5. a) Kaplan-Meier curves for overall survival according to tumor volume **b)** Kaplan-Meier curves for overall survival according to tumor volume

In addition, tumor localizations were divided into two groups as thigh and non-thigh localizations. While only 1 of the 4 patients with tumor localized in thigh had metastasis, all of the patients with tumor localized in regions other than thigh were metastatic, but the difference was not statistically significant (p=0.143).

The 5-year survival rate was 100% in patients whose tumor volume was below 30 mL and 40% in patients with tumor volume of 30 mL or above, and there was no significant difference in survival rates (log-rank test; p=0.204; Figure 5a). The 5-year survival rate was 75% in patients with tumor volume below 50 mL and 50% in patients with tumor volume of 50 mL or above, and there was no significant difference in survival rates (log-rank test; p=0.446; Figure 5b).

Discussion

Vascular anomalies are a heterogeneous group consisting of conditions associated with abnormal growth or expansion of the vessels (10). Due to the diversity of these pathological structures and the similar appearance of many of these diseases, the indefinite terminology is prevalent in these lesions thus causes misdiagnoses, inappropriate interventions and treatment delays. Many vascular lesions are called hemangiomas with incorrect use, and the rate of use of misnamed lesion as hemangioma is reported to be as high as 71.3% (11,12).

ASPS is a rare, highly-vascularized malignant soft tissue tumor. Sometimes a murmur can be heard clinically and may be confused with arteriovenous malformations (7,8). Furthermore, according to a recently published study, MRI findings of ASPS may be misdiagnosed as benign tumors, pseudo-tumors, particularly intramuscular benign vascular tumors or vascular malformations (13).

It is estimated that 90% percent or more of vascular anomalies can be diagnosed simply by anamnesis and physical examination. Indications for imaging tests include the diagnosis of atypical lesions, the examination of larger and deeper lesions, and planning treatment for mixed lesions (venous or lymphatic malformations, etc.). An incisional biopsy is essential for the diagnosis before the final treatment plan in cases in whom anamnesis, physical examination and imaging findings do not match. Three of the 8 cases in this study were operated in other centers with a pre-diagnosis of a benign vascular lesion and required bed resection. In case of preliminary diagnosis of a vascular lesion, we recommend a more careful preoperative evaluation for malignancy, and if necessary, referring the patient to a hospital experienced in tumoral diseases (2,5,6,9,12,14)

The aim of this study was to investigate the factors affecting the prognosis of patients with ASPS whichwas a very rare soft tissue sarcoma. It is known that ASPS is an insidious disease and is often metastatic at the time of diagnosis (9,15-17). In ASPS, we examined the risk factors for the presence of lung metastases, and when we considered $p<0.05$ as significant, we could not find a significant result. Because this was a very rare tumor, we analyzed the data with a significance level of $p<0.20$ and found that the age at the time of diagnosis and tumor localization were significant prognostic factors in terms of lung metastasis.

ASPS is typically more common in adolescents and young adults and women aged between 15 and 35 years (15). However, patients can be seen in a wide range of age. Recently, ASPS has been reported in the tongue in a 11-month- girl (18). In our study, the mean age was 33.5 years, but 62% of the patients were male, which was not consistent with the literature. When we divided the patients into two groups as patients over 28 years of age and under 28 years of age, age older than 28 years was found as a risk factor for lung metastasis (Table 3).

ASPS is most commonly seen in the thigh (16,17,19) and it was seen in 50% of the patients in our study. In our study, when we divided the patients into two groups as patients with primary tumor located in the thigh and patients with non thigh localization , non-thigh localization was found as a risk factor for lung metastasis (Table 3).

ASPS has slow growth characteristics, but 20% to 40% of patients have a high metastatic rate at the time of diagnosis. Metastasis occurs primarily in the lung, including the bone and brain. Five-year survival was reported to be between 52% and 88% (8,9). In our study, the rate of metastatic patients was high (62%) and at the time of diagnosis, 5 of the 8 patients had lung metastases. In all cases in our study, the removal of the primary tumor with wide margins could be performed and the 5-year survival rate was 62.5%.

Previously, factors affecting survival in the literature have been reported as stage, surgical margins and tumor size (3,15,17). We reported that age older than 28 years and non-thigh localization of tumor in extremity were the risk factors for lung metastasis Treatment of primary, non-metastatic soft tissue sarcomas is resection with wide margins. Chemotherapy is recommended for advanced, inoperable and/or metastatic soft tissue sarcomas (STS) (20). However, advanced or metastatic ASPS is generally not sensitive to conventional cytotoxic chemotherapy. Current studies have

shown that ASPS is characterized by its sensitivity to the effect of vascular endothelial growth factor receptor (VEGFR)-predominant tyrosine kinase inhibitors (TKIs) compared with other STSs (21,22). Especially in recent years, there have been studies indicating that antiangiogenic agents such as pazopanib, crizotinib, sorafenib, anlotinib, sunitinib and cedirranib could be effective in ASPS (23).

There were some limitations in this study. Firstly, the study was retrospective . Also, since it was a very rare tumor, the number of cases was relatively low. The low number of cases reduced the statistical power of the study, and therefore, the survival rates reported in our article were poor in reflecting the reality.

Conclusion

When the demographic data were analyzed, the average age in our study was similar with the literature, but in contrast with the literature , the tumor was more common in men in our study. It was found that age older than 28 years at the time of diagnosis and the non- thigh location of the tumor inextremity increased the risk of lung metastasis. It was found that 37.5% of the patients underwent inadequate operation with the pre-diagnosis of vascular related benign tumors. So, a good preoperative evaluation for the differential diagnosis of ASPS is needed when interfering with hemangioma-like vascular associated tumors.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Written informed consent was obtained from the patient's legal custodian or first-degree relatives to use the individual medical records.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Concept: Design: Data Collection or Processing: Analysis or Interpretation: Literature Search: Writing:

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

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

References

1. Christopherson WM, Foote FW Jr, Stewart FW. Alveolar soft-part sarcomas; structurally characteristic tumors of uncertain histogenesis. Cancer. 1952;5(1):100–11. http://dx.doi.org/10.1002/1097-0142(195201)5:1<100::AID-CNCR2820050112>3.0.CO;2-K.
2. Portera CA Jr, Ho V, Patel SR, Hunt KK, Feig BW, Respondek PM, et al. Alveolar soft part sarcoma: clinical course and patterns of metastasis in 70 patients treated at a single institution. Cancer 2001;91:585-91.
3. Ogose A, Yazawa Y, Ueda T, Hotta T, Kawashima H, Hatano H, et al. Alveolar soft part sarcoma in Japan: multi-institutional study of 57 patients from the Japanese Musculoskeletal Oncology Group. Oncology 2003;65:7-13.
4. Günay C, Atalar H, Kaygusuz G, Yildiz Y, Sağlik Y. Alveolar soft part sarcoma of the extremities: an evaluation of four cases. Acta Orthop Traumatol Turc 2007;41:326-31.
5. 5. Viry F, Orbach D, Klijanienko J, Fréneaux P, Pierron G, Michon J, et al. Alveolar soft part sarcoma – radiologic patterns in children and adolescents. Pediatr Radiol 2013;43: 1174-81.
6. Kayton ML, Meyers P, Wexler LH, Gerald WL, LaQuaglia MP. Clinical presentation, treatment, and outcome of alveolar soft part sarcoma in children, adolescents, and young adults. J Pediatr Surg 2006;41:187-93.
7. Cho YJ, Kim JY. Alveolar soft part sarcoma: clinical presentation, treatment and outcome in a series of 19 patient. Clin Orthop Surg 2014;6:80-6.
8. Lin YK, Wu PK, Chen CF, Chen CM, Tsai SW, Chih-Hsueh CP, et al. Alveolar soft part sarcoma: Clinical presentation, treatment, and outcome in a series of 13 patients. J Chin Med Assoc 2018; 81:735-41.
9. Ozturk R, Aydın M, Arıkan ŞM, Şimşek MA, Toptaş E, Güngör BŞ. Extremity soft tissue sarcomas of uncertain differentiation: Presentation, treatment, and outcomes in a clinical series of 59 patients. Med J Bakirkoy 2018;14:31-9.
10. Nosher JL, Murillo PG, Liszewski M, Gendel V, Gribbin CE. Vascular anomalies: A pictorial review of nomenclature, diagnosis and treatment. World J Radiol 2014;6:677-92.
11. Greene AK, Liu AS, Mulliken JB, Chalache K, Fishman SJ. Vascular anomalies in 5,621 patients: guidelines for referral. J Pediatr Surg 2011;46:1784-89.
12. Leszczynska M, Jodeh DS, Reed D, Lynskey EM, Bittles MA, Mayer JL, et al. A case report of alveolar soft part sarcoma demonstrating principles for uncommon vascular lesions. Pediatr Int 2019;20.
13. Crombé A, Brisse HJ, Ledoux P, Haddag-Miliani L, Bouhamama A, Taieb S, et al. Alveolar soft-part sarcoma: can MRI help discriminating from other soft-tissue tumors? A study of the French sarcoma group. Eur Radiol. 2019;29:3170-82.
14. Ozturk R, Arıkan ŞM, Bulut EK, Kekeç AF, Çelebi F, Güngör BŞ. Distribution and evaluation of bone and soft tissue tumors operated in a tertiary care center. Acta Orthop Traumatol Turc 2019;53:189-94.
15. Ogura K, Beppu Y, Chuman H, Yoshida A, Yamamoto N, Sumi M, et al. Alveolar soft part sarcoma: a single-center 26-patient case series and review of the literature. Sarcoma 2012;2012:907179.
16. Daigeler A, Kuhnen C, Hauser J, Goertz O, Tilkorn D, Steinstraesser L, et al. Alveolar soft partsarcoma: clinicopathological findings in a series of 11 cases. World J Surg Oncol 2008;6:71.
17. Pennacchioli E, Fiore M, Collini P, Radaelli S, Dileo P, Stacchiotti S, et al. Alveolar soft part sarcoma: clinical presentation, treatment, and outcome in a series of 33 patients at a single institution. Ann Surg Oncol 2010;17:3229-33.

18. Ruffle A, Cameron M, Jonas N, Levine S, Mills C, Hook CE, et al. Lingual Alveolar Soft Part Sarcoma in a 1-Year-Old Infant : Youngest Reported Case With Characteristic ASPSCR1-TFE3 Fusion. Pediatr Dev Pathol 2019;22:391-5.
19. Orbach D, Brennan B, Casanova M, Bergeron C, Mosseri V, Francotte N, et al. Paediatric and adolescent alveolar soft part sarcoma: A joint series from European cooperative groups. Pediatr Blood Cancer 2013;60:1826-32.
20. Kaya V, Yilmaz S, Atalay IB, Gungor BS. Assessment of Surgical Treatment and Long-Term Follow-up Results of Extremity Liposarcomas: A Single Center Experience. J Ortho Bone Disord 2018;2:000168.
21. Toğral G, Güngör BŞ. Management of suspected cases of soft tissue sarcoma, bone invasion: 16 Case Study. Acta Oncol Tur 2019;52:121-6.
22. Paoluzzi L, Maki RG. Diagnosis, Prognosis, and Treatment of Alveolar Soft-Part Sarcoma A Review. JAMA Oncol 2019;5:254-60.
23. Wang Y, Min L, Zhou Y, Tang F, Luo Y, Zhang W, et al. Cancer Manag Res 2019;11:3583-91.

Original Article

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Evaluation of the Effectiveness of Simulation and Web Based Training Methods in the Development of Knowledge and Skills of Urinary İncontinence Management in Nursing Students

Hemşirelik Öğrencilerinin Üriner İnkontinans Yönetimi Bilgi ve Becerilerinin Geliştirilmesinde Simülasyon ve Web Tabanlı Eğitim Yöntemlerinin Etkinliğinin Değerlendirilmesi

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ABSTRACT

Objective: The aim of this study was to evaluate the effectiveness of simulation and web based training methods in developing knowledge and skills of urinary incontinence (UI) management in nursing students.

Methods: This study was a single blind, randomized controlled study. It was conducted with 75 period 2 nursing students. The research was carried out in 3 stages. In the first stage; all students were given theoretical training about UI management and pretest was applied. Then, students were divided into three groups, each of which consisted of 25 students, by block randomization method (Intervention 1 group, intervention 2 group and control group). In the second stage, intervention 1 group was trained with the simulation training, and intervention 2 group was trained with web-based training. The control group underwent no intervention. The third stage was initiated after 3 months in order to evaluate the effectiveness of knowledge and skills in the long term. All of the students' skills were evaluated on a real patient with UI and posttest was applied.

Results: It was found that the change in knowledge level in intervention 1 and intervention 2 groups was similar (p=0.086), but the level of knowledge in both groups was increased more than

ÖZ

Amaç: Hemşirelik öğrencilerinin üriner inkontinans (Üİ) yönetimi bilgi ve becerilerinin geliştirilmesinde simülasyon ve web tabanlı eğitim yöntemlerinin etkinliğinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Tek kör, randomize kontrollü olarak yapılan bu çalışma, ikinci sınıftaki toplam 75 hemşirelik öğrencisi ile üç aşamada gerçekleştirilmiştir. Birinci aşamada; öğrencilerin tamamına Üİ yönetimiyle ilgili teorik bilgi verilip ön test uygulanmıştır. Daha sonra öğrenciler blok randomizasyon yöntemiyle; müdahale1, müdahale 2 ve kontrol grubu olmak üzere 25'er kişiden oluşan üç gruba ayrılmıştır. İkinci aşamada; müdahale 1 grubu simülasyon eğitim yöntemiyle, müdahale 2 grubu web tabanlı eğitim yöntemiyle eğitilmiş, kontrol grubuna ise herhangi bir müdahalede bulunulmamıştır. Üçüncü aşamada eğitimlerden üç ay sonra grupla rarasında bilgi ve becerilerin uzun vadede etkinliğini belirlemek amacıyla öğrencilerin tamamının becerileri Üİ'si olan gerçek hasta üzerinde değerlendirilmiş ve öğrencilere son test uygulanmıştır.

Bulgular: Müdahale 1 ve müdahale 2 gruplarındaki bilgi düzeyi değişiminin benzer düzeyde olduğu (p=0,086) ancak her iki gruptaki bilgi düzeyinin kontrol grubuna göre daha da arttığı belirlenmiştir

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the control group (p<0.001). In addition, the skills level was the highest in the intervention 1 group and the lowest in the control group (p<0.05).

Conclusion: Although simulation and web based trainings have a positive and similar effect on the level of knowledge, it is seen that simulation training has more impact on skill level than web-based training.

Keywords: Simulation training, web based training, urinary incontinence management, nursing students

(p<0,001). Ayrıca beceri düzeyinin müdahale 1 grubunda en yüksek, kontrol grubunda en düşük olduğu saptanmıştır (p<0,05).

Sonuç: Simülasyon ve web tabanlı eğitimin öğrencilerin bilgi düzeyi üzerinde olumlu ve benzer etkisi görülse de; beceri düzeyinde simülasyon eğitimi web tabanlı eğitime göre daha etkilidir.

Anahtar Sözcükler: Simülasyon eğitimi, web tabanlı eğitim, üriner inkontinans yönetimi, hemşirelik öğrencileri

Introduction

Nursing is a practical health discipline covering the processes for the realization of cognitive, affective and psychomotor learning (1,2). Today, with the development of technology, in addition to traditional training methods, innovative training methods are preferred for students to develop cognitive, affective and psychomotor skills. In nursing education, especially the increasing number of students, the appropriate clinical practice area and the low number of trainers have made it necessary to integrate innovative training methods such as simulation training and web-based training into nursing education (1-3).

Simulation training allows students to learn by gaining experience in many subjects such as providing patient safety and developing evaluation skills for psychiatric nursing; allows students to develop their cognitive, affective and psychomotor skills in these subjects in the short and long term (3-5); and reduces the fear and anxiety of making mistakes and enables students to adequately reflect their knowledge and skills into real patient care even after three to six months (6-8). In a pretest-posttest evaluation study conducted on nursing students to examine the development of basic information in intensive care nursing, it was determined that the persistence of knowledge in students increased significantly 3 months after simulation training (9). In another study to determine the effect of simulation training on nursing students on cognitive skills and confidence level, it was determined that cognitive skills improved significantly after 6 months, but there was no significant difference in confidence levels (10). Web-based training is a cost-effective and useful practice that aims to improve students' cognitive, affective and psychomotor skills (11). Web-based training is considered to be an important training method for eliminating time and limit barriers, providing 24-hour access to information and supporting learning (12). In a study that evaluated the effect of web-based training on hand washing knowledge and skills on nursing students, it was determined that knowledge and skills increased significantly after 8 weeks (13).

Urinary incontinence (UI) is a major and widespread problem worldwide, affecting the psychological, physical, social and economic well-being of individuals and their families (14,15). UI is reported to be more common in women and about 10% of all women face this problem. Its prevalence increases as age increases, affecting more than 40% of women aged 70 years (14,16). The prevalence of UI in women has been reported to vary between 25-45% (17) in the world and 20-25% in Turkey (18,19). It is important to consider and evaluate this problem carefully considering that the rates of UI are quite high and people/families are affected psychologically, physically, socially and economically. UI, which is a preventable problem and is very common, requires the nursing profession to be better equipped in this regard. The acquisition of this equipment requires studies that assess the impact of innovative training methods such as simulation training and web-based training on the persistence of knowledge and skills in the long term. It was thought that this study would make an important contribution to the literature at this point.

Aim and Questions of the Study

The aim of this study was to evaluate the effectiveness of simulation and web-based training methods in the development of nursing students' knowledge and skills in UI management. The following study questions were created in line with the purpose of the study.

Is there a difference between groups (simulation training, web-based training and control group) in terms of nursing students' knowledge development related to UI management?

Is there a difference between groups (simulation training, web-based training, and control group) in terms of nursing students' skills development related to UI management?

Methods

Form of the Study

This study was conducted as a single blind randomized controlled trial.

Universe and Sample of the Study

The universe of the study consisted of 130 students in the nursing department of a university in Ankara who took the course of "Internal Medicine Nursing" between December 2018 and March 2019. The sample of the study consisted of 75 students who agreed to participate in the study.

Criteria for Inclusion in the Study:

1. To be enrolled in the course of "Internal Medicine Nursing",

2. Active participation in the course of "Internal Medicine Nursing",

3. Agreeing to participate in the study.

Criteria for Exclusion from the Study:

1. Not participating to theoretical education of the course of "Internal Medicine Nursing",

2. Not participating in simulation and video based training,

3. Not participating in clinical practice of the course of "Internal Medicine Nursing",

4. Not working with a patient with UI,

4. Refusing to participate in the study.

Data Collection Forms

Demographic information including the age and gender of the participants were collected and the "Assessment Form (Form 1) on knowledge level related to UI management" and the "Skills Assessment Form (Form 2) for management of UI" were used. The final versions of these forms prepared by the researchers in accordance with the literature were formed by taking opinions of 5 experts.

Assessment Form (Form 1) on Knowledge Level Related to Urinary Incontinence management; this form was created by the researcher by scanning the literature to measure the level of knowledge of nursing students on what urinary incontinence meaned, why it occured, risk factors, diagnostic methods, conservative (pelvic floor muscle exercises, bladder training, toilet programs, etc.), medical and surgical treatment methods, and nursing care of UI (5,14-17). The form was prepared on a multiple choice basis and contained a total of 20 questions. The score that was taken from each correctly answered question was 5 and the score range of the form varied between 0 and 100 points.

Skills Assessment Form (Form 2) for Management of Urinary Incontinence; this form was created by the researcher by scanning literature to evaluate nursing students' skills related to urinary incontinence (6,14-17).The form contained a total of 20 items and included options for each item that could be marked as "not observed", "missing/incorrect" and "correct/complete", and these categories were rated 0, 1, and 2, respectively. The score that could be taken from each "correct/complete" answer was 2 and the score range of the form varied between 0 and 40 points. Performance scores were obtained by converting the sum of the scores in this form to a scale of 0-100**.**

Application of the Study

The study was carried out in three stages (Figure 1).

First Stage:

Theoretical knowledge about management of UI was given by the researchers to all students (75 students) during a lecture hour by expression and demonstration method. At the end of the training, a question-answer session was held. Then, pre-test was applied to all the students who participated in the study and the knowledge levels of the students were evaluated. Students were divided into three groups (25 students, intervention 1 group; 25 students, intervention 2 group; 25 students, control group) using the block randomization method. By block randomization method, the first three students were included in group I, II and III, respectively; then the second three in group II, III and I, respectively and then the third three in group III, I and II,

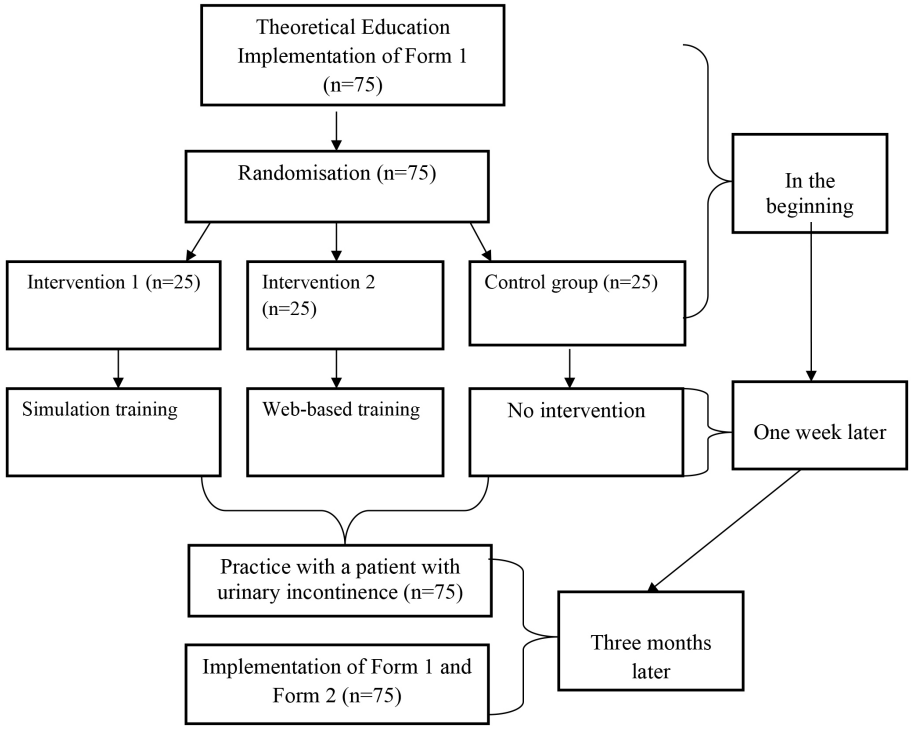

Figure 1. Stages of the study

respectively. Then, they were distributed to the groups in the same way.

Second Stage:

1. Intervention 1 group was given a new 20-minute training about UI management one week later with demonstration method and with standard patient accompaniment. The training given by the researchers was about what urinary incontinence meaned, why it occured, risk factors, diagnostic methods, conservative (pelvic floor muscle exercises, bladder training, toilet programs, etc.), medical and surgical treatment methods, and nursing care of UI. After the training, the students were released to self-study with the standard patient. Student applications were recorded on video during the study. The analysis session was then conducted. During the analysis session, the videotaped applications of the students were monitored by both the student and the researcher. In the meantime, students were given feedback on their practice skills.

2. Intervention 2 group was given web-based training on UI management one week later. The researchers prepared a video about what UI meaned, why it occured, risk factors, diagnostic methods, conservative (pelvic floor muscle exercises, bladder training, toilet programs, etc.), medical and surgical treatment methods, and nursing care of UI. The video was uploaded to the web environment for students to reach and was watched by the students.

3. To q control group was not interfered other than theoretical training.

Third Stage:

The third stage of the study was carried out three months later. Three months after simulation and web-based theoretical and practical training, each student in the three groups performed a practice on a female patient with UI during the clinical practice. During this application, the students' skill levels were evaluated using the "Skills assessment form on UI management (Form 2)" by the two instructors who were not involved in the study. These two faculty members did not know which group the students were in. The final test was applied to all the students who participated in the study and their knowledge levels were re-evaluated at the end of the third month.

Limitations of the Study

Considering that UI was more common in women, only female patients were used in the actual patient practice of the study. It is also recommended that male patients be included in other studies on this subject.

Ethical Aspects of the Study

The authorization and ethical approval of the study was taken from Ankara Yıldırım Beyazit University (2018/86). The aim of the study was explained to the students and their written consent was obtained. It was stated to the students that whether or not they participated in the study was not part of the education and would never affect the educational process. During the clinical practice, the female patients with UI were informed about the study and their approval was obtained.

Statistical Analysis

The distribution of information and performance scores in the study was examined with the Shapiro-Wilk test. All scores were expressed in mean ± standard deviation and median (min-max). Knowledge and performance scores were obtained by converting the sum of the scores in the relevant form to a scale of 0-100. The knowledge and performance scores of the groups were compared with the Kruskal-Wallis test. The Bonferroni-Dunn Correction was applied for binary comparisons. The variation of information scores in groups was compared with the F1-LD-F1 design. As a result of this test, a p value for Anova-type-statistic was given for intergroup differences and group*test time interaction. A p value <0.05 was accepted as statistically significant. For statistical analysis and calculations, IBM SPSS Statistics21. 0 program (IBM Corp. Releasedin 2012. IBM SPSS Statistics for Windows, Version21.0. Armonk, NY: IBM Corp.) was used and for graphic drawing, Microsoft Office Excel 2013 was used.

Results

The average age of 75 students in the study was 20.7±0.8 years and the majority (84%) were female (Table 1).

The median of the pretest knowledge score was 35 [minimum-maximum (min-max): 20-65] in intervention 1 group, 35 (min-max: 15-70) in intervention 2 group and 35 (min-max: 20-65) in control group (Table 2; Figure 2). There was no difference between the groups in terms of pretest knowledge score (p=0.911). The posttest knowledge score was significantly higher in intervention 1 group and intervention 2 group than in control group (p<0.05). There was no significant difference between the intervention 1 and Intervention 2 groups in terms of the posttest knowledge score (p=0.260).

When pretest and posttest knowledge scores were examined, it was determined that there was a significant change in intervention 1

Table 1. Characteristics of students (n=75)

Characteristics	Intervention 1 group (n=25)	Intervention 2 group (n=25)	Control group (n=25)	Total
Age (years)				
Average ± standard deviation	20.6±0.6	20.6±0.8	20.7±0.8	20.7±0.8
Gender				
Female	21 (84%)	22 (88%)	20 (80%)	63 (84%)
Male	4 (16%)	3 (12%)	5 (20%)	12 (16%)

and intervention 2 groups (p<0.001) and that knowledge scores remained at a similar level in the control group (p=0.423). When information score changes were compared, it was found that the change in intervention 1 and intervention 2 groups was similar (p=0.086) but the scores in both groups increased compared to the control group (p<0.001).

The performance score distributions of the groups are given in Table 2 and Figure 3. Performance score was found to be highest in intervention 1 group and lowest in control group (p<0.05)

Discussion

It is observed that innovative training methods such as simulation training and web-based training are applied in order to gain sufficient knowledge and skills and to provide cognitive, affective and psychomotor learning in nursing education (5,11). When these training methods are applied separately, it is seen that they provide long-term knowledge and skills persistence for nursing students (9,10,13). When the literature was examined, it was observed that a limited number of studies were conducted on the employees to assess the effectiveness of these training methods on the persistence of knowledge and skills in the long term (20-22). However, it has not been observed that the effects of these training methods on the long-term persistence of knowledge and skills have been determined by evaluating them together. There has also been no study on the management of UI in this area. Based on this point, this study was conducted as a randomized controlled trial to evaluate the effectiveness of simulation and web-based training methods in the development of the knowledge and skills in the management of UI of nursing students.

In a randomized controlled trial, where simulation and web-based training methods were compared on nurses, it was determined that knowledge levels in both methods were similarly increased in the short term and long term (at the end of the second month). The skills of nurses who received simulation training were found to be higher in the short term and in the long term (at the end of the second month) (20). In a study where simulation and web-based trainings about intravenous administration were given to radiography specialists, it was found that both methods increased the level of knowledge, but the increase in simulation training was more without reaching statistical significance. In both groups, it was observed that the persistence of knowledge after six months was ensured (21). In a semi-experimental study comparing simulation and web based training methods on midwives, it was determined that there was a significant improvement in midwives with both methods and no difference was found between groups (22). In a randomized controlled trial, simulation and web based training methods were

Table 2. Comparison of knowledge and skill scores of intervention 1, intervention 2 and control groups

	Intervention 1	Intervention 2	Control	Intergroup comparison
Pretest knowledge score				0.911
Average ± standard deviation	35.20±10.65	35.20±12.46	36.00±10.51	
Median (min-max)	35 (20-65)	35 (15-70)	35 (20-65)	
Posttest knowledge score				**<0.001**
Average ± standard deviation	51.00±11.64	47.20±13.08	36.80±11.08	
Median (min-max)	45 (40-85)	45 (35-80)	35 (20-60)*	
In-group comparison	**<0.001**	**<0.001**	0.423	
Skill score				**<0.001**
Average ± standard deviation	84.10±8.89	66.10±8.81	31.30±9.44	
Median (min-max)	85.0 (60.0-97.5)*	67.5 (52.5-82.5)*	30(2.5-45.0)*	

Kruskal-Wallis testi, *Indicates that the group is different from the other two groups, min: Minumum, max: Maximum

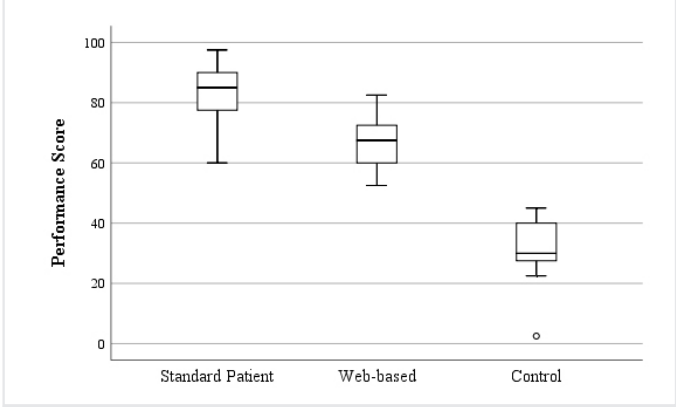

Figure 3. Distribution of skill level of groups

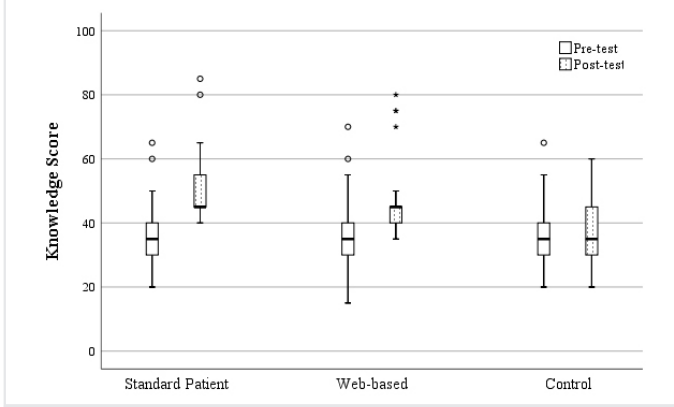

Figure 2. Distribution of knowledge level of groups

used on midwives for postpartum hemorrhage volume estimation and it was determined that there was a significant improvement in midwives with both methods and no difference was found between groups (23). Similarly, when changes in knowledge level were compared between the groups, it was determined that the change in intervention 1 and intervention 2 groups was similar ($p=0.086$) and that the knowledge level in both groups was more increased compared with control group ($p<0.001$). In addition, skill levels were found to be highest in intervention 1 group and lowest in control group ($p<0.05$). Although simulation and web-based trainings had a positive and similar effect on knowledge level, simulation training had more impact on skill level than web-based training. This was thought to be related to providing students with a realistic learning environment where they experienced real-life situations through simulation training (24-26). It was also thought that the analysis session affected this result. It is known that effective learning is achieved through feedback during the analysis session and positive aspects of skill are reinforced. This enables the student to relate theoretical knowledge with practice and enables the performance permanent (27,28).

Conclusion

Although both innovative training methods such as simulation training and web-based training had a positive and similar effect on knowledge level, simulation training had more impact on skill level than web-based training. Further research is needed assessing the effectiveness of simulation and web-based training methods on gaining knowledge and skills in the management of urinary incontinence in nursing students.

Ethics

Ethics Committee Approval: The authorization and ethical approval of the study was taken from Ankara Yıldırım Beyazit University (2018/86).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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

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

References

1. Cooper S, Endacott, R, Cant R. Measuring nontechnical skills in medical emergency care: A review of assessment measures. Emergency Medicine 2010;2:7-16.
2. Gillespie BM, Polit DF, Hamlin L, Chaboyer W. Developing a model of competence in the OR: Psycometric validation of perceived perioperative competence scale-revised. International Journal Nursing Studies 2012;49:90-101.
3. Robinson-Smith G, Bradley PK, Meakim C.Evaluating the use of standardized patients in undergraduate psychiatric nursing experiences November. Clinical Simulation in Nursing 2009;5(6):e203–e211. doi:10.1016/j.ecns.2009.07.001.
4. Robertson B, Kaplan B, Atallah H, Higgins M, Lewitt MJ, Ander DS. The use of simulation and a modified team STEPPS curriculum for medical and Nursing student team training. The Journal of the Society for Simulation in Healthcare 2010;5:332-7.
5. Crowe S, Ewar L, Derman S. Theimpact of simulation based education on nursing confidence, knowledge and patient outcomes on general medicine units. Nurse Education in Practice 2018;29:70-5.
6. Houghton CE, Casey D, Shaw D, Murphy K. Students' experiences of implementing clinical skills in the real word of practice. Journal of Clinical Nursing 2013;22:1961-9.
7. McNett S. Teaching nursing psychomotor skills in a fundamentals laboratory: A literature review. Nurse Education Perspectives 2012;33:328-33.
8. Ross JG. Simulation and psychomotor skill acquisition: A review of the literature. Clinical Simulation in Nursing 2012;8:e429-e435.
9. Hoffmann R, O'Donnell J, Kim Y. The effects of human patient simulators on basic knowledge in critical care nursing with undergraduate senior baccalaureate nursing students. Simulation in Healthcare 2007;2:110-4.
10. Brannan J, White A, Bezanson J. Simulator effects on cognitive skills and confidence levels Journal of Nursing Education 2008;47:495-500.
11. Hadjiconstantinou M, Byrne J, Bodicoat D H, Robertson N, Eborall H, Khunti K, Davies M. J. Do web-based interventions improve well-being in type 2 diabetes? A systematic review and meta-analysis. Journal of Medical Internet Research 2016;18:270.
12. Elgaphar SMA, El Gafar SIA. Effect of tele-nursing (phone-basedfollow-ups) on self efficacy healthy lifestyle and glycemic control in diabetic patients IOSR Journal of Nursing and Health Science (IOSR-JNHS) 2017;6:67-76.
13. Bloomfield J, Roberts J, While A. The effects of computer assisted learning versus conventional methods on the acquisition and retention of handwashing theory and skills in pre-qualification nursing students: a randomized controlled trial. International Journal of Nursing Studies 2010;47:287-94.
14. Milsom I, Gyhagen M. The prevalence of urinary incontinence, Climacteric 2018;1-6. DOI: 10.1080/13697137.2018.1543263
15. Wagner T, Moore K, Subak L, De Wachter S, Dudding T. Economics of urinary and faecal incontinence, and prolapse. In:Abrams P, Cardozo L, Wagg A, Wein A, eds. Incontinence. 6th ed. Paris: Health Publications Ltd; 2016:17–24
16. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int 2011;108:1132-8.

17. Milsom I, Altman D, Cartwright R, et al. Epidemiology of urinary incontinence (UI) and other lower urinary tract symptoms (LUTS), pelvic organ prolapse (POP) and anal (AI) incontinence. In: Abrams P, Cardozo L, Wagg A, Wein A, eds. Incontinence. 6th ed. Paris: Health Publications Ltd; 2016:17–24
18. Maral I, Özkardeş H, Peskircioğlu L,Bumin MA. Prevalence of stres urinary incontinence in both sexes at or after age 15 years: a cross-sectional study. J Urol 2001;165:408-12
19. Özerdoğan N, Beji NK, Yalçın O. Urinary incontinence: its prevalance, risk factors and effects on the quality of life of women living in a region of Turkey. Gynecol Obstet Invest 2004;58:145-50
20. Rutherford-Hemming T, Kelsey NC, Grenig DL, Feliciano M, Simko L, Henrich CM. Multisite single-blinded randomized control study of transfer and retention of knowledge and skill between nurses using simulation and online self-study module. Simulation in Healthcare 2016;11:264-70.
21. Aura SM, Paakkonen HJ, Metsavainio K, Saano SSM, Selander TA, Jordan SE, TurunenHE. Simulation- and web-based learning of intravenous pharmacotherapy: A 2-group comparison with 6 months' follow-up. Journal of Radiology Nursing 2017;36:117-24.
22. Fakari FR, Kordi M, Mazloom SR, Khadivzadeh T, Tara M, Akhlaghi F. Comparing the effect of traditional, web based and simulation training on midwifery students' clinical competence in postpartum hemorrhage management. J Mazandaran Univ Med Sci 2015;25:65-77.
23. Kordi M, Fakari FR, Mazloom SR, Khadivzadeh T, Akhlaghi F, Tara M. Comparison of the effect of web-based, simulation-based, and conventional training on the accuracy of visual estimation of postpartum hemorrhage volume on midwifery students: A randomized clinical trial. J EducHealthPromot 2016;5:22.
24. Harrington KL, Palley JE, Pfeiffer CE. Impact of thesite specialty of a continuity practice on students' clinical skills: Performance with standardized patients. Teaching and Learning in Medicine 2010;22:191-5.
25. Kim JK. Standardized patient identification and specimen labeling: A retrospective analysis on improving patient safety. Journal of the American Academy of Dermatology 2012;68:53-6.
26. Lucktar-Flude M, Wilson B, Larocque M. Evaluating high fidelity human simulators and standardized patients in an undergraduate nursing health assessment course. Nurse Education Today 2012;32:448-52.
27. Jeffries PR. Simulation in nursing education: From Conceptualization to Evaluation. New York, NY: National League for Nursing. 2007.
28. Jeffries PR. A framework for Designing, Implementing, and Evaluating. Nursing Education, Perspectives 2005;26:96-103.

Original Article

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Evaluation of Retinopathy of Prematurity: Four-year Follow-up Study in a Newly Established Tertiary Neonatal Intensive Care Unit in Turkey

Prematüre Retinopatisinin Değerlendirilmesi: Türkiye'de Yeni Kurulan Yenidoğan Yoğun Bakım Ünitesinde Dört Yıllık Takip Çalışması

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ABSTRACT

Objective: Retinopathy of prematurity (ROP) is one of the leading causes of childhood vision loss in both developed and developing countries. In this study, we aimed to assess the results of ROP screening and treatment, and to evaluate the risk factors in our newly established unit. We also compared our data with other studies reported in Turkey.

Methods: Two-hundred and forty eight (33.9%) infants were enrolled in ROP screening between January 2012-January 2016. The results of ROP screening and treatment, and the risk factors for ROP in infants followed up in a newly established neonatal intensive care unit were determined.

Results: ROP was observed in 25.8% of premature infants in different stages and zones. In the logistic regression analysis, we found an increased risk of ROP development in those patients with the following risk factors: Low gestational age [p=0.0001, odds ratio (OR)=0.73], sepsis (p=0.003, OR=0.57), and bronchopulmonary dysplasia (p=0.0035, OR=0.41).

Conclusion: Good antenatal care, improving unit conditions, and regular screening will decrease the ROP incidence in our facility to the level of developed countries. Hopefully, this will help to reduce the future sequelae of visual function loss in these patients. The awareness of the risk factors and the complications of ROP will decrease the incidence of the disease in unexperienced and newly organized NICUs.

Keywords: Retinopathy of prematurity, risk factors, Turkey, neonatal intensive care unit

ÖZ

Amaç: Prematüre retinopatisi (ROP) hem gelişmiş hem de gelişmekte olan ülkelerde çocukluk çağı görme kaybının önde gelen nedenlerinden biridir. Bu çalışmada, yeni kurulan ünitemizdeki ROP taraması ve tedavisinin sonuçlarını ve risk faktörlerini değerlendirmeyi amaçladık. Sonuçlarımızı Türkiye'de yapılan diğer çalışmalarla da karşılaştırdık.

Yöntemler: Ocak 2012-Ocak 2016 tarihleri arasında iki yüz kırk sekiz (%33,9) bebek ROP taramasına dahil edildi. Yeni kurulan yoğun bakım ünitesinde takip edilen bebeklerde ROP tarama ve tedavi sonuçları ile risk faktörleri belirlendi.

Bulgular: Prematüre bebeklerin %25,8'inde farklı evre ve bölgelerde ROP gözlendi. Lojistik regresyon analizinde, aşağıdaki risk faktörleri olan hastalarda artan ROP gelişme riski bulduk: Düşük gebelik yaşı (p=0,0001, OR=0,73), sepsis (p=0,003, OR=0,57) ve bronkopulmoner displazi (p=0,0035, OR=0,41).

Sonuç: Doğum öncesi iyi bakım, ünite koşullarının iyileştirilmesi ve düzenli tarama, ünitemizdeki ROP insidansını gelişmiş ülkeler seviyesine ulaştıracaktır. Umut ediyoruz ki bu da hastalarda görme fonksiyonlarının gelecekteki sekelini azaltmaya yardımcı olacaktır. Risk faktörleri ve komplikasyonlarla ilgili farkındalığın artması özellikle deneyimsiz ve yeni kurulan yenidoğan yoğun bakım ünitelerinde hastalığın görülme sıklığını azaltacaktır.

Anahtar Sözcükler: Prematürite retinopatisi, risk faktörleri, Türkiye, yenidoğan yoğun bakım ünitesi

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Introduction

Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy characterized by the abnormal vascularization of retinal blood vessels in premature infants (1-5). It is an important cause of childhood blindness in countries with a high human development index and low socio-economic income (1-5). This disease occurs in different stages ranging from mild to severe. In addition to blindness, each year 2,300 newborns are influenced by the late sequelae, such as retinal detachment, myopia, and strabismus (2-4). In the first three years of life, premature infants face several types of strabismus or refractive errors. Therefore, premature infants require regular eye examinations whether or not they are diagnosed with ROP (6). Timely screening and treatment are crucial to the outcomes in these patients (1).

The prevalence of ROP remains high today due to the increasing survival rates of extremely low birth weight (BW) babies (4-7). Hitherto, there have been 3 epidemics of ROP. The first one occurred between 1940 and 1945 due to uncontrolled oxygen use. After the development of neonatal nursing, the second one developed between 1960 and 1970. The third one was reported in 1980 and still continues today (2,5,8). Low BW, low gestational age (GA), and oxygen therapy are among the factors responsible for ROP (6,9).

In this study, we aimed to assess the results of ROP screening and treatment, and to evaluate the risk factors for ROP in babies followed up in our newly established neonatal intensive care unit (NICU). We also compared our data with other studies reported in Turkey.

Methods

Study Design and Data Collection

This retrospective trial was conducted in the NICU at the …… Hospital in …., Turkey, between January 2012 and January 2016, using the unit's database. This study was approved by the local ethical board (22.06.2016/386). It was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. The neonates included in this research had BWs of 1,500 grams or less, and/or GAs of 32 weeks or less. We also included larger infants with unstable clinical situations, based on the recommendations of the American Academy of Pediatrics, Academy of Ophthalmology, and American Pediatric Ophthalmology and Strabismus Academy (10). Seven-hundred and thirty-one premature infants were followed up during the study, and 248 of these were admitted into ROP screening programs. All of these were inborn patients.

The demographic characteristics of the patients, potential risk factors for ROP, eye examinations, and type and course of treatment were recorded. Those neonates who died before the ROP screening began were excluded from this research.

Screening Procedure

The ROP screening began at 4-6 weeks of age or between 31 and 33 weeks of age. One hour before the examination, 0.5% tropicamide and 2.5% phenylephrine HCl were applied to both eyes every five minutes for a total of 3 doses. After sufficient pupil dilatation was achieved, the eye examinations were completed with using eyelid speculums with a 28 D lens indirect ophthalmoscope under topical anesthesia (proparacaine HCL, 0.5%). Scleral indentation was used for the ocular rotation. All of the examinations and treatments were performed by the same ophthalmologist (A.K.) over the course of the study (four years). The infants were monitored during the examination, and were provided with 24% sucrose and a pacifier if analgesia was needed.

The ROP stage and zone classification were outlined for each eye using the International Classification of Retinopathy of Prematurity (ICROP) (11). The babies without ROP were followed up until they reached a 45-week GA, every 2-3 weeks, until the peripheral retinal vascularization fully developed. The infants with ROP were treated and followed up according to the criteria of the Early Treatment for Retinopathy of Prematurity Cooperative Group (12). These patients were treated with transpupillary diode laser photocoagulation and intravitreal bevacizumab, which was used in aggressive ROP cases.

Statistical Analysis

The statistical analysis of the data was performed using SPSS version 17 (SPSS Inc., Chicago, IL). Thet-test was used to analyze the continuous variables, whereas the chi-squared test was used for the categorical variables. The logistic regression analysis was conducted to define the variables that affected the development of ROP. A p value<0.05 was considered to be statistically significant.

Results

A total of 731 premature infants were monitored in the NICU during the four-year study period. Of these, 248 (33.9%) infants were enrolled in ROP screening; 119 (48%) females and 129 (52%) males. ROP was observed in 64 (25.8%) premature babies in different stages and zones. Of these patients, 36 (56.3%) had stage I, 17 (26.6%) had stage II, and 9 had (14.1%) stage III diseases. Aggressive ROP was detected in 2 (3.1%) patients; however, stages IV and V were not observed. The mean GA of the infants with ROP was 29.11±2.92 weeks (range=22-35 weeks), and the mean BW was 1224.57±474.54 g (range=485-2480 g). There was a statistically significant difference between the groups with and without ROP, according to the GA and BW (p=0.0001). The demographic features and risk factors for the babies with and without ROP are given in Table 1.

ROP regressed in 48 (75%) of the infants. Of the patients who were treated, the mean GA was 27.31±2.87 weeks, and the mean BW was 1015.00±331.15 g. The mean GA and BW in the treatment group were lower than those in the non-treated group, and the statistical difference was significant (p<0.005 and p<0.045, respectively). Diode laser photocoagulation and intravitreal bevacizumab were used in babies at rates of 18.8% (n=12) and 6.3% (n=4), respectively. There were no complications in either treatment modality.

We found a significant relationship between the GA, BW, respiratory distress syndrome (RDS), sepsis, intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), apnea, anemia, blood transfusion, oxygen therapy, and ROP by using the Chi-squared analysis (p value for each parameter = 0.0001, for apnea p = 0.013). However, there was no significant association between the gender, type of delivery, antenatal steroids, preeclampsia, multiple births, intrauterine growth restriction (IUGR), necrotizing enterocolitis (NEC), and ROP (p>0.05). In the logistic regression analysis, we found an increased risk of ROP development in those patients with the following risk factors: Low GA (p=0.0001, OR=0.73), sepsis (p=0.003, OR=0.57), and BPD [p=0.0035, odds ratio (OR)=0.41] (Table 2).

Discussion

ROP is one of the leading causes of childhood vision loss in both developed and developing countries (1-5). Recently, the increasing number of multiple pregnancies with assisted reproductive technology and the development of nursing care in the NICU have increased the incidence of ROP (6). According to the American Pediatric Ophthalmology and Strabismus Academy, 14,000 infants are diagnosed as having ROP in the US every year. Of these children, 1,100-1,500 exhibit severe forms of this disease, with 400-600 children going blind (2). However, the incidence is generally low in developed countries (13,14).

Table 1. Demographic features and the risk factors of the patients screened for ROP

Risk factor	ROP (+) (n=64)	ROP (-) (n=184)	p
GA (week)*	29.03±2.96	32.43±2.20	0.0001
BW (gram)*	1218.09±473.60	1852.46±571.18	0.0001
Gender (F/M)	29/35	90/94	0.62
Delivery mode (C/S)	55	154	0.67
Antenatal steroid	33	83	0.37
Preeklampsia	23	57	0.47
Twins	7	32	0.22
IUGR	5	3	0.44
RDS	70	45	0.0001
Sepsis	42	38	0.0001
NEC	6	2	0.97
IVH	18	10	0.0001
PDA	18	14	0.0001
BPD	19	2	0.0001
Apnea	13	16	0.013
Anemia	43	31	0.0001
Blood transfusion	30	12	0.0001

Abbreviations: ROP: Retinopathy of prematurity, GA: Gestational age, F: Female, M: Male, C/S: Caeserean section, IUGR: Intrauterine growth retardation, RDS: Respiratory distress syndrome, NEC: Necrotizing enterocolitis, IVH: Intraventricular hemorrhage, PDA: Patent ductus arteriosus, BPD: Bronchopulmonary dysplasia

Hwang et al. (15) reported that the incidence of ROP was 34.1% in Korea. In one study conducted in Northern Iran, incidence of ROP was 45% (16). Research conducted in Egypt found the incidence to be 36.5%, with the number of patients without follow up results being very high (17). The study by Öner et al. (18) reported a ROP incidence of 20.9%, with a mean GA of 31.35±3.5 weeks and a mean BW of 1,504.27±499.09 g. Additionally, Ekinci et al. (19) reported a 30.8% incidence of ROP, but the infants included in their study were larger premature babies. The incidence of ROP was 36.3% in the research conducted by Özbek et al. (20), who reported that 1.5% of the cases had stage V in their study group. In research from the middle of the Black Sea region, the incidence was reported as 30.8% (21). Moreover, Hanedar et al. (22) reported their ROP incidence as 23.7%. The ratio of ROP cases that required treatment was 8% in the trial conducted by Esen et al. (23). Furthermore, the ROP incidence was 56.8% in the study by Sönmez et al. (24). In our study, the prevalence of ROP was lower than the studies which screened for ROP in our country, but the incidence was higher than the studies conducted in developed countries.

A low GA, low BW, RDS, anemia, hyperbilirubinemia, apnea, IVH, NEC, oxygen therapy, and blood transfusion were the risk factors reported for ROP (6,25-27). The most important ones were a low BW and low GA (27-29). Hwang et al. (15) found PDA and invasive ventilation to be risk factors for ROP in cases with stage III or above disease. In a study from Iran, the main risk factors were identified as multiple births, a low BW, and oxygen therapy longer than 5 days (16). In the study by Yilmaz et al. (30) from our country, a low BW, low GA, ventilator use, and blood transfusion were the risk factors most commonly associated with the development of ROP. Ekinci et al. (19) showed that the BW, GA, and oxygen therapy were independent risk factors. However, Sönmez et al. (24) found that the GA, BW, phototherapy, RDS, mechanical ventilation, and continuous positive airway pressure (CPAP) support were risk factors for ROP, but multiple births, sepsis, and blood transfusion were not. A low GA, low BW, and blood transfusion were found to be risk factors for ROP in another study from Turkey (31).

Table 2. Multivariate Logistic Regression Analysis of Risk Factors for ROP

Risk factor	Wald	OR	95% CI (min-max)	P
GA	14.95	0.73	0.62-0.85	0.0001
Sepsis	8.57	0.57	0.39-0.83	0.003
BPD	4.42	0.41	0.18-0.94	0.035

Abbreviations: ROP: Retinopathy of prematurity, GA: Gestational age, BPD: Bronchopulmonary dysplasia, CI: Confidence interval, min: Minimum, max: Maximum

In our research, the risk factors of ROP were similar with recent studies: A low GA, low BW, RDS, sepsis, IVH, PDA, BPD, apnea, anemia, and blood transfusion were identified as risk factors. However, antenatal steroids were not protective against ROP. In our logistic regression analysis, we found that the GA, sepsis, and BPD were independent risk factors that influenced the development of ROP.

Peripheral retinal ablation with cryotherapy was determined to be the appropriate treatment based on the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study (32). In 1999, the laser ablation criteria were identified by the Early Treatment for Retinopathy of Prematurity (ET-ROP) study, which found it to be more successful than cryotherapy (12). We also applied the ET-ROP criteria in our treatment plan. Diode laser photocoagulation (18.8%) was applied to those patients who underwent treatment, and no complications were observed during or after the treatment. In the study by Ekinci et al. (19), 6.2% of the cases were given laser treatment, and the success rate in that group of infants was 80%. In that study, the mean BW and GA of the treated babies were 1,249.8±334.2 g and 29.1±3.1 weeks, respectively (19). Beden et al. (21) treated 11% of the patients in their study, in which they evaluated babies with GAs of less than 37 weeks old. Moreover, Hanedar et al. (22) treated 28.8% of their patients, while the treatment rate was 8.6% in one study from the capital of Turkey (26).

The role of VEGF in the pathogenesis of ROP is well-understood. In 2004, the FDA approved the use of intravenous (IV) bevacizumab in the treatment of metastatic colon cancer. Since then, it has also been used in the field of ophthalmology in the treatment of proliferative retinal diseases (33). Bevacizumab was preferred in zone I or II disease stage 3 proliferative retinopathy (PR) plus (+) in the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study (34). However, the systemic absorption of the drug during treatment and the long-term effects on the baby are not known (35). Intravitreal bevacizumab may be preferred in aggressive zone I disease cases or those infants who are unable to tolerate the laser. In our patient group, 4 (6.3%) infants underwent intravitreal bevacizumab treatment, and no complications were seen during the treatment, follow-up, or after the application.

In this study, we aimed to determine the incidence, course, treatment outcomes, and risk factors for ROP in premature infants. Our results were within the acceptable limits for our country, although our NICU was newly established and consists of new residents and nurses with low levels of experience. With the increasing experience in the care of premature infants in the coming years, we hope the cases of ROP will decrease.

Study Limitations

Some limitations of our study should be noted. For example, this was a retrospective study with the related limitations. In addition, fluctuations in the oxygenation were not documented in our cases. Finally, the number of infants participating in our research was not as large as it could have been, because we included only inborn patients.

Conclusion

Not losing patients during the follow-up depends on how well informed the families are, as well as how closely the neonatal team follows the patients after discharge. Good antenatal care, improving NICU conditions, and regular screening, monitoring, and treatment will push the ROP incidence in our facility to the level of developed countries. Hopefully, this will help to reduce the future sequelae of visual function loss in these patients. The awareness of the risk factors and the complications of ROP will decrease the incidence of the disease in unexperienced and newly organized NICUs.

Ethics

Ethics Committee Approval: This study was approved by the local ethical board (22.06.2016/386).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: B.T.B., Design: B.T.B., Z.M., Data Collection or Processing: B.T.B., Analysis or Interpretation: B.T.B, S.B., İ.A.K., Literature Search: BT.B., Writing: B.T.B.,

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References

1. Bas AY, Koc E, Dilmen U, ROP Neonatal Study Group. Incidence and severity of retinopathy of prematurity in Turkey. Br J Ophthalmol 2015;99:1311-4.
2. Broxterman EC, Hug DA. Retinopathy of prematurity: a review of current screening guidelines and treatment options. Missouri Medicine 2016;113:187-90.
3. Yonekawa Y, Thomas BJ, Thanos A, Tedorich B, Drense KA, Trese MT, et al. The cutting edge of Retinopathy of Prematurity care expanding the boundaries of diagnosis and treatment. Retina 2017;37:2208-25.
4. Sen P, Rao C, Bansal N. Retinopathy of Prematurity: An Update. Sci J Med & Vis Res Foun 2015;vol XXXIII:93-6.
5. Shah PK, Prabhu V, Karandikar SS, Ranjan R, Narendran V, Kalpana N. Retinopathy of prematurity: Past, present and future. World J Clin Pediatr 2016;5:35-46.
6. Zhu T, Zhang L, Zhao F, Qu Y, Mu D. Association of maternal hypertensive disorders with retinopathy of prematurity: A systematic review and meta-analysis. PLoS One 2017;12:e0175374.
7. Fang JL, Sorita A, Carey WA, Colby CE, Murad MH, Alahdab F. Interventions To Prevent Retinopathy of Prematurity: A Meta-analysis. Pediatrics 2016;137:e20153387.

8. Suelves AM, Shulman JP. Current screening and treatments in retinopathy of prematurity in the US. Eye and Brain 2016:837-43.
9. Yau GS, Lee JW, Tam VT, Liu CC, Yip S, Cheng E, et al. Incidence and Risk Factors of Retinopathy of Prematurity From 2 Neonatal Intensive Care Units in a Hong Kong Chinese Population. Asia Pac J Ophthalmol 2016;5:185-91.
10. Section on Ophthalmology American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2006;117:572-6.
11. International Committee for the Classification Retinopathy of Prematurity. The international classification of retinopathy of prematurity. Arch Ophthalmol 2005;123:991-9.
12. Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-50.
13. Goble RR, Jones HS, Fielder AR. Are we screening too many babies for retinopathy of prematurity? Eye 1997;11:509-14.
14. Gilbert C, Fielder A, Gordillo L, Quinn G, Semiglia R, Visintin P, et al. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implications for screening programs. Pediatrics 2005;115:e518-25.
15. Hwang JH, Lee EH, Kim EA. Retinopathy of prematurity among very-low-birth-weight infants in Korea: incidence, treatment, and risk factors. J Korean Med Sci 2015;30:S88-94.
16. Rasoulinejad SA, Montazeri M. Retinopathy of prematurity in neonates and its risk factors: a seven year study in northern Iran. Open Ophthalmol J 2016;10:17-21.
17. Nassar MM. Screening for retinopathy of prematurity: a report from Upper Egypt. Int J Ophthalmol 2016;9:262-5.
18. Öner A, Özkırış A, Güneş T, Karaküçük S, Erkılıç K, Çetin N. Prematüre retinopatisi: 2 yıllık tarama sonuçlarımız. Erciyes Tıp Dergisi 2005;27:104-9.
19. Ekinci A, Akçakaya AA, Yaylalı SA, Sadıgov F. Prematüre retinopatisi: dört yıllık tarama sonuçlarımız. Okmeydanı Tıp Dergisi 2015;31:75-81.
20. Özbek E, Genel F, Atlıhan F, Güngör İ, Malatyalı R, Menteş J, ve ark. Yenidoğan yoğun bakım ünitemizde premature retinopatisi insidansı, risk faktörleri ve izlem sonuçları. İzmir Behçet Uz Çocuk Hast. Dergisi 2011;1:7-12.
21. Beden Ü, Demir S, Aygün C, Küçüködük Ş, Erkan D. Screening for retinopathy of prematurity (ROP) in the middle Black Sea region of Turkey. Turk J Pediatr 2012;54:223-9.
22. Hanedar A, Göncü T, Adıbelli FM, Çakmak A, Oğuz H. Prematüre retinopatisi tarama ve tedavi sonuçları. Harran Üniversitesi Tıp Fakültesi Dergisi 2015;12: 274-80.
23. Esen E, Erdem E, Yar K, Demircan N, Soylu M. Prematüre retinopatisi tarama sonuçlarımız: ideal tarama programı nasıl olmalı? Turk J Ophthalmol 2014;44:42-6.
24. Sönmez K, Özcan PY, İlhan B, Koçak Altıntaş AG. Yenidoğan yoğun bakım ünitesindeki bebeklerde prematüre retinopatisi sıklığı, gelişiminde etkili risk faktörleri ve tedavi sonuçları. Ret-Vit 2011;19:225-30.
25. Seiberth V, Linderkamp O. Risk factors in retinopathy of prematurity. Ophthalmologica 2000;14:131-5.
26. Küçükevcilioğlu M, Mutlu FM, Sarıcı SÜ, Ceylan OM, Altınsoy HI, Kılıç S, et al. Frequency, risk factors, and outcomes of retinopathy of prematurity in a tertiary care hospital in Turkey. Turk J Pediatr 2013;55:467-74.
27. Zengin N, Özer EA, Zengin MÖ, Türe G, Sütçüoğlu S, Talay E. Prematüre retinopatisi sıklığı ve risk faktörlerinin değerlendirilmesi. Çocuk Sağlığı ve Hastalıkları Dergisi 2014;57:87-96.
28. Günay M, Topçuoğlu S, Çelik G, Gürsoy T. Prematüre retinopatisi: sıklık azalıyor mu? Zeynep Kamil Tıp Bülteni 2013;44:214-20.
29. Mutlu FM, Altinsoy HI, Mumcuoğlu T, Kerimoglu H, Kiliç S, Kul M, et al. Screening for retinopathy of prematurity in a tertiary care unit in Turkey: frequency, outcomes, and risk factor analysis. J Pediatr Ophthalmol Strabismus 2008;45:291-8.
30. Yılmaz R, Ünüvar Ş, Karaaslan E, İnce DA, Demir S, Demir HD. Prematüre retinopatisi taraması yapılan elli dokuz bebeğin retrospektif değerlendirilmesi. Journal of Contemporary Medicine 2013;3:161-5.
31. Altunbaş HH, Kır N, Ovalı T, Dağoğlu T. Prematüre retinopatisi: klinik seyir ve risk faktörleri. T Oft Gaz 2002;32:286-90.
32. Cryotherapy for Retinopathy of Prematurity Cooperative Group. 15-year outcomes following threshold retinopathy of prematurity. Arch Ophthalmology 2005;123:311-8.
33. Micieli JA, Surkont M, Smith AF. A systematic analysis of the off-label use of bevacizumab for severe retinopathy of prematurity. Am J Ophthalmol 2009;148:536-43.
34. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med 2011;364:603-15.
35. Lien R, Yu MH, Hsu KH, Liao PJ, Chen YP, Lai CC, et al. Neurodevelopmental outcomes in infants with retinopathy of prematurity and bevacizumab treatment. PLoS One 2016;11:e0148019.

Original Article

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Comparison of the Role of Endocan With Other Laboratory Tests in Diagnosis of Acute and Perforated Appendicitis in Children

Endokanın Çocuklardaki Akut ve Perfore Apandisit Tanısındaki Rolünün Diğer Laboratuvar Testleri ile Kıyaslanması

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ABSTRACT

Objective: In this study, we aimed to determine the role and efficacy of endocan and other routine laboratory tests to diagnose of acute appendicitis (AA) and determining perforation.

Methods: One hundred patients under the age of 16 who were diagnosed appendicitis were included the study. The patients were divided into two groups as acute and perforated appendicitis. Complete blood count, C-reactive protein (CRP) and endocan values were evaluated on admission and on postoperative 48th hour. Obtained endocan samples and concomitantly obtained CRP, white blood cell (WBC) count, and neutrophil lymphocyte ratio (NLR) parameters were compared preoperatively and postoperatively in terms of perforated and non-perforated (acute) appendicitis.

Results: In this study, 74.2% of the patients were acute and 25.8% were perforated. In both groups, more than half of the patients had an endocan value of less than 50 ng/mL. Specificity and sensitivity of endocan were lower than other inflammation markers to determine AA and perforation. It was shown that the combined evaluation of CRP and NLR values of <9 and <15 respectively, were the best data to diagnose AA and perforation.

Conclusion: The efficacy of endocan was significantly lower than the other routine laboratory markers to determine AA and perforation. It seems more beneficial to use CRP and NLR together to detect infection during early and late period.

Keywords: Endocan, child, appendicitis

ÖZ

Amaç: Bu çalışmada, endokan ve diğer rutin laboratuvar testlerinin akut apandisit (AA) tanısında ve perforasyonun belirlenmesindeki rolünü ve etkinliğini belirlemeyi amaçladık.

Yöntemler: Çalışmamıza 16 yaşından küçük, apandisit tanısı konmuş 100 hasta dahil edildi. Hastalar akut ve perfore apandisit olarak iki gruba ayrıldı. Tam kan sayımı, C-reaktif protein (CRP) ve endokan değerleri başvuru sırasında ve ameliyat sonrası 48. saatte bakıldı. Elde edilen endokan örnekleri ve aynı zamanda alınan CRP, beyaz kan hücresi sayısı (WBC) ve nötrofil lenfosit oranı (NLR) parametreleri, preoperatif ve postoperatif olarak perfore ve perfore olmayan (akut) apandisit açısından karşılaştırıldı.

Bulgular: Bu çalışmada hastaların %74,2'si akut, %25,8'i perfore apandisit tanısı aldı. Her iki grupta da hastaların yarısından fazlasında endokan değeri 50 ng/mL'den daha az olarak saptandı. AA ve perforasyonu belirlemek için endokanın özgüllüğü ve duyarlılığı diğer inflamasyon belirteçlerinden daha düşük bulundu. CRP <9 ve NLR <15 olan olgularda birlikte değerlendirilmeleri AA tanısı ve perforasyonun ayırıcı tanısında en uygun belirteçler olduğu gösterildi.

Sonuç: Endokanın AA ve perforasyonu belirlemedeki etkinliği diğer rutin laboratuvar belirteçlerinden anlamlı derecede düşük bulundu. Erken ve geç dönemde enfeksiyonun saptanması için CRP ve NLR'nin birlikte kullanılması daha yararlı olduğu gösterildi.

Anahtar Sözcükler: Endokan, çocuk, apandisit

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Introduction

Appendicitis is one of the causes of abdominal pain in children that requires urgent surgery. Early diagnosis and treatment of this progressively inflammatory disease is very important. Delay in diagnosis and surgical intervention may lead to serious complications such as abscess mostly localised to subhepatic and retroperitoneum regions, ileus, bacteremia, sepsis, necrotizing fasciitis and appendico-vesical fistula which increase mortality and morbidity (1,2). On the contrary, it is stated that early surgical interventions due to uncertain diagnosis increase the rate of negative appendectomy (3,4). In children, it is difficult to diagnose acute appendicitis, hence they easily get agitated with physical examination and the history of the patient and symptoms are obtained indirectly. That's why, patients with acute appendicitis (AA) can often be confused with some conditions clinically (such as., familial mediterranean fever (FMF), invagination, gastroenteritis, pneumonia, urinary system infections, ovarian torsion and pelvic inflammatory disease) (2,5,6). In addition to history, physical examination and radiological evaluation, the most commonly used laboratory tests to support AA diagnosis include white blood cell count (WBC), neutrophil lymphocyte ratio (NLR) and C-reactive protein (CRP). However, many markers that are known to have accuracy in inflammatory reactions (such as erythrocyte sedimentation rate, procalcitonin, interleukin 6,8, haptoglobin, granulocyte colony-stimulating factor, lactoferrin, calprotectin, mid platelet volume, plateletcrit) have been proposed to support the diagnosis (7). As in those laboratory tests, many recently developed clinical scoring systems have been found to be inadequate for AA diagnosis in routine practice (8-11).

Endocan is a proteoglycan released from the vascular endothelial surface. Its release is regulated by cytokines and growth factors such as vascular endothelial growth factor (12). Since endocan is mainly released from endothelium of lungs and kidneys, it is seen that studies in the literature largely focuse on these two systems (13-16). There are also many studies showing the importance of endocan in the diagnosis and prognosis of acute and chronic infections, as well as sepsis and septic shock (17-20). In some studies, endocan has been shown to increase earlier than some infectious markers such as CRP and procalcitonin at the onset of infection and decreased later than the others (12,21). Endocan has also been shown to be elevated in FMF, which is often confused with AA, and those elevated levels have been shown to persist in non-exacerbated periods as well (20). In literature, we did not find any study in which endocan was used as a diagnostic marker in children with AA.

In this study, we evaluated the correlation of serum endocan levels detected in the early and late phase of an appendicitis together with some other inflammatory markers (such as,. WBC, NLR and CRP) and whether it could be helpful or not in distinguishing acute or perforated appendicitis.

Methods

Ethics approval: Erzurum Regional Education and Research Hospital Ethics Committee approved this study (20.05.2014 / 10-3).

Between March 2015 and May 2016, 100 patients under the age of 16 who were operated with the diagnosis of appendicitis were prospectively included in the study. Patients' parents were informed about the study during the admission. Written consents were obtained from the parents on the basis of volunteerism. The patients were divided into two groups as acute and perforated appendicitis. Appendicitis diagnosis was made with physical examination, history, laboratory tests (WBC, NLR, and CRP) and abdominal ultrasonography.

Antibiotic therapy with ampicillin-sulbactam (150 mg/kg/day, divided into four equal doses) was initiated in all patients with AA pre-diagnosis prior to surgery. Metranidazole (30 mg/kg/day, divided into three equal doses) and amikacin (15 mg/kg/day, divided into two equal doses) were added to the patient's initial terapy who were presented with perforation during surgery. The distinction between the presence or absence of perforation in the patients who underwent surgery was made with intraoperative evaluation and the afterwards histopathological examination. Patients who were diagnosed with additional clinical presentations other than appendicitis such as invagination, Meckel diverticulum, over torsion, mesenteric lymphadenitis and primary peritonitis were excluded. Three patients who were diagnosed as having appendicitis were excluded from the study, due to personal excuses. Patients who agreed to participate in the study were tested for complete blood counts and CRP at the admission and at 48 hours after the surgery. In addition, blood samples were taken to another hemogram tube simultaneously to measure endocan level. Samples were centrifuged at 4000 rpm for 10 min at + 4 °C. Serum samples were aliquoted and transferred to eppendorf tubes and placed in the deep freezer at -80°C and held there till the day they were analyzed. Endocan levels in the serum samples were measured in the direction of the manufacturer's firm using the "Human Endocan / esm-1 ELISA Kit" (SuNLRng Biotech Co., Ltd., Lot No.: SL2210Hu, China) via Enzyme-Linked Immunosorbent Assay (ELISA) method. The analysis was performed with BioTek Power Wave ST microplate spectrophotometer (USA). Concomitant CRP, complete WBC, and NLR parameters were compared simultaneously with the endocan levels preoperatively and postoperatively in both patients with acute and perforated appendicitis.

Statistical Analyses

Data were analyzed with Minitab Statistical package (PA, USA) and checked for distribution by using Anderson-Darling formula. As none of the parameters had normal distribution, they were converted into log 10 scale. Following this conversion, LNR values had normal distribution but the other data, except a slight improvement, did not distribute normally. Therefore, non-parametric Kruskal-Wallis test was used to analyze the data in terms of age, sex, diagnosis (acute and perforated appendicitis) and time (pre- and post-operative). An additional attempt was made to test whether there were any interactions between the parameters studied. For that purpose, generalized linear model (GLM) was used to find out the effects of each parameter and their interactions. GLM procedure resulted in similar levels of significance for each parameter. Furthermore, there were no interactions between any of the parameters . Correlation analyses were carried out by using Spearman rho. The data

were presented as mean ± SEM and p≤0.050 was denoted as statistically significant. Although analyses were carried out with log 10 converted values, results were presented as original values.

Results

Of the 97 patients in sum, 72 patients (74.2%) had acute and 25 patients (25.8%) had perforated appendicitis. There was no difference between the groups in terms of age. The number of males was higher in both groups, and male gender was more pronounced in the perforated appendicitis group (Table 1).

WBC did not change by age (p=0.415) but males had higher WBC values than the females (p=0.002). Additionally, WBC values were higher in perforated appendicitis than acute appendicitis (p<0.001) and were higher in pre-op period than post-op period (p<0.001). If WBC counts >6.25 were used to describe (or diagnose) perforated appendicitis, both specifity and sensitivity were between 90-100%. However, as new WBC count criteria (>5, >7 etc.) were applied, both the sensitivity and specificity decreased (Figure 1).

CRP did not change by age (p=0.193) or by sex (P=0.426). However CRP values were higher in perforated appendicitis than acute appendicitis (P<0.001) and were higher in post-op period than pre-op period (p<0.001). If CRP levels >1 were used to describe (or diagnose) perforated appendicitis, specificity was between 40-50% and sensitivity was between 90-100%. However, as specificity increased by new CRP criteria (>3, >5 etc), sensitivity decreased. The graph also shows that both the sensitivitiy and specificity are between 60-100% if CRP criteria >9 are used (Figure 2).

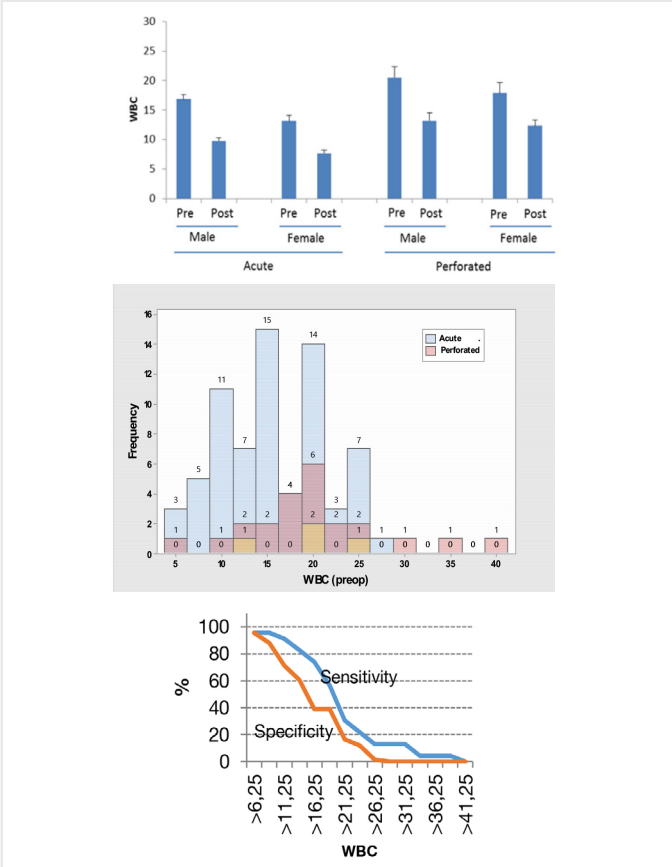


Figure 1. WBC values and WBC's specificity and sensitivity
WBC: White blood cell count

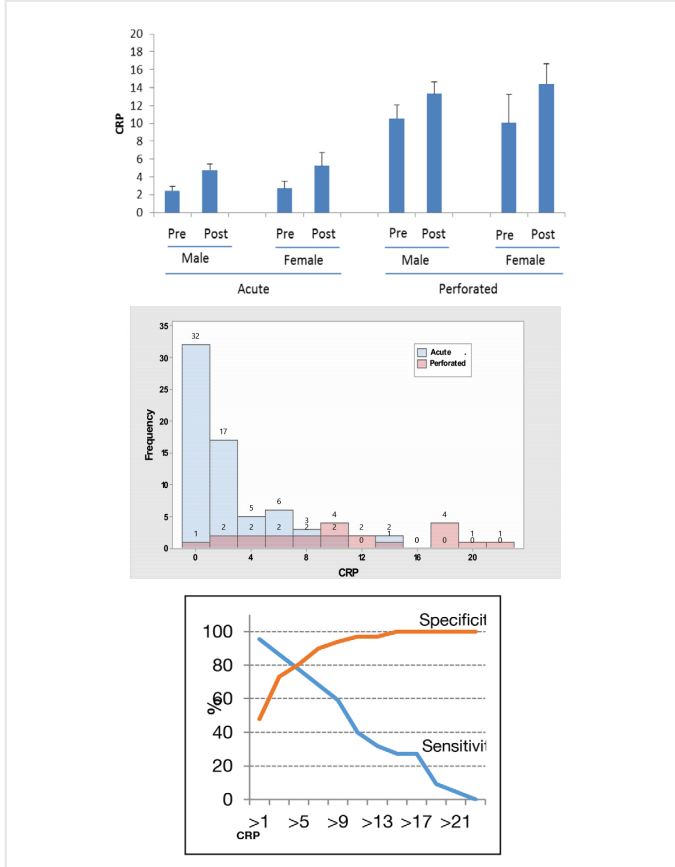


Figure 2. CRP values and CRP's specificity and sensitivity
CRP: C-reaktive protein

Table 1. Age and gender distribution of patients

	Non-perforated preoperative n (72)	Non-perforated postoperative n (72)	P	Perforated preoperative n (25)	Perforated postoperative n (25)	p
Age (years)	10.7±2.9	10.7±2.9		9.2±37	9.2±37	0.62
Male/female	49/23	49/23		20/5	20/5	
male (%)	68.1	68.1	0.002	80	80	0.003
female (%)	31.9	31.9		20	20	

NLR did not change by age p=0.247) and by sex (p=0.173). However, NLR values were higher in perforated appendicitis than acute appendicitis (p<0.001) and were higher in pre-op period than post-op period (p<0.001). If N/L ratios >3 were used to describe (or diagnose) perforated appendicitis, specificity was around 10% and sensitivity was 100%. However, as specificity increased by new N/L ratio criteria (>5, >7 etc), sensitivity decreased (Figure 3).

Correlation of pre-op CRP and N/L ratio in relation to diagonsis (acute versus perforated appendicitis) can be seen from the graphic 1. CRP levels <9 and N/L ratio <15 described the most of the data as being acute. According to this criteria, sensitivity was 80 % and specificity was 95.7% (Graphic 1).

Endocan values changed by age (p<0.001), being the highest in the age groups of 2, 5 and 16 years than the other age groups (4, 7, 8, 9, 10, 11, 12, 13, 14, 15). Additionally, males had higher endocan levels than females (p=0.018). However, endocan values did not differ between perforated and acute appendicitis groups (p=0.979) and between pre-op and post-op periods (p=0.281). If endocan levels >50 were used to describe (or diagnose) perforated appendicitis, both specificity and sensitivity were between 40-60%. However, as specificity increased by new endocan criteria (>150, >250 etc), sensitivity decreased to zero (Figure 4). Pre-op and pos-top endocan levels were positively and significantly correlated (R-sq=0.636 and p<0.001) (Graphic 2).

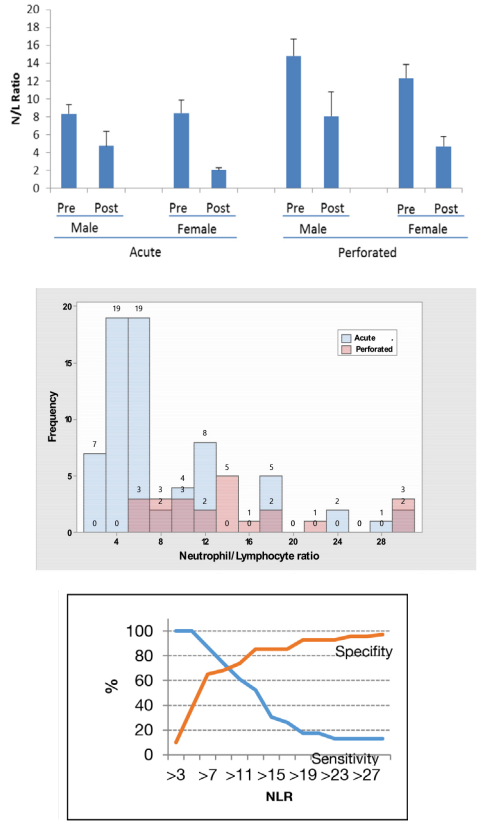


Figure 3. NLR values and NLR's specificity and sensitivity
NLR: Neutrophil lymphocyte ratio

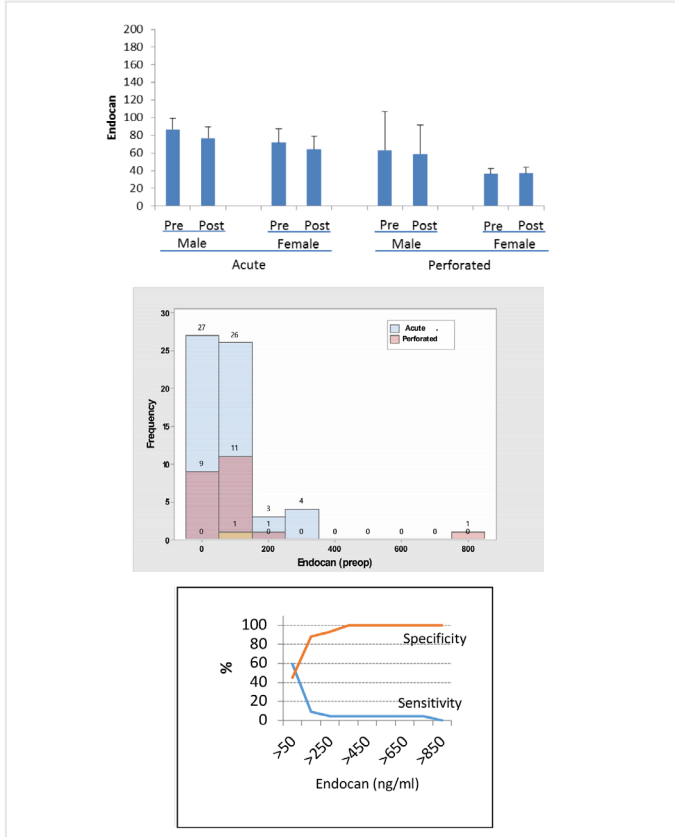
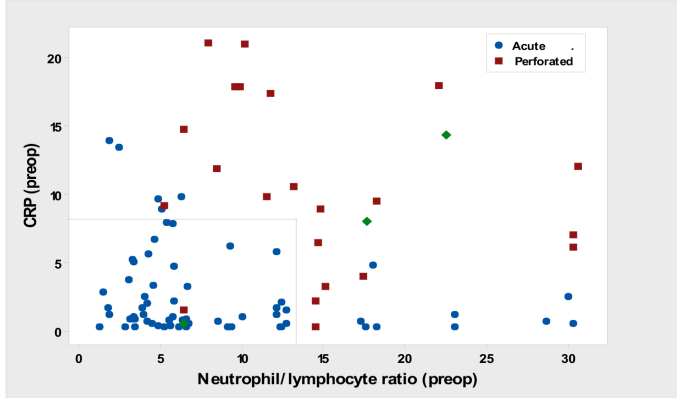


Figure 4. Endocan values and endocan's specificity and sensitivity

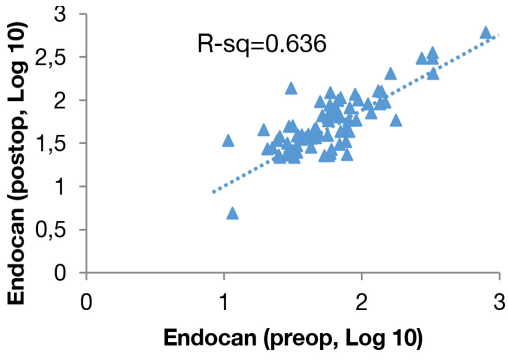


Graphic 1. Correlation of preoperative CRP level and N/L ratio
CRP: C-reaktive protein, NLR: Neutrophil lymphocyte ratio

Discussion

Appendicitis is one of the causes of abdominal pain in which urgent surgery is needed inchildren. However, distinguishing this situation from other causes of abdominal pain is particularly difficult in young children and the perforation rate increases with younger age.

For this reason, early diagnosis and treatment of the disease is very important. In this study, endocan levels were higher in male



Graphic 2. Correlation of preoperative and postoperative endocan levels

patients than in females, the highest levels were obtained in the ages of 2.5 and16 years and varied significantly with age. We could not find any meaningful reason to explain the difference in age and gender. When the preoperative endocan values over 50 ng/mL were taken as basis, the specificity and sensitivity on diagnosis of perforated appendicitis were found between 40-60%. When these base values were taken higher than 150 ng/mL, the specificity was significantly increased and the sensitivity was decreased. However, the mean preoperative endocan values in our study were 52.3 ng/mL in the perforated appendicitis group and 52.9 ng/mL in the acute appendicitis group. In both groups more than half of the patients had an endocan value of less than 50 ng/mL. Based on this value, both the sensitivity and specificity of endocan were lower in the diagnosis of perforated appendicitis compared to the other classical markers. In addition, there was no statistically significant difference between the preoperative and postoperative endocan values and it was noticed that there was a significant positive correlation between the two values. Endocan has been shown to be a useful marker for monitoring prognosis and the efficacy of the treatment in serious infections requiring long-term therapy exceeding more than one week (12,17-19). However, in our study, because of the similarity of the serum endocan values detected at 48th hour with the preoperative values, it could be said that endocan was not as effective as other laboratory markers in diagnosing diseases requiring short-term treatment such as appendicitis and demonstrating the treatments efficacy.

When we looked at the accuracy of the markers in diagnosis of AA and detecting perforation; we saw that WBC increased in 70% of the reasons that caused pain in the right lower quadrant, for this reason diagnostic value of WBC was low. Instead of WBC, NLR was reported as more valuable in the diagnosis and a significant inflammatory index for appendicitis, which was above 85% (20,22). In our study, in acute and perforated appendicitis, preoperative WBC and NLR values were significantly higher than postoperative values. It was shown that WBC was more sensitive (sensitivity was above 80%) in showing perforated appendicitis between the values of 10- 16×10^3 and the specificity was around 60%. At higher WBC values, both specificity and sensitivity were significantly decreased. Therefore, it could be said that the values of 16×10^3 and below were more reliable when the WBC value was used to detect perforated appendicitis, and the probability of a wrong diagnosis increased when values above 16×10^3 were considered. When we looked at the neutrophil and lymphocyte distribution ratio, it was observed that NLR was higher in males and this ratio did not change with age. In addition, preoperative values were higher in both groups, which were more prominent in perforated appendicitis. The lower values of NLR were found to be more valuable in determining the perforation. The specificity was low (10-60%) and the sensitivity was high (> 80%) in the values where the rate was low (range 3-7). At the intersection point where both sensitivity and specificity were 70%; NLR value was 9. Sensitivity was found to decrease significantly in the values where the ratio was higher, but specificity was found to increase.

In the inflammatory events, CRP starts to be synthesized 4-6 hours after tissue damage begins, but reaches its peak value after 36-50 hours. Therefore, CRP is more sensitive in the late period of appendicitis. In other words, it is known that the sensitivity of CRP in the first 12 hours is relatively low in case of perforation or abscess. In their study, Xharra et al. showed that the diagnostic value of CRP was not superior to that of WBC and NLR, more likely it indicated the severity of AA and the elapsed time (19). In many studies it has been shown that the combined use of these three markers (WBC, LNO, and CRP) is more reliable in determining AA and perforation (23-25). CRP values at the 48th hour after operation were significantly higher in both groups in our study. According to these results were considered, AA diagnosis could not be excluded when CRP levels in the first 24 hours and WBC and NLR levels after 48 hours were low. In their study, Kharbanda et al. found that children with acute appendicitis who were followed up with abdominal pain less then 24 hours were found to have a higher serum WBC value, children who had a 24-48-hour pain were found to have higher CRP values (26). Considering this result, it can be said that these markers are more sensitive in showing the duration of symptoms since the onset, rather than deciding whether the situation is acute or perforated. So that, whether it is acute or perforated, the results obtained within the first 24 hours or after that may differ independently from the patients' clinical situation. Our laboratory results were similar with this study. Although there were no trustworthy data on how long ago the patients' symptoms began at the time of admission, the higher values of WBC and NLR in the first samples and the higher CRP in the 48th hour samples supported the relationship of those markers with time independently from the patients' clinic situation. When we evaluated the correlation of CRP levels with perforated appendicitis in the perforation group, CRP was found to be significantly higher. When these markers were used alone, the sensitivity and specificity were usually reversed, while one was increasing, the other decreased. Therefore, it appears to be more useful to use these markers in combination to determine appendicitis and perforation. In our study, CRP <9 and NLR <15 in the pre-op period were found to be the best predictors to show AA. In the diagnosis of perforated appendicitis; sensitivity and specificity were found to be 80% and 95.7%, respectively.

Study Limitations

Our study had its own limitations. Limited assessment of endocan at 48 hours as an inflammatory marker appeared to be the most important restriction of this study. For this reason, we thought that the patient group with appendicitis was not very suitable for studying this marker. In addition, the fact that the time between the onset of symptoms and the presence of AA was not objectively determined, led to limitations in assessing the effectiveness of markers in diagnosis of AA and perforation.

Conclusion

As a result, endocan, which was known to be an important marker in diagnosis and prognosis of diseases presenting with chronic inflammation and some infections was not shown to be effective in distinguishing acute and perforated appendicitis. Combined evaluation of 2 of the routine laboratory tests and their defined cut-off values, CRP<9 and NLR<15, were found to be the best for diagnosis of AA and determination of perforation. We think it would be more helpful to use the combination of routine laboratory tests to enhance clinical and radiological assessment which can reduce unnecessary surgery and delays on diagnosis with the error margin.

Ethics

Ethics Committee Approval: Erzurum Regional Education and Research Hospital Ethics Committee approved this study (20.05.2014 / 10-3).

Informed Consent: Written consents were obtained from the parents on the basis of volunteerism.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.N.C., Data Collection or Processing: E.Ş., M.Ş., Analysis or Interpretation: S.S.K., Literature Search: M.N.C., Writing: M.N.C.

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

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

References

1. Kim JS. Acute abdominal pain in children. Pediatr Gastroenterol Hepatol Nutr 2013;16:219-224.
2. Huckins DS, Simon HK, Copeland K, Spiro DM, Gogain J, Wandell M. A novel biomarker panel to rule out acute appendicitis in pediatric patients with abdominal pain. Am J Emerg Med 2013;9:1368-75.
3. Benito J, Acedo Y, Medrano L, Barcena E, Garay RP, Arri EA. Usefulness of new and traditional serum biomarkers in children with suspected appendicitis. Am J Emerg Med 2016;34:871-6.
4. Garcia peña BM, Cook EF, Mandl KD. Selective imaging strategies for the diagnosis of appendicitis in children. Pediatrics 2004;113:24-8.
5. Trout AT, Sanchez R, Ladino-Torres MF, Pai DR, Strouse PJ. A critical evaluation of US for the diagnosis of pediatric acute appendicitis in a real-life setting: how can we improve the diagnostic value of sonography? Pediatr Radiol 2012;42:813-23.
6. Buyukbese SS, Sarac F. Diagnostic value of white blood cell and C-reactive protein in pediatric appendicitis. Biomed Res Int. 2016 May 4.
7. Allister L, Bachur R, Glickman J, Horwitz B. Serum markers in acute appendicitis. J Surg Res 2011;168:70-5.
8. Mandeville K, Pottker T, Bulloch B, Liu J. Using appendicitis scores in the pediatric ED. Am J Emerg Med 2011;29:972-7.
9. Samuel M. Pediatric appendicitis score. J Pediatr Surg 2002;37:877-81.
10. Macco S, Vrouenraets BC, DE Castro SM. Evaluation of scoring systems in predicting acute appendicitis in children. Surgery 2016;160:1599-604.
11. Peyvasteh M, Askarpour S, Javaherizadeh H, Besharati S. Modified alvarado score in children with diagnosis of appendicitis. Arq Bras Cir Dig 2017;30:51-2.
12. Seo K, Kitazawa T, Yoshino Y, Koga I, Ota Y. Characteristics of serum endocan levels in infection. PLoS One 2015;10:e0123358.
13. Kim JH, Park MY, Kim CN, Kim KH, Kang HB, Kim KD, et al. Expression of endothelial cell-specific molecule-1 regulated by hypoxia inducible factor-1α in human colon carcinoma: impact of ESM-1 on prognosis and its correlation with clinicopathological features. Oncol Rep 2012;28:1701-8.
14. Leroy X, Aubert S, Zini L, Franquet H, Kervoaze G, Villers A, et al. Vascular endocan (ESM-1) is markedly overexpressed in clear cell renal cell carcinoma. Histopathology 2010;56:180-7.
15. Kupeli I, Salcan S, Kuzucu M, Kuyrukluyıldız U. Can endocan be a new biomarker in ventilator-associated pneumonia? Kaohsiung J Med Sci 2018;34:689-94.
16. Kiral E, Dinleyici EC, Bozkurt-Turhan A, Bor O, Akgun Y, Akgun NA. Serum endocan levels in children with febrile neutropenia. Hematol Rep 2016;8.
17. Scherpereel A, Depontieu F, Grigoriu B, Cavestri B, Tsicopoulos A, Gentina T, et al. Endocan, a new endothelial marker in human sepsis. Crit Care Med 2006;34:532-7.
18. Pauly D, Hamed S, Behnes M, Lepiorz D, Lang S, Akin I, et al. Endothelial cell-specific molecule–1/endocan: Diagnostic and prognostic value in patients suffering from severe sepsis and septic shock. J Crit Care 2016;31:68-75.

19. Xharra S, Gashi-Luci L, Xharra K, Veselaj F, Bicaj B, Sada F, et al. Correlation of serum C-reactive protein, white blood count and neutrophil percentage with histopathology findings in acute appendicitis. World J Emerg Surg 2012;7:27.
20. Ozalper V, Kara M, Tanoglu A, Cetındaglı I, Ozturker C, Hancerlı Y, et al. Evaluation of endothelial dysfunction in patients with familial Mediterranean fever: the relationship between the levels of asymmetric dimethylarginine and endocan with carotid intima-media thickness and endothelium-dependent vasodilation. Clin Rheumatol 2017;36:2071-7.
21. Andersson RE, Hugander AP, Ghazi SH, Ravn H, Offenbartl SK, Nyström PO, et al. Diagnostic value of disease history, clinical presentation, and inflammatory parameters of appendicitis. World J Surg 1999;23:133-40.
22. Keskek M, Tez M, Yoldas O, Acar A, Akgul O, Gocmen E, et al. Receiver operating characteristic analysis of leukocyte counts in operations for suspected appendicitis. Am J Emerg Med 2008;26:769-72.
23. Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. Br J Surg 2013;100:322-9.
24. Daly MC, Von Allmen D, Wong HR. Biomarkers to estimate the probability of complicated appendicitis. J Pediatr Surg 2018;53:437-40.
25. Atema JJ, Gans SL, Beenen LF, Toorenvliet BR, Laurell H, Stoker J, et al. Accuracy of white blood cell count and C-reactive protein levels related to duration of symptoms in patients suspected of acute appendicitis. Acad Emerg Med 2015;22:1015-24.
26. Kharbanda AB, Cosme Y, Liu K, Spitalnik SL, Dayan PS. Discriminative accuracy of novel and traditional biomarkers in children with suspected appendicitis adjusted for duration of abdominal pain. Acad Emerg Med 2011;18:567-74.

Review

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Inherited Epilepsies

Kalıtsal Epilepsiler

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ABSTRACT

Mutations in genes encoding the formation of ion channels may cause epileptic syndromes. These epileptic syndromes are generally divided into generalized and partial epilepsies. Among the causative agents of generalized epilepsy showing mendelian or non-mendelian inheritance; mutations in sodium channel, calcium channel, GABAA receptor and nicotinic receptor can be listed. Generalized epilepileptic syndromes with mendelian inheritance are Genetic Epilepsy With Febrile Seizures Plus, Autosomal Dominant Juvenile Myoclonic Epilepsy, and Epilepsy Associated With *CLCN2* Gene Mutation. Generalized epileptic syndromes with non-mendelian inheritance are JME and Juvenile Absence Epilepsy With Generalized Tonic-Clonic Seizures. The epilepsies of newborns and infants with a single gene inheritanceare classified into three categories: Benign Familial Neonatal Convulsions, Benign Familial Infantile Convulsions, and Benign Familial Neonatal-Infantile Seizures. Autosomal dominant partial epilepsies are examined under the headings of Autosomal Dominant Nocturnal Frontal Lobe Epilepsy, Familial Mesial Temporal Lobe Epilepsy, Familial Lateral Temporal Lobe Epilepsy, and Autosomal Dominant Partial Epilepsy With Auditory Features. While various mutations in different ion channels can produce similar phenotypes, a certain mutation on the same gene can cause different phenotypes. This review provides a summary of the epilepsy classification on the genetic basis and pathophysiological effects of neural channelopathies causing epileptic syndromes.

Keywords: Epilepsy, channelopathies, inherited epilepsy, genetic mutations

ÖZ

İyon kanallarının oluşumunu kodlayan genlerde meydana gelen mutasyonlar epileptik sendromlara neden olabilir. Bu epileptik sendromlar genel olarak jeneralize ve parsiyel olarak ikiye ayrılmaktadır. Kendi içerisinde mendelyan ve non-mendelyan geçiş gösteren jeneralize epilepsilere neden olan etkenler arasında sodyum kanalı, kalsiyum kanalı, GABAA reseptör ve nikotinik reseptör mutasyonları gösterilebilir. Mendelyan geçiş gösteren jeneralize epilepileptik sendromlar; febril nöbetler ile karakterize, otozomal dominant formlu juvenil miyoklonik, *CLCN2* gen mutasyonuyla ilişkili, kalsiyum kanalı alt birimlerindeki mutasyonlarla ilişkili epilepsiler şeklinde farklılaşmaktadır. Non-mendelyan geçiş gösteren jeneralize epileptik sendromları ise juvenil miyoklonik ve juvenil absans jeneralize tonik-klonik nöbetli epilepsilerdir. Parsiyel özellik gösteren tek gen kalıtımı ile gerçekleşen Yenidoğan ve Süt Çocuğu Epilepsileri, Selim Ailesel Neonatal, Selim Ailesel İnfantil Konvülzionlar ve Selim Ailesel Neonatal-İnfaltil Nöbetler başlıklarıyla 3 sınıfta toplanmaktadır. Otozomal dominant parsiyel epilepsiler ise Otozomal Dominant Noktürnal Frontal Lob, Ailesel Meziyal Temporal Lob, Ailesel Lateral Temporal Lob, Değişken Odaklı Ailesel Parsiyel Lob Epilepsisi başlıkları altında incelenmektedir. Farklı iyon kanallarında meydana gelen çeşitli mutasyonlar benzer fenotipler oluşturabilirken, aynı gen üzerinde meydana gelen belli bir mutasyon da farklı fenotiplere neden olabilir. Bu derleme epileptik sendromlara neden olan nöral kanalopatilerin genetik tabanı ve patofizyolojik etkileri üzerinden epilepsi sınıflandırmasına ait bir özet sunmaktadır.

Anahtar Sözcükler: Epilepsi, kanalopati, kalıtsal epilepsi, genetik mutasyon

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Inherited Epilepsy Syndromes

Introduction

Epilepsy describes a heterogeneous group of paroxysmal diseases thought to occur as a result of disturbances in neural networks. Around 50 million people around the world live with epilepsy. The estimated rate of patients with active epilepsy who still have seizures or need treatment is between 4 and 10 per 1000 people in the general population. This rate is between 7 and 14 per 1000 people in low-and middle-income countries. Globally, an estimated 2.4 million people are diagnosed as having epilepsy each year. In high-income countries, the incidence is between 30 and 50 per 100,000. In low-and middle-income countries, this figure has been recorded as double or higher. About 80% of people with epilepsy live in low-and middle-income countries. Epilepsy accounts for 0.6% of the global disease burden and leads to significant economic burden due to health care needs, early death and lost work productivity (1).

Studies show that the most common forms of idiopathic epilepsy in particular have inherited characteristics (2-6). Genes inherited by individuals from their families cause conformational mutations in ion channels. As a result of these mutations, unwanted neuronal firing occurs as a result of electrical potential changes in the cell and thus seizures are observed (1).

Ion channels play an important role in the creation and control of neuronal stimulation. With the discovery of mutations in genes that encode the formation of the ion channel, it has been shown that the issue is less or more stimulation of the affected tissues in various inherited neurological diseases. Ion channel disorders in other words, channelopathies are epilepsies in the idiopathic form, accounting for one-third of all epilepsies (7). Neuronal ion channels including voltage-gated channels (Na^+, K^+, Ca^{2+}, Cl^-) and ligand-gated channels (nicotinic ACh receptors, GABA receptors) have a role in the formation of hereditary epilepsies.

The genotype-phenotype relationship in epilepsy is quite complex. Different mutations in the same gene can cause phenotypes of various types (allelic heterogeneity), while mutations occurring in multiple different ion channels can cause similar phenotypes (locus heterogeneity). In addition, due to factors such as age and maturation of the brain, even the same mutation in the same gene can cause different phenotypes (2-6). These genetic changes and the epilepsies caused by them are given in Table 1.

Neuronal channelopathies were originally described based on genetic chain studies. Increased number of epileptic syndromes are usually included in neuronal channelopathies, and these canalopathies often begin at a certain age. The channelopathies include generalized epilepsies such as Genetic Epilepsy With Febrile Seizures Plus (GEFS+) associated with sodium channel and GABRG2 ($GABA_A$) receptor mutations (8). Also focal epilepsies such as BFNC associated with potassium channel mutations and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) associated with neuronal nicotinic receptor mutations are found in these channelopathies. Juvenile Myoclonic Epilepsy (JME) and Absans Epilepsy, which are forms of idiopathic generalized epilepsy, may be due to mutations in Ca^{2+} channels. Furthermore, mutations in Cl^- channel gene were found to be associated with certain types of epilepsies (9).

The aim of this study is to explain the types of hereditary epilepsies and the causes of these epilepsies. For this purpose, Mendelian and non-Mendelian idiopathic generalized epilepsy syndromes will be explained in the first part of the article. Then, partial epilepsies observed in newborn and children with single gene inheritance and partial epilepsies with automosomal dominant transition will be discussed. Later, types of epilepsy associated with paroxysmal dyskinesias, episodic ataxia and myokymia will be evaluated under the main heading of "channelopathies associated with epilepsies and other paroxymal neurological disorders". Finally, we will focus on epilepsy genes that are not associated with the ion channel.

Generalized Epilepsy Sydromes

Mendelian Idiopathic Generalized Epilepsy Syndromes

Genetic Epilepsy With Febrile Seizures Plus (GEFS+)

GEFS+ was first described in 1997 by two scientists, Ingrid Scheffer and Samuel Berkovic (10). Febrile seizures (seizures occuring when body temperature is >38 °C) are the most common neurological disorder affecting 3% of children under 6 years of age Gardiner, M. In GEFS+, fever seizures often begin at age before 6 months and continue after 6 years of age with or without fever (11). The SCN1A, SCN2A, SCN1B and GABRG2 ion channel genes are thought to have a role in GEFS+ epilepsy (12). Mutations in these genes result in epilepsy syndromes belonging to the GEFS+ family showing autosomal dominant inheritance (13). As a result of mutations in these genes, epilepsy syndromes belonging to the GEFS + family that show autososomal dominant transition given in Table 2 (14). The most common phenotype is FS+; where febrile seizures (FS) continue after 6 years of age as tonic-clonic seizures without fever. Less common phenotype is myoclonic-astatic epilepsy syndrome with febrile seizures which is characterized by absance, myoclonic or atonic seizures (10,14,15).

The genetic heterogeneity of GEFS+ has been expressed in detail through loci. First locus (19q) was defined on the long arm of 19th chromosome (GEFS1) and corresponded to the gene encoding the sodium channel β1 subunit (SCN1B). Second locus (2q) was defined on the long arm of 2nd chromosome (GEFS2) and corresponded to the gene encoding the sodium channel alpha subunit (SCN1A). To date, 9 different missense mutations have been reported in SCN1A. The missense mutation in the *SCN2A* gene, which encodes the sodium channel α2 subunit, is also localized on 2q and has been identified for the first time in a Japanese family (9). Voltage-gated sodium channels are essential in the production and propagation of the action potential in neuronal tissues. Biochemically, these channels consist of

one large alpha subunit and 1 or 2 smaller beta subunits. The alpha subunit alone can show all the functional properties of the voltage-gated sodium channel, but requires beta subunits for normal inactivation kinetics. The mutations identified in sodium channel α and β subunits cause subtle changes in channel gating (increases in persistent sodium current, shifts in the voltage-dependence of steady state inactivation and/or resistance to frequency-dependent cumulative inactivation) which are thought to increase neuronal excitability and thus to predispose affected individuals to seizures (9,16).

Molecular studies have shown that gene mutations in the $GABA_A$ receptor subunit occur in GEFS+ syndromes and in the classic idiopathic generalized epilepsy family. In particular *GABRG2* gene mutations have been reported to be seen in GEFS+ and childhood absance epilepsy phenotypes. Mutations in the sodium channel subunit have been found mostly in GEFS+, but these mutations can also be seen in classical idiopathic generalized epilepsies (IJE) (13).

Autosomal Dominant Juvenile Myoclonic Epilepsy

JME is a type of seizure that occurs around puberty, characterized by bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks (MJ), observed mostly in the upper extremities. JME accounts for 5-10% of all epilepsies and 20-27% of IJE. The starting age of the JME often varies between the ages of 8-26 years, particularly 12-18 years (11,17). JME is often accompanied by generalized tonic-clonic seizures (JTKN) and less often by also absence seizures. Seizures can usually occur shortly after waking up or with sleep deprivation.

Table 1. Hereditary neurological diseases associated with neuronal ion channels

Disease	Channel protein	Responsible gene
Benign Familial Infantile Epilepsy	Nav2.1: Sodium channel, voltage-gated, type II, α subunit	SCN2A
Benign Familial Neonatal Epilepsy	Kv7.2: Potassium channel, voltage-gated, KQT-like sub-family, member 2	KCNQ2
	Kv7.3: Potassium channel, voltage-gated, KQT-like sub-family, member 3	KCNQ3
Childhood deficiency epilepsy	γ- Aminobutyric acid A receptor, α1 subunit	GABRA1
	γ- Aminobutyric acid A receptor, α6 subunit	GABRA6
	γ- Aminobutyric acid A receptor, β3 subunit	GABRB3
	γ- Aminobutyric acid A receptor, γ2 subunit	GABRG2
	Cav3.2: Calcium channel, voltage-gated, T-type, α1H subunit	CACNA1H
Early infantile epileptic encephalopathy type 7	Kv7.2: Potassium channel, voltage-gated, KQT-like sub-family, member 2	KCNQ2
Early infantile epileptic encephalopathy type 11	Nav2.1: Sodium channel, voltage-gated, type II, α subunit	SCN2A
Early infantile epileptic encephalopathy type 13	Nav1.6: Sodium channel, voltage-gated, type VIII, α subunit	SCN8A
Early infantile epileptic encephalopathy type 14	KCa4.1: Potassium channel, sub-family T, member 1	KCNT1
Familial hemiplegic migraine type 3	Nav1.1: Sodium channel, voltage-gated, type I, α subunit	SCN1A
Generalized epilepsies with febrile seizures plus	Navβ1: Sodium channel, voltage-gated, type I, β subunit	SCN1B
	Nav1.1: Sodium channel, voltage-gated, type I, α subunit	SCN1A
	γ- Aminobutyric acid A receptor, γ2 subunit	GABRG2
Juvenil myoclonic epilepsy	γ- Aminobutyric acid A receptor, α1 subunit	GABRA1
	Cavβ4: Calcium channel, voltage-gated, β4 subunit	CACNB4
Nocturnal frontal lobe epilepsy type 1	Cholinergic receptor, neuronal nicotinic, α4 subunit	CHRNA4
Nocturnal frontal lobe epilepsy type 3	Cholinergic receptor, neuronal nicotinic, β2 subunit	CHRNB2
Nocturnal frontal lobe epilepsy type 4	Cholinergic receptor, neuronal nicotinic, α2 subunit	CHRNA2
Nocturnal frontal lobe epilepsy type 5	KCa4.1: Potassium channel, sub-family T, member 1	KCNT1
Generalized epilepsy with paroxysmal dyskinesia	KCa1.1: Potassium channel, calcium-activated, wide conductivity, M family, α1 subunit	KCNMA1
Dravet syndrome	Nav1.1: Sodium channel, voltage-gated, type 1, α subunit	SCN1A
	γ- Aminobutyric acid A receptor, γ2 subunit	GABRG2

JME is a heterogeneous disease associated with several mutations. Major genetic loci thought to cause JME have been identified as epilepsy juvenile myoclonic 1 (EJM1), epilepsy juvenile myoclonic 2 (EJM2), and epilepsy juvenile myoclonic 3 (EJM3). A mutation in the GABRA1 gene on chromosome 5q34-q35 was identified in 14 members of a French-Canadian family with JME. In that family, the mode of inheritance of JME was autosomal dominant. The cause of seizures is the degradation of ligand-gated ion channels and the reduction of GABA. JME may also occur due to dysfunction in the β4 subunit of voltage-gated calcium channels as a result of mutation in the *CACNB4* gene on the 2q22-q23 locus (18). In addition, Cl^- channels have been affected as a result of a mutation in the *CLCN2* gene on locus 3q26 and JME has developed. It has therefore been determined that various channelopathies can lead to JME. In JME, maternal transition associated with EJM1 has also been shown. JME is transmitted five times more to children from mother than from father (19).

Epilepsy Associated With CLCN2 Gene Mutation

CLC-2, a chlorine channel found in the brain, is particularly found in neurons inhibited by GABA and has the role in providing the low intracellular Cl^- concentration required for the response of the inhibitory GABA (20,21). Disturbance of neuronal inhibitory system controlled by the inward current of Cl-can result in epilepsy. The *CLCN2* gene mutation encoding CLC-2 (voltage-gated Cl^- channel) has been found to be associated with IJE in three families. Two families were found to have inherited autosomal dominant patterns, and the third family had epilepsy in only one generation. The phenotype is very diverse, including patients with JME, absence epilepsies (childhood absence epilepsy and juvenile absence epilepsy) and isolated generalized tonic-clonic seizures (GTCS) (20,21).

Epilepsy Associated With Mutations in Calcium Channel Subunits

Mutations in CACNB4, the calcium channel ß4 subunit gene, have been identified in two small families with two affected individuals in each. In one of these families, the phenotypes overlapped with JME. In a small family with childhood absence epilepsy, another calcium channel subunit gene, CACNA1, was found to be mutated. Functional analysis of the mutation (R2162H) has shown that P/Q type CA++ channels have function gain by influencing G-protein modulation (22).

Non-Mendelian Idiopathic Generalized Epilepsies

It shows a complex inheritance of IJEs. In IJE, the original characteristic features of symptoms often overlap, and different IJE syndromes are collected in a single lineage. A locus identified on chromosome 18 is responsible for various IJE syndromes with adolescent onset including JME and juvenile epilepsy with absence and generalized tonic-clonic seizures (10). Analyses with polymorphism based on a single nucleotide have shown that the malic enzyme 2 haplotype increases the risk of IJE in homozygous cases. This enzyme is found in the neuronal synthesis of GABA. Blocking GABA synthesis facilitates the emergence of adolescent-onset IJE (12).

Fokal (Parsiyel) Epilepsies

Idiopathic Focal Epilepsies of Newborns and Infants Associated With Single Gene Inheritance

Benign Familial Neonatal Convulsions (BFNC)

Benign familial neonatal convulsions (BFNC) is a rare epileptic syndrome with dominant heredity characterized by frequent and short seizures that typically begin in the early days of life and disappear spontaneously after weeks or months. In very rare cases, adulthood epilepsy occurs (~10% of people). Although it has been recognized as generalized epilepsy in the ILAE classification in 1989, seizures have several clinical manifestations including tonic attacks, apnea, clonic, focal, and autonomic features (23). The majority of patients with BFNC have *KCNQ2* gene mutations on chromosome 20q13.3 and some of them have *KCNQ3* gene mutations on chromosome 8q24. In the nervous system, the products of the *KCNQ2* and *KCNQ3* gene combine to form potassium channels that produce M-current (24). M-current regulates neuronal excitability by reducing the tendency for repetitive firing. Neuronal M-currents are activators of other neurotransmitter receptor types but are inhibited by muscarinic acetylcholine agonists. Mutations in KCNQ2 or KCNQ3 decrease function in K^+ channels encoded by negative mechanism, consistent with autosomal dominant inheritance patterns of BFNC (16,25). Detailed examination of the KCNQ2/KCNQ3 complex, which contained one of the KCNQ2 mutations, showed that neonatal epilepsy was the result of mutation leading to changes in the K^+ channel gate and the M-current (26).

Benign Familial Infantil Convulsions (BFIC)

BFIC is an autosomal dominant disease seen in infancy. It is characterized by motor arrest along with short seizures and slow deviation of the head and eyes to one side. During the seizure, bruising, hypertonia and unilateral lip wobble are observed. Seizures begin at age of 3-12 months. Three locuses are responsible for the occurrence of this epilepsy. A mutation has been observed in 4 Italian families on chromosome 19q, in 7 French and Argentine families on chromosome 16p12-q12 (short arm of 16th chromosome) and on chromosome 2q24 in another 8 Italian families. No phenotypic differences have been observed between families with symptoms associated with mutations in these different chromosomes (27).

Benign Familial Neonatal-Infantil Convulsions (BFNIC)

Benign familial neonatal-infantil convulsions (BFNIC) syndrome is one of the autosomal dominant benign familial epilepsy syndromes seen in the first year of life. BFNIC syndrome begins in the range of 2 days to 7 months and shows symptoms that remain phenotypically between BFNC and BFIC. The mutation in the subunit gene SCN2A, which encodes the Na^+ channel, is the main cause of this disease and BFNIC have been found in 8 families until today (28).

Autosomal Dominant Partial Epilepsies

Genetic etiology is widely accepted in generalized epilepsies, but focal or partial epilepsies are mostly based on environmental

factors such as birth accidents, trauma, infections, and brain lesions such as tumors and vascular damage. Despite this, there has been an increase in the diagnosis of families with dominant hereditary partial epilepsies over the past decade. Major familial focal epilepsies are ADNFLE, familial mesial temporal lobe epilepsy (FMTLE), familial lateral temporal lobe epilepsy (FLTLE), and familial partial epilepsy with variable foci (FPEVF) (29,30). So far, responsible genes have been identified only in ADNFLE (genes encoding ion channel subunits) and FLTLE (genes encoding non-ion channel subunits) (9,31).

ADNFLE is seen in almost every period from early childhood to adulthood, but most often starts around the age of 10 years. Almost all seizures occur in sleep. Mesial temporal lobe epilepsy was first described in 1994. A year later it was determined that the gene responsible for causing this epilepsy was on region 20q13.2. The gene CHRNA4 that encoded the neuronal nicotinic acetylcholine receptor (nACh-R) was then sequenced (this was also the first gene found in 1995). Another localization that causes this type of epilepsy has been found on the 15q region where different neuronal nicotinic acetylcholine receptor subunits exist. Mutations of $\alpha 4$ and $\beta 2$ subunits of nicotinic acetyl choline receptor (CHRNA+ and CHRNB2) are the proven causes of ADNFLE (32).

Channelopathies Associated With Epilepsies or Other Paroxysmal Neurological Diseases

Epilepsies Associated With Paroxysmal Dyskinesias

Infantile convulsions and choreoathetosis (ICCA) syndrome is a syndrome associated with familial infantile convulsions that occur in association with paroxysmal choreoathetosis. Afebrile partial seizures occur between 3-12 months. Seizures begin with psychomotor arrests and deviation of the head and eyes, and sometimes become secondary generalised. Paroxysmal choreoathetosis begins in most patients between the ages of 5 and 9 years and tends to decrease in adulthood. A mutation on the 16p12-q12 locus has been observed to cause ICCA syndrome (33).

Generalized epilepsy and paroxysmal dyskinesia is a syndrome that accompanies generalized epilepsy, and paroxysmal dyskinesia is linked to chromosome 10q22. The mutation has been identified in the alpha subunit of the calcium-sensitive potassium channel. The mutant calcium-sensitive potassium channel has a noticeably larger macroscopic current. Single channel records show an increase in open-channel probability due to a 3-5-fold increase in Ca^{++} sensitivity. It has been suggested that increasing calcium-sensitive potassium channels in vivo would induce rapid repolarization of the action potential, leading to increased excitability, and would result in generalized epilepsy and paroxysmal dyskinesia, allowing these neurons to fire at a faster rate (34).

Epilepsies Associated With Episodic Ataxia

Another ion channel disorder with impaired excitability in the central nervous system is Episodic ataxia type 1 (EA-1) with myokymia. The disorder is mostly in the cerebellum. Patients complain of short kinesiogenic walking attacks, limb ataxia, or cerebellar dysarthria. In addition, partial epileptic seizures have also been reported in four families. Genetic analyses with EA-1 have indicated a link to chromosome 12p13. Mutations have also been found in the KCNA gene encoding the K^+ channel Kv1.1 (35).

Episodic ataxia type 2 (EA-2) with IJE: Mutations in the CACNB4 gene encoding the voltage-gated calcium channel on chromosome 2q22-23 cause IJEs and hereditary episodic ataxia (36). This gene encodes the $\beta 4$ subunit of the protein that regulates the function of P/Q-type neuronal calcium channels. Voltage-gated calcium channels, especially P/Q-type channels, are important for neurotransmitter release in the central nervous system. The same gene has been also reported to be mutant in patients with sole IJE.

Absans epilepsy with episodic ataxia: A heterozygous mutation in the CACNA1A gene encoding the subunit of the P/Q type voltage-gated Ca^{+2} channel is the cause in individuals with complex phenotypes where absence epilepsy is associated with episodic ataxia (37).

Myokymia-Associated Epilepsies

BFNC that occur after myokymia have been described in two families. Muscular over-excitability resulted from the variable excitability of the lower motor neuron. Unlike other neurological diseases identified associated with epilepsy mentioned above, myokymia activity is continuous (38). Mutations in KCNNQ2 can cause typical BFNC and peripheral nerve stimulation that are not related to epilepsy, but also cause epilepsies of neonatal and early infancy with myokymia (39).

Non-Ion Channel Epilepsy Genes

Autosomal dominant partial epilepsy with auditory features (ADPEAF) is characterized by simple partial seizures with hallucinations or illusions, dream state, visual illusions, or speech disorders suggesting a lateral temporal source. If it spreads to the mesial temporal or extratemporal structures, it may develop into complex partial seizures (40). Magnetic resonance imaging results of patients are mostly normal. The onset time of the disease varies between youth and early adulthood. A genetic examination has shown a mutation in the LGI1 gene (leucine-rich glioma inactivated-1) on chromosome 10q24. This gene is involved in protein-protein interaction with ligand binding and in the development of the nervous system. LGI1 is the only gene responsible for temporal lobe epilepsy. This gene is also the only non-ion channel gene (40) that can be identified in idiopathic epilepsy. In some families with IJE (JME or lone GTCS), a second gene, EFHC1, which is not a direct ion channel gene, is mutant. This gene encodes a protein that interacts with R-type voltage-gated calcium channels and modulates these channels and has apoptotic activity. The third gene is the ATP1A2 Na^+, K^+-ATPase pump gene (41) on chromosome 1q23. This gene does not encode an ion channel but is involved in ion transport. This gene has been found to be a mutant in a family that includes patients with an idiopathic form of epilepsy and migraine (9).

Conclusion

In general, idiopathic epilepsies can be evaluated as ion channel pathologies (38,42). All mutations cause functional change. It is thought that channelopathies can reduce the transmembrane chloride gradient required for GABAergic inhibition, leading to membrane depolarization and hyperexcitability. There are many other diseases, episodic or non-episodic, caused by channel pathologies other than epilepsy. But channel pathologies are not the only cause of epilepsy. Non-ion channel genes, LGI1 and ARX, have emerged as major causes of specific epilepsy syndromes during the past years (26). As new genes are discovered and the functional consequences of disease-causing mutations are revealed, the genetic field of epilepsies will continue to evolve.

With genetic information from spontaneous mutant or genetically mutantized epilepsy animal models, or from epileptic humans, it has been understood that certain epilepsy syndromes are ion channel diseases. Idiopathic epilepsies are usually caused by mutations in genes that encode ion channels (9). Therefore, dysfunction in ion channels is associated with epilepsy. The complete elucidation of the functioning and genetic structure in ion channels will lead to the emergence of new approaches in the treatment of epilepsies mentioned above.

Ethic

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: H.A.V., Design: H.A.V., Data Collection or Processing: M.Y.B., Analysis or Interpretation: M.Y.B., Literature Search: H.A.V., Writing: H.A.V., M.Y.B.

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References

1. World Health Organization. Epilepsy [Internet]. [cited 2019 Jan 28]. Available from: https://www.who.int/news-room/fact-sheets/detail/epilepsy
2. Inouye E. Observations on forty twin index cases with chronic epilepsy and their co-twins. J Nerv Ment Dis. 1960;130:401-16.
3. Corey LA, Berg K, Pellock JM, Solaas MH, Nance WE, DeLorenzo RJ. The occurrence of epilepsy and febrile seizures in Virginian and Norwegian twins. Neurology 1991;41:1433-6.
4. Marshall AG, Hutchinson EO, Honisett J. Heredity in common diseases: A retrospective survey of twins in a hospital population. Br Med J. 1962;5270:1-6.
5. Schiottz-Christensen. GENETIC FACTORS IN FEBRILE CONVULSIONS An Investigation of 64 Same-Sexed Twin Pairs. Acta Neurol Scand. 1972;48:538-46.
6. Sillanpää M, Koskenvuo M, Romanov K, Kaprio J. Genetic factors in epileptic seizures: evidence from a large twin population. Acta Neurol Scand 1991;84:523-6.
7. Lerche, H., Jurkat-Rott, K., Lehmann-Horn F. Ion channels and epilepsy. Am J Med Genet - Semin Med Genet. 2001;106:146-59.
8. Scheffer IE, Zhang YH, Jansen FE, Dibbens L. Dravet syndrome or genetic (generalized) epilepsy with febrile seizures plus? Brain Dev [Internet]. 2009;31:394-400.
9. Kurian M, Picard F. Inherited epilepsy syndromes and channelopathies. Epileptologie. 2006;23:75-85.
10. Scheffer IE, Berkovic SF. The genetics of human epilepsy. Trends in Pharmacological Sciences. 2003.
11. Dervent A, Gökyiğit A. Çocukluk ve ergenlikte başlayan idiyopatik jeneralize epilepsiler. Epilepsi 2014;20:13-22.
12. Gardiner M. Genetics of idiopathic generalized epilepsies. Epilepsia [Internet] 2005;46(Suppl 9):15-20.
13. Zhang, Y-H. ve Scheffer I (2010). Generalized epilepsy with febrile seizures plus and classical idiopathic generalized epilepsy. Neurol Asia 2010;15(Supplement 1):3-4.
14. Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT, Zuberi SM, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007;13:843-52.
15. Scheffer IE, Berkovic SF. Generalized epilepsy with febrile seizures plus. A genetic disorder with heterogeneous clinical phenotypes. Brain 1997;120:479-90.
16. Wallace RH, Scheffer IE, Barnett S, Richards M, Dibbens L, Desai RR, et al. Neuronal Sodium-Channel 2001;859-65.
17. Renganathan R, Delanty N. Juvenile myoclonic epilepsy: under-appreciated and under-diagnosed. Postgrad Med J [Internet] 2003;79:78-80.
18. Robyn Wallace. Identification of a New JME Gene Implicates Reduced Apoptotic Neuronal Death as a Mechanism of Epileptogenesis. Epilepsy Curr 2005;5:11-3.
19. Turan OD. Juvenil myoklonik epilepsi hastaları ve asemptomatik akrabalarında uyku deprivayonlu kısa dönemli uykuda EEG özellikleri ve kognitif fonksiyonların değerlendirilmesi. 2009.
20. D'Agostino D, Bertelli M, Gallo S, Cecchin S, Albiero E, Garofalo PG, et al. Mutations and polymorphisms of the CLCN2 gene in idiopathic epilepsy. Neurology 2004;63:1500-2.
21. Saint-Martin C, Gauvain G, Teodorescu G, Gourfinkel-An I, Fedirko E, Weber YG, et al. Two novel CLCN2 mutations accelerating chloride channel deactivation are associated with idiopathic generalized epilepsy. Hum Mutat 2009;30:397-405.
22. Heyes S, Pratt WS, Rees E, Dahimene S, Ferron L, Owen MJ, et al. Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. Prog Neurobiol [Internet] 2015;134:36-54.
23. Zhang YH, Burgess R, Malone JP, Glubb GC, Helbig KL, Vadlamudi L, et al. Genetic epilepsy with febrile seizures plus. Refining the spectrum. Neurology 2017;89:1210-9.
24. Rogawski MA. Rogawski00 2000;1-6. Available from: papers3://publication/uuid/CAF83C20-944B-4128-B979-5B120146CE99
25. Schroeder, B.C., Kubisch, C., Stein, V. Ve Jentsch TJ. Moderate loss of function of cyclic-AMP-modulated KCNQ2/KCNQ3 K+ channels causes epilepsy. Macmillian Publ Ltd Nature 1998;396.

26. Bebek N. ve Baykan B. Epilepsilerin genetik yönü ve idyopatik epilepsi genetiğinde son gelişmeler. J Neurol Sci [Turkish] 2006;23:70-83.
27. Callenvach, P.MC., De Coo, R.FM., Vein, A.A., Arts, W.F.M., Oosterwijk, J.C., Hageman, G., Houten, R.T., Terwindt, G.M., Lindhout, D., Frants, R.R. ve Brouwer OF. Benign familial infantile convulsions: a clinical study of seven Duch families. Eur J Paediatr Neurol 2002;6:269-83.
28. Herlenius, E., Heron, S.E., Grington, B.E., Keay, D., Scheffer, I.E., Mulley, J.C. ve Berkovic SF. SCN2A mutations and benign familial neonatal-infantile seizures: the phenotypic spectrum. Epilepsia 2007;48:1138-42.
29. Engel J. Mesial Temporal Lobe Epilepsy: What Have We Learned? Neurosci [Internet] 2001;7:340-52.
30. Cersósimo R, Flesler S, Bartuluchi M, Soprano AM, Pomata H, Caraballo R. Mesial temporal lobe epilepsy with hippocampal sclerosis: Study of 42 children. Seizure 2011;20:131-7.
31. De Marco E V., Gambardella A, Annesi F, Labate A, Carrideo S, Forabosco P, et al. Further evidence of genetic heterogeneity in families with autosomal dominant nocturnal frontal lobe epilepsy. Epilepsy Res 2007;74:70-3.
32. Trivisano M, Terracciano A, Milano T, Cappelletti S, Pietrafusa N, Bertini ES, et al. Mutation of CHRNA2 in a family with benign familial infantile seizures: Potential role of nicotinic acetylcholine receptor in various phenotypes of epilepsy. Epilepsia. 2015;56:e53-7.
33. Rochette J, Roll P, Fu YH, Lemoing AG, Royer B, Roubertie A, et al. Novel familial cases of ICCA (infantile convulsions with paroxysmal choreoathetosis) syndrome. Epileptic Disord 2010;12:199-204.
34. Guerrini R, Sanchez-Carpintero R, Deonna T, Santucci M, Bhatia KP, Moreno T, et al. Early-onset absence epilepsy and paroxysmal dyskinesia. Epilepsia 2002;43:1224-9.
35. Akay, A., Turanlıgil-Sümer, N.C., Uyanıkgil Y. İyon kanalları ve epilepsi patojenezindeki rolleri. Arşiv Kaynak Tarama Derg 2010;19:72.
36. Escayg, A., De Waard, M., Lee, D.D., Bichet, D., Wolf, P., Mayer, T., Johnston, J., Baloh, R., Sander, T., ve Meisler MH. Coding and noncoding variation of the human calcium-channel ß4-Subunit gene CACNB4 in patients with idiopathic generalized epilepsy and episodic ataxia. Am J Hum Genet 2000;66:1531-9.
37. Reid CA, Berkovic SF, Petrou S. Mechanisms of human inherited epilepsies. Prog Neurobiol 2009;87:41-57.
38. Dedek K, Kunath B, Kananura C, Reuner U, Jentsch TJ, Steinlein OK. Myokymia and neonatal epilepsy caused by a mutation in the voltage sensor of the KCNQ2 K+ channel. Proc Natl Acad Sci U S A [Internet] 2001;98:12272-7.
39. Weckhuysen S, Mandelstam S, Suls A, Audenaert D, Deconinck T, Claes LRF, et al. KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. Ann Neurol [Internet] 2012;71:15-25.
40. Browne, T.R. ve Holmes GR. Epilepsi El Kitabı. İstanbul: İstanbul: Güneş Tıp Kitabevleri; 2013.
41. Deprez L, Weckhuysen S, Peeters K, Deconinck T, Claeys KG, Claes LRF, et al. Epilepsy as part of the phenotype associated with ATP1A2 mutations. Epilepsia 2008;49:500-8.
42. Fujiwara T, Sugawara T, Mazaki-Miyazaki E, Takahashi Y, Fukushima K, Watanabe M, et al. Mutations of sodium channel α subunit type 1 (SCN1A) in intractable childhood epilepsies with frequent generalized tonic-clonic seizures. Brain 2003;126:531-46.

Review

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Nursing Approach Based on Watson's Theory of Human Caring in Treatment Adherence in Hemodialysis Patients

Hemodiyaliz Hastalarında Tedaviye Uyumda Watson İnsan Bakım Kuramına Dayalı Hemşirelik Yaklaşımı

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ABSTRACT

Hemodialysis is the most common renal replacement therapy in the treatment of chronic kidney disease. Adherence to treatment is important in hemodialysis which is a complex treatment process. Adherence to treatment includes fluid intake, diet, drug management and participation in dialysis sessions. In hemodialysis patients, many problems may arise due to nonadherence to treatment. Watson's Theory of Human Caring (THC) is the one of the important theories used to understand these problems and adaptation difficulties and to develop appropriate coping methods. Watson's THC enables individuals to be evaluated in a holistic manner, adapt to the disease and treatment process, and recover. This review, which was prepared as a result of the literature review, was prepared to raise awareness about nursing care based on Watson's THC in ensuring compliance with treatment in individuals undergoing hemodialysis therapy.

Keywords: Compliance, nursing, renal dialysis, Watson's Theory of Human Caring

ÖZ

Hemodiyaliz, kronik böbrek hastalığının tedavisinde en sık uygulanan renal replasman tedavisidir. Karmaşık bir tedavi süreci olan hemodiyaliz yönteminde bireylerin tedaviye uyumu önemlidir. Tedaviye uyum süreci ise sıvı alımı, diyet, ilaç yönetimi ve diyaliz seansına katılımı içermektedir. Hemodiyaliz uygulanan bireylerde tedaviye uyumsuzluğa bağlı birçok sorun ortaya çıkabilmektedir. Bu sorunların ve uyum güçlüklerinin anlaşılması ve uygun başetme yöntemlerinin geliştirilmesi için yararlanılan önemli kuramlardan biri de Watson'ın İnsan Bakım Kuramı'dır (THC). Kuram bireylerin bütüncül olarak değerlendirilmesini, hastalık ve tedavi sürecine uyumunu ve iyileşmesini sağlamaktadır. Literatür taraması sonucu hazırlanan bu makale, hemodiyaliz tedavisi uygulanan bireylerde tedaviye uyumun sağlanmasında Watson'ın THC üzerinde temellendirilmiş hemşirelik bakımına ilişkin farkındalık oluşturmak amacıyla hazırlanmıştır.

Anahtar Sözcükler: Uyum, hemşirelik, hemodiyaliz, Watson İnsan Bakım Kuramı

Introduction

Chronic kidney disease (CKD) is an important health problem that continues to increase in the world and in our country. The World Health Organization's report, published in 2018, stated that 1.2 million individuals died from kidney disease in 2015, and that an estimated 2.3-7.1 million people with end-stage kidney disease died without access to chronic dialysis in 2010, and that mortality has increased by 32% since 2005. In the same report, it was reported that 2.1 million individuals received dialysis treatment in 2010 and that by 2030, individuals receiving dialysis treatment would reach double that (1). In our country, according to the Turkish Nephrology Society's 2017 report, the prevalence of end-stage kidney disease requiring renal replacement therapy (RRT) was 956.7 per million population, 77,311 individuals

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received RRT and the most frequently administered RRT was hemodialysis therapy (76%) (2).

The hemodialysis method involves a complex treatment process and it is important that individuals adapt to the treatment. The process of adaptation to treatment in hemodialysis method includes diet, fluid intake, drug management, participation in dialysis sessions and completion of Sessions (3). Due to the adaptation problems experienced by individuals, hemodialysis treatment and the problems that can be seen due to the treatment; the individuals have problems in terms of physical, mental and socioeconomic aspects and their quality of life is negatively affected (4,5).

Understanding of individuals' disease behavior, psychological responses and adaptation difficulties and implementing holistic care initiatives to support the development of appropriate coping methods are needed. To provide this, nursing-specific theories and models are used as guides (6). One of the important theories used in nursing is the Watson' Theory of Human Caring (THC). Watson based his theory on the view that humans cannot be treated as objects, nor can they be separated from their own selves, from other people, from nature and the universe. THC is seen as a philosophical and moral basis for professional nursing (7,8).

This review is intended to raise awareness of nursing approaches based on Watson's THC in ensuring compliance with treatment in patients undergoing hemodialysis therapy.

Adaptation to Treatment in Individuals Undergoing Hemodialysis Therapy

Hemodialysis is the most common and safe treatment method among renal replacement treatments, providing fluid electrolyte balance, homeostasis, normal plasma pH and removal of nitrogenous waste products from the body (9). However, individuals' compliance with diet, fluid intake and drug management and participation in dialysis sessions affect the success of the treatment process (10). Failure to adapt to treatment leads to increased complications, morbidity and mortality (11,12).

Incompatibility with fluid intake is one of the most common problems in individuals undergoing hemodialysis therapy. Rate of incompatibility with fluid intake was found in the international literature as 22-77% (13-16) and in our country as 60-95% (17-19). Excessive fluid intake causes shortness of breath, headache, abdominal distension, edema, hypertension and heart failure (20). It also causes disorders in cognitive functions, an increase in hospitalization and mortality (11).

Individuals are required to adapt to the intake of many components such as calories, sodium, protein, potassium, phosphorus, calcium in their diet (21). Non-compliance with dietary intake was found in the international literature at rates of 41-84% (13,16,22,23) and in our country at rates of 64-98% (18,19). Incompatibility in each dietary component causes different problems in individuals. The lack of compliance with sodium intake leads to excessive fluid intake and associated increase in total body fluid and interdialytic weight; incompatibility in phosphorus uptake leads to disorders in mineral metabolism and cardiovascular diseases; incompatibility in potassium uptake leads to arrhythmias and increase in mortality; incompatibility in protein uptake leads to complications and increase in mortality due to increase in urea (24-26).

Non-compliance with the treatment regime can be seen as deliberate incompatibility in the form of changing, delaying or skipping medication doses, or as non-intentional incompatibility in the form of forgetfulness, lack of information or lack of communication. In the literature, incompatibility with drug intake was found to be 22-56%. Non-compliance with drug intake in individuals leads to an increase in complications, mortality and hospitalization (27,28).

Participation in hemodialysis sessions and completion of sessions are important in removing waste materials and fluid from the body. Failure to attend a single session leads to a 1.4-fold increase in hospitalization rate and a 2.2-fold increase in mortality in individuals within 30 days (29). In the literature, incompatibility to session attendance or shortened session rate was found to be 7-32% (29-31).

By properly addressing individuals experiencing non-compliance problems, improving participation and compliance awareness in diet and fluid restriction, drug management and dialysis sessions will contribute to improving the quality of life of individuals by reducing the risk of complications. It is emphasized that the role of health professionals is important in this change (14,32). It is the nursing theories that will guide these initiatives of nurses. Nursing theories provide systematic presentation of the care given (6). One of the important theories utilized in nursing care is the Watson's THC.

The Conceptual Framework of the Watson's Theory of Human Care

The Watson's THC is a theory focusing on transpersonal relationships and life experiences developed by Jean Watson from 1975-1979. Watson's theory states that nursing care should be humane, conscious and purposeful. In theory, nursing is defined as helping the individual achieve high harmony within the mind, body and spirit, and it is stated that this harmony can be achieved through care interactions involving transpersonal care relationship (6,7,33). The theory consists of three components: (a) the caritas processes, (b) the transpersonal caring relationship, and (c) the caring occasion or caring moment (7).

The theory is widely used in nursing applications. According to Watson, nursing care is not traditional nursing practice. The nurse should focus on the physical needs of the individual as well as the integrity of mind and spirit. "Care is the heart of nursing" and is a must for patients, families, communities and the entire universe. The nurse communicates transpersonal communication while giving care and a vital consciousness is formed when care is given by the nurse and taken by the patient (7,34).

Transpersonal Caring Relationship

Transpersonal care relationship is defined as establishing a special communication between the nurse and the individual in the process of care, improvement, or authentic relationship that involves connecting and adopting each other's spirit. The transpersonal care relationship seeks for deeper sources of internal healing as well as leading to cure illness or problems. Traditional nursing practices turn into conscious and professional nursing practices when authentic relationship is established with improvement processes. Both the patient and the nurse are in recovery process (8,34).

In the interpersonal care relationship, the nurse establishes a sincere, trustworthy, natural, loving and conscious authentic relationship with the patient, which includes mimics, colors, emotions and words. In order for care to begin, the nurse must enter the existential space of the individual. The individual's existential space consists of his/her thoughts, goals, expectations, needs, feelings and spiritual needs and is unique to the individual (6). The following examples of questions are suggested in order to reach the existential domain of the individual.

- Can you talk about yourself?
- Can you talk about your experiences in life?
- Can you talk about what you feel physically?
- Can you talk about your spiritual and cultural beliefs?
- Can you talk about your goals and expectations? (6).

In the transpersonal care relationship, the nurse provides the strengthening of the individual's state of well-being, increasing the harmony and comfort of the individual by reaching the existential area of the individual (6,8).

The Caring Occasion or Caring Moment

The state of care is the ability to interact between the nurse and the individual's life stories and phenomenal fields at the moment of giving care to the individual. The phenomenal field of the individual is defined as life experiences consisting of thoughts, expectations, feelings, beliefs, bodily perceptions and environmental factors (6,8).

According to Watson, at the time of care the nurse and the individual have an opportunity to present their life stories and phenomenal fields when they come together. Communication established at the time of care transcends time and space, reaching a deeper level than physical interaction. It enables the individual to be satisfied with care and to strengthen the healing process (7,8).

The Caritas Processes

The caritas processes were developed by Watson in 1979 and revised by her in 1985 and 1988 and were described as the essence of nursing. Processes include the concepts of value, love, appreciation. Nurses must internalize and adopt these concepts in their approach and care to the individual. There as 10 caritas processes (6,7):

- Values system of humanism and dedication
- Faith - hope vaccination
- Sensitivity to self and others
- Helpful and reassuring caring relationship
- Expressing positive and negative emotions
- Creative problem solving in caring process
- Individual learning-teaching
- Supportive, protective and/or corrective mental, physical, social and spiritual environment
- Helping people's needs
- Existential-phenomenological-spiritual forces (8).

The cavitas processes are the guide to nursing initiatives and constitute the science, art and philosophy of nursing care. Processes are related to each other, all processes can be used together or can be applied separately. In the care given through the caritas processes, the individual is treated as a whole which reinforces the individual's well-being and harmony (6,35).

Nursıng Care Based on Watson's Theory of Human Care in Patıents Undergoing Hemodialysis

Nursing care based on Watson's THC in patients undergoing hemodialysis is expected to support the process of adaptation to treatment including diet, fluid restriction, drug management and participation in dialysis sessions by establishing transpersonal care relationship and to increase their well-being and quality of life by supporting spirituality, which is one of the important elements of the theory, and to strengthen them psychosocially. In Watson's THC, nursing is centered on helping the individual achieve a higher level of harmony within the mind, body and soul, and it is emphasized that this harmony can be achieved through care interactions involving transpersonal care relationships (33).

Establishment of Transpersonal Care Relationship and Initiation of Caring Moment

The establishment of a reassuring, respectful, sensitive and intimate transpersonal communication with the individual enables the individual to express his/her problems that he or she has experienced during the disease and his/her anxiety and stress about non-compliance with the treatment. In addition, transpersonal care relationship produces mind-body-spirit harmony between the care taker and the giver and provides an energy during the caring moment (7).

Authentic relationship and healing environment concepts are important elements of the theory (6). The authentic relationship between the nurse and the individual in the transpersonal care relationship and at the caring moment makes it easier for the individuals to understand and express their feelings, thoughts

and needs. In the authentic relationship, the nurse should focus not only on the individual's illness or problem, but on care, healing and wholeness (7, 8).

The healing environment ensures that the individual is physically, emotionally and spiritually comfortable and peaceful in all physical and non-physical environments. The environment in which caring is given, should be regulated as a healing environment. For example, the physical environment should be created as clean, comfortable and reliable; and the emotional environment should be specific to the individual and should be created according to the wishes of the individual; while the spiritual environment should be created according to what the individuals want to do according to their beliefs (7,34).

The Caritas Processes

The caritas processes are the first concept of the THC. Processes are implemented throughout the caring and recovery process. The cavitas processes enable the nurse and the individual to be creative in solving problems (8).

Values System of Humanism-dedication

Care is based on universal humanistic values. These values are tolerance, empathy, love for oneself and others, and begin with childhood experiences, are developed through faith, culture and art. Devotional values are defined as the satisfaction we receive from the value we give ourselves. Adopting these values enables us to approach the individual and ourselves with love, compassion and tolerance. It also forms the basis of human care and provides professional care. It constitutes the first and most fundamental factor for science and care ethics (6,8). In this caritas process, it is important to listen effectively to the individual, to pay attention to privacy at the time of data collection, transpersonal communication and care, to accept the individual as he/she is, to respect, to honor the person's values and abilities.

Instilling Faith and Hope

The process of instilling hope and belief is to know the feelings, thoughts and beliefs that the individual experiences in his or her inner world and to instill positive and promising thoughts and words. The belief of the individual is supported, honoured, and in this way it is ensured that the individual improves and sustains his or her health (7,34). In this cavitas process; the individual should be seen not as an object but as a human being; the individual should be addressed by name, eye contact and touched; the individual should be helped to believe in herself/himself, and the hope should be supported (8,33).

For example;

- The nurse should talk with the individual about the positive and negative developments in hemodialysis treatment and adaptation process, support the positive aspects of faith-hope and try to strengthen them.
- In the next process, the individual should be informed that communication can be established.

Being Sensitive to Self and Others

Most of the time people don't want to express their feelings. In order to develop sensitivity to oneself and other people, the individual needs to recognize and feel their emotions. Nurses can recognize and encourage others to do so if they feel their own feelings. Being sensitive to individuals who are sick, especially in nursing, makes the individual comfortable and allows us to support the healing process and show that we are on the side of the individual (6,36). In this caritas process, we should be more sensitive to the needs and feelings of the individual, showing that we are willing to explore the feelings, beliefs and values of the individual (7,8).

For example;

- The individual should be asked about the positive/negative experiences in his/her life and how he/she copes with the negative situations he/she has experienced and the individual should be asked to talk about his/her experiences during the time he/she is diagnosed as having chronic kidney failure and undergoes hemodialysis treatment.
- It should be ensured that the individual shares his/her feelings and thoughts about the process of adaptation to treatment and about his/her later life.

Development of Helpful-reassuring Relationship

The caring relationship is an transpersonal process, and in this process it is important to respect the individual, to make the individual feel that we are listening to him/her, to connect with the individual's soul that goes beyond physicality. Development of helpful and reassuring relationship enables the individual to feel safe and reduce incompatibility issues (7,37). In this caritas process, unconditional love and respect should be shown to the individual, non-judgmental attitudes should be displayed. The nurses should be honest, sincere, sensitive and open in communication and should allow the individual to choose the best time to talk about his/her concerns (7,8).

For example;

- Individuals should be supported to talk about their problems with fluid restriction, diet, drug management and dialysis sessions.

Encouraging the Individuals to Express Their Positive and Negative Emotions and Accepting Them

Thoughts, behaviors and experiences need to be considered and accepted in the human care process. In the caritas process, the care relationship becomes deeper, more honest, and more authentic if the nurses focus on the feelings of the individuals and understand them. Also, listening to and honoring the feelings of individuals are important for the individual's healing and harmony (8,35). During this caritas process, the individual should be encouraged to express himself/herself and supported to reflect his/her feelings and experiences. Praying and spiritual relief should be offered, the individual should be helped to see the good aspects of his/her situation, the individual should be accepted and supported to cope with negative emotions (6,7).

For example;

- The individual should be asked to express his/her feelings and thoughts about the disease process and the individual should be asked questions
- Can you tell me what you went through during that illness?
- What are the symptoms of chronic kidney failure and do you have any difficulties about it?
- How did that illness affect your social life?
- What do you think it means to adapt to disease and treatment?
- The individual should be asked to express their fears about the disease process.
- Can you talk about your fears about your illness? What does frighten you during the disease process ?

Systematic Use of Scientific Problem Solving Method in Caring Process

Professional nursing is to use problem solving methods and a creative approach in the nursing process. This process includes information, technology, skills, instincts, ethics and personal information. It is suggested to be in a scientific, systematic, logical framework and to use technology when giving care (34,38). In this caritas process, the individual should be encouraged to ask questions. A healing environment should be created: Sound, authenticity, artistic expression, art therapy, keeping a diary, game, humour, fun, spontaneity, music, readiness, breathing, relaxation, daydreaming, imagination, and volunteering, eye contact, smile, positive attitude, active listening, light and noise protection should be regarded as effective elements in the planning of care (7,8).

For example;

- The individual should be educated about the importance of diet, fluid control, drug compliance and participation in dialysis sessions.
- The individual should be encouraged to speak and ask questions.
- Is there a question you would like to ask me about fluid restriction, diet and drug management or anything?

Promoting Transpersonal Teaching-learning

It involves learning and teaching according to the individual's needs and understanding method when an individual needs information. The role of nurses in education is focused solely on providing information. In this process, an appropriate, friendly learning and teaching environment is created with the individual, providing self-learning, self-coaching, healing and harmony (8,39). In this caritas process, cooperation should be made with the individual, calm and respectful conversation should be made with the individual, the individual's readiness to learn and knowledge level should be evaluated, the individual should be helped to express his/her concerns and questions to health workers (6,35).

For example;

- The individuals should be asked about their experiences and knowledge about fluid restriction, diet, drug management and dialysis sessions.
    - Can you tell me what you're doing with that fluid restriction, diet, drug management and dialysis sessions?
    - Can you tell me a little bit about your relationship with that fluid intake?
    - Can you tell me a little bit about your relationship with that diet management?
    - Can you tell me about your relationship with those drugs?
    - Can you tell me a little bit about your dialysis sessions?
- The individual can be encouraged to speak and ask questions.

Providing a Supportive, Protective Physical, Sociocultural and Spiritual Environment

The purpose of creating such an environment is to provide quality care and to ensure recovery. A comfortable, clean, aesthetic, private and safe environment needs to be created. Creation of a healing environment promotes the use of improvement, adaptation and caring methods. For example, applications such as imagery, visualization, relaxation, music, touch, art are utilized to create a healing environment (6,40). In this caritas process; space must be created to establish a relationship with the individual, the individual must rest carefully, the needs of the individuals must be predicted in advance, and their routines and rituals must be learned (8,39).

For example;

- A physically, emotionally and spiritually comfortable and healing environment should be created.
- The privacy of the individual should be protected during the hemodialysis treatment process.
- The individual must express himself/herself.
- The individual's problems related to hemodialysis and adaptation to treatment should be tried to be corrected.

Helping People's Needs

To help individuals meet their physical, emotional and spiritual needs. During the caritas process, not only the physical needs must be met, but the individual's soul must also be touched. All needs are linked to each other, and all needs for the caring-healing process are equally important and valuable (8,41). In this caritas process; the individual should be evaluated in a holistic way and be helped to meet his/her needs. The individuals' needs should be respected. The nurses should be sensitive to the individual's family and loved ones, and ensure the participation of family and other important persons (7,34).

For example;

- Is there a question you would like to ask me about fluid restriction, diet, drug management and dialysis sessions or anything?

Existential-phenomenological-spiritual Powers

It incorporates the mystique, philosophy, and metaphysical aspects of human experiences and phenomena that do not conform to traditional science. It consists of belief systems of the individual, the family and the nurse that express the meaning of life and death. This belief system includes cultural beliefs, myths and metaphors (8,42). In this caritas process, miracles should be allowed to happen for the individual, the individual's hope should be supported and nurtured, the individual's feelings should be accepted, and what is important for the individual should be known (6,36).

For example;

- The individual should be able to share feelings and thoughts about the hemodialysis treatment process and adaptation process.
- The spiritual needs of the individual should be respected and supported.

Conclusion

Watson's THC is a model that provides the application of nursing care within love, respect, compassion and trust, which assesses the individual in mind-body-spirit harmony, which ensures that not only the physical needs of the individuals but also their emotional and spiritual needs are met. Individuals undergoing hemodialysis treatment encounter many negative factors during the disease and treatment process. Adaptation to hemodialysis treatment in individuals is an important process, and Watson's THC is an effective and easy to implement theory in dealing with these adversities and adaptation problems. The theory ensures that individuals are evaluated on a holistic basis and that individuals are given care after that, and thus, individuals' recovery, compliance with the disease and treatment process and satisfaction are increased.

It is proposed to use Watson's THC as a guide in creating the conceptual framework of nursing care, and to apply and evaluate the model in different disease groups.

Ethics

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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References

1. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. Bulletin of the World Health Organization 2018;96:414.
2. Süleymanlar G, Ateş K, Seyahi N. [Registry of The Nephrology, Dialysis And Transplantation in Turkey-Registry 2017]. Türk Nefroloji Derneği Yayınları, Ankara. 2017.
3. Ok E, Kutlu FY. Hopelessness, Anxiety, Depression and Treatment Adherence in Chronic Hemodialysis Patients. International Journal of Caring Sciences 2019;12:423-9.
4. Ibrahim S, Hossam M, Belal D. Study of non-compliance among chronic hemodialysis patients and its impact on patients' outcomes. Saudi Journal of Kidney Diseases and Transplantation 2015;26:243.
5. Mukakarangwa MC, Chironda G, Bhengu B, Katende G. Adherence to Hemodialysis and Associated Factors among End Stage Renal Disease Patients at Selected Nephrology Units in Rwanda: A Descriptive Cross-Sectional Study. Nursing research and practice 2018;2018.
6. Smith MC, Parker ME. Nursing theories and nursing practice. Fourth Edition ed. Philadelphia, America: FA Davis; 2015.
7. Watson J. Human Caring science. A theory of Nursing Second Edition ed. Burlington, MA: Jones & Barlett Learning; 2012.
8. Watson J. Unitary Caring Science: Philosophy and Praxis of Nursing: University Press of Colorado; 2018.
9. Grossman S. Acute Renal Injury and Chronic Kidney Disease. In: Grossman S, Porth CM, Conelius J, Gerard SO, Moriber N, O'Shea ER, et al., editors. Porth's pathophysiology: Concepts of altered health states. 9th Edition ed. Philadelphia, PA: Wolters Kluwer Health | Lippincott Williams & Wilkins.; 2014. p. 1112-31.
10. Lins SMdSB, Leite JL, Godoy Sd, Tavares JMAB, Rocha RG, Silva FVC. Treatment adherence of chronic kidney disease patients on hemodialysis. Acta Paulista de Enfermagem 2018;31:54-60.
11. Naalweh KS, Barakat MA, Sweileh MW, Al-Jabi SW, Sweileh WM, Sa'ed HZ. Treatment adherence and perception in patients on maintenance hemodialysis: a cross–sectional study from Palestine. BMC nephrology 2017;18:178.
12. Tohme F, Mor MK, Pena-Polanco J, Green JA, Fine MJ, Palevsky PM, et al. Predictors and outcomes of non-adherence in patients receiving maintenance hemodialysis. International urology and nephrology 2017;49:1471-9.
13. Beerendrakumar N, Ramamoorthy L, Haridasan S. Dietary and fluid regime adherence in chronic kidney disease patients. Journal of caring sciences 2018;7:17.
14. Edison C. Adherence to dialysis therapy management in hemodialysis patients. UI Proceedings on Health and Medicine 2018;3.
15. Jampour L, Dehzad S, Eftekhari MH, Akbarzadeh M. The Evaluation of Adherence to Dietary and Liquid Intake Recommendations in Hemodialysis Patients. International Journal of Nutrition Sciences 2018;3:92-8.
16. Khalil AA, Darawad MW. Objectively measured and self-reported nonadherence among J ordanian patients receiving hemodialysis. Hemodialysis International 2014;18:95-103.

17. Efe D, Kocaoz S. Adherence to diet and fluid restriction of individuals on hemodialysis treatment and affecting factors in Turkey. Japan journal of nursing science : JJNS 2015;12:113-23.
18. Korkmaz Y. Evaluation of the hemodialysis patients' self– efficacy, adherence and non-adherence to treatment and fluid restriction [Master's]. AnkaraTurkey: Başkent University; 2016.
19. Mollaoğlu M, Kayataş M. Disability is associated with nonadherence to diet and fluid restrictions in end-stage renal disease patients undergoing maintenance hemodialysis. International urology and nephrology 2015;47:1863-70.
20. Wong M, Ghebleh P, Phillips S. Tips for Dialysis Patients With Fluid Restrictions. Journal of Renal Nutrition 2017;27:e35-e8.
21. Lambert K, Mullan J, Mansfield K. An integrative review of the methodology and findings regarding dietary adherence in end stage kidney disease. BMC nephrology 2017;18:318.
22. Ahrari S, Moshki M, Bahrami M. The Relationship Between Social Support and Adherence of Dietary and Fluids Restrictions among Hemodialysis Patients in Iran. Journal of caring sciences 2014;3:11-9.
23. Chironda G, Bhengu B. Engagement with Fluid and Dietary Restriction among Chronic Kidney Disease (CKD) Patients in Selected Public Hospitals of KwaZulu-Natal (KZN) Province, South Africa. Health Science Journal 2016;10:1.
24. Beerappa H, Chandrababu R. Adherence to dietary and fluid restrictions among patients undergoing hemodialysis: An observational study. Clinical Epidemiology and Global Health. 2018.
25. Umeukeje EM, Mixon AS, Cavanaugh KL. Phosphate-control adherence in hemodialysis patients: current perspectives. Patient preference and adherence 2018;12:1175.
26. Ko GJ, Obi Y, Tortoricci AR, Kalantar-Zadeh K. Dietary protein intake and chronic kidney disease. Current opinion in clinical nutrition and metabolic care 2017;20:77.
27. Ahlawat R, Tiwari P, D'Cruz S. Prevalence and predictors of medication non-adherence in patients of chronic kidney disease: Evidence from a cross sectional study. J Pharma Care Health Sys 2016;3:2376-0419.
28. Ghimire S, Castelino RL, Jose MD, Zaidi STR. Medication adherence perspectives in haemodialysis patients: a qualitative study. BMC nephrology 2017;18:167.
29. Gray KS, Cohen DE, Brunelli SM. In-center hemodialysis absenteeism: prevalence and association with outcomes. ClinicoEconomics and outcomes research: CEOR 2017;9:307.
30. Obialo C, Zager PG, Myers OB, Hunt WC. Relationships of clinic size, geographic region, and race/ethnicity to the frequency of missed/shortened dialysis treatments. Journal of nephrology 2014;27:425-30.
31. Nicholas SB, Kalantar-Zadeh K, Norris KC. Socioeconomic disparities in chronic kidney disease. Advances in chronic kidney disease 2015;22:6-15.
32. Ghimire S, Castelino RL, Lioufas NM, Peterson GM, Zaidi STR. Nonadherence to medication therapy in haemodialysis patients: a systematic review. PloS one 2015;10:e0144119.
33. Suliman WA, Welmann E, Omer T, Thomas L. Applying Watson's nursing theory to assess patient perceptions of being cared for in a multicultural environment. Journal of Nursing Research 2009;17:293-300.
34. Lukose A. Developing a practice model for Watson's theory of caring. Nursing Science Quarterly 2011;24:27-30.
35. Costello M. Watson's Caritas Processes® as a Framework for Spiritual End of Life Care for Oncology Patients. International Journal of Caring Sciences 2018;11:639-44.
36. Davidson AW, Ray MA, Turkel MC. Nursing, caring, and complexity science: For human environment well-being: Springer Publishing Company; 2011.
37. Helming MB. Relationships. In: Dossey BM, Keegan L, editors. Holistic nursing: A handbook for practice: Jones & Bartlett Publishers; 2013. p. 439-62.
38. Bolima DC, Estes T. The Sixth Caritas Process®: Use Creative Scientific Problem-Solving Methods for Caring Decision Making—and Creative Solution-Seeking. In: Kathleen S, Jean W, editors. Caring Science, Mindful Practice. New York: Springer Publishing Company; 2018. p. 119-34.
39. Clark C. Watson's human caring theory: Pertinent transpersonal and humanities concepts for educators. Humanities 2016;5:21.
40. İlkay Arslan Özkan, Okumuş H. [A Model Where Caring and Healing Meets: Watson's Theory of Human Caring]. Turkish Journal of Research & Development in Nursing 2012;14:61-72.
41. Swartley N, Caron SJ. The Ninth Caritas Process®: Assist With Basic Physical, Emotional, and Spiritual Human Needs. In: Kathleen S, Jean W, editors. Caring Science, Mindful Practice. New York: Springer Publishing Company; 2018. p. 167-82.
42. Laws D, Beck MD. The Tenth Caritas Process®: Open to Mystery and Allow Miracles to Enter. In: Kathleen S, Jean W, editors. Caring Science, Mindful Practice. New York: Springer Publishing Company; 2018. p. 183-96.

Review

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Study Protocol Preparation for Randomized Controlled Trials: Recommendations and Protocol Recording

Randomize Kontrollü Çalışmalar için Protokol Hazırlama: Öneriler ve Protokol Kaydı

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ABSTRACT

The World Health Organization (WHO) considers the registration of the study protocol as the publication of an internationally recognized set of information on the design, conduct, and management of clinical trials. Writing a detailed study protocol with all the correct and necessary steps is an important step before starting randomized controlled trials. WHO says that study protocols should be included in a standardized registration system and published on a publicly accessible website. From an ethical point of view, the Helsinki Declaration emphasizes that study protocols should be registered in a public database. In addition, before the implementation process of the RCTs has started, obtaining the registration number (protocol ID) in public databases has become an important necessity for the studies to be published in quality journals. The purpose of this review is to review, consider recommendations and provide guidance for protocol registration during protocol preparation, which is the most important stage of a correctly planned RCT process. It is seen that the culture of planning and adhering to this protocol has not yet become widespread in the researchers in our country as they begin the RCT process, according to the principles of the study protocol preparation. It is thought that the information in this review will guide the researchers at this point.

Keywords: Study protocol, clinical trials, randomized controlled study, nursing

ÖZ

Dünya Sağlık Örgütü (DSÖ), çalışma protokolü kaydını, klinik çalışmaların tasarımı, yürütülmesi ve yönetimi ile ilgili uluslararası kabul görmüş bir bilgi dizisinin yayınlanması olarak kabul etmektedir. Doğru ve gerekli tüm basamakları içeren ayrıntılı bir çalışma protokolü yazmak, randomize kontrollü çalışmalara (RKÇ) başlamadan önce önemli bir adımdır. DSÖ çalışma protokollerini standartlara uygun bir kayıt sisteminde yer alması ve bu bilgilerin herkes tarafından erişilebilen bir web sitesinde yayınlanması gerektiğini söylemektedir. Etik açıdan bakıldığında Helsinki Bildirgesi'de çalışma protokollerinin halka açık bir veri tabanında kayıtlı olması gerektiğini vurgulamaktadır. Ayrıca hazırlanan protokollerin RKÇ'nin uygulama süreci başlamadan önce uluslararası veri tabanlarında kayıt edilmesi ve kayıt numarasının (protokol ID) alınması, çalışmaların kaliteli dergilerde yayına dönüşmesi için oldukça önemli bir zorunluluk haline gelmiştir.

Bu derlemenin amacı, kanıt değeri yüksek, doğru planlanmış bir RKÇ sürecinin en önemli aşaması olan protokol hazırlama sırasında, dikkate edilmesi gereken noktaları gözden geçirmek, öneriler vermek ve protokol kaydı için rehberlik sağlamaktır. Ülkemizdeki araştırmacılarda RKÇ sürecine başlarken, çalışma protokolü hazırlama ilkelerine göre çalışmalarını planlama ve bu protokole bağlı kalarak sürdürme kültürünün henüz yaygınlaşmadığı görülmektedir. Bu derlemede yer alan bilgilerin araştırmacılara bu noktada rehberlik ederek yol göstereceği düşünülmektedir.

Anahtar Sözcükler: Çalışma protokolü, klinik araştırmalar, randomize kontrollü çalışma, hemşirelik

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Introduction

Evidence is information that decision-makers in the health care system can reach, based on a scientific assessment of the practice. It is also a tool that can be used to make sure patients receive the best care available (1,2). Evidence- based practice (EBP) is the process of using the best available evidence to support clinical decisions (3,4). It is also defined as integrating the best research evidence obtained by systematic research into personal experience, clinical decision-making ability obtained by clinical practice, and patient values and preferences (5,6).

Evidence-based nursing is a process in which the evidence obtained from scientific research is critically evaluated with the participation of the patient according to status, preferences, and availability of resources of patients and healthy individuals to assure the provision of best nursing care (5). The purpose of EBP is to enable nurses to enrich their clinical training and experience with up-to-date research. EBP enables nurses to learn from many researches, gain knowledge and EBP skills that exist in nursing and enables them to research, evaluate and practice literature in the clinic. It has been reported that experimental studies have increased in the last 20 years and that more than half (67%) of these studies are randomized controlled trials (RCT) (7). RCTs are trials conducted to assess the effects of one or more interventions on individuals or groups. It can also be called interventional trials. These interventions include drugs, cell and other biological products, surgical procedures, radiological procedures, devices, behavioral treatments, changes in care process, and preventive care (8). The importance of RCTs in terms of nursing is that these trials provide the opportunity to draw causal conclusions that will help to demonstrate the effectiveness of the interventions used by nurses. In order to achieve these results, the effectiveness of the initiatives must be demonstrated in a certain system. The synthesis of research evidence using systematic and rigorous methods has become an important feature of evidence-based medicine. It is very important to work with RCT protocols that determine the effectiveness of the intervention to create this systematics (9).

In order to implement EBPs, it is necessary to develop the skills of nurses to critically evaluate research and to establish a culture of basing their practice on scientific knowledge (10,11). Nurses need to know and evaluate the levels of evidence so that EBPs can be transferred to them. Evidence levels reflect how strong the method of studies is (11). Gray and Chambers (12) classified the power of evidence into five categories. Various systems have been developed for the grading of evidence, and evidence and recommendation level classifications adopted by the Joanna Briggs Centre are used for the evaluation of evidence levels in nursing (13). According to the evidence level classification, the strongest evidence comes from at least one systematic review and meta-analysis which are based on well-designed RCTs (14). In evaluating the effectiveness of the initiative, RCT is considered to be the best research design. RCTs shown as evidential source of information provide second level of evidence in making decision for interventions and are the basic source for systematic reviews and meta-analyses which are accepted to be the first level of evidence for interventions (15). A meta-analysis is a quantitative analysis of the findings of the researches involved in the systematic review using statistical analysis techniques (16). Therefore, the main purpose of systematic review and meta-analysis is to synthesize the results of numerous researches on a particular subject and present the most accurate evidence to health professionals. In these studies, synthesis is mostly performed using the results obtained from RCTs (17). It is very important that RCTs are based on a document called a protocol, detailing the rationale, proposed methods and organization of the intervention (18).

It is possible for nurses to benefit the individuals they care for by using the evidence obtained from the RCTs, if the trials are well-designed and implemented, reported openly and transparently. A well-prepared study protocol is needed to ensure that RCTs, which are a type of clinical research with a high level of evidence, have the chance to be based in clinical practice and directly utilized in decision-making (19). Furthermore, the quality of the evidence obtained from the RCTs depends on the detailed planning of each phase of the study, and the way to obtain these details is through the preparation of a well-planned study protocol (20).

The working protocols prepared with insufficient methodological approach can have high scientific value and appear to be excellent from a theoretical point of view. However, when the study is started, there may be some deficiencies, glitches and inappropriate points. These deficiencies may include who the participants are, which Initiative is targeted, how the participants respond to the initiative is measured, and financial and expert support (21). Proper development, evaluation and implementation of clinical trial protocols is of great importance in avoiding these deficiencies (22,23).

The study protocol is a document that defines the objectives, design, methodology, statistical evaluation and organization of the work to be performed (24). The protocol is a resource that clearly states the logic and structure behind a research project (25). According to another definition, the study protocol is a document that describes each step of the research and answers questions on issues such as what goals the study will achieve, how much power it has (26). In addition, the study protocol demonstrates the guidelines needed to carry out the research. A clinical trial protocol involves processes such as planning, conducting, reporting and transferring the study to practice. A well-written protocol allows evaluation of scientific, ethical and safety issues such as suitability of the study before the study begins, execution of the study, and implementation of the results after the study is completed (27).

It is seen that the culture of planning their study according to the principles of study protocol preparation and continuing their study by adhering to the protocol have not yet become widespread in nursing researchers. A study published in a nursing journal showed that more than two-thirds of the studies

published between the years 2011-2016 were not registered and that 54% of them were recorded after the study was initiated. It was also reported that whole study protocol was published in only 9% of the published studies and that vast majority of the published studies lacked of whole study protocol (28). These rates raise the importance of a guideline on the subject. In line with this information, it is thought that the researchers in the field of nursing have insufficient awareness of the importance of preparing a working protocol when starting a RCT. Although preparing a working protocol is a new approach in Turkey especially in the field of nursing, there are hardly any resources that can provide guidence in this regard. In addition, it has become a very important necessity to make registration in the international databases and to take protocol ID before implementation process of the RCT is started, for the studies to be published in quality journals in the future.

The purpose of this review is to increase the level of knowledge at the point of preparing and recording protocols by increasing the awareness of researchers in the field of nursing. In addition, it is thought that this review will provide researchers with guidance on making recommendations and recording the protocol by reviewing the points to be considered during the preparation of the protocol, which is the most important stage of a properly planned RCT process with high evidential value.

Study Protocol Registration, Aims and Benefits

The World Health Organization (WHO) recognizes the study protocol register as the publication of an internationally recognized series of information on the design, conduct and management of clinical trials. Details about the study are recorded in a registration system that complies with WHO standards and this information is published on a publicly accessible website (29). One of the most important journals in the field of nursing recommends that non-registered RCTs should not be published and that the authors' work could be recorded retrospectively, but that an explanation should be made about the cause. They also stated that it was ideal for the authors to publish the study protocols in a peer-reviewed journal as a full text (28). To register the working protocol in web-based databases means to obtain registration in a way. These registrations involve both the ethical and scientific aspects of the study. At the same time, the registrations provide an ethical function in ensuring that everyone is informed about ongoing and previous work. Many groups including the International Committee of Medical Journal Editors (ICMJE) argue that registrations should be managed by a non-profit organization and free for both registrars and users. Records also contribute to researchers, journal editors, and referees in the context of understanding research results (30).

It is also accepted as a scientific, ethical and moral responsibility. The Declaration of Helsinki states that "every clinical trial must be registered in a public database before the first participant is included in the study." The objectives of a study protocol are summarized below.

Objectives of a study protocol

- √ Raising the question to be investigated and clarifying its importance,
- √ Gather available information and discuss the efforts of other researchers working on relevant questions (literature review),
- √ Formulating hypothesis and goals,
- √ Clarify ethical considerations and obtain ethical approval,
- √ Propose the methodology necessary to solve the question and achieve the goals,
- √ Discuss requirements and limitations for achieving goals,
- √ Provide funding for the current study,
- √ To ensure that all working team members are in the same denominator in terms of expectation and contribution (26).

The benefits of registering the working protocols are summarized below.

Benefits of study protocol registration

- Shows what to do by explaining the necessary points in the study and how it is carried out.
- Allows the researcher to plan and study the steps of the project.
- Serves as a guide throughout the research.
- Speeds up time and budget estimates.
- Explains participants' suitability, duration of study, drugs and related tests (31).
- Makes it easier to identify ongoing clinical trials and identify gaps in clinical trials.
- Knowledge of the study protocol makes it easier for researchers and potential participants to participate in the study.
- Enables researchers and health care practitioners to identify research they may be interested in, and to collaborate more effectively among researchers.
- Referees in the relevant database who control the data as part of the registration process identify potential problems early in the research process, enabling improvement in the quality of clinical trials.
- Journal editors and referees can determine whether the study protocol given to the journal meets the protocol design described in the first registration.
- In addition, it allows journal editors to review ongoing and previously unpublished research on the same topic (32-34).

Study Protocol Preparation Steps and Format

One of the most important stages of working protocol preparation is to obtain a protocol registration number. In order to obtain this registration number, the required information must be entered into the system of the database to be registered after preparing the working protocol in the appropriate format and the compliance of the research methodology must be confirmed through the process of refereeing in the system. In order to present the required information in these databases, it is important to prepare the study protocol in an accurate and valid format for each database. One of the most important and valid of these formats is the study protocol preparation format proposed by the WHO (29,33,34).

The key points of the protocol are that it contains the rationale for why the study is necessary and the detailed plan of the study (25). Therefore, the most difficult stage of conducting a research project is the preparation of a short but comprehensive document (protocol) that clearly outlines the project. The protocols prepared should be accurate, easy to read and free of typos.

It is important to understand the steps in developing a research protocol to accomplish what is planned and achieve reliable results. The extra time spent writing a good protocol will help with the analysis as well as prevent errors at a later stage. If the protocol is poorly prepared or it is not followed, there will be little chance of getting the expected results from the project (31,35).

The format of the study protocol proposed by the WHO in Table 1 is capable of guiding researchers to prepare a good protocol. This table contains suggestions and tips for both the study protocol proposed by the WHO and all study protocol formats available to all researchers. According to the format proposed by the WHO, the study protocols consist of two parts. This table lists suggestions and tips for each section and subsections (20,24,25,31,33,34,36). A similar format is summarized in Table 2 according to the information obtained from more recent references.

Randomized Controlled Study Protocol Preparation Guidelines

RCTs which are transparent, well-designed, well-managed, and based on a good protocol in terms of providing solid evidence, provide solid evidence for use in patient care and health policy decisions. Therefore, careful assessment of the quality of the study is needed before relying on the evidence that RCT provides (37). To make this assessment, the CONSORT (Consolidated Standards of Reporting Trials) report is widely used around the world as a guide for the development of registration of RCTs (38).

Table 1. Study protocol preparation format, tips and suggestions

Part 1	Tips and suggestions
Project Summary	√ Like the summary of a research article, the project summary should be no more than 300 words and no more than one page (font size 12, single space). √ Preferably on a separate page, it should outline all key elements of the protocol, e.g. rationale, purposes, methods, populations, timeframe and expected outcomes.
General information • Protocol headline, protocol identification (ID) number and date • Name and address of sponsor/funder • Names and titles of the researchers responsible for conducting the research; addresses and telephone numbers and the responsibilities of each researcher • Names and addresses of clinical laboratory (laboratories) and other medical and/or technical department(s) and/or institutions involved in the research	√ Title is one of the most important features of the protocol. Because it attracts potential readers. Therefore, it should be short and in the way that addresses the problem. The main objective should be clear, convey the main objective of the research and indicate the target audience. It should convey information about the subject in a few words, provide information about the research area and should be in such a way as not to exceed 12-15 words. The title should be followed by another short title. √ The research protocol must start with the description of the person who will coordinate the entire study, e.g. all details of the main researcher must be reported in the first paragraph. This will allow each participant to know who to contact in case of doubt or criticality during research. √ A protocol must be administered by a principal investigator. √ The health status of the participants should be checked regularly by members of the research team to ensure the safety and effectiveness of the study. √ If the study is approved by the Ethics Committee, it would be appropriate to include the decision number of the Ethics Committee.
Introduction and purpose	√ The introduction of the project should reflect the essence of the study and direct readers directly to the subject. Attention should be paid to the positive and negative aspects and limitations of the studies cited in the introduction. √ The introduction should be concluded by explaining how the current study will benefit society. √ It should include the latest publications in the field and the title of the study should be selected only after the literature review is completed and gaps in the field to be studied are identified.
References References can also be listed at the end of Part 1.	√ It should not be more than two pages, reducing the number of articles cited to less than 20 would probably be good practice. √ It should briefly answer the importance of the subject, the gaps in the literature, the purpose of the study and its benefits to society. √ The research question must be explained in a conclusive and concise way. Because the research question will be the basis of the study design. √ The problem being addressed must be clear to readers to be able to properly understand its true meaning. The information involving size and frequency of the problem, the geographical areas affected, ethnic and gender factors, etc. should be included.

Table 1 contiuned

Aims and objectives of the study	√ The objectives should be clearly stated. These should be limited to what is intended to be achieved in the study and should be determined as a result of the literature review. Objectives must be simple and specific. √ Goals are broad statements that lead to purpose. After the expression of the primary goal, secondary goals can be mentioned. √ More than 4-5 goals should be avoided in order not to reduce the accuracy of the project when determining the objective. It would be appropriate to use verbs as "to show", "to evaluate", "to verify", "to improve", "to reduce" and "to compare".
Study design The scientific integrity of the study and the reliability of the study data depend heavily on the study design and methodology.	√ The design of the study should include information about the type of study, the research community or sampling. √ It should include information about participants (inclusion and exclusion criteria, polling criteria, etc.) and should include information such as the expected duration of the study. √ Explanation should be given about why the design is chosen. Methods to collect and analyze data should be explained.
Methodology The methodology section is the most important part of the protocol. The methodology reveals that the hypothesis will be confirmed or rejected. It also provides a comprehensive strategy for achieving goals (27).	√ It should contain detailed information about interventions to be made, procedures to be used, precautions to be taken, observations to be made, laboratory examinations to be done, etc. √ The intervention/drug/device being tested must be explained in detail. √ Standardized or documented procedures/techniques must be explained. In the tools to be used for collecting information (surveys, guides, observation report forms, case report forms, etc.) should be introduced in detail. √ In the case of a randomized controlled trial, additional information about the process of randomization and blinding, and identification of the inclusion and exclusion criteria of individuals for a part or all of the study is required. √ The study design must be shown in detail, along with all procedures and timing, using a graphic outline and a flow diagram.
Study population (sample)	√ Detailed information about all aspects of sample selection procedure and sample size calculation should be provided. √ Inclusion to sampling, exclusion from sampling and continuation criteria must be specified. √ The process of blinding and randomization should be explained in detail.
Sample size	√ Detailed explanation of how the sample size is calculated is suggested for economic and ethical reasons. √ The randomization that will be used to obtain a representative sample for your target population should be mentioned. √ Details on "informed consent " should also be stated.
Data collection methods and tools used	√ Data collection tools may include retrospective data (medical records), questionnaires, interviews (structured, semi-structured) laboratory tests and clinical examination. √ The definition of the data collection tools used, the tools used in data collection and the methods used to test the validity and reliability of the device should be explained.
Management of the study	√ By preparing a work flow plan, a draft of all the steps to be carried out according to the planned timescale should be laid out. Making this flow plan in accordance with this timeline will ensure organization while implementing the study. √ The team members (researchers, assistants, lab technicians, etc.) involved in the study or collecting data should be properly trained.
Strengths and limitations	√ Talking about the strengths and limitations of the study is important to prevent unnecessary use of resources and to indicate what results may or may not be achieved.
Safety considerations	√ The safety of its participants during research is the most important. The safety aspects of the research should always be kept in mind and the information presented in the protocol should be provided on how to ensure the safety of the research participants.
Follow-up	√ The research protocol should clearly state what will be followed up and for how long it will be followed up in participants.

Table 1 contiuned

Data management and statistical analysis	√ This section should be written after receiving statistical advice from a statistician. The names of the statistical tests to be used, the names of the variables to be used in the analysis, and the names of the statistical analyses to be performed to evaluate the results should be listed. √ If computer programs are to be implemented, it is important to specify the software used and its version. √ The protocol should provide information on how to manage data, including coding for computer analysis, monitoring and verification. √ Procedures for the selected sample size, for the strength of the study, for the level of importance to be used and for incomplete or false data should be prepared.
Quality assurance	√ The protocol should define the quality control and assurance system based on guidelines and procedures such as the WHO-established clinical trial practice guide, SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Checklist.
Expected results of the study	√ The protocol should also show how the study will contribute to science, how the results will be used, and how it will affect health services, health systems or health policies.
Generalization of results and publication policy	√ The protocol should include information about the spread of results not only in the scientific media but also to the community and participants, and for policymakers to take these results into account when setting policy. √ The publishing policy should be openly discussed. (For example, who will lead publications, who will provide and organize their spread, etc.)
The duration of the project	√ The protocol must specify a probable period for each phase of the project
Expected issues	√ This part should discuss issues that could prevent researchers from successfully completing their projects within the prescribed time frame and within the requested funding. It should also offer possible solutions to deal with these problems.
Management of the project	√ This part must define the role and responsibility of each member of the team.
Ethical aspect	√ It should not be limited to providing information on how and by whom ethics approval is to be received, but also it should document issues that are likely to cause an ethics violation. √ It should be stated whether the procedures to be followed are in accordance with the Helsinki Declaration. √ In all cases, the study should not be initiated unless the approval of the Ethics Committee is obtained.
Informed consent forms	√ Researchers must also explain how they plan to obtain informed consent from research participants (the process of informed consent). √ If the research involves multiple groups of individuals, for example health care workers and health care providers, it should include a separate personalized informed consent form for each group. This allows each group of participants to receive the information they need to make an informed decision.
Part 2	Tips and suggestions
Budget	√ The budget section should be written in detail of the requested funds and by indicating a rationale for each item.
Other support for the project	√ This part must provide information about funding received from other funding agencies or expected fundings for this project.
Collaboration with other researchers or research institutions	√ It should be ensured that links to other projects are indicated and that the CVs of the responsible researcher and each researcher are indicated
Other research activities of researchers	√ The responsible researcher must list all existing research projects he or she has participated in, the source of funding for these projects, the duration of these projects, and the percentage of time spent on each.
Financing and insurance	√ Financing and insurance information should be disclosed if it exists. √ If investigators seek financial support, all sources obtained must be listed to avoid a conflict of interest.

Table 2. Summary of the main sections and subsections that should be included in the study protocol

Responsible investigator
Name
Address
Telephone/fax
E-mail
Number of related centers (for multicenter studies)
Specify reference center
Name of the study
Protocol number (abbreviated form)
Keywords (up to 7 specific keywords)
Rationale for the research (explain with available scientific evidence supporting the research)
Study design
Monocentric/multisentric
Prospective/retrospective
Controlled/uncontrolled
Open label/single blind or double blind
Randomized/non-randomized
Experimental/observational
Others
Priority target
Expected results
Criteria analyzed
Basic variables
Main variables
Security variables
Visits and examinations (interventions)
Study population
Short definition of main inclusion and exclusion criteria
Sample size
Estimation of duration of study
Requested funds
Additional features

Preparing a randomized RCT protocol contains more specific details, unlike reporting RCC results. The EQUATOR web page, which contains quality control lists for each type of research, is widely preferred by researchers on this topic, and contains two guidelines for protocol preparation (39). One of these is the PRISMA-P checklist that researchers can use when preparing a systematic review protocol (40). The other is the SPRIT 2013 checklist. The SPIRIT recommendations are a guide for the authors preparing a RCT protocol. Although randomized controlled study protocols are the basis for study planning, execution, reporting and evaluation, they differ greatly in content and quality. To address this issue, SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) was published in 2013. SPIRIT provides an evidence-based list based on the substances proposed for inclusion in the RCT protocols. SPIRIT 2013 is proposed as a guide for researchers who will prepare a RCT protocol (41).

Accessible Databases Where Study Protocol Can Be Registered

The databases where the working protocol can be registered and the registration number can be obtained are quite varied. The WHO International Clinical Research Registration Platform covers all these databases and collects them all under one roof. Table 3 contains the most commonly used web addresses of these databases and information from The Who's International Clinical Trials Registry Platform (8,42-44). In the vast majority of these databases, protocols go through the process of arbitration before the registration number is given.

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Conclusion

It is thought that the information contained in this review will guide the researchers at the point of preparing RCT protocol. With this guide, researchers will be able to understand the importance and benefits of study protocol preparation and how they should form these steps. They will also be able to access the necessary information for the registration of the study protocols they have created.

Writing a detailed protocol that contains all the correct and necessary steps is an important step before starting study. The protocol should be written simply and accurately, but clarify all aspects of the protocol. For this purpose, the use of the study protocol preparation format proposed by the WHO provides both ease in registering the protocol of the study and allows to describe the design and course of the study in detail.

From an ethical point of view, the Declaration of Helsinki also stresses that study protocols must be registered in a public database. Researchers are advised to evaluate the study protocols according to their internationally valid check lists before registering and to register the study protocols in international databases. The registration number obtained from these databases will be included in the protocol part of the study, and when researchers reach the publication stage, this condition will be used by many quality journals. A RCT based on the study protocol preparation steps will be a good source of evidence for use in EBPs and will contribute to the improvement of the quality of RCT and the increase of the value of evidence.

Table 3. Databases in which study protocols can be registered

Database name	Web address	Explanations
Clinical trials	https://clinicaltrials.gov/	√ "ClinicalTrials.gov" is a database in which the results of human clinical studies conducted throughout the world are recorded open to public and which is supported by the United States in particular. √ It is often preferred by researchers, while the majority of RSCs are registered in this database and the registration number (protocol ID) is taken. √ In order to become a member of this database, a password must be obtained from the institution that the researcher is affiliated to by contacting the administrator designated by ClinicalTrial. √ After the protocol of the study is registered in the database, the protocol registration number is given if it is considered appropriate by the referees.
The Australian New Zealand Clinical Trials Registry (ANZCTR)	http://www.anzctr.org.au/	√ The Australian New Zealand Clinical Trials Registry (ANZCTR) is the database in which the protocol registration of clinical trials is provided. √ In 2007 the ANZCTR was one of the first three trial registries to be recognised by the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) as a Primary Registry. The ANZCTR contributes data to the WHO ICTRP, which was developed in 2007.
ISRCTN registry	https://www.isrctn.com/	√ The ISRCTN registry is a primary clinical trial registry recognised by WHO and ICMJE that accepts all clinical research studies (whether proposed, ongoing or completed), providing content validation and curation and the unique identification number necessary for publication. √ All study records in the database are freely accessible and searchable. √ ISRCTN supports transparency in clinical research, helps reduce selective reporting of results and ensures an unbiased and complete evidence base.
WHO International Clinical Trials Registry Platform (ICTRP)	http://apps.who.in c t/ trialsearch/	 √ The mission of the WHO ICTRP is to ensure that research can be conducted fully for everyone involved in health care decision-making. This platform regularly receives data from the following databases. **Databases where data flow is provided every week** √ ClinicalTrials.gov √ The Australian New Zealand Clinical Trials Registry (ANZCTR) √ ISRCTN √ Chinese Clinical Trial Registry, √ EU Clinical Trials Register (EU-CTR) √ The Netherlands National Trial Register, **Databases where data flow is provided every month** √ Brazilian Clinical Trials Registry (ReBec) √ Clinical Trials Registry-India √ Clinical Research Information Service-Republic of Korea √ Cuban Public Registry of Clinical Trials √ German Clinical Trials Register √ Iranian Registry of Clinical Trials √ Japan Primary Registries Network √ Pan African Clinical Trial Registry √ Sri Lanka Clinical Trials Registry √ Thai Clinical Trials Registry (TCTR) √ Peruvian Clinical Trials Registry (REPEC)

Ethics

Peer-review: Internally peer reviewed.

Authorship Contributions

Concept: A.D.A., Z.Ö., Design: A.D.A., Z.Ö., Analysis or Interpretation: A.D.A., Z.Ö., Literature Search: A.D.A., Writing: A.D.A.

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References

1. Senyuva E. Hemşirelik Eğitimi ve Kanıta Dayalı Uygulamalar. Florence Nightingale Hemşirelik Dergisi 2016;24:59-65.
2. Closs S, Cheater F. Evidence for nursing practice: a clarification of the issues. Journal of Advanced Nursing 1999;30:10-7.
3. Arslan S, Şener DK, Küçük Ö. Pediatri kliniğinde çalişan hemşirelerin kanita dayali uygulamalara ilişkin görüşleri. Yildirim Beyazit Üniversitesi Hemşirelik E-Dergisi. 2016;3.
4. Kocaman G. Hemşirelikte Kanıta Dayalı Uygulama. Hemşirelikte Araştırma Geliştirme Dergisi 2006;2:61-9.
5. Scott K, McSherry R. Evidence-based nursing: clarifying the concepts for nurses in practice. Journal of clinical nursing 2009;18:1085-95.
6. Ingersoll GL. Evidence-based nursing: what it is and what it isn't. Nursing outlook 2000;48:151-2.
7. Baldi I, Dal Lago E, De Bardi S, Sartor G, Soriani N, Zanotti R, et al. Trends in RCT nursing research over 20 years: mind the gap. British journal of nursing (Mark Allen Publishing) 2014;23:895-9.
8. WHO. International Clinical Trials Registry Platform (ICTRP) 2018 [cited 2018 December 15].
9. Boden C, Bidonde J, Busch A. Gaps exist in the current guidance on the use of randomized controlled trial study protocols in systematic reviews. Journal of Clinical Epidemiology 2017;85:59-69.
10. Closs SJ, Cheater FM. Evidence for nursing practice: a clarification of the issues. J Adv Nurs 1999;30:10-7.
11. Kocaman G. Hemşirelikte Kanıta Dayalı Uygulama. Hemşirelikte Araştırma Geliştirme Dergisi 2003;2:61-9.
12. Gray J, Chambers LW. Evidence-based healthcare: how to make health policy & management decisions. Canadian Medical Association Journal 1997;157:1598.
13. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? Bmj 2008;336:995-8.
14. Donaldson L. Evidence-based health care, by J A Muir Gray1997. 615- p.
15. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plastic and reconstructive surgery 2011;128:305-10.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine 2009;6:e1000097.
17. Grove SK, Burns N, Gray J. The practice of nursing research: Appraisal, synthesis, and generation of evidence: Elsevier Health Sciences; 2012.
18. Association WM. Declaration of Helsinki. Ethical principles for medical research involving human subjects. http://www wma net/e/policy/b3 htm. 2008.
19. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
20. Cameli M, Novo G, Tusa M, Mandoli GE, Corrado G, Benedetto F, et al. How to Write a Research Protocol: Tips and Tricks. Journal of cardiovascular echography 2018;28:151-3.
21. Chow S-C, Liu J-p. Design and analysis of clinical trials: concepts and methodologies: John Wiley & Sons;2008.
22. ECCRT(European Centre For Clinical Research Training). Writing Clinical Research Protocols 2016 [cited 2018 December 10].
23. DeRenzo E, Moss J. Writing clinical research protocols: Ethical considerations: Elsevier; 2005.
24. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. Bmj 2013;346:e7586.
25. O'Brien K, Wright J. How to write a protocol. Journal of orthodontics 2002;29:58-61.
26. wiki.ecdc.europa. Writing a Study Protocol 2016 [cited 2018 December, 6].
27. Gonzalez CD, Bolaños R, de Sereday M. Editorial on hypothesis and objectives in clinical trials: superiority, equivalence and non-inferiority. Thrombosis journal 2009;7:3.
28. Gray R, Badnapurkar A, Thomas D. Reporting of clinical trials in nursing journals: how are we doing? Journal of Advanced Nursing 2017;73:2782-4.
29. WHO. Trial Registration 2018 [cited 2018 December, 15
30. Zarin DA, Keselman A. Registering a clinical trial in ClinicalTrials. gov. Chest 2007;131:909-12.
31. Al-JunDi A, Sakka S. Protocol writing in clinical research. Journal of clinical and diagnostic research: JCDR 2016;10:ZE10.
32. Huang GD, Bull J, Johnston McKee K, Mahon E, Harper B, Roberts JN. Clinical trials recruitment planning: A proposed framework from the Clinical Trials Transformation Initiative. Contemporary Clinical Trials 2018;66:74-9.
33. WHO ICTRP. International Clinical Trials Registry Platform Searh Portal 2018 [cited 2018 December, 22]. Available from: http://apps.who.int/trialsearch/.
34. WHO. Recommended format for a Research Protocol 2018 [cited 2018 December, 15].
35. Eaton KA, Santini A. An Introduction to Research for Primary Dental Care Clinicians Part 3: Stage 5. Writing a Protocol. Primary Dental Care 2011;18:91.
36. Bhandari M, Devereaux PJ, Montori V, Cina C, Tandan V, Guyatt GH. Users' guide to the surgical literature: how to use a systematic literature review and meta-analysis. Canadian journal of surgery Journal canadien de chirurgie 2004;47:60-7.

37. Smith BA, Lee HJ, Lee JH, Choi M, Jones DE, Bausell RB, et al. Quality of reporting randomized controlled trials (RCTs) in the nursing literature: application of the consolidated standards of reporting trials (CONSORT). Nursing outlook 2008;56:31-7.

38. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC medicine 2010;8:18.

39. equator network. Enhancing the QUAlity and Transparency Of health Research 2019 [cited 2019 5 May,].

40. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews 2015;4:1.

41. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine 2013;158:200-7.

42. ClinicalTrials.gov. ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world 2018 [cited 2018 December,13].

43. ANZCTR. The Australian New Zealand Clinical Trials Registry 2019.

44. BMC Part of Springer Nature. ISRCTN registry 2019.

Review

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Effect of Pregnancy Process on Urinary System and Pelvic Floor and Nursing Approach

Gebelik Sürecinin Üriner Sistem ve Pelvik Taban Üzerine Etkisi ve Hemşirelik Yaklaşımı

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ABSTRACT

The pelvic floor is a structure composed of layers of muscles and fascia that support the opening of the vagina, rectum and urethra together with the abdominopelvic cavity. Pelvic floor includes structures effective in maintaining continence and sexual function. Although chronic cough, obesity, constipation, vaginal surgeries, trauma, race and advancing age are responsible for the deterioration of pelvic integrity with increased intraabdominal pressure; the most important reasons for this are pregnancy and giving birth. In this review, the effects of pregnancy on urinary system and pelvic floor were examined and discussed in the light of current literature.

Keywords: Pelvic floor, pelvic floor in pregnancy, pelvic floor disorders

ÖZ

Pelvis tabanı, abdominopelvik kaviteyle birlikte vajina, rektum ve üretranın dışa açıldığı noktaları destekleyen kas ve fasya tabakalarından oluşan bir yapıdır. Pelvik taban, kontinensin sağlanmasında ve cinsel fonksiyonda etkili olan yapıları içermektedir. Pelvik bütünlüğün bozulmasında intraabdominal basıncın artmasıyla seyreden; kronik öksürük, obezite, konstipasyon, vajinal ameliyatlar, travma, ırk ve ilerleyen yaş sorumlu tutulsa da en önemli sebepler gebelik ve doğumdur. Bu derlemede gebelik sürecinin üriner sistem ve pelvik taban üzerine etkileri incelenerek, güncel literatür doğrultusunda tartışıldı.

Anahtar Sözcükler: Pelvik taban, gebelikte pelvik taban, pelvik taban bozuklukları

Introduction

The pelvic floor consists of the muscle and fascia layers that support the openings of the vagina, rectum and urethra, along with the abdominopelvic cavity. It refers to all support structures that include pelvic organ support. The pelvic floor provides active support to the pelvic organs and muscles, while the fascia and ligaments provide passive support (1). The most important factor providing pelvic integrity is the pelvic muscles and endopelvic fascia (2). The endopelvic fascia is loose connective tissue that surrounds the pelvic organs, connecting them loosely to the muscles that support them and to the bone structures of the pelvis. As is known, connective tissue is a type of biological tissue with a large extracellular matrix that supports, binds and protects organs. The extracellular matrix is a complex structure which is located between cells and support them. It contains structural proteins such as hyaluronic acid, chondroitin sulfate, collagen, elastin. The endopelvic fascia is a biological fabric that is three-dimensional and has the appearance of cobwebs (3). Collagen, elastin, adipose tissue, nerves, veins and lymph channels are composed of smooth muscle. Endopelvic fascia anchors and supports pelvic organs. In addition, it provides the movement needed for urine and gaita storage, parity, coitus and defecation. The uterosacral ligament, cardinal ligament and broad ligaments are thickening in the

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endopelvic fascia and are not actually ligaments. The role of the endopelvic fascia in supporting the bladder, urethra, vagina and other pelvic organs is great.

The term "pelvic diaphragm" is used for the levator ani muscle and the fascias that surround it. Pelvic diaphragm is composed of M. Levator Ani, M.Coccygeus and the fascias surrounding these muscles, and is the lowest part of the abdominal cavity. Rectum, urethra and vagina open into the the pelvic diaphragm. The pelvic diaphragm muscles are arranged as a "U" the end of which is located at the front. The open part of U is called the "urogenital hiatus". M. Levator Ani muscle makes up the bulk of the pelvic floor. It is composed of pubococcygeus and iliococcygeus muscles. The pubococcygeus muscle originates from the pubic bones and clings to the anococcygeal raphe (the anococcygeal raphe is the fibrous band between the anus and the upper surface of the coccyx) and the superior part of the coccyx. The most medial fibers of this muscle are close to the vagina. For this reason, it is called as the "pubovaginal muscle". The greater part of the muscle in the lateral is at the back of the anus and has two layers; the superficial muscle layer ends in the ligamentum anococcygeum. Contraction of this muscle causes elevation of the urethra, although it is not directly connected to the urethra. The deep layer (upper layer) fibers combine behind the rectum with the fibers of the opposite side to form a ring. These fibers are also called as the "puborectalis muscle" because of their close relationship with the rectum. The puborectalis muscle is adjacent to the vagina and clings to the vagina. M. Coccygeus is at the rear-top of the M. Levator Ani and has a triangular shape. It originates from the upper part of Spina Ischiadiaca and the sacrospinal ligament and ends at the last segment of the sacrum and the side of the os coccyx. If trauma and relaxation occur in the pelvic floor muscles, the pelvic floor opens, and if intraabdominal pressure increases, the vagina is left under low external pressure. Ligaments contribute to the adhesion of the vagina for a short time. If the muscles do not close the opening of the pelvic floor during this time, the level and location of the vagina will change.

Most of the muscle fibers found in M. Levator Ani are type 1 slow-contracting muscle fibers and provide continuous toning. The perianal and periurethral parts have type 2 fast-contracting muscle fibers. The continuous tonus provided by type 1 fibers closes the urogenital hiatus while the person is standing, reducing the load found on the passive connective tissue support of the pelvic viscera. Type 2 fibers respond quickly in moments of stress such as coughing, sneezing, and sudden intraabdominal pressure change (4). Iliococcygeus muscle has assumed a shelf-like barrier on the urogenital gap; it supports the uterus, vagina, bladder, and other pelvic organs, but also forms a muscle layer that avoids pelvic organs to prolapse from the urogenital range against increased intra-abdominal pressure. The pubococcygeus and puborectalis muscles surround the urethral and anal sphincters like a sling, helping to increase the intrinsic smooth muscle tone and provide tonic-phasic pressures. When intra-abdominal pressure increases, these muscles maintain continence by increasing the urethral and anal sphincter pressure (5).

For urinary control, it is necessary to store urine at low pressure and sufficient amount in the bladder, and a healthy bladder neck, an active distal urethral sphincter (sphincter formed by skeletal muscle) and strong pelvic floor muscles are necessary. The inability of the bladder to respond to the excess amount of urine with increasing pressure, in other words, impaired compliance is an important part of the incontinence mechanism. The bladder contracts together with the voluntary sphincter, which is made of skeletal muscle, before intraabdominal pressure increases, maintaining urinary control. In women, the bladder neck is weak compared to men and may be easily inadequate. The most important part of the urinary control mechanism is the voluntary sphincter and the active force in closing the bladder outlet. Pelvic floor muscles provide anatomical support. When intraabdominal pressure increases, the urethra becomes trapped between pressure and intact pelvic floor tissue. If the pelvic floor muscles weaken, this compression is insufficient and results in incontinence (6).

Although chronic cough, obesity, chronic constipation, diseases such as COPD, vaginal surgeries, trauma, race and advancing age are responsible for the deterioration of pelvic integrity; the most important reasons for this are pregnancy and giving birth (2,7). Pregnancy causes differences in the structure of all organs, but the data about how it affects the pelvic floor are very limited. It is not clear whether pregnancy or childbirth contributes more to pelvic floor disorders, and studies supported by numerical data are few (8,9).

Pelvic floor muscle power decreases beginning from 20th gestation week to postpartum 6th week. Changes in local tissues caused by the effect of relaxin and reproductive hormones lead to negative effects on pelvic floor muscles. The hormone relaxin softens the connective tissue in the pelvic floor to allow it to prepare for birth (10). Hormonal changes in pregnancy cause physiological changes in all organs. The placement of the fetus in the pelvis and the effect of hormonal differences on the physiology of the pelvis are influential on pelvic floor and pelvic floor support (2).

In pregnant women, the tensile strength of fascias is found to be less than in non-pregnant women. As the uterus grows during pregnancy, intraabdominal pressure increases and the pelvic organs are pushed downwards. This condition exposes the pelvic floor muscles to constant stress and strain and negatively affects pelvic support throughout pregnancy. In the early stages of pregnancy, when viewed with perineal ultrasound, it is observed that the pelvic floor is displaced in the downward direction. It is stated that the contractions of the pelvic floor muscles decrease at a certain rate, the mobility of the bladder and urethra is increased, and that this mobility increase occurs more in the late gestational period (8).

The effects of pregnancy on the urinary system;

- Renal pelvises are disproportionately enlarged. The right renal pelvis is measured in the range of 5 mm (5-25) and the left renal pelvis is measured in the range of 5 mm (3-8) (11).

- Due to the right rotation of the uterus and the left sigmoid colon having a cushion effect on the left urethra, the right urethra is more dilated than the left (11).
- The fact that urethral dilation is below the pelvic girdle shows the mechanical effect of the growing uterus. This dilation is seen in the 8th week and reaches the highest level in the 2nd trimester, all of which are not fully explained by mechanical factor and hormonal factors are thought to have an effect (12).
- Ureters of term pregnant women hold 200 mL more volume compared with women without pregnancy.
- Urethral dilation recedes until the 3rd postpartum month (11).
- The functional length of the urethra during pregnancy reaches from 30 mm to maximum 35 mm in the third trimester, decreasing to 28 mm in the postpartum period. This occurs when the bladder shifts upwards and forwards (12).
- Increased blood volume causes increased blood flow to the pelvic organs (11).
- Increase in hormone production leads to relaxation of the musculoskeletal system in the whole body, especially the pelvis (11).
- Blood and edema in the pelvic diaphragm also contribute to the relaxation of this layer (11).
- In the middle of pregnancy, bladder capacity reaches from 410 mL to 460 mL. But in the late third trimester it falls again to 272 mL due to relaxation of the uterus sub-segments and the fetal head being engaged in the pelvis (12).

Increase in bladder and urethra pressure in pregnancy is 2-3 times more than intraabdominal pressure and thus urination is provided. Another mechanism that explains the incidence of stress urinary incontinence in pregnancy needs to be effective. The looseness of pelvic muscles and connective tissue is one of the causes of stress incontinence. Despite increased bladder pressure in women who experience stress incontinence during pregnancy, urethral pressure is insufficient (11). Pregnancy and especially vaginal delivery, negatively affect bladder neck support and its drop by valsalva maneuver, but this has not been correlated with incontinence.

Causes of pelvic floor dysfunction in pregnancy; baby's birth weight, body mass index (BMI), smoking, genetic predisposition, age, intraabdominal pressure and nutrition (13). Hormones throughout pregnancy influence the biochemical composition of the extracellular matrix and the hydration of pelvic floor tissue. It causes the diameter of the collagen fibers and the convoluted structure of the collagen fibrils to change. Such effects in pregnancy can affect viscoelastic features in the vaginal wall, pubovisceral muscles, and the perianal region. Changes in collagen cause increased mobility of the bladder neck and stress incontinence. As the collagen component of connective tissue contributes to the structural support of the neck of the bladder, abnormalities in collagen can increase the risk of incontinence. As the amount of collagen is reduced in pregnancy, the tension property of connective tissue is also reduced (14).

Pelvic floor disorders including pelvic organ prolapse, urinary system/defecation dysfunctions, sexual dysfunction and pelvic pain can be seen in pregnancy.

Pelvic organ prolapse is the prolapse of the anterior and/or posterior walls of the vagina, uterus (cervix) and the vaginal vault downwards in patients with a history of hysterectomy. This finding is present with symptoms and is usually seen at hymen level or below levels. It is a major health problem in developed and developing countries. There is little data on pelvic organ prolapse in pregnancy. But the level of prolapse is thought to increase in pregnancy.

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There are studies that show that the third trimester of pregnancy and the postpartum period cause prolapse more than the first trimester. This means that pregnancy weakens pelvic support regardless of birth. The effects of hormonal change in pregnancy on collagen structure, growth of the uterus throughout pregnancy, increased tension of pelvic floor muscles weakening the uterus, reduce pelvic floor support. As the amount of collagen in the endopelvic fascia decreases; pelvic floor support is also reported to decrease and pelvic support injury occurs before birth (9).

During pregnancy, the first and most affected area of prolapse in pregnant women is the "Aa" point according to the POP-Q (Pelvic Organ Prolapse-Quantification) classification system (2,15,16). Pregnant nullipars and non-pregnant nullipars were compared and stage-2 was detected in 47.6% of pregnant women, whereas no further prolapse than stage-1 was reported in non-pregnant women. In this context nullipar pregnancy in women is related to more advanced pelvic organ prolapse (2).

There are several risk factors for urinary incontinence (UI), including age, birth, menopause, and smoking. Stress urinary incontinence (SUI) is defined by the International Continence Society (ICS) as urinary incontinence from the urethra along with increased intrabdominal pressure during physical activity (6). Prevalence of SUI in gestation has been found between 18.6% and 75% (17,18). Pregnancy is one of the main risk factors for SUI development. Pregnancy is be associated with a decrease in pelvic floor muscle strength, which may lead to

a decrease in the strength, supporting function and sphincter function of the pelvic floor muscle. However, the mechanism of pregnancy-related SUI is not fully understood. Huebner stated that UI prevalence increased in the second half of pregnancy in the study conducted with 411 pregnant women. Milsom's study found that the prevalence of UI increased in pregnancy (especially in the second trimester) and then gradually decreased in the first months of the first year after birth (19).

The pelvic floor muscle plays a complementary role in maintaining the continence mechanism by actively supporting the pelvic organs and closing the urethral sphincter during contraction. When coughing, sneezing, laughing, or moving, intra-abdominal pressure increases and this pressure is transmitted to the bladder. When the pressure in the bladder is greater than the urethral closure pressure along with the weakness of the urethral sphincter, this results in incontinence or SUI (17).

However, SUI seen in women during pregnancy can be prevented and improved with pelvic floor muscle exercise (PFME). PFME aims to increase pelvic floor muscle (PFM) strength to support the bladder, ureter and urethra; increase the effectiveness of sphincteric function of the urethra during exertion; and improve the continence mechanism after proper contraction of the pelvic floor.

Oliveira et al. reported that PFME led to a significant increase in PFM pressure and force during pregnancy. PFME is therefore recommended as the first intervention that prevents and improves the symptoms of pregnancy and postpartum SUI before considering other interventions.

In pregnancy, difficulty in micturation is quite common. During early gestation (up to 12^{nd}-14^{th} gestation weeks), the cause of urinary retention is the retrovert uterus. This creates mechanical pressure on the bladder neck and urethra. Urinary retention may develop as a result of the uterus compressing the bladder during late gestation (11).

As a result of frequent urination (frequency) in pregnancy, The increase in plasma volume during early pregnancy and the pressure of expanding uterus on the bladder are reported as the causes of frequent urination in pregnancy. A study performed in women in the 32^{nd} gestation week suggested that the expanding uterus caused upward displacement of the bladder, resulting in frequent urination due to pressure on the bladder (11).

Pregnancy and childbirth also cause defecation disorders. Anal incontinence occurs in 1.3%16% of pregnant womens (20). Coordination integrity between the neuromuscular body of the colon and rectum and the anal sphincter plays an important role in maintaining defecation control and continence.

Innervation of internal anal sphincter, transmission of impulse to circular muscle layer and enteric nervous system of rectum, close relationship between external anal sphincter and pelvic floor muscles, especially puborectalis muscle and the coordination of puborectalis muscle, longitudinal muscle of rectum and anal canal muscles play important role in this coordination integrity (2). In addition, another important factor in maintaining defecation control and continence is the increase of anorectal angle as a result of contraction of the puborectal muscle, which allows for greater retention of feces (2).

Ischiocavernosus, bulbocavernosus, and levator ani muscles and pelvic floor muscles which are effective on sexual function, pull the rectum, vagina and anterior part of urethra towards the pubic bone and close the lumen during vaginal penetration and orgasm. The literature states that strong pelvic floor muscles, especially the ischiocavernosus muscle, have an important role in achieving genital arousal and orgasm (21). The strong pelvic muscles provide strong lubrication, arousal and an increase in orgasm. Sexual pain disorders are seen if excessive tonus increase occurs in pelvic muscles. Vaginal sensitivity, decrease in orgasm intensity and UI during sexual intercourse are seen if hypotonia occurs (22).

Pelvic pain is pain felt in the lower quadrant of the abdomen and pelvis (23). A fifth of women in pregnancy experience pelvic pain (15). The etiology of pelvic pain seen in pregnancy is not fully understood (24).

Nurses should plan training and provide information for preventing and protecting pelvic floor dysfunction for pregnant women 13. A comprehensive anamnesis should be taken to determine the factors that may cause risk in pregnant women. The woman's health behaviors during pregnancy affect her pregnancy, birth and the health of the newborn 25. Pregnant women should be supported to gain healthy lifestyle behaviors (controlling all behaviors that may affect the health of the individual, choosing and regulating behaviors appropriate to the health condition while performing daily life activities with the ability to make decisions and making these behaviors habitually) (26). Pregnant women should be given training on PFME (27). In the literature, there are studies that report that UI can be prevented in pregnant women who perform PFME in the last trimester and after birth (28). PFME increases PFM strenght and reduces the risk of pelvic organ prolapse. It also prevents hemorrhoids and increases excretory control and orgasm (10,29). Furthermore, pregnant women should be informed about taking care of weight gain during pregnancy, consuming fibrous foods to prevent constipation, consuming enough fluids, not lifting heavy, not smoking, avoiding valsalva maneuvers as much as possible (13,30).

Conclusion

As a result, pregnancy causes changes in the pelvic floor and urinary system. Urinary incontinence, pelvic organ prolapse, fecal incontinence and pelvic pain are caused by the inability of the pelvic floor. Training should be given to pregnant women in order to maintain the function of the pelvic floor.

Ethics

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Authorship Contributions

Concept: N.K.B., G.S., Design: N.K.B., G.S., G.Ç., Analysis or Interpretation: N.K.B., G.S., G.Ç., Literature Search: N.K.B., G.S., G.Ç., Writing: G.S.

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References

1. Sarıcı DY, Boran AB. Üriner İnkontinans Tedavisinde Pelvik Taban Egzersizleri Nöromodülasyon-biofeedback İçin Evde Egzersiz Eğitim Uygulaması Kısa Dönem Sonuçları. Uzmanlık Tezi. İstanbul, 2009;4-5.
2. Kumtepe Y. Pelvis tabanı, gebelik ve doğum. Yalçın Ö (Editör). Temel Ürojinekoloji. İstanbul: Nobel Tıp Kitabevleri; 2009;61-5.
3. 3Üçgül İ, Aras S, Elibüyük U. Ekstraselüler matris yapısı ve görevleri. Uludağ University Journal of The Faculty of Engineering, 2018;23:295-310.
4. Dere F, Karın duvarları ve pelvis, "Anatomi" 2. Baskı, Adana, s,1990, 166-204.
5. Aydın ÇEN. Gebelikte başlayan pelvik taban bozukluğu sıklığının belirlenmesi ve doğum sonrası 6. Ayda sebat eden olguların özelliklerinin öngörülmesi, Ankara Üniversitesi Tıp Fakültesi, Doğum ve Kadın Hastalıkları Anabilim Dalı, Tıpta Uzmanlık Tezi. 2016;21-2.
6. Demircan N, Özmen Ü, Köktürk F, Küçük H, Ata Ş, Harma M, Arıkan, İİ. What are the probable predictors of urinary incontinence during pregnancy. Peer J 2016;4:e2283.
7. Sancak, P. Pelvik organ prolapsusu ve/veya inkontinansı olan kadınlarda cinsel disfonksiyon ve pelvik organ prolapsusu/idrar inkontinans cinsel fonksiyon sorgulaması (PISQ-12) formunun validasyonu. TC Sağlık Bakanlığı Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği Uzmanlık Tezi 5. 2008.
8. Akbayrak T, Kaya S, Tedavi F. Gebelik ve egzersiz. Hacettepe Üniversitesi Sağlık Bilimleri Fakültesi, Fizik Tedavi Ve Rehabilitasyon Bölümü Klasmat Matbaası, Ankara. 2008.
9. Bozkurt M, Yumru AE, Şahin L. Pelvic floor dysfunction, and effects of pregnancy and mode of delivery on pelvic floor. Taiwanese Journal of Obstetrics and Gynecology 2014;53:4,452-8.
10. Dönmez S, Kavlak O. Gebelikte pelvik taban kas egzersizi. Balıkesir Sağlık Bilimleri Dergisi,2014; 3:1,45-49.
11. Dinç A. Üriner İnkontinans Şikâyeti Olan Gebelerde Gebelik ve Postpartum Dönemde Uygulanan Pelvik Taban Kas Egzersizlerinin Bu Şikâyetin Giderilmesindeki Etkinliği", İstanbul Üniversitesi Sağlık Bilimleri Enstitüsü, Doğum ve Kadın Hastalıkları Hemşireliği Anabilim Dalı, Doktora Tezi. 2004.5-6
12. Gollin YG. Gebelik sırasında ve puerperium'da idrar yollarında görülen değişiklikler. ürojinekoloji ve pelvik rekonstrüktif cerrahi temel bilgiler, Çev. Önay Yalçın. Mcgraw-Hill, Türkiye Klinikleri 2007;203-8.
13. Kahyaoğlu Süt H. Gebelik ve doğumun pelvik taban yetersizlikleri üzerine etkisi: önlenmesi ve korunmada hemşirenin rolü. Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi 2015;4:292-304.
14. Abrams P, Cardozo L, Wagg A, Wein A. Incontınence, 6 th Internatıonal Consultatıon on Incontınence, Tokyo 2016;378-9.
15. Turan İ. (2016). Pelvik taban cerrahisinin seksüel fonksiyon ve yaşam kalitesi üzerine etkisinin incelenmesi, Pamukkale Üniversitesi Tıp Fakültesi, Doğum ve Kadın Hastalıkları Anabilim Dalı, Tıpta Uzmanlık Tezi. 17-20.
16. Liddle SD, Pennick V. Interventions for preventing and treating low-back and pelvic pain during pregnancy. Cochrane Database of Systematic Reviews 2015;9.
17. Sangsawang B. Risk factors for the development of stress urinary incontinence during pregnancy in primigravidae: a review of the literature. European Journal of Obstetrics & Gynecology and Reproductive Biology 2014;178:27-34.
18. Luo D, Chen L, Yu X, Ma L, Chen W, Zhou N, Cai W. Differences in urinary incontinence symptoms and pelvic floor structure changes during pregnancy between nulliparous and multiparous women. PeerJ 2017;5:e3615.
19. Milsom I, Altman D, Cartwright R, Lapitan MC, Nelson R, Sjöström S, et al. Epidemiology of urinary incontinence (UI) and other lower urinary tract symptoms (LUTS), pelvic organ prolapse (POP) and anal incontinence (AI). In: Abrams P, Cardozo L, Wagg A, Wein A editor(s). Incontinence: 6th International Consultation on Incontinence, Tokyo, September 2016. 6th Edition. Vol. 1, Bristol (UK): International Continence Society (ICS) and International Consultation on Urological Diseases (ICUD) 2017:1-141.
20. Rogers RG, Ninivaggio C, Gallagher K, Border AN, Qualls C, Leeman LM. Pelvic floor symptoms and quality of life changes during first pregnancy: a prospective cohort study. International urogynecology journal 2017;28:1701-7.
21. Ceylan Çelik F. Pelvik taban elekromyografik aktivite cevabı ve abdominal kas kuvvetinin, kadın cinsel fonksiyonu ile ilişkisinin değerlendirilmesi, 2013.
22. Polat B. Pelvik taban kas zayıflığı olan kadınlarda pelvik taban eğitiminin cinsel fonksiyon ve yaşam kalitesi üzerine etkisi. MS thesis. Sağlık Bilimleri Enstitüsü, 2017.
23. 23.Demir F. Kronik pelvik ağrıda jinekolojik, ürolojik, psikiyatrik etkenlerin araştırılması: Diagnostik laparoskopinin kronik pelvik ağrıdaki yeri. Diss. SDÜ Tıp Fakültesi, 2006.
24. Hall H, Cramer H, Sundberg T, Ward L, Adams J, Moore C, Lauche R. The effectiveness of complementary manual therapies for pregnancy-related back and pelvic pain: A systematic review with meta-analysis. Medicine 2016;95:38.

25. Ural A. Gestasyonel diabetes mellitus ve sağlıklı yaşam biçimi davranışları. Düzce Üniversitesi Sağlık Bilimleri Enstitüsü Dergisi 2016;6:120-2.
26. Kostak MA, Kurt S, Süt N, Akarsu Ö, Ergül GD. Hemşirelik ve sınıf öğretmenliği öğrencilerinin sağlıklı yaşam biçimi davranışları. TAF Preventive Medicine Bulletin 2014;13:3.
27. Aktas D, Sahin E, İlknur MG. Kadın sağlığını etkileyen, sık görülen bazı jinekolojik problemler ve hemşirelik yaklaşımları. Ankara Sağlık Bilimleri Dergisi 2012;1:37-53.
28. Woodley SJ, Boyle R, Cody JD, Markved S, Hay Smith EJC. Doğum öncesi ve doğum sonrası kadınlarda idrar ve dışkı idrar kaçırmalarının önlenmesi ve tedavisi için pelvik taban kas eğitimi. Sistematik incelemelerin cochrane veri tabanı 2017;12.
29. Rivalta M, Sighinolfi M.C, Micali S, De Stefani S, Bianchi G. Sexual function and quality of life in women with urinary incontinence treated by a complete pelvic floor rehabilitation program (biofeedback, functional electrical stimulation, pelvic floor muscles exercises, and vaginal cones). The journal of sexual medicine 2010;7:1200-8.
30. Demir R, Taşpınar A. Kadın sağlığının korunmasında kegel egzersizlerinin önemi ve ebelik yaklaşımı. Ege Üniversitesi Hemşirelik Fakültesi Dergisi 2018;34:77-88.

Case Report

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Acute Respiratory Distress Syndrome and Myocarditis Caused by Human Metapneumovirus in a Child

Çocukta İnsan Metapneumovirüs'ün Neden Olduğu Akut Solunum Sıkıntısı Sendromu ve Miyokardit

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ABSTRACT

Human metapneumovirus (hMPV), a recently described paramyxovirus, has commonly been associated with upper and lower respiratory tract infections in young children. Severe infections including cardiovascular disease associated with hMPV have been particularly reported in older and immunocompromised patients; however, there has been no previous report of hMPV causing myocarditis in a child. In this article, we present a rare case with acute respiratory distress syndrome and myocarditis associated with hMPV in a child.

Keywords: Human metapneumovirus, myocarditis, child

ÖZ

Son yıllarda tanımlanan bir paramiksovirüs olan insan metapnömovirüsü (hMPV), küçük çocuklarda genellikle üst ve alt solunum yolu enfeksiyonları ile ilişkilendirilmiştir. hMPV ile ilişkili kardiyovasküler hastalık dahil olmak üzere şiddetli enfeksiyonlar özellikle yaşlı ve immün yetmezliği olan hastalarda bildirilmiştir. Literatürde çocuklarda miyokarditle seyreden bildirilmiş hMPV olgusu yoktu. Bu yazıda, hMPV'ye bağlı akut solunum sıkıntısı sendromu ve miyokardit birlikteliği bulunan nadir bir çocuk hasta sunulmuştur.

Anahtar Sözcükler: İnsan metapneumovirus, miyokardit, çocuk

Introduction

Human metapneumovirus (hMPV), a recently described paramyxovirus, is a non-segmented, negative-sense RNA virus (1). Since its discovery in the Netherlands in 2001, hMPV has been recognized as one of the most commonly causes of upper and lower respiratory tract infections in children (2). Although hMPV can infect adults and the elderly, the highest incidence of infection is among children under the age of 5 (3). It can cause various infectious diseases including rhinitis, bronchiolitis and pneumonia. The disease caused by hMPV is usually mild or moderate in severity and recovers spontaneously, but rarely may cause severe illnesses that requires admission to an intensive care unit. We report the case of a 2.5-month-old boy with acute respiratory distress syndrome and myocarditis secondary to the hMPV.

Case Report

A previously healthy 2.5-month-old boy was hospitalized because of nonproductive cough lasting ten days. On the third day in this hospital, his clinical condition and breathing worsened and cardiomegaly was detected. He was intubated and referred to our department of pediatric intensive care unit for intensive care management and investigation of cardiomegaly. The patient was admitted to intensive care unit with a diagnosis of acute respiratory distress syndrome. His physical examination showed that his body temperature was 36.9 °C, oxygen saturation 96%, blood pressure 76/48 mm Hg and heart rate 160/min. He had cutis marmorata. Capillary refill time was >5 seconds. Auscultation of the lungs revealed obvious bilateral thin rales and bilateral rhonchus. Abdominal examination revealed a liver enlargement

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of 5 cm below subcostal margin. His other examination findings were normal. Laboratory tests showed a white blood cell count of 11300/μL (normal range, 4000-10000), hemoglobin level of 8.56 g/dL, thrombocyte count of 225 bin/μL, C-reactive protein level of 16 mg/L (normal range=0-5), and normal biochemistry values. His arterial blood gas results were as follows: PH=7.35, $PCO_{2=}$52, HCO_3=22 mmol/L, lactate=5, O_2 saturation=97%. Chest X-ray (CXR) showed cardiomegaly and bilateral diffuse opacities, suggesting bilateral pulmonary edema (Figure 1). Ventilation was started with high positive end-expiratory pressure (PEEP) on synchronized intermittent mandatory ventilation (SIMV) mode of mechanical ventilator. Blood, urine and tracheal aspirate cultures were taken and empirical antibiotic treatment with vancomycin and meropenem were started. Dopamine supplement was initiated for sepsis and secondary circulatory disorder. Electrocardiogram showed sinus tachycardia, widespread QRS voltage decrease, and ST elevation (Figure 2). Echocardiogram demonstrated a depressed ejection fraction of 36% with severely dilated left ventricle. Troponin-I level was 8 ng/mL. Brain natriuretic peptide (BNP) level was 3200 pg/mL. A dose of 2 g/kg intravenous immunoglobulin (IVIG) was given to the patient who was diagnosed as having myocarditis according these findings. Intravenous (IV) diuretic and positive inotropic agents were started (furosemide 3 mg IV, milrinone 0.5 mcg/kg/min IV infusion). On the third day of his hospitalization, the patient in whom oxygenation did not recover carbon dioxide retention developed was taken to airway pressure release ventilation (APRV) mode. His echocardiographic examination showed that ejection fraction increased to 38%. The referral hospital reported that respiratory viral reverse transcriptase polymerase chain reaction (PCR) performed in the nasopharyngeal swab sample with FilmArray® Multiplex PCR (BioFire, Biomerieux Diagnostics, France) was positive only for hMPV but negative for microorganisms most commonly causing pulmonary infection, including adenovirus, respiratory syncytial virus, influenza A, influenza B, parainfluenza, coronavirus, clamydia and mycoplasma. On the sixth day of his hospitalization, CXR findings also markedly improved. On the 10th day of admission, the patient was extubated and his echocardiographic examination showed that ejection fraction increased to 48% and there was mild mitral regurgitation. Bilateral diffuse opacities and cardiomegaly improved on CXR (Figure 3). Dopamine infusion was stopped and digoxin was started. Blood, urine and tracheal aspirate cultures remained sterile. The antibiotic treatment was continued for 14 days. Finally, the patient was diagnosed as having hMPV infection complicated by ARDS and myocarditis. On the 16th day of admission, the patient recovered without any serious sequelae and he was discharged home on furosemide and digoxin.

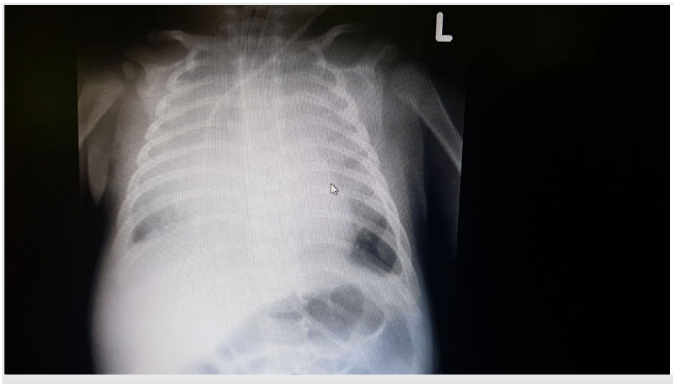

Figure 1. Chest X-ray shows cardiomegaly and bilateral diffuse opacities

Discussion

Human metapneumovirus (hMPV) was identified in 2001 by van den Hoogen et al. (1) from nasopharyngeal aspirates of children with respiratory tract infections. Since then, it has been reported worldwide as one of the most common causes of upper and lower respiratory tract infections (4). Clinical manifestations of hMPV infections are similar to that of respiratory syncytial virus and range from coryza to mild or moderate upper respiratory tract infections and severe lower respiratory tract infections requiring hospitalization (5). Mortality is rare and may occur in 5-10% of children with hMPV infections who are admitted to the intensive care units. Although hMPV can cause infection in all age groups, studies have shown that mostly infants and young children are affected by hMPV infections (6). Human metapneumovirus is commonly associated with acute respiratory tract infections in children but it can affect different organ systems including

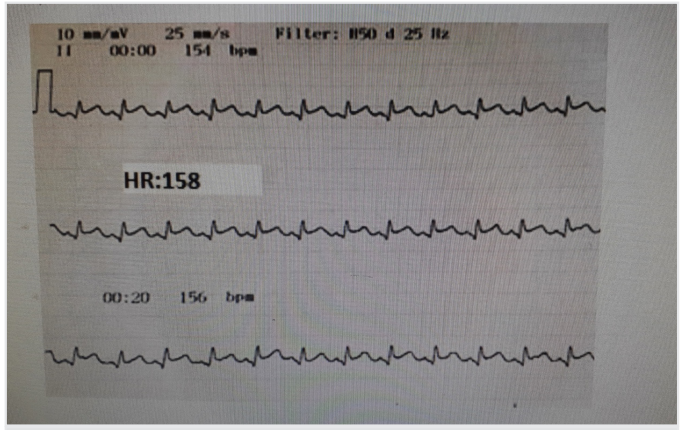

Figure 2. Electrocardiogram shows sinus tachycardia, widespread QRS voltage decrease, and ST elevation

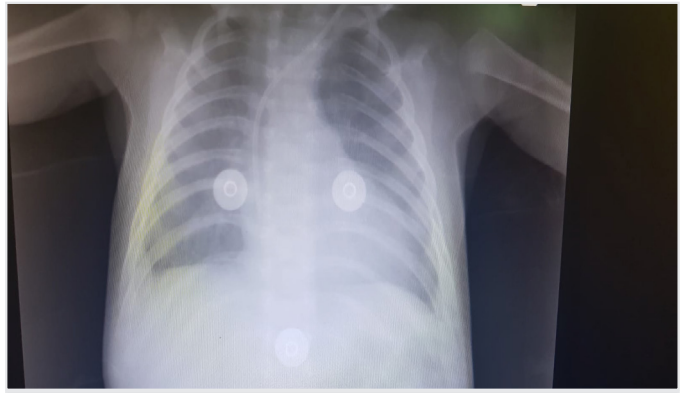

Figure 3. On the 10th day of hospitalization chest X-ray shows improved cardiomegaly and bilateral diffuse opacities

cardiovascular system (7). Viral infections are the most commonly identified cause of myocarditis in children. These pathogens include enteroviruses, particularly Coxsackie B virus, adenovirus, parvovirus B19, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus and influenza virus (8). Human metapneumovirus infections may be distinguished from the other respiratory tract infections due to more common accompanying cardiovascular diseases (9). In one of the few case reports, hMPV infection in a 25-year-old patient who was complicated by acute myocarditis was reported (10). A Korean pediatric study showed analysis of the medical records of 33 patients with myocarditis. Human MPV was one of the etiologic agents of acute myocarditis (11). We experienced a rare case of hMPV infection in an infant complicated by acute respiratory distress syndrome and myocarditis that resolved after intensive care management. Our patient presented with acute respiratoy failure and severe systolic dysfunction in the setting of a 10-day history of lower respiratory infection. Endomyocardial biopsy is the gold standard for diagnosis of myocarditis but it is an invasive test and may have complications. Therefore, it can be used in selected patients with unexplained diagnosis or those with cardiomyopathy who are unresponsive to treatment. Cardiovascular magnetic resonance (CMR) is a highly sensitive non-invasive imaging technique for the early diagnosis of myocarditis in children. CMR shows characteristic tissue changes such as edema, hyperemia, necrosis and fibrosis (12,13). We made the diagnosis of myocarditis with clinical manifestations, elevated inflammatory markers, cardiac troponin I levels, and echocardiogram with reduced ejection fraction. Treatment of viral myocarditis is mainly supportive with unclear role of anti-inflammatory therapy, IVIG, steroids, and anti-viral therapy. Our patient was treated with high dose IVIG, intravenous diuretics and positive inotropic agents. In the present case, although a bacterial pathogen was not isolated, antibiotics were administered because of concerns regarding concomitant bacterial pneumonia.

Conclusion

Severe infections including cardiovascular diseases associated with hMPV are particularly reported in older and immune compromised patients. However, our patient was an infant. He responded well to high dose IVIG, intravenous diuretics and positive inotropic agents. He was discharged home after 16 days of intensive care hospitalization. Although hMPV is generally associated with acute respiratory tract infections in children, it should still be kept in mind that it can cause myocardial involvement.

Ethics

Informed Consent:

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: İ.E., K.T., Design: K.Y., B.V., İ.E., K.T., Data Collection or Processing: K.Y., İ.E., Analysis or Interpretation: K.Y., B.V., İ.E., Literature Search: K.Y., B.V., Writing: K.Y., İ.E.

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References

1. van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719-24.
2. Kim CK, Choi J, Callaway Z, Kim HB, Chung JY, Koh YY, et al. Clinical and epidemiological comparison of human metapneumovirus and respiratory syncytial virus in seoul, Korea, 2003-2008. J Korean Med Sci 2010;25:342-7.
3. Principi N, Esposito S. Paediatric humanmeta pneumovirus infection: epidemiology, prevention and therapy. J Clin Virol 2014;59:141-7.
4. Garcia J, Sovero M, Kochel T, Laguna-Torres VA, Gamero ME, Gomez J, et al. Human metapneumovirus strains circulating in Latin America. Arch Virol 2012;157:563-8.
5. Heikkinen T, Osterback R, Peltola V, Jartti T, Vainionpää R. Human metapneumovirus infections in children. Emerg Infect Dis 2008;14:101-6.
6. Nascimento-Carvalho CM, Cardoso MR, Ruuskanen O, Lappalainen M. Sole infection by human metapneumovirus among children with radiographically diagnosed community-acquired pneumonia in a tropical region. Influenza Other Respir Viruses 2011;5:285-7.
7. Panda S, Mohakud NK, Pena L, Kumar S. Human metapneumovirus: review of an important respiratory pathogen. Int J Infect Dis 2014;25:45-52.
8. Tunuguntla H, Jeewa A, Denfield SW. Acute Myocarditis and Pericarditis in Children.
9. Pediatr Rev 2019;40:14-25.
10. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. J Infect Dis 2012;206:56-62.
11. Weinreich MA, Jabbar AY, Malguria N, Haley RW. New-Onset Myocarditis in an Immunocompetent Adult with Acute Metapneumovirus Infection. Case Rep Med 2015;2015:814269.
12. Kim HJ, Yoo GH, Kil HR. Clinical outcome of acute myocarditis in children according to treatment modalities. Korean J Pediatr 2010;53:745-52.
13. Martinez- Villar M, Gran F, Sabaté-Rotés A, Tello-Montoliu A, Castellote A, Figueras-Coll M, et al. Acute Myocarditis with Infarct-like Presentation in a Pediatric Population: Role of CardiovascularMagnetic Resonance. Pediatr Cardiol 2018;39:51-6.
14. Lv J, Han B, Wang C, Wang J, Jiang D, Zhao L, et al. The Clinical Features of Children With Acute Fulminant Myocarditis and the Diagnostic and Follow-Up Value of Cardiovascular Magnetic Resonance. Front Pediatr 2019;7:388.