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The effects of MDR-1 gene polymorphisms on the clinical course of chronic hepatitis B infection

Hakan Şıvgın[1], Abdülkerim Yılmaz[2], Aydın Rüstemoğlu[3], Banu Öztürk[4], Şafak Şahin[1], Türker Taşlıyurt[1]

[1]Department of Internal Medicine, Faculty of Medicine, Tokat Gaziosmanpaşa University, Tokat, Turkey
[2]Department of Gastroenterology, Medicana Sivas Hospital, Sivas, Turkey
[3]Department of Medical Biology, Faculty of Medicine, Aksaray University, Aksaray, Turkey
[4]Department of Medical Oncology, Antalya Training and Research Hospital, University of Health Sciences, Antalya, Turkey

ABSTRACT

Aims: Chronic HBV infection is associated with a high morbidity and mortality rate due to the increased risk of hepatic cirrhosis and hepatocellular cancer. Treatment modalities and resistance are currently being investigated. Several mechanisms underlie drug resistance. P-glycoprotein (P-gp), the product of the multidrug resistance gene (MDR-1), is a well-known mechanism of the MDR phenotype. MDR gene C1236T polymorphism is associated with decreased p-gp function. The mutation of the MDR gene can affect the clinical course of the disease and response rate to treatment. The aim of our study was to investigate the relationship between MDR gene polymorphism and clinical course and treatment responses in chronic HBV infection.

Methods: A total of 90 (male/female: 69/21) patients with chronic HBV infection under Lamivudine treatment were enrolled in this study. Mean ages were 49.8±12.6 (range: 22-75) years. The patients were categorized as: Treatment-respondent (group 1: HBV-DNA is negative at the 24th week) and treatment-refractory (group 2: HBV-DNA is still positive after the 24th week). Group 1 consisted of 51 (M/F: 38/13) and group 2 consisted of 39 (M/F: 31/9) patients. There was no significant difference between the ages and genders of the two groups. Histologic activity indexes (HAI), total bilirubin, AST and ALT levels, and HBV-DNA titers were significantly higher in the patients in group 2 than in group 1 ($p<0.05$).

Results: Genotype distributions; homozygous CC genotype was in 8 (15.7 %), heterozygous CT genotype was in 37 (%72.5), and homozygous TT genotype was in 6 (11.8%) in patients in group 1. The homozygous CC genotype was in 13 (33.3%), the heterozygous CT genotype was in 21 (53.8%), homozygous TT genotype was in 5 (12.8%) in patients in group 2. CC genotype was more common in group 2 than in group 1 ($p=0.044$). C and T alleles' frequencies in groups 1 and 2 were 51.96% and 60.26%, 48.04%, and 39.74%, respectively ($p>0.05$). In group 2 (n:11) patients with a YMDD mutation, 5 (45%) had the CC genotype, 5 (45%) had the CT genotype, and 1 (9%) had the TT genotype. Three (37%) of the patients with a negative YMDD mutation in group 2 (n: 8) had the CC genotype, while five (63%) had the CT genotype. CC genotype was more common in the patients with a positive YMDD mutation than in group 1 ($p=0.043$). Furthermore, the CC genotype was more common in patients with HBV-DNA positivity than in group 1 at the 12th month of Lamivudine treatment ($p=0.042$).

Conclusion: Consequently, MDR-1 and p-gp polymorphisms are important factors in the clinical course of chronic HBV infection and may influence treatment responses. In the current study, it was found that the CC genotype of the MDR-1 gene C1236T was more common in patients with lamivudine-resistant HBV infection.

Keywords: Hepatitis B, Lamivudine resistance, MDR-1 gene polymorphism

INTRODUCTION

Chronic hepatitis B is a major health problem and one of the most common infectious diseases. Liver cirrhosis and cancer, which are fatal liver diseases, develop in 25% of chronic hepatitis B patients.[1,2]

Lamivudine is the first nucleoside analogue approved for the treatment of chronic hepatitis B. However, the relapse of the disease and the development of drug resistance after an average of 3-6 months following the discontinuation of the treatment are the limitations of lamivudine treatment.[1]

MDR1 gene (Multidrug Resistance) encodes a transmembrane transporter protein named P-glycoprotein (P-gp). P-gp controls the intracellular entry and exit routes of many drugs and chemicals. Response to drugs and drug-related adverse events vary across individuals in the same population due to genetic changes in drug-metabolizing enzymes. This difference may be explained by the increased expression of MDR genes that lead to drug resistance.[3,4]

The increased expression of the MDR1 gene product, P-gp, is the most well-studied among the mechanisms that create the MDR phenotype. It has been reported in various studies that single nucleotide polymorphisms manifested in the MDR1 gene lead to alterations in P-gp expression and/or function.[4] It is considered that P-gp expression is high in some alleles, and this causes resistance to drugs and some substances.[5] P-gp

Corresponding Author: Hakan Şıvgın, sivginhakan@gmail.com

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is expressed in various organs and is associated with drug distribution in intestinal erythrocytes, endothelial cells of brain capillaries, proximal tubule and hepatic canalicular cells.[6]

The three commonly observed SNPs in the MDR1 gene and the most emphasized in the literature are C3435T, G2677T and C1236T, and these SNPs are common haplotype components.

In this study, the association between treatment response rates and C1236T polymorphism in the MDR1 gene in chronic hepatitis B patients was investigated.

METHODS

Ninety patients treated for Chronic Hepatitis B that applied to Gaziosmanpaşa University Faculty of Medicine Gastroenterology Clinic between 2009 and 2012 and received lamivudine, were enrolled in the study. In this study, which was approved by the Ethics Committee of Gaziosmanpaşa University Faculty of Medicine by the decision dated 30.03.2012 and numbered 2012-30, all genetic and laboratory analyzes were performed in Gaziosmanpaşa University Faculty of Medicine Genetics Laboratory.

Selection of Cases

Patients with positive HBS Ag results detected by the ELISA method and significant HBV-DNA levels detected by PCR method were included in the study. YMDD mutation analysis was done in lamivudine resistant cases via HBV Quantitative & YMDD Mutation Real Time PCR Kit (Shanghai ZJ Bio-Tech Co.,Ltd, China, HD-0003-04).

Patients enrolled in the study were divided into two groups.

Group 1: Patients on lamivudine therapy for chronic hepatitis B and responding to treatment with negative HBV-DNA titer.

Group 2: Patients non-responsive to treatment with an increase or no significant decrease in HBV-DNA titer during monitoring of the patients with chronic hepatitis B on lamivudine therapy. YMDD mutation was studied in patients in group 2 and YMDD mutation was examined in two subgroups as positive/negative.

A total of 90 patients diagnosed with chronic hepatitis B were included in the study. Patients with negative HBV-DNA titer at week 24 during lamivudine therapy were considered to be responsive to treatment (Group 1, n:51). Patients applied to the hospital at the 24th and later weeks on lamivudine therapy and still showed positive HBV-DNA titers were considered treatment-resistant (Group 2, n:39). There were 51 (Male/Female:38/13) patients in group 1 and 39 (Male/Female:31/8) patients in group 2. There were 11 patients with YMDD mutation who were non-responsive to lamivudine therapy in group 2, 11 patients with positive YMDD mutation, and 8 patients with negative YMDD mutation and 20 patients whose YMDD mutation could not be detected as positive/negative due to technical issues.

Genetic Analysis

Genomic DNA isolation was performed from the blood sample collected from the patients in a 5-cc EDTA tube via the Invitrogen Genomic DNA Isolation Mini Kit (K1820-02, Invitrogen Life Technologies, Carlsbad, CA, USA). Afterwards, PCR was performed for the MDR1 gene C1236T locus using the appropriate primers as previously defined. The fragmented PCR products were resolved in 3% Nusieve 3:1 agarose gels containing 0.5 mg/ml of ethidium bromide and they were visualized by using Vilber–Lourmat Gel Quantification and Documentation System QUANTUM-ST4 (Vilber Lourmat BP 66, Torcy, France). Genotyping was performed based on the restriction lengths obtained (Allele T: 269+97 bp and Allele C: 269+62+35 bp).

Statistical Analysis

Statistical analyses were performed using SPSS 15.0. Visual and analytical methods (Kolmogorov-Smirnow/Shapiro-Wilk tests) were used to confirm that the data was normally distributed. Values are given as mean±standard deviation. The T-test was used to compare numerical variables between independent groups and the chi-square test was used to compare categorical variables. The Mann-Whitney U test was used to compare the parameters that did not fit the normal distribution.

The allelic/genotypic frequencies for SNP in patient groups and haplotype frequencies were determined by the Arlequin 3.11 software program. Fischer's exact chi-square test was used to detect genotype frequencies. SPSS 15.0 was used to compare the data from the patient and control groups and to calculate the OR (Odds Ratio). $p<0.05$ was considered as statistically significant.

RESULTS

A total of 90 (M/F:69/21) patients diagnosed with chronic hepatitis B were included in the study. The mean age of the patients was 49.8±12.6 (range; 22-75) years. The patients were divided into 2 main groups:

The mean age of the patients in the first group was 50.78±12.66 years, and 74.5% of the patients were male while 25.5% were female. The mean age of the second group was 48.62±12.69 years, and 79.5% of the patients were male while 20.5% were female. In the second group, the mean age of the patients with positive YMDD mutation was 50.64±12.20 years, 81.8% of the patients were male while 18.2% were female, and the mean age of the patients with negative YMDD mutation was 45.38±11.04, 82.5% of the patients were male while 17.5% were female. No statistically significant difference was found between the mean age and sex of both groups ($p>0.05$). The clinical and laboratory features of the patients are given in **Table 1**.

Table 1: Clinical and laboratory features of patient groups prior to treatment

Feature	Responsive to Lamivudine N:51	Resistant to Lamivudine N:39	P
Age, year	50.78±12.66	48.62±12.69	0.324
Sex			0.624
Male	38 (74.5%)	31 (79.5%)	
Female	13 (25.5%)	8 (20.5%)	
HBV-DNA, IU/ml	1483696.02 ±7298719.11	5842435.95 ±17252984.918	0.001*
HAI	9.20±3.40	10.62±3.70	0.036*
Fibrotic stage			0,117
Stage 1	12 (23.5%)	10 (25.6%)	
Stage 2	21 (41.2%)	9 (23.1%)	
Stage 3	9 (17.6%)	15 (38.5%)	
Stage 4	2 (3.9%)	3 (7.7%)	
Stage 5	1 (2%)	1 (2.6%)	
Stage 6	6 (11.8%)	1 (2.6%)	
Lamivudine duration, months	33.05±22.1	16.97±12.26	0.001*
AST, U/L	36.21±17.41	60.07±43.99	0.002*
ALT, U/L	46.07±32.24	94.41±75.71	0.001*
Albumin, gr/dl	4.43±0.36	4.40±0.39	0.416
T. Bilirubin, g/dl	0.69±0.48	0.83±0.44	0.042*

The CC, CT and TT gene mutations of MDR1 C1236T were compared genotypically between the treatment-respondent group and the treatment-resistant group. In group 1, CC gene mutations were found in 8 (15.7%), CT gene mutations in 37 (72.5%), and TT gene mutations in 6 (11.8%) patients. In group 2, CC gene mutations were found in 13 (33.3%), CT gene mutations in 21 (53.8%), and TT gene mutations in 5 (12.8%) patients. In the treatment-resistant group (group 2), CC gene mutations were found in 5 (45%) patients with positive YMDD mutation, CT gene mutations in 5 (45%) patients, TT gene mutation was found in 1 (9%) patient while CC gene mutations were detected in 3 (37%) patients with negative YMDD mutation and CT gene mutations were detected in 5 (63%) patients. YMDD mutation rate in patients with treatment resistance was found 12.2% (11/90) (**Table 2**).

The CC, CT, and TT genotype distributions were investigated among the patient groups (**Figure 1**). While CT and TT genotypes were detected at similar rates Group 1 and 2, CC genotype was present by 15.7% in Group 1 and 33.3% in Group 2. The difference was statistically significant (p=0.044) (OR 2.69%; 95% CI: 0.99-7.27).

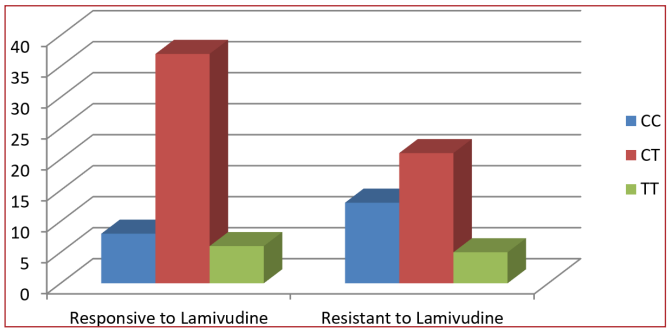

Figure 1: C1236T genotype distribution among patient groups

Allele frequencies between groups were compared. Allele C frequency was 51.96% in Group 1 and 60.26% in Group 2. Allele T frequency was 48.04% in Group 1 and 39.74% in Group 2. When the groups were compared in terms of the frequency of both alleles, no statistically significant difference was found (p>0.05).

CC, CT, TT mutations of 11 patients in group 2 with positive YMDD mutation and 8 patients with negative mutation were found to be genotypically similar (p>0.05). 11 lamivudine-resistant patients with positive YMDD mutation and group 1 which consists of 51 patients sensitive to lamivudine, were compared in terms of genotypic CC mutation, and the difference between the two groups was found to be statistically significant (p=0.043) (OR=4.48, 95% CI: 1.15 – 17.38).

10 of 11 YMDD-positive patients in group 2 carry the allele C. In terms of CC mutation, when 8 patients with positive YMDD mutation with a detected lamivudine resistance in group 2 and whose total duration of lamivudine use did not exceed 12 months, and 51 lamivudine sensitive patients were compared, a statistically significant difference was found (p=0.046 OR=5.38 95% CI 1.20-24) (**Table 2**).

CC mutation was detected in 8 (15.69%) patients in group 1 and in 8 (38.1%) patients in group 2 with a 12-month duration of Lamivudine use, and the difference regarding CC mutation was found statistically significant (p=0.042) (OR 3.31, 95%). CI: 1.06 – 10.33) (**Table 2**).

DISCUSSION

Lamivudine is a nucleoside analogue approved by the FDA in 1998 for the treatment of chronic hepatitis B. The only limitation, when compared to other anti-viral agents used in the treatment of chronic hepatitis B, is drug resistance, which may arise during lamivudine therapy.[7-15]

Factors that may be associated with the development of lamivudine resistance in the literature have been reported as the patient's age, sex, body-mass index, HBeAg positivity, HBV genotype, pathological condition of the liver prior to treatment, pre-treatment serum ALT and HBV-DNA levels.[7,8,12,16]

In this study, apart from the factors triggering the development of resistance mentioned in the literature, it has been investigated whether MDR1 gene polymorphism is associated with the development of lamivudine resistance.

Yuen et al.[8] reported that YMDD motif mutation occurrence was associated with pre-treatment serum ALT and HBV-DNA levels. In a similar vein, in our study, we have found a significantly higher HBV-DNA level in the treatment-resistant group when compared with the sensitive group (p=0.001).

The study conducted by Suzuki et al.[17] presented that the development of a YMDD motif mutation was directly associated with the duration of treatment. Accordingly, they reported that the YMDD motif mutation frequency, which was detected as 12.5% at the end of the 1st year, reached 43% at the end of the 3rd year and 63% at the end of the 5th year. In our study, although a higher rate of lamivudine resistance was found when compared with the previous findings in the literature, the YMDD mutation rate in patients with treatment resistance was found to be consistent with the literature findings as 12.2%.

The pharmacokinetic and pharmacodynamic efficacy of drugs is affected by enzymes responsible for the metabolism of drugs, drug transporters, and genetic variations on receptors

Table 2: Genotypic and allelic distribution of MDR1 gene C1236T polymorphism in patients with HBV based on Lamivudine response, YMDD mutation, and duration of Lamivudine therapy

Genotype	The response to Lamivudine		YMDD Mutation			Lamivudine Resistant Duration of Use	
	Responsive	Resistant	Positive (n:11)		Negative		
			Lamivudine Use 6-12 months	Lamivudine Use > 12 months		<12 months	>12 months
CC	8 (15.7%)	13 (33.3%)*	4 (36%)	1 (%9)	3 (%37)	8 (38.1%)**	5 (27.7%)
CT	37 (72.5%)	21 (53.8%)	4 (36%)	1 (9%)	5 (63%)	11 (52.4%)	10 (55%)
TT	6 (11.8%)	5 (12.8)	0	1 (9%)	0	2 (9%)	3 (16.6%)
Total	51	39	8	3	8	21	18
Allele							
C	53(51.96%)	47(60.26%)	12	3	11	27	20
T	49(48.04%)	31(39.74%)	4	3	5	15	16

*- Among lamivudine responsive and resistant patients, p=0.044, **- Among drug-resistant and responsive patients on Lamivudine <12 months, p=0.042 (OR, 3.31; 95% CI, 1.06-10.33)

or cofactors.[18] The P-glycoprotein encoded by the MDR1 gene is a factor that has an influence on the drug metabolism.[19,20]

For the first time, in a study conducted by Tsurua et al.[21] it was shown that vincristine accumulated in the cell due to the use of trifluoperazine and verapamil in P-gp positive mouse leukemic cells with MDR phenotype, and it was reported that P-gp-associated multi-drug resistance could be reversed. Studies were carried out with the aim of reducing the expression and function of P-gp with anti-MDR-1 oligonucleotides or decreasing the expression of MDR-1 with protein kinase C inhibitors such as staurosporine as well.[22] It was reported that verapamil and trifluoperazine eliminated the resistance to adriamycin in P-gp positive cells.[23]

Schwab et al.[20] emphasized that drug kinetics and the response to drugs vary between societies and individuals based on genetic structure, and they brought forward the development of a "patient-tailored treatment" approach by using genetic databases to be obtained from different populations.[27] In our study, we investigated the presence of other genetic factors affecting lamivudine resistance, apart from YMDD mutation, and the impact of MDR1 gene polymorphism on resistance. The CC genotype was found to be significantly higher in both the lamivudine-resistant group and the resistant patients with YMDD mutation.

More than 50 SNPs (Single Nucleotide Polymorphism) have been identified in the MDR1 gene up to the present, and are increasing in number day by day.[18] Kimichi – Sarfaty et al.[28] reported that the three most observed and emphasized SNPs in the MDR1 gene were C3435T, G2677T/A and C1236T.

Schwab et al.[20] concluded that C3435T and C1236T polymorphisms were silent (synonymous) polymorphisms that did not lead to amino acid replacement, and although C3435T and C1236T were silent polymorphisms.

C3435T polymorphism is the most associated with diseases or drug resistance.[23,24,26,29] It has been reported that C3435T, one of the silent polymorphisms, may be associated with ribavirin resistance in chronic hepatitis C infection.[30] In our study, we investigated whether another silent polymorphism, C1236 T, was associated with lamivudine resistance in chronic hepatitis B patients.

The CT genotype (72.5%) was higher in the lamivudine-responsive group in comparison to the non-responsive group (53.8%), however, no statistical difference was noted. The CC genotype was higher in the lamivudine-resistant group (33.3%) in comparison to the responsive group (15.7%) (p=0.044). When the groups were compared in terms of alleles, allele C was higher in the resistant group (60.26% vs 51.96%), while allele T was higher in the sensitive group (48.04% vs 39.4%). Allele frequencies were determined as similar between the groups. Similarly, CC genotype and allele C were found to be higher in the lamivudine non-responsive group and in the patient group with positive YMDD. The CC genotype was significantly higher in patients who developed resistance in the first year of treatment when compared with the group that responded to lamivudine. In light of these findings, it was concluded that the CC genotype played a role in the development of lamivudine resistance. The elevated CC genotype and allele C frequency in patients with YMDD mutation also support this hypothesis.

The MDR1 genotype is of great importance in terms of disease risk and treatment outcome in AIDS because HIV protease inhibitors used in the treatment of this disease are the substrates of P-gp. Fellay et al.[29] detected a significant increase in CD4+ cells in patients with the C3435TT genotype following 6 months of antiretroviral treatment. As a result, it was concluded that TT genotype was associated with a better response rate and virus resistance to a lesser extent in HIV treatment or allele C was linked to a failure in viral immune response. The data on the C1236T polymorphism in our study also supports this study to a large extent. It was found that Allele C frequency and CC genotype were associated with lamivudine resistance in the treatment of chronic hepatitis B.

When compared with other nucleoside analogues, the rate of development of resistance to lamivudine is higher. The findings of our study have put forth that MDR1 gene mutation may affect response rates to treatment in patients with hepatitis B, especially for lamivudine.

CONCLUSION

Polymorphisms in the MDR-1 gene and its product, P-glycoprotein, are important factors that affect the treatment response during chronic hepatitis B. In our study, MDR1 C1236T CC genotype was more commonly found in the lamivudine-resistant group. We are of the opinion that MDR gene polymorphisms will guide clinicians in the selection and duration of treatment in chronic hepatitis B treatment in the upcoming years. Further and more comprehensive research is needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziosmanpaşa University Faculty of Medicine Research and Application Hospital Clinic Ethics Committee (Date: 30/03/2012, Decision No: 30).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Preoperative anxiety in parents of pediatric patients: related factors and the role of health literacy

Şule Özdemir[1], Ayşe Çeçen[2], Doğukan Özdemir[2]

[1]Department of Public Health, Faculty of Medicine, Samsun University, Samsun, Turkey
[2]Department of Otolaryngology, Faculty of Medicine, Samsun University, Samsun, Turkey

ABSTRACT

Aims: In this study, it was aimed to determine preoperative anxiety levels, related factors, the relationship between health literacy and anxiety in parents of pediatric patients.

Methods: This descriptive cross-sectional study was conducted on the parents of children who will be operated in a tertiary hospital between 15 June and 15 September 2022. The number of 82 people were included in the study. Information form introducing children and families, Health Literacy Scale(HLS), State Trait Anxiety Inventory(STAI) questionnaires were applied to parents. $p<0.05$ was considered significant in statistical analysis.

Results: The state anxiety score of the parents participating in the study was 37.51±9.50, trait anxiety score was 42.55±8.83, HLS 45.46±14.34. Preoperative state anxiety level of mothers(39.63±9.97) was higher than that of fathers(34.36±8.71) ($p=0.040$), trait anxiety level was similar($p=0.189$), mothers' health literacy(40.36±11.11) was found to be lower (48.11±15.19) than fathers($p=0.019$). The state anxiety level of parents whose income is equal to expenditure was found to be the lowest(33.43±7.33)($p<0.001$). While the state anxiety score was found to be significantly lower($p=0.024$), the trait anxiety score was similar($p=0.560$) and the health literacy score was higher($p=0.042$), among the parents who had knowledge about anesthesia. The relationship between state anxiety score and health literacy score was negative and significant($p<0.001$).

Conclusion: It is seen that the anxiety levels of parents with low health literacy increase before the surgery It is important to know the factors related to the anxiety levels of the parents before the surgery.

Keywords: Health literacy, anxiety, pediatric patients, parents, surgery

INTRODUCTION

Surgery a medical procedure involving anesthesia, is a stressful event. Therefore, anxiety experienced before surgery is an important problem in children who are scheduled for surgery and their parents.[1] Anxiety is a physiological response such as fear, worry, restlessness, and nervousness that occurs when a person does not feel safe in the face of an undefined danger or an unknown threat.[2] It is known that every year millions of pediatric patients undergo surgery and undergo a number of procedures.[3] Children are a more vulnerable population than adults and their ability to cope with stressful events is less developed. In addition, children are dependent on others and have limited ability to make sense of their experiences.[4] There is also a state of emotional dependence between parents and children. Conditions such as fear and anxiety experienced by parents are important determinants of children's lives.[5] Even when people hear the word "Surgery", they may experience fear, anxiety and depression. For this reason, it has been shown that there is a positive relationship between pre- and post-operative anxiety levels due to reasons such as pain, complications and fear of death in most of the children who are planned to have surgery and in their parents.[1,6-8]

Intense stress and anxiety experienced by parents cause difficulties in giving support and care to their children in the pre-operative period. More than half of the parents of children who will undergo surgery are concerned about surgical procedures and surgery.[3] High level of anxiety in parents is an important risk factor for preoperative anxiety in children. Studies have shown that pain and anxiety scores are high in children of parents with moderate or severe preoperative anxiety.[9] Anxiety of parents may also negatively affect health workers while performing health services for the child.[3] In order to eliminate the effect of anxiety in pediatric patients and their parents, it is important to know the conditions that increase anxiety before surgery.[10] Anxiety levels of parents decrease when they have sufficient information about their children's medical condition, anesthesia and surgery plan, possible anesthesia and surgical complications.[11-14] In addition to these, they should be able to evaluate and correctly interpret the health information given about these issues. Health literacy is defined as the cognitive and social skills related

Corresponding Author: Sule Özdemir, sule.ozdemir@samsun.edu.tr

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to the ability and desire of individuals to access, understand and use information about health in order to maintain and improve well-being in health. Health literacy leads to the sharing of responsibilities between health care providers and patients receiving health care services, and for both parties to better understand each other during communication. Having a high level of health literacy is an important factor for people to understand the information they receive from the physician, and to make decisions about treatment and care in health by testing the accuracy and reliability of the information.[15] For this reason, the level of health literacy may be one of the effective factors in parental anxiety.

In this study, it was aimed to determine preoperative anxiety levels, related factors, the relationship between health literacy and anxiety in parents of pediatric patients.

METHODS

The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 01.06.2022, Decision No: 2022/2/3). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This descriptive cross-sectional study was conducted in Samsun Training and Research Hospital, Department of Otorhinolaryngology, between 15 June and 15 September 2022 on the parents of children who will undergo surgery. In order to determine the number of samples to be taken for the study, power analysis was performed using the G* power 3.1.9.7 program.[16] According to Cohen's effect size coefficients; While the effect size was d=0.30, the type 1 error level was calculated as α=0.05, the power 1-β (β=type 2 error probability) =0.80 and the sample size calculated as a minimum of 72 people. Parents of children between the ages of 0 and 18 who will have surgery between the specified dates were included in the study. Parents of children who were planned to have surgery were all included in the study, without making any distinction between surgery indication and diagnosis. The research was completed with 82 people. Necessary explanations were given the day before the surgery to the volunteers from the parents determined by simple randomization, after obtaining written and verbal consent from the individuals, data collection tools were applied using face-to-face interview technique.

Data Collection Tools

Information Form Introducing Children and Their Families: In the form prepared by the researchers, there are sociodemographic information about the parents and the child (11 questions) and questions about the disease status (8 questions).

State-Trait Anxiety Inventory (STAI) scale: It was developed by Spielberg et al.[17] Turkish validity-reliability study was performed by Öner and Le Compte.[18] The internal consistency and reliability of the State Anxiety Inventory (STAI-S) were between 0.83 and 0.92, and between 0.86 and 0.92 for the Trait Anxiety Inventory (STAI-T). The items in the scale are in 4-point Likert type. STAI-S determines how an individual feels at a particular moment and in a situation. It is widely used in preoperative anxiety measurement. STAI-T determines how a person generally feels, regardless of the individual's situation and circumstances. Scores obtained from both scales range from 20 (low anxiety) to 80 (high anxiety). An increase in the score obtained from the scale indicates a high level of anxiety.

Health Literacy Scale (HLS): The 47-item Health Literacy Survey in Europe scale (HLS-EU), developed by Sorensen et al.[19] was simplified to 25 items (HLS-EU, Health Literacy Index) by Sorensen et al.[19] and Toçi et al.[20] The Turkish validity and reliability of this scale was performed by Aras and Bayık Temel.[21] The cronbach alpha value of the scale was found to be 0.92. The scale is in 5-point Likert type and consists of four sub-dimensions. In sub-dimensions; It consists of 25 items, 5 items being access to health information, 7 items understanding health information, 8 items appraising/evaluating health information, and 5 items are applying/using health information. A minimum of 25 and a maximum of 125 points are taken from the scale. Low scores indicate insufficient, problematic and poor health literacy, while high scores indicate adequate and very good. The higher the score, the higher the individual's health literacy level.[21]

Statistical Analysis

SPSS 22.0 package program was used for the statistical analysis of the data obtained in this study. Results were expressed using mean±standard deviation(min-max) (median (quarters)) and number (%) according to data. For those who fit the normal distribution in the analysis of the data; Student-t test and One-Way ANOVA test were used. For those who do not follow the normal distribution; Mann Whitney-U, Kruskal Wallis test was used. Spearman correlation analysis was used in the correlation analysis. Statistical significance level of $p<0.05$ was accepted for all tests.

RESULTS

The mean age of the participants in the study was 36.52±5.92(25.0-59.0) years. Of the participating parents, 65.9% were mothers, 34.1% were fathers, 26.8% were university graduates, 65.9% were living in the city center. The mean age of the children scheduled for surgery was 6.51±2.77 (1.0-14.0) years, and 53.7% were girls (**Table 1**).

According to the analysis of the parents' possible causes of anxiety; It was found that 13.4% of them were not given sufficient information about the surgery, 32.9% were afraid of the success of the surgery, 53.7% were afraid of the complications of the surgery, 54.9% were afraid of the complications of anesthesia (**Table 2**). When the child's surgery decision time was questioned, 19.5% (n=16) two months ago, 42.7% (n=35) one month ago, 34.1% (n=28) one week ago, 3.7% (n=3) one day ago surgery was decided.

The STAI-S score of the participating parents was 37.51±9.50, the STAI-T score was 42.55±8.83, and the HLS total score was 45.46±14.34 (**Table 3**).

Among the participating parents, the fathers' STAI-S score average (34.36±8.71) was lower than the mothers' STAI-S mean score (39.63±9.97)($p=0.040$), and their STAI-T scores were similar ($p=0.186$). In addition, the fathers' total HLS score (48.11±15.19) was found to be higher than the mean score of the mothers (40.36±11.11) ($p=0.019$). While the mean STAI-S score was similar in their education level ($p=0.689$), the mean STAI-T score of those with secondary school and below education (48.00±8.32, $p<0.001$) was found to be significantly higher than the mean score of those in the other group. The mean HLS score of the parents who graduated from university or higher was found to be higher than the others ($p<0.001$). According to the monthly income perception of the parents, the STAI-S mean score of those whose income is more than their expenses (44.75±13.77) was the highest, while the STAI-S mean score of those whose income was equal to their expenses (33.43±7.33) was found to be the lowest ($p<0.001$) (**Table 4**).

Table 1. Demographic features (n=82)

Variables	n=82	%
Parent		
Fathers	28	34.1
Mothers	54	65.9
Age		
<40 years	60	73.2
≥40 years	22	26.8
Education status		
Secondary school and below	29	35.4
High school graduate	31	37.8
University graduate and above	22	26.8
Working status		
Yes	42	51.2
No	40	48.8
Number of children		
1 child	5	6.1
≥2 children	77	93.9
Children age		
0-4 ages	16	19.5
5-8 ages	52	63.4
9-14 ages	14	17.1
The person's perception of the monthly income of the family		
Income less than expenses	28	34.1
Income equals expense	42	51.2
Income more than expenses	12	14.7
Living place		
Province center	54	65.9
Town center	24	29.2
Village/town	4	4.9
Sex of the child		
Male	38	46.3
Female	44	53.7
Age (years)	36.52±5.92 (25.0-59.0) *	
Number of children	2.33±0.61 (1.0-4.0) *	
Child's age (years)	6.51±2.77 (1.0-14.0) *	

*; Mean±Standart Deviation (minimum-maximum)

Table 2. Responses to possible causes of anxiety in parents

Possibilities causing anxiety	Yes (n, %)	No (n, %)
Presence of congenital disease in the child	6 (7.3)	76 (92.7)
Has the child ever had surgery before?	16 (19.5)	66 (80.5)
Has the child been hospitalized before?	24 (29.3)	58 (70.7)
İnformation about the surgery	82 (100.0)	0 (0.0)
İnformation about the plan of anesthesia	71 (86.6)	11 (13.4)
Was the information given about the operation sufficient?	71 (86.6)	11 (13.4)
Fear of surgical success	25 (32.9)	55 (67.1)
Fear of anesthesia related complications	45 (54.9)	37 (45.1)
Fear of surgery related complications	44 (53.7)	38 (46.3)
Fear of pain in the child after surgery	47 (57.3)	35 (42.7)
Fear of late discharge of the child	19 (23.2)	63 (76.8)

Table 3. Distribution of participating parents according to the scores they got from the scales

Scales	Mean±Standart Deviation	Min-Max	Median (Quarters)
HLS	45.46±14.34	25.0-75.0	44.0(33.0-57.0)
Access/obtain health information	9.62±4.02	5.0-19.0	9.0(5.0-14.0)
Understand health information	13.23±4.81	7.0-24.0	12.5(9.0-17.0)
Process/appraise health information	14.07±4.80	8.0-24.0	13.5(10.0-18.0)
Apply/use health information	8.54±3.04	5.0-16.0	8.5(6.0-11.0)
STAI-S	37.51±9.50	22.0-68.0	37.0(31.0-44.0)
STAI-T	42.55±8.83	27.0-62.0	42.0(35.0-49.0)

HLS; Health Literacy Scale, STAI-S; State Anxiety Inventory, STAI-T; Trait Anxiety Inventory

Table 4. Evaluation of the scores of the scales according to the sociodemographic variables of the participant parents

Variables	STAI-S	STAI-T	HLS
Parent			
Fathers	34.36±8.71	40.75±9.22	48.11±15.19
Mothers	39.63±9.97	43.48±8.56	40.36±11.11
p Value	0.040*	0.186+	0.019*
Age			
<40 years	38.25±10.23	43.43±8.04	44.98±14.77
≥40 years	35. 50±9.94	40.14±10.53	46.77±13.34
p Value	0.171+	0.135+	0.620*
Education status			
Secondary school and below[1]	38.69±8.51	48.00±8.32	43.76±7.38
High school graduate[2]	37.16±8.11	40.48±8.43	37.19±11.05
University graduate and above[3]	36.45±12.43	38.27±6.37	59.36±15.47
p Value	0.689++	<0.001**	<0.001++
1-2[a]		0.001	0.085
1-3[a]		<0.001	<0.001
2-3[a]		0.576	<0.001
Working status			
Yes	37.60±10.86	40.45±8.06	46.43±16. 14
No	37.43±7.96	44.75±9.17	44.45±12. 30
p Value	0.936*	0.027+	0.533+
Number of children			
1 child	37.73±9.61	42.79±8.85	45.60±20.84
≥2 children	34.20±7.66	38.80±8.55	45.45±14.01
p Value	0.425*	0.331+	0.983*
Children age			
0-4 ages	38.83±8.15	46.14±8.21	43.78±8.98
5-8 ages	39.94±8.44	42.64±8.17	43.59±9.14
9-14 ages	37.58±7.78	44.72±8.84	44.62±8. 68
p Value	0.196**	0.072**	0.146++
The person's perception of the monthly income of the family			
Income less than expenses[1]	44.75±13.77	45.04±8.26	43.64±11.39
Income equals expense[2]	40.54±7.29	40.14±8.57	43.69±14.79
Income more than expenses[3]	33.43±7.33	45.17±9.37	55.92±15.53
p Value	<0.001++	0.039**	0.022++
1-2[a]	0.328	0.057	0.899
1-3[a]	<0.001	0.999	0.012
2-3[a]	0.013	0.180	0.013
Living place			
Province center	37.61±10.00	42.00±9.63	46.48±15.21
Town center	37.71±9.14	43.50±7.66	43.38±13.45
Village/town	35.00±4.61	44.25±1.5	44.25±5.18
p Value	0.866++	0.733++	0.673++

HLS; Health Literacy Scale, STAI-S; State Anxiety Inventory, STAI-T; Trait Anxiety Inventory, *; Student-t test, **; One Way ANOVA test, +; Mann-Whitney-U test, ++; Kruskall Wallis test, a; Mann Whitney U test with Bonferroni correction.

While the mean STAI-S score of parent whose child has a congenital disease was 42.33±3.07 and higher than those who did not (37.13±9.74) (p=0.007), the STAI-T score did not differ significantly (p=0.410). In addition, the mean HLS score of Parent whose child has a congenital disease was low (p=0.005). While the mean STAI-S score of parents who had knowledge about anesthesia (33.55±4.98) was found to be significantly lower than the mean score of STAI-S (38.13±9.90) of parents who did not have knowledge about anesthesia (p=0.024), the STAI-T mean scores were similar (p=0.560), and the HLS level was found to be higher in parents who had knowledge about anesthesia (p=0.042). While the STAI-S mean score(41.00±6.74) was higher in those who were afraid of the late discharge of their child after the surgery (p=0.048) than those who were not afraid (36.46±9.99), there was no significant difference between STAI-T mean scores and HLS mean scores (p=0.756) (Table 5).

Table 5. Evaluation of the scores of the scales according to the possible causes of anxiety of the parents

Variables	STAI-S	STAI-T	HLS
Presence of congenital disease in the child			
Yes	42.33±3.07	42.78±9.01	36.00±5.89
No	37.13±9.74	39.67±5.82	46.21±14.57
p Value	0.007+	0.410+	0.005*
Has the child ever had surgery before?			
Yes	34.19±8.84	44.31±8.56	43.38±12.33
No	38.32±9.54	42.12±8.91	45.97±14.83
p Value	0.119*	0.377+	0.520*
Has the child been hospitalized before?			
Yes	36.29±8.89	43.83±9.03	40.83±11.27
No	38.02±9.77	42.02±8.77	47.38±15.11
p Value	0.458+	0.401*	0.035*
The child's surgery decision time			
Two months ago	42.31±7.05	47.31±9.33	42.63±11.05
One month ago	37.23±8.79	43.77±8.01	46.46±15.43
One week ago	34.79±10.86	38.82±8.05	46.29±14.87
One day ago	40.67±8.50	37.67±10.26	41.33±16.28
p Value	0.078++	0.058++	0.775++
Information about the plan of anesthesia			
Yes	33.55±4.98	42.77±8.43	46.34±14.38
No	38.13±9.90	41.09±11.46	39.82±13.39
p Value	0.024*	0.560+	0.042+
The person who informs about the surgery			
Surgeon	38.36±10.05	43.89±8.95	45.67±14.10
Anesthesiologist	42.00±8.54	48.00±3.36	40.00±5.56
Surgeon and anesthesiologist	37.17±10.01	39.91±7.07	48.48±15.68
p Value	0.712**	0.101++	0.558++
Was the information given about the operation sufficient?			
Yes	40.00±7.65	42.77±8.66	45.97±14.41
No	37.13±9.74	41.09±10.22	42.18±14.11
p Value	0.354*	0.560+	0.418*
Fear of surgical success			
Yes	38.44±8.94	44.07±8.98	43.78±15.68
No	35.63±10.47	39.44±7.79	46.29±13.72
p Value	0.211*	0.025*	0.854+
Fear of anesthesia related complications			
Yes	37.44±10.12	46.35±9.09	43.59±11.07
No	37.59±8.82	39.42±7.34	47.00±16.53
p Value	0.944+	<0.001*	0.270+
Fear of surgery related complications			
Yes	37.93±10.33	41.82±9.26	43.87±11.05
No	37.03±8.55	43.39±8.35	46.84±16.68
p Value	0.670*	0.424+	0.339+
Fear of pain in the child after surgery			
Yes	36.34±8.17	41.68±9.23	41.30±12.88
No	39.09±10.96	43.71±8.25	51.06±14.47
p Value	0.198*	0.306+	0.002*
Fear of late discharge of the child			
Yes	41.00±6.74	43.11±9.82	43.53±14.02
No	36.46±9.99	42.38±8.59	46.05±14.50
p Value	0.048+	0.756*	0.505*
Has the parent had surgery before?			
Yes	37.64±8.57	41.44±8.12	47.16±13.54
No	38.98±10.11	43.13±9.15	50.87±14.36
p Value	0.244*	0.372+	0.172*

HLS; Health Literacy Scale, STAI-S; State Anxiety Inventory, STAI-T; Trait Anxiety Inventory, *; Student-t test, **; One Way ANOVA test, +; Mann-Whitney-U test, ++; Kruskall Wallis test.

The relationship between HLS and STAI was examined by correlation analysis. HLS total score (r=-0.579, p<0.001), access to information sub-dimension (r=-0.631, p<0.001), understanding information sub-dimension (r=-0.604, p<0.001), information evaluation sub-dimension (r=-0.484, p<0.001), application/use sub-dimension (r=-0.553, p<0.001) and a negative correlation was found between the STAI-S total score. HLS total score (r=-0.327, p=0.011), access to information sub-dimension (r=-0.254, p=0.048), understanding information sub-dimension (r=-0.667, p<0.001), applying/using information sub-dimension (r=-0.163, p=0.026) and a negative correlation was found between the STAI-T total score.

DISCUSSION

It has been shown that the level of anxiety increases in the parents of children who are planned for surgical operation, and that increased anxiety creates problems in children and even increases the postoperative recovery period.[11,22-24] While parental anxiety is effective on both the child and the family, it negatively affects many situations, including surgical decision and informed consent.[25] Health literacy is an important determinant of anxiety in parents. In the pediatric surgical setting, parental health literacy is important in understanding the role of surgery in the treatment of the child, obtaining valid informed consent, and following pre/post operative instructions. Despite the importance of parental health literacy, there are few studies in the literature investigating its possible impact on parental anxiety. Therefore, in our study, we evaluated preoperative anxiety levels, factors affecting this, the relationship between health literacy and anxiety in parents of children who will undergo surgery.

In studies conducted in the literature, the STAI-S threshold used to determine the level of anxiety, which indicates how an individual feels at a certain moment and in a given situation, is 39-40, whereas in different studies performed on patients for the preoperative anxiety measurement, the threshold varies between 36-45 points.[26-28] In our study, the preoperative STAI-S score average of the parents was found to be 37.51 and this value was found to be compatible with the literature. In addition, in our study, it was found that the state anxiety levels of the mothers were higher than the fathers, but the trait anxiety scores were similar in the parents. This result is consistent with other studies showing that women are more anxious before surgery than men.[22,23,29-31] The fact that mothers generally have a protective nature towards their children and spend longer time with their children may have caused higher levels of anxiety. In our study, while STAI-T scores of parents varied according to education level and employment status, it was found that STAI-S scores were not related to these variables. In addition, it was found that the level of state anxiety was high and health literacy was low in parents who had a congenital disease in their child and were not informed about the anesthesia to be applied. We think that this may have had a negative impact on the person's health literacy, possibly due to the motivation to cope with complex health-related situations. In a study by Ayenew et al.[3] it was shown that insufficient knowledge of parents about anesthesia increases anxiety, similar to our results. Information exchange between parents and healthcare professionals and trust in healthcare personnel are effective in reducing parental anxiety in the preoperative period.[13,32]

As a result of our study, it was found that the health literacy levels of the participating parents were low (45.46 points). In many studies, it is seen that the HL score is higher than the scores obtained from this study.[21,33,34] In the study of Çimen and Bayık.[33] the mean HLS was 87.96, in the study of Aras and Temel.[21] the mean HL score was 90.30. In our study, health literacy levels were associated with parents'

education level, socioeconomic status (income more than expenditure according to income perception). Our results are consistent with previous studies in parents. Walker et al.[35] found that among hospitalized patients, those with sufficient health literacy were significantly associated with socioeconomic status and education. Yin et al.[36] showed that it was significantly associated with low health literacy level in parents with high school or lower education and low income parents. The low results in our study may be due to the difference between the education levels of the people included in the study.

Another important result of our study was that health literacy was related to the preoperative anxiety levels of the parents and as the health literacy level decreased, the anxiety level of the parents increased. Our results are similar with studies examining the relationship between health literacy and anxiety.[37,38] Kampouroglou et al.[37] found in their study, similar to our results, that parents with lower health literacy levels were more anxious before the surgery. Rowland et al.[38] in his study on patients with coronary heart disease, he reported that patients with low health literacy had higher levels of anxiety than those with adequate health literacy. It is thought that parents' obtaining information about health in the preoperative period, understanding and evaluating this information, and interpreting it correctly will contribute to good management of the preoperative situation and decrease the level of anxiety.

CONCLUSION

In the preoperative state anxiety levels of the parents; parent's being a mother, income status, congenital disease in the child, giving information about anesthesia and surgery were found to be related factors. It is seen that the anxiety levels of parents with low health literacy increase before the surgery. Our study is descriptive and our results cannot be generalized to the general population. However, factors affecting the preoperative anxiety levels of parents should always be considered and it is important to take steps to reduce anxiety. In particular, a screening tool can be used to determine the health literacy level of parents. In this way, using a plain language that parents with low health literacy in written and verbal communication can understand can contribute to reducing their anxiety levels.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun University Clinical Researches Ethics Committee (Date: 01.06.2022, Decision No: 2022/2/3).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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The effects of donepezil on anxiety- and depression-like behaviors in diabetic rats and the role of nitric oxide modulators

Mehmet Öz[1], Kısmet Esra Nurullahoğlu Atalık[2], Durmuş Ali Aslanlar[2]

[1]Department of Physiology, Faculty of Medicine, University of Aksaray, Aksaray, Turkey
[2]Department of Pharmacology, Faculty of Meram Medicine, University of Necmettin Erbakan, Konya, Turkey

ABSTRACT

Aims: The aim of the present study was to evaluate the effect of an acetylcholinesterase inhibitor donepezil on the diabetes-induced anxiety and depression and the role of nitric oxide in these effects.

Methods: Thirty male Wistar rats were randomly divided into 5 groups (6 rats each): (I) normal control group, (II) untreated diabetic group, and Groups (III-V) diabetic rats received donepezil at a dose of 4 mg/kg orally for twenty days after the first 30 days of diabetes. Group 4 also received 20 mg/kg i.p., L-NAME simultaneously with donepezil for the last 20 days, while group 5 received 40 mg/kg i.p., L-Arginine during this period. A single dose of streptozotocin was used to induce experimental type 1 diabetes.

Results: Anxiety-like behaviors were assessed using the open field test (OFT), and depression-like behaviors were estimated using the forced swim test (FST). In the OFT, all diabetic rats spent less time in the center and engaged in less exploratory behavior than the control group. The number of lines crossed where locomotor activity was assessed did not differ significantly between groups. In the FST, duration of immobility increased significantly in diabetic groups compared to the control. Donepezil administration did not affect either depression or anxiety responses. Moreover, donepezil plus L-arginine increased diabetes-induced depression significantly.

Conclusion: These findings may suggest that cholinergic and nitrergic systems may interact on depression-like behaviors in diabetic rats.

Keywords: Diabetes, depression, anxiety, acetylcholinesterase, nitric oxide

INTRODUCTION

Diabetes mellitus (DM) is one of the main global public health problems that is becoming more serious over time, and it is frequently associated with depression, which leads to a lower quality of life and a worse long-term prognosis.[1] Essentially, as seen in major chronic diseases, there is a reciprocal relationship between diabetes and depression, such that those with diabetes are more likely to develop depression, while those with depression are more likely to develop diabetes.[2] Because the consequences of each condition are aggravated by the presence of the other, a vicious circle develops spontaneously and has a negative impact on disease pathogenesis. Nonetheless, this bidirectional relationship is not entirely clear, and the pathophysiologic mechanisms underlying between these two diseases remain a mystery. Hyperglycemia is independently associated with depression.[1] However, the exact mechanism of anxiety and depression development under the influence of hyperglycemia has not been fully characterized. Understanding the etiology of diabetes and identifying the points of intersection of its close relationship with depression will thus be critical for the development of treatment strategies.

Cholinergic transmission is known to play a crucial role in cognitive functions containing learning and memory.[3-6] In line with this perspective, changes in acetylcholine (ACh) levels are involved in the regulation of learning and memory or depression-like behaviors, it is known that brain ACh levels are elevated in depressed patients and remain at this level as long as depression persists,[7] and acetylcholinesterase (AChE) activity is the main regulator of ACh levels.[8] However, there are inconsistent results regarding the effect of AChE activity on these functions in cognitive dysfunctions. While decreased AChE activity, which results in increased ACh levels, is associated with impaired cognitive function,[4] others have shown that increased AChE activity similarly leads to impaired cognitive function.[5,6] A similar contradiction is seen in depression-like behavior in experimental animals after

Corresponding Author: Mehmet Öz, ozmhmt@gmail.com

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pharmacologically reducing ACh release or increasing its expression. In a study using physostigmine, an AChE inhibitor, depression-like behaviors were observed to increase,[3] while there is also a report showing that increasing the amount of acetylcholine through ACh inhibition exhibits antidepressant properties.[9] Nitric oxide (NO), another neurotransmitter known to have an effect on depression and anxiety, is defined as a durable gaseous free radical and is also referred to as an crucial biomodulator in the body.[10] The neuromodulatory role of NO in the central nervous system and its possible role in central nervous system-related disorders have been observed in experimental studies, where L-arginine, an NO precursor, shows an anti-anxiogenic (anxiolytic) effect due to restraint stress in rats. A similar effect was observed at low dose (10 mg/kg) of L-NAME, a nitric oxide synthase (NOS) inhibitor, whereas high dose L-NAME (50 mg/kg) further worsened the existing behavioral impairment.[10] Furthermore, NOS inhibitors, L-NAME,[11,12] 7-nitroindazole (7-NI),[11] and aminoguanidine,[13] are known to improve stress-induced anxiety and depression in different stress models causing anxiety and depression, and this improvement is dose-dependent,[11,13] and these inhibitors achieve this improvement by different mechanisms,[11] L-NAME modulates plasma NO and corticosterone, while 7-NI modulates brain NO stimulation. As it can be understood from the reports, the dose-dependent change in the responses and sometimes paradoxical results at similar doses; in addition, the biphasic properties of these substances increase the confusion of the researchers on the subject and reveal the importance of new studies in determining the mechanism of action of NO on depression and anxiety. This study was designed to investigate the effect of donepezil, an AChE inhibitor, on depression- and anxiety-like behaviors in STZ-induced diabetic rats and also the role of NO modulators; precursor (L-arginine) and inhibitor (L-NAME) in these effects

METHODS

Experimental Design

This study was carried out at Necmettin Erbakan University Experimental Medicine Research and Application Center after obtaining ethics committee approval (2022/015). Wistar albino rats, 12-15 weeks of age, with an average weight of 200-250 g were used in the study. All rats were housed in normal rat cages, four per cage, in a controlled environment at 22±2 °C, 50% humidity and quiet conditions, with ad libitum access to water and food, under 12/12 h light-dark cycles.

Formation of Groups

Our study was completed using 30 rats (n=6) in 5 groups, and the rats were randomly assigned to the groups. Diabetes was induced experimentally in all groups except the control group (CON). Diabetes groups were seperated into four subgroups as diabetic control group (DIA), donepezil group (DON), donepezil plus L-NAME (L-NAME) group and donepezil plus L-arginine (L-arg) group. Injections were administered by the same investigator at the same time of the day, and an equal volume of vehicle was either injected or gavaged into the rats that received no supplementation. At the end of the study, all rats were subjected to behavioral tests. The experimental protocol in the present study is schematically represented in **Figure 1**.

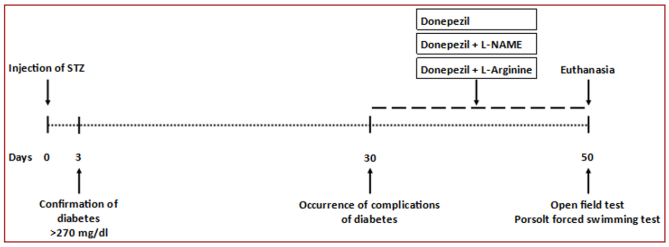

Figure 1. Schematic presentation of the protocol used for the study

Induction of Diabetes

STZ was used to induce experimental diabetes. All rats in the diabetes groups were administered 55 mg/kg dose of STZ intraperitoneally as a single dose after 12-hour fasting.[14] STZ was dissolved in citrate buffer (10 mM, pH 4.5), the control group was injected with the same volume of citrate buffer only.[14] Blood was taken from the tail vein 72 hours after the injections and blood glucose levels were measured. Rats with blood glucose levels above 270 mg/dl were considered diabetic and included in the study.

Drugs and Administration

After STZ induced diabetes was confirmed, we waited for 30 days to occur the complications of diabetes. Subsequently, donepezil at a dose of 4 mg/kg was administered orally by gavage to the DON, L-NAME and L-arg groups at the same time every day.[15] In another group, L-NAME was administered intraperitoneally 30 minutes after the administration of donepezil in a volume of 20 mg/kg.[16] The rats in the L-arg group were administered L-arginine 40 mg/kg intraperitoneally at the same time as the rats in the L-NAME group.[17] Donepezil, L-NAME and L-arginine were administered for a total of 20 days and behavioral tests were performed on the last day of administration. All drugs were obtained from Sigma-Aldrich Chemical Co.

Behavioral Tests

Behavioral tests were performed in a separate room that was never used during any phase of the study. The room did not contain any noise or odor to distract the animals. There was at least a 2-hour interval between behavioral tests and all rats were acclimated to the room environment before the tests began. Behavioral tests were achieved and videotaped by the alike person. The recordings were evaluated blindly by the other investigators.

Open Field Test

In our study, we applied an open field test to assess anxiety-like behaviors. Each rat was gently placed in the middle of a well-lit open field arena (80 cm×80 cm, height 40 cm, made of black acrylic material) and permitted to explore the arena freely for 5 minutes. The open field arena was separated into 16 equal squares, and the 4 sections in the center and 12 sections on the edge were named center and periphery, respectively. The time spent in the center was recorded by calculating the time spent in the 4 squares located in the middle zone. Rearing number (vertical movement) was scored as 1 point if the rats stood on their hind legs and crossing number (horizontal movement) was scored as 1 point if at least 3 paws entered the same square.[18]

The arena was cleaned with ethanol after each trial to ensure that the residual odor did not affect the next rat

Forced Swim Test

Rats were placed in an acrylic cylinder (24 cm diameter and 60 cm height) filled with 25°C water and allowed to swim freely. The depth of the water was such that their tails did not touch the ground, they could not get out, and they could swim freely (40 cm). Rats were considered immobile when they swam in the water without struggling and keeping their heads above water. They were subjected to a 15 min acclimatization test the day before the test, followed by another 5 min of forced swimming on the day of the test. The first and last 1 min were subtracted and the immobility time in seconds was recorded for the intervening 3 min.[18] The rats were dried with a towel and left to dry completely in a heat source for 20 min after each swimming session. The cylinders were prepared for a new test by refilling with water at the same temperature after each session.

Statistical Analysis

All results were expressed as mean value±standard deviation (SD). Statistical differences were determined by analysis of variance (ANOVA, SPSS 20.0) followed by Tukey post-hoc analysis. The statistical significance level was determined as $p<0.05$.

RESULTS

Forced Swimming Test

The forced swim test was used to assess depression-like behavior by measuring the immobility time of each rat (**Figure 2**). Duration of immobility increased significantly in all diabetic groups compared to the control group (p=0.000 vs all other groups). According to these results, our study shows that STZ-induced diabetes causes depression-like behaviors in rats. Rats in the L-NAME treated group showed similar results as in the DIA and DON groups. But, in donepezil administered diabetic rats, L-arginine increased diabetes-induced depression-like behaviors significantly (p=0.000 vs CON; p=0.001 vs DIA; p=0.014 vs DON; p=0.004 vs LNAME).

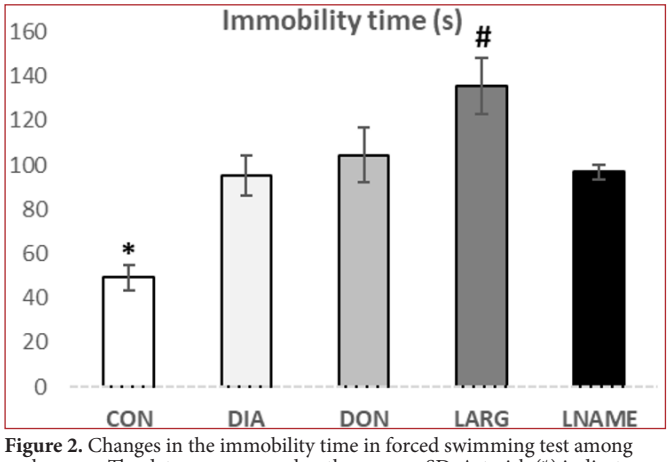

Figure 2. Changes in the immobility time in forced swimming test among each group. The data are expressed as the means±SD. Asterisk (*) indicates significance compared with other groups. Hash (#) indicates significance compared with other diabetes groups. p<0.01; one-way ANOVA.

Open Field Test

The open field test was used to assess anxiety-like behavioral responses in a novel environment. The time spent in the center was found to be lower in diabetic rats compared to the control group (p=0.003 vs DIA; p=0.005 vs DON and LARG; p=0.006 vs LNAME; **Figure 3A**). There was no significant difference between all diabetic groups in terms of time spent in the center (p>0.05, **Figure 3A**). In addition, the number of rearings, which we used as an indicator of exploratory behavior, was also higher in the CON group than in the diabetic groups (p=0.000 vs DIA, LARG and LNAME; p=0.001 vs DON; **Figure 3B**). The movement of the rats in the horizontal plane (crossing count) was used to evaluate locomotor activity. This activity was higher in the CON group compared to the diabetes groups, but this trend did not reach statistical significance (**Figure 3C**). It was found that donepezil, L-NAME or L-arginine administration to diabetic rats did not cause a significant difference in terms of both vertical movements and movements in the horizontal plane (p>0.05).

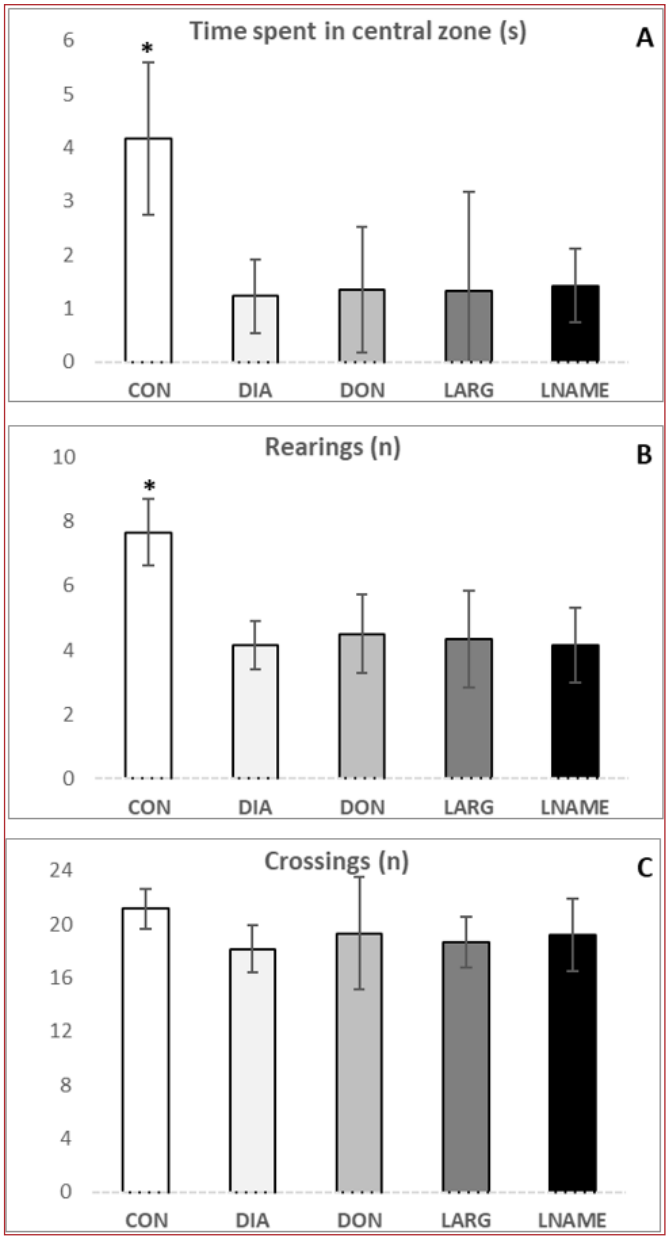

Figure 1. Effect of donepezil, L-NAME and L-Arginine on (A) time spent in central zone (B) number of rearing (C) number of crossing in the open field test in stz-induced diabetic rats. The data are expressed as the means±SD. Asterisk (*) indicates significance compared with other groups. p<0.01; one-way ANOVA.

DISCUSSION

The current study used a well-established method for creating diabetes in order to examine the effect of donepezil, an acetylcholinesterase inhibitor on diabetes-induced anxiety and depression and the role of NO.

To the best of our knowledge, our study is the first to demonstrate the effect of donepezil on depression and anxiety-like behaviors in STZ-induced diabetic rats and the role of NO in this effect. In this study, diabetes-induced reduction both in time spent in the center and exploratory activity in the OFT and increase in duration of immobility in the FST. Donepezil had no effect on either anxiety- or depression-like behavior in diabetic rats. However, L-arginine, administered rats, there was an increase in the duration of immobility in the FST associated with increased levels of depression.

Injection of STZ in rats leads to persistent hyperglycemia within approximately 48 hours and, in fact, hyperglycemia is responsible for diabetes-related complications, including cognitive and behavioral ones.[1] In fact, the pathophysiology of these complications is multifactorial and may be interrelated in some way and this complex relationship may often turn into a vicious circle. In our study, blood glucose levels were measured from the tail vein 72 hours after STZ injection and those above 270 mg/dl were considered diabetic. During the study period, blood glucose levels were above 270 mg/dl in all diabetic groups and there was no statistically significant difference between the all-diabetic groups (DON, L-NAME and L-ARG) in weekly measurements, so the relevant data are not presented here. Diabetes was accompanied by loss of weight in all groups (data not given). There was no significant difference in body weight between all diabetic groups and this was the same until the end of the study.

In our study, immobility time, which is considered as an indicator of depression in the forced swim test, increased in the diabetic groups compared to the control group (**Figure 2**). In the open field test, the time spent in the center and the number of rearing, which we evaluated as exploratory behavior, were lower in the diabetic groups (**Figure 3A-B**), indicating that anxiety was induced in the diabetic groups. Neurobiological studies suggest different mechanisms for the occurrence of depression-like behaviors in diabetic rats. Diabetes causes increased hippocampal levels of proinflammatory cytokines, such as TNF-α, NF-κB and IL-6, decreased neurotrophic factors, such as BDNF, NGF and IGF-1,[19] increased hippocampal lipid peroxidation and plasma glycated hemoglobin levels, and decreased antioxidant status as assessed by GSH,[20] and decreased insulin receptor phosphorylation in rat hippocampus, decreased ATP and glucose transporter 4 (GLUT4) expression,[21] decreased levels of glutamate, serotonin and dopamine in the hippocampus and associated hippocampal neuron apoptosis,[22] impaired regulation of hippocampal oxidative enzymes (GSH, SOD, CAT, LOOH),[23] increased brain proinflammatory cytokines (TNF-α, IL-6 and IL-1β) and MDA levels, and reduced SOD; CAT and GSH activity.[24] One of the important neurotransmitters in the pathophysiology of diabetic depression is ACh, and patients suffering from depression have high brain ACh levels and remain at this level as long as depression persists.[7] Donepezil is a synthetic AChE inhibitor that enhances cholinergic function by increasing the amount of ACh in the central nervous system and thus its interaction with the relevant receptors. Pharmacologic inhibition of AChE improves serum IL-6, brain noradrenaline and serotonin levels in diabetic rats, and donepezil is suggested to act through these mediators in the recovery of diabetes-induced brain oxidative damage.[25] However, donepezil was not effective in the regulation of proinflammatory cytokines such as hippocampal TNF-α and IL-1β and antioxidant enzymes such as GSH-SOD in type 2 diabetic rats.[26] Moreover, according to the available evidence, pharmacologic inhibition of AChE showed anxiogenic[3] and anxiolytic[9] effects, indicating that the subject is still in need of clarification and new studies are needed in this field. In this study, we do not know the effect of donepezil on these parameters (proinflammatory cytokines, oxidative parameters, etc.), which is the first limitation of our study. Nevertheless, we know that the effect of donepezil on diabetes-induced depression-like behaviors was not statistically significant in our study ($p>0.05$, **Figure 2**). These differences in the results may be attributed to the differences in the dose and duration of administration of the drug, the differences in the age, race and perhaps sex of the animals used, and the differences in the experimental stress models; a recent study reported that low doses of donepezil showed antidepressant effects but high doses had no effect,[27] which indicates that our results are not surprising.

Increased experimental evidences suggests that NO is associated with mood disorders such as anxiety and depression, which affect large numbers of people globally and have increasing morbidity. Epithelial and neuronal-derived NOS have been shown to be expressed in brain regions responsible for depression-anxiety responses and memory formation, such as the hypothalamus, hippocampus and amygdala.[28-30] Stress-inducing conditions lead to an increase in hippocampal NO levels in experimental animals, and NO induces the production of proinflammatory cytokines via microglia and these inflammatory mediators are involved in the occurrence of neuronal damage leading to the emergence of deviated behavioral symptoms associated with anxiety and depression. The reduction of NO levels as a result of L-NAME administration, which is responsible for the prevention of damage by modulating the production of inflammatory mediators,[31] indicates the magnitude of the effect of NO in the physiopathology of depression. NO not only induces depressive behaviors by inducing the production of proinflammatory cytokines, but also leads to impairments in oxidative stress parameters.[13] Essentially, proinflammatory cytokine production and this condition interact with each other in a vicious circle. Other studies demonstrating the effect of systemic NO inhibition on stress-induced anxiogenic behaviors suggest that L-NAME,[11] and L-NAME and 7-NI[12] cause anxiolytic effects. In our study, rats receiving L-arginine showed high immobility time in the forced swim test than the other diabetes groups, which means that the increased amount of nitric oxide by L-arginine administration worsens the depression-like behavior and is consistent with the studies mentioned above. In our study, diabetic rats receiving L-arginine were also receiving donepezil and we cannot say whether this effect is due to L-arginine alone or its interaction with donepezil, which is another limitation of our study. Nonetheless, NO modulates ACh release, especially exogenous NO is more effective in the upward induction of ACh release than endogenous NO.[32] Our speculative, but at the same time, need-to-be-proven explanation for the fact that the group receiving L-arginine exhibited more severe depressive behaviors than the other diabetes groups is as follows: Increasing the amount of NO by systemically administering L-arginine leads to an increase in ACh release, and since ACh and NO individually induce depressive behaviors, this result observed in the L-ARG group is a result of a cumulative effect due to **a)** the increase in NO by administering L-arginine and the stimulation of ACh release by NO **b)** and the increase in the amount of ACh by decreasing

AChE enzyme activity due to donepezil administration. On the other hand, there are also experimental evidences that points in the opposite direction. In contrast to the mentioned studies, L-arginine supplementation positively modulates stressor-induced cognitive impairments and plasma and brain tissue biochemical changes in animal studies in which anxiety and depression are induced, as well as improves cognitive impairment in Alzheimer's disease model induced by type-2 diabetes,[33] improves anxiety in a stress model induced by electric shock,[34] and anxiotic signs induced by restraint stress and assessed by elevated plus-maze, anxiety-like behavior (EPM).[10,35] The use of NO donors or NOS inhibitors in experimental models has produced conflicting results, but also similar effects in the same study. Both L-arginine and L-NAME administered locally to the basolateral amygdala region reduced stress-induced anxiety and depression,[34] while L-arginine and low doses of L-NAME improved anxiety induced by restraint stress and assessed by EPM.[10] In addition, while the use of L-arginine alone did not cause any effect, it decreased the antidepressant effect of lithium when used with lithium, L-arginine supplementation improved aminophylline-induced anxiety-like behaviors, while anxiety level increased after L-NAME supplementation. However, L-NAME improved the number of seizures and mortality rate that developed as a result of aminophylline administration, whereas L-arginine had a negative effect. Considering all these reports, the fact that both NO precursor and inhibitor lead to the same result under the same conditions, and the interaction with different systems leads to unpredictable results suggest that NO is a neuromodulator that interacts with other factors such as stress factor, dose and duration of administration rather than a unique mechanism of action in the physiopathology of mood disorders such as anxiety and depression. The existence of bidirectional relationship between diabetes and depression, beyond the confusion of whether diabetes causes depression or depression causes diabetes, an important fact that should not be overlooked is that many psychological symptoms accompany diabetic individuals. Good management of depression and/or anxiety symptoms is clinically very important in the control of diabetes. The difficulty of preventing the complications of diabetes and the frequent overlook of the psychiatric disorders observed during diabetes cause these two comorbid conditions to worsen. Determining the underlying mechanisms of depression and/or anxiety states observed during diabetes will contribute to the explanation of the physiopathology of this comorbid condition. For this reason, many experimental animal studies are carried out for this purpose, but a clear answer has not been found yet, so it is thought that more comprehensive studies are needed in this area.[1,2,36]

CONCLUSION

Taken together, in this study, we demonstrated that STZ-induced diabetes caused both anxiety and depression in rats. Furthermore, AChE inhibition by donepezil had no effect on anxiety and depression levels in diabetic rats. An increase in the level of depression was observed in the L-arginine-treated group, while the non-specific NOS inhibitor L-NAME had no statistically significant effect. Our findings suggest that the depressive effects of L-Arginine may be related to the increase in ACh release by NO and the increase in the amount of ACh as a result of the effect of AChE inhibitor.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out at Necmettin Erbakan University Experimental Medicine Researches and Application Center after obtaining Ethics Committee approval (2022/015).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Evaluation of vitamin D status of pregnant women in the Western Black Sea region of Turkey

Mehmet Can Nacar[1], Görker Sel[2]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Adıyaman University, Adıyaman, Turkey
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Bülent Ecevit University, Zonguldak, Turkey

ABSTRACT

Aims: Vitamin D (Vit-D) is an essential fat-soluble vitamin for the body whose central role is to regulate phosphorus and calcium homeostasis. Various studies have shown that Vit-D deficiency in pregnant women can have adverse consequences for the mother and the fetus. Therefore, in this study, we aimed to evaluate the Vit-D level in first trimester pregnant women in the Western Black Sea region of Turkey. We then examined the relationship between these levels and age.

Methods: In this cross-sectional study, 214 first trimester pregnant women who applied for medical examination at the Obstetrics and Gynecology outpatient clinic between 2015 and 2018 were included. The demographic characteristics and obstetric histories of pregnant women were recorded. Maternal serum Vit-D levels were compared. Vit- D < 12 ng/mL was considered a Vit-D deficiency, and 12–20 ng/mL was considered a Vit-D insufficiency.

Results: The records of 214 pregnant women aged 17 to 44 were reviewed. The mean Vit-D level in pregnant women was 21.08±16.45 ng/mL. We divided women into four groups based on their Vit-D levels: normal, deficiency, insufficiency, and high levels. There were 30 (14.01%) pregnant women with normal Vit-D levels, 91 (42.52%) pregnant women with deficiency, and 91 (42.52) pregnant women with insufficiency. Then, we divided women into two groups: those under 30 and those over 30. There were 139 (64.95%) women under 30 years old and 75 (35.05%) women 30 years and older. The proportion of those under 30 years old who had Vit-D deficiency and insufficiency levels was 60/91 (65.9%) and 61/91 (67.03%), respectively. Vit-D deficiency and insufficiency were found in 31/91 (34.06%) and 30/91 (32.96%) of those aged 30 and older, respectively. There was no significant relationship between Vit-D levels and age (p=0.381).

Conclusion: We found that Vit-D deficiency is more common in first trimester pregnant women in the Western Black Sea region of Turkey. Pregnant women should take Vit-D supplements to reduce morbidity and its effects on fetuses and newborns.

Keywords: Pregnant women, vitamin D, age

INTRODUCTION

As a steroid prohormone, Vitamin D (Vit-D) is an essential fat soluble vitamin for the body, whose central role is to regulate phosphorus and calcium homeostasis, resulting in bone mineralization.[1] Sunlight (90%) is the primary source of Vit-D in humans, followed by food (10%) as the next major source of Vit-D.[2] After the skin is exposed to the sun's ultraviolet B rays and protected against hypovitaminosis D, Vit-D2 (ergocalciferol) and Vit-D3 (cholecalciferol) are transferred to the liver and hydroxylated to 25-hydroxyvitamin D (25(OH) D).[3] 25(OH)D is the normal state of Vit-D circulation in the body.[4]

Vit-D deficiency is a common global deficiency,[5] and it can lead to immune system dysfunction, an increased risk of cancer, neurological dysfunction, muscle weakness, chronic pain, and exposure to various diseases, including cardiovascular disease, diabetes, and rheumatic disease.[6] Vit-D in pregnant women has an important role in fetal health, embryogenesis, calcium homeostasis, and fetal skeletal development.[7] A balanced maternal diet before, and during pregnancy supports optimal growth and development in the fetus and offspring.[8] Various articles have shown that Vit-D inadequacy in pregnant women can have adverse consequences for the mother and the fetus, including small for gestational age, gestational diabetes mellitus (GDM), and preeclampsia.[9] A systematic review found that Vit-D has a significant relationship with increasing mean birth weight and height for up to a year and lowering the risk of small-for-gestational-age, recurrent or persistent wheezing, and offspring recurrent or persistent asthma for up to three years.[10] Although all of these effects have been confirmed in many studies, Vit-D deficiency has a high prevalence rate, ranging from 20% to 85% in pregnant women.[2] In a study conducted in two regions of Turkey, Gür et al.[11] reported that the prevalence of Vit-D deficiency in pregnant women ranged from 27.8 to 76.3%.

Corresponding Author: Mehmet Can Nacar, mcannacar@gmail.com

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Therefore, in this study, we aimed to evaluate the Vit-D level in pregnant women in the Western Black Sea region of Turkey. We then examined the relationship between these levels and age.

METHODS

The study was carried out with the permission of Zonguldak Karaelmas University Research Ethics Committee (Date: 21.11.2018, Decision No: 2018/22). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

This retrospective study evaluated the laboratory data of 214 first trimester pregnant women (mean age±SD: 27.68±5.35 years) attending the Department of Gynecology and Obstetrics, Faculty of Medicine, Zonguldak Karaelmas University, Zonguldak, Turkey, between February 2015 and December 2018. None of the women were taking Vit-D supplements prior to blood sampling. The patient population was not taking vitamin D because pre-conception vitamin D measurement was not routinely performed and patients did not have information about the need for prophylactic vitamin D intake. After obtaining the approval of the Institutional Ethics Committee of the same hospital, we used the hospital's electronic database of pregnancy-related variables.

Vit-D Level Analysis

The Vit- D status of the participants is determined using serum 25(OH)D analysis. After collecting venous blood samples from participants, the samples are analyzed by the liquid chromatography mass spectrometry method. The criteria for these cut points are as follows: Less than 12 ng/mL of serum 25(OH)D indicates deficiency, 12 to 20 ng/mL indicates insufficiency, and 20 to 50 ng/mL indicates adequate levels.[12]

Statistical Analysis

Statistical analysis was performed using the IBM SPSS (Statistical Package for the Social Sciences) program, version 21, and the Open Epi Info software, version 3.01 (source: www.openepi.com). Results were given as mean±standard deviation (S.D.). The X2 test was used to examine the relationship between women's ages and Vit-D levels. A p-value less than 0.05 was considered statistically significant.

RESULTS

The records of 214 first trimester pregnant women between the ages of 17 to 44 were examined. The mean Vit-D level in pregnant women was 21.08±16.45 ng/mL. The baseline findings for pregnant women are shown in Table 1.

The pregnant women were divided into four groups based on the accepted cut-off values for Vit-D levels: normal, deficient, insufficient, and high. There were 30 (14.01%) pregnant women with normal Vit-D levels, 91 (42.52%) pregnant women with deficiency, and 91 (42.52%) pregnant women with deficiency. The level in 2 (0.93%) was above the average level.

Then we divided the women into two groups; under 30 years old and those over 30 years old. There were 139 (64.95%) women under 30 years old and 75 (35.05%) women 30 years and older. The proportion of those under 30 years old who had Vit-D deficiency and insufficiency levels was 60/91 (65.9%) and 61/91 (67.03%), respectively. Vit-D deficiency and insufficiency were found in 31/91 (34.06%) and 30/91 (32.96%) of those aged 30 and older, respectively. There was no significant relationship between Vit-D levels and age (p=0.381). The results are shown in Table 2.

Table 1. Baseline findings of pregnant women

Ages, years mean (SD) min-max	27.68 ±5.35 (17-44)
Vitamin D level, ng/mL, mean (SD)	21.08±16.45
Education level, n (%)	
Illiterate	1 (0.5)
Primary school	43 (20.1)
Middle school	87 (40.7)
High school	42 (19.6)
University	41 (19.2)
Education level of husbands, n (%)	
Illiterate	1 (0.5)
Primary school	45 (21)
Middle school	63 (29.4)
High school	60 (28)
University	45 (21)
Pre-pregnancy doctor referral, n (%)	
Yes	38 (17.8)
No	176 (82.2)
Pregnancy planning, n (%)	
Planned	124 (57.7)
Not Planned	90 (42.3)
Smoking, n (%)	
Yes	25 (11.7)
No	189 (88.3)
Use of folic acid before pregnancy, n (%)	
Yes	27 (12.6)
No	187 (87.4)
Delivery, n (%)	
Normal delivery	129 (60.3)
Cesarean section	85 (39.7)
Gravidity, n (%)	
Primigravid	68 (31.8)
Multigravid	146 (68.2)
Parity, n (%)	
Primiparous	87 (40.7)
Multipararous	127 (59.3)

Data is presented as n (%). Values are mean±SD or numbers and percentages.

Table 2. Vit-D levels in pregnant women

	Vit-D levels				p
	Deficiency (<12 ng/mL) n:91 (%)	Insufficiency (12-20 ng/mL) n:91 (%)	Normal (20-50 ng/mL) n:30 (%)	High (>50 ng/mL) n:2 (%)	
Ages					0.381
<30 years	60 (65.93)	61 (67.03)	16 (53.34)	2 (100)	
≥30 years	31 (34.06)	30 (32.96)	14 (46.66)	0 (0)	

Data is presented as n (%).

DISCUSSION

During periods of rapid cell division in the fetus, tissues and organs of the body undergo critical growth.[13] Any stimulus or problem in fetal planning or during the developmental period can affect the life of the fetus.[14] Significant changes occur in the mother's Vit-D and calcium metabolism in order to meet the fetus's need for mineralization and bone growth. During the first trimester of pregnancy, the fetus accumulates 2 to 3 mg of calcium in the skeleton daily, reaching 4 to 6 mg in the last trimester of pregnancy.[15] Recent studies examining the effects of Vit-D deficiency in pregnant women have shown links

between Vit-D deficiency and various problems, including increased cesarean delivery rates, insulin resistance, pre-eclampsia, GDM, and bacterial vaginosis.[16] A study of pregnant women also found that taking 4,000 IU/d could reduce complications such as cesarean section, preterm delivery, or maternal infections.[17] In our study, there was no additional increase in cesarean section rates in pregnant women who spent the first trimester and preconceptional period without vitamin D supplementation.

Vit-D deficiency in women of reproductive age continues to be one of the major problems for women worldwide. Pregnant women can develop Vit- D deficiency due to a lack of sunlight exposure, frequent use of sunscreen creams, dark skin color, closed clothing styles, lack of support for Vit- D during pregnancy, living in a polluted city environment, and disorders in Vit- D metabolism. There are many studies examining the link between low maternal Vit-D levels and many diseases in their babies.[18,19] Prasad et al.[20] assessed 88% of pregnant women for Vit- D deficiency. In Boyle et al.[21] study, Vit-D deficiency was detected in 53% of pregnant women, and in 4.4% severe Vit-D deficiency was detected. In our study, it is thought that there is a high rate of vitamin D insufficiency and deficiency due to the lack of pre-pregnancy doctor consultation and the geographical conditions and clothing style.

In Turkey, a program for pregnant women has been implemented since May 2011 in which women should receive 1200 IU of Vit-D daily from the twelfth week of pregnancy. This program will continue for up to six months after the baby is born. Preconceptional vitamin D prophylaxis has not yet been implemented by the Ministry of Health. Many studies in Turkey have examined Vit-D levels in pregnant women. A study on the concentration of Vit-D in pregnant women in the Middle East showed that this amount is <25 nmol/L for women in early pregnancy.[22] In a meta-analysis, Alpdemir et al.[23] evaluated that Vit-D deficiency in pregnant women was 76.3% in Turkey. A study conducted in the East Black Sea region of Turkey found that Vit-D deficiency (≤20 ng/mL) and severe Vit-D deficiency (≤5 ng/mL) were observed in between 94.2% and 24.2% of mothers, respectively.[24] Ozdemir et al.[25] observed that mean Vit- D levels were significantly lower in pregnant women in the Istanbul district. A study by Cakır et al.[26] found that summer levels of Vit-D in pregnant women were significantly higher than in winter in Turkey. In a study conducted by Ateş et al.[27] 45.9% of the pregnant women had severe Vit-D deficiency. These results are also consistent with our data and we think that this deficiency is obvious because there is no vitamin D level examination in the pre-pregnancy routine screening and the society has less use from the sun.

In our study, we aimed to evaluate the level of Vit-D in pregnant women in the Western Black Sea region. The average Vit-D level was found to be 21.08±16.45 ng/mL. We classified the 214 first trimester pregnant women who took part in the study as having deficiency, insufficiency, or normal Vit-D status. Two of the women had Vit-D levels that were higher than the accepted cut-off value. The total number of women with Vit-D deficiency or insufficiency was 182/214 (85.04%). Our results were found to be compatible with many studies in our country. We then evaluated the Vit-D levels in women under the age of thirty and over the age of thirty. We wondered if vitamin D levels were related to age and health knowledge experience. Although our results were not statistically significant, Vit-D deficiency and insufficiency were more common in the group under 30 years of age (**Table 2**). This could be because the majority of the patients included were under the age of 30. We predict that vitamin D level is higher over the age of thirty due to aging and the related increase in health literacy and experience gained from previous pregnancies.

Study Limitations

Our study has some limitations. First, our samples consisted only of pregnant women in the Western Black Sea region and first trimester pregnants. These data may not reflect the whole country and all pregnancy period. Another limitation is that the Vit-D analysis was not evaluated according to months. It is a known fact that Vit-D levels are lower in the winter months. However, it is an advantage of our study that the data obtained from the Western Black Sea region can guide the pregnancy support programs in the region.

CONCLUSION

In order for newborn babies to be healthy, it is necessary to provide optimal conditions in the mother's womb. Our findings show that Vit-D deficiency is common in pregnant women in the Western Black Sea region. It is necessary to investigate the causes of Vit-D deficiency and insufficiency in the group under the age of 30 and take precautions accordingly. Pregnant women should consider taking Vit-D supplements to reduce morbidity and the effects of pregnancy and lactation on fetuses and newborns. It can also be envisaged that the vitamin D level should be included in the routine screening program before pregnancy planning.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Zonguldak Karaelmas University Research Ethics Committee (Date: 21.11.2018, Decision No: 2018/22).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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Candida spp. infection frequency and risk factors in malignant critical care patients

Burcu İleri Fikri[1], Alev Öztaş[1], Hazal Özsağıroğlu[2], Güldem Turan[1]

[1]Department of Intensive Care Unit, Başakşehir Çam and Sakura City Hospital, University of Health Sciences, İstanbul, Turkey
[2]Department of Anaesthesiology and Reanimation, Başakşehir Çam and Sakura City Hospital, University of Health Sciences, İstanbul, Turkey

ABSTRACT

Aims: *Candida* spp. can cause fatal infections in the person in case of immunosuppression such as malignancy. The aim of our study is to examine the frequency, prognosis and risk factors of *Candida*-related infections in our patients with malignancies followed in our intensive care unit (ICU).

Methods: ICU patients with malignancy with fungal infection accepted as the case group and the patients without *Candida* were considered as the control. Demographic characteristics, risk factors and *Candida* risk scores were recorded and compared in both groups.

Results: *Candida* spp. reproduction was observed at a very high rate with 24%. However, there was no difference in mortality between the two groups with and without *Candida* infection. In our study; *Candida* risk score, presence and duration of central venous catheter, antibiotic and steroid use in the last 1 month were found to be the factors determining the risk of *Candida* infection.

Conclusion: The contribution of the presence of fungal infection to mortality in our cancer patients does not seem different from others. However, in this patient group, it is difficult to distinguish colonization from invasive fungal infections. At this stage, the use of treatment decisions using risk factors and risk scoring comes to the fore.

Keywords: ICU, malignancy, *Candida* spp., mortality.

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INTRODUCTION

Infections due to *Candida* spp. cause severe problems associated with increased morbidity and mortality in ICUs.[1,2] Candidemia constitutes 10% of nosocomial infections and is associated with mortality defined as high as 40%.[3] The number of patients followed in ICUs with the diagnosis of malignancy is relatively high, and these patients have risks for *Candida* infection due to their immunosuppressed status. Except for mortality, *Candida* infections remain serious with increasing duration of stay and cost, and there may still be different approaches among clinicians in both diagnosis and treatment phases. It usually delays the diagnosis of *Candida* spp. infections as a result of the time required to obtain a positive blood culture, and this delay may cause mortality in our malignant patients. To start an effective early treatment, the diagnosis of *Candida* infections must be made quickly. Evaluation of risk factors is important for clinical guidance so that the patient to be treated can be determined as soon as possible.

The primary aim of our study was to evaluate whether there was a difference in mortality between the two groups in the ICU, and secondarily, it was aimed to reveal the difference in *Candida* risk factors statistically.

METHODS

Our study was approved by the Ethics Committee of Başakşehir Çam and Sakura City Hospital, with the decree dated 13/01/2022 and numbered 2022.01.13. All patients with malignancy were reached by retrospectively scanning through the hospital registry system among all patients hospitalized in the Level 3 ICU between 01/01/2021-30/11/2021. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Inclusion Criteria

- ICU patients over the age of 18 with a diagnosis of malignancy.
- Patients with ongoing malignancy (chemotherapy, radiotherapy processes).
- All patients who will undergo or have undergone surgery for their active malignancy.

Exclusion Criteria of the Study

- Patients in remission whose malignancy has been treated more than 1 year after the remission period.
- Patients with a duration of stay in ICU less than 24 hours.

Corresponding Author: Burcu İleri Fikri, drburcuileri@hotmail.com

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These patients were divided into 2 groups patients with fungal reproduction in at least one of the culture samples taken during ICU admission and patients with no reproduction at all. Demographic characteristics of these 2 groups, which organ malignancy they have, APACHE-II, Sofa scores, ICU length of stay, first month and 3rd-month mortality, discharge data, fungal growth in which culture, whether they received treatment, if any, which antifungal agent was given, and risk factors were examined. *Candida* Risk Score Criteria (total parenteral nutrition (TPN) given, undergone surgery, presence of severe sepsis and multiple colonization), presence and duration of central venous chateter (CVC), long duration of stay in ICU, antibiotics, steroids, or other immunosuppressive treatments (chemotherapy) in the last 1 month agents) were investigated in our study as risk factors.

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, first quartile, third quartile, frequency, percentage, minimum, maximum) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. Independent groups t-test was used for comparisons between two groups of normally distributed quantitative variables, and the Mann-Whitney U test was used for comparisons between two groups of non-normally distributed quantitative variables. Pearson chi-square test, Fisher's exact test, and Fisher-Freeman-Halton exact test were used to compare qualitative data. Statistical significance was accepted as $p<0.05$.

RESULTS

Our study was carried out retrospectively in Başakşehir Çam ve Sakura City Hospital ICU, covering the date range of 01/01/2021-30/11/2021. There were 111 patients in our study, and the group with *Candida* spp. reproduction consisted of 27 patients, and the group without reproduction consisted of 84 patients. The ages of the cases ranged from 18 to 89, with a mean age of 61.32±13.26 years. 47.7% (n=53) of the participants were female and 52.3% (n=58) were male. The APACHE II values of the cases ranged from 2 to 47, and the mean value was 20.07±11.20. Sofa scores range from 0 to 21, with an average sofa score of 7.85±5.60. The duration of ICU hospitalization in the cases ranged from 1 to 155 days, and the mean duration of hospitalization was 14.22±21.12. When ICU discharge routes were examined, it was observed that 64% (n=71) of the cases were dead, 34.2% (n=38) were transferred to the service, 0.9% (n=38) were transferred to palliative, and 0.9% of them (n=1) were transferred to another ICU and left the intensive care unit. Mortality at the end of the first month was observed in 56.8% (n=63) of the participants, and mortality at the end of the third month in 64% (n=71) of the participants. Reproduction was observed in 22.2% (n=6) blood, 18.5% (n=5) urine, 7.4% (n=2) tracheal aspiration sample, 3.7% (n=1) wounds, 48.1% (n=13) multi-areas. When the reproducing fungal species were examined, it was observed that 74.1% (n=20) of those with growth were *C. albicans*, 40.7% (n=11) C. Non-albicans, and 7.4% (n=2) other (rare fungi). Antifungal treatment was started in 81.5% (n=22) of the cases. Azole group was started in 19 of our patients and the echinocandin group was started in 2 patients considering their antifungal resistance. Demographic characteristics, ICU exit patterns and mortality rates according to the groups of the patients are shown in **Table 1**, and reproduction rates and antifungals used in the treatment are shown in **Table 2** and **Figure 1**.

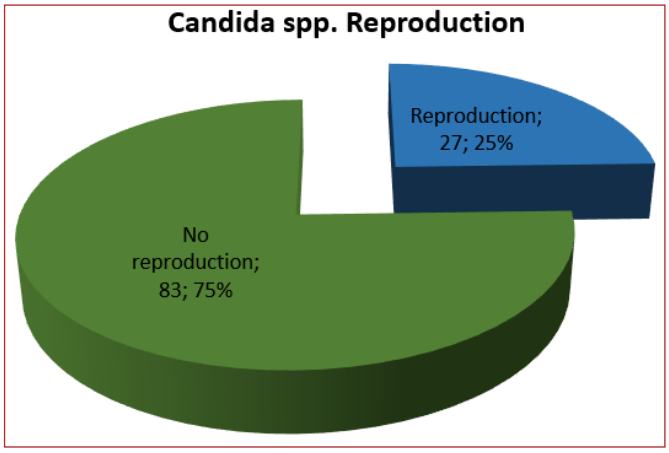

Figure 1: *Candida* reproduction distribution

Table 1: Evaluation of Demographic Characteristics by Groups

	Candida		
	Reproduction (+) (n=27)	Reproduction (-) (n=84)	p
Age			[a]0.688
Mean±SD	62.22±14.85	61.04±12.79	
Median (min-max)	63 (18-87)	61 (25-89)	
Gender			[b]0.624
Female	14 (51.9)	39 (46.4)	
Male	13 (48.1)	45 (53.6)	
Apache score			[c]0.441
Mean±SD	18.11±7.05	20.70±12.21	
Median (min-max)	17 (6-36)	20 (2-47)	
SOFA score			[c]0.441
Mean±SD	7.30±4.03	8.02±6.03	
Median (min-max)	7 (1-17)	8 (0-21)	
Intensive care hospital stay (days)			[c]0.001**
Mean±SD	35.33±32.09	7.43±8.79	
Median (min-max)	27 (1-155)	3 (1-37)	
Mortality at the end of 1st month			[b]0.554
No	13 (48.1)	35 (41.7)	
Yes	14 (51.9)	49 (58.3)	
Mortality at the end of 3rd month			[b]0.086
No	6 (22.2)	34 (40.5)	
Yes	21 (77.8)	50 (59.5)	
ICU discharge route			[d]0.221
Ex	19 (70.4)	52 (61.9)	
Transfer to service	7 (25.9)	31 (36.9)	
Transfer to palliative	1 (3.7)	0 (0)	
Transfer to another intensive care	0 (0)	1 (1.2)	

aStudent t Test, bChi Square Test, cMann Whitney U Test, dFisher Freeman Halton Test, **p<0,01

Table 2: Reproduction Results and Cure Rates

Area, in case of reproduction (n=27)	
Blood	6 (22.2)
Urine	5 (18.5)
Tracheal aspiration	2 (7.4)
Wound	1 (3.7)
Multiple	13 (48.1)
• Reproducing mushroom species (n=27); n(%)	
C. albicans	20 (74.1)
C. Non-albicans	11 (40.7)
Other (rare fungi)	2 (7.4)
Antifungal started? (n=27); n(%)	
Not started	5 (18.5)
Started	22 (81.5)
If started, which (n=22); n(%)	
Azol group	20 (90.9)
Echinocandins	2 (9.0)

•More than one option is marked.

When Risk Factors are examined in detail, 17.1% (n=19) of the cases received total parenteral nutrition (TPN) and 36.9% (n=41) underwent surgery. Multiple fungal colonization was observed in 14.4% (n=16) of the patients, and severe sepsis was observed in 49.5% (n=55) of the patients. The total *Candida* scores of the cases ranged from 0 to 5 and the mean score was determined as 1.66±1.36. 59.1% (n=55) of the participants in the study had CVC, and the mean duration of CVC was 10.85±20.56. 50.5% (n=47) of the cases used antibiotics within the last 1 month, 25.8% (n=24) used steroids within the last 1 month, and 17.2% (n=16) used non-steroidal immunosuppressive therapy (chemotherapy) within the last 1 month. The distribution of Risk Factors is shown in **Table 3**.

Table 3. Distribution of Risk Factors

		n (%)
TPN	Did not receive	92 (82.9)
	Received	19 (17.1)
Surgery	Underwent	70 (63.1)
	Did not undergo	41 (36.9)
Multiple colonization	No	95 (85.6)
	Yes	16 (14.4)
Severe sepsis	No	56 (50.5)
	Yes	55 (49.5)
Total *Candida* score	Mean±SD	1.66±1.36
	Median (min-max)	2 (0-5)
CVC	No	56 (50.5)
	Yes	55 (49.5)
CVC duration	Mean±SD	10.85±20.56
	Median (min-max)	3 (0-150)
Antibiotic use in the last 1 month	No	64 (57.7)
	Yes	47 (42.3)
Steroid use in the last 1 month	No	87 (74.8)
	Yes	24 (21.6)
Immunosuppressive therapy in the last 1 month	No	95 (85.6)
	Yes	16 (14.4)

ICU length of stay in cases with *Candida* reproduction was statistically significantly higher than those without reproduction (p=0.001; p<0.01) **Figure 2**.

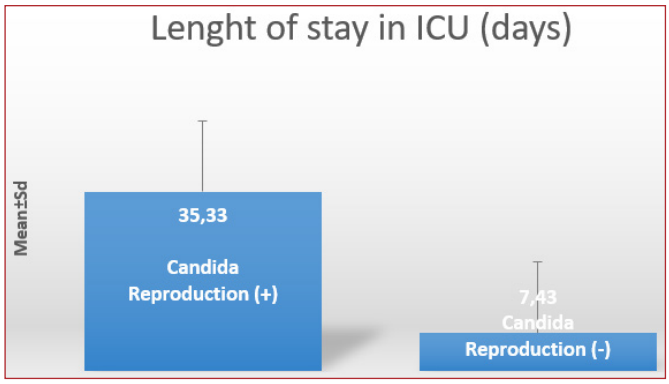

Figure 2: Distribution of intensive care unit stay according to the presence of *Candida* reproduction

Age, gender, APACHE II and Sofa scores of the cases, mortality rates at the end of the 1st and 3rd months, and the route they were discharged from the ICU did not show a statistically significant difference according to the presence of *Candida* reproduction (p>0.05). According to the incidence of *Candida* reproduction, the incidence of TPN and surgery did not show a statistically significant difference (p>0.05). The incidence of multiple sewage in those with *Candida* reproduction was found to be statistically significantly higher than in those without reproduction (p=0.001; p<0.01). The incidence of severe sepsis in those with *Candida* reproduction was found to be statistically significantly higher than in those without reproduction (p=0.001; p<0.01). The total *Candida* scores of the cases with *Candida* reproduction were found to be statistically significantly higher than those without reproduction (p=0.001; p<0.01). The incidence of CVCs in those with *Candida* reproduction was found to be statistically significantly higher than in those without reproduction (p=0.002; p<0.01). CVC times of cases with *Candida* reproduction were found to be statistically significantly higher than those without reproduction (p=0.001; p<0.01). The rate of antibiotic use in the last 1 month in those with *Candida* reproduction was found to be statistically significantly higher than those without reproduction (p=0.001; p<0.01). The rate of steroid use in the last 1 month in those with *Candida* reproduction was found to be statistically significantly higher than those without reproduction (p=0.023; p<0.05). There was no statistically significant difference between the rates of using other immunosuppressive treatments in the last 1 month according to the *Candida* reproduction rate (p>0.05).

DISCUSSION

As ICU physicians, we designed this study based on the question of whether our fungal infections are more common in patients with malignancy among chronic-comorbid diseases such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease and cerebrovascular diseases.

There was a reproduction in the blood culture of 16 of our patients and these patients were referred to as "candidemia". In other words, our candidemia frequency was found to be 15.8% in all patients. Although breeding is considered the gold standard for candidemia, its sensitivity varies between 21-71%.[4] In our study, especially patients with a diagnosis of malignancy hospitalized in the tertiary ICU were selected, and when we looked at our patients' APACHE and SOFA scores, we encountered a patient group with a very low life expectancy. Regardless of the underlying disease in ICUs, the crude mortality rate due to *Candida* infections has been shown in studies to be 30-50%.[5] It was shown in many studies that many more patients with malignancy result in death compared to other chronic diseases.[6,7]

All the patients in our study were patients diagnosed with malignancy, admitted after surgery for malignancy, hospitalized with a complication related to malignancy, or patients whose general condition deteriorated after chemotherapy and indicated for ICU admission. In our patients, the mortality at the end of the 1st month was 56.8% and the mortality at the end of the 3rd month was 64.0%. When we divided all our patients into 2 groups those with and without fungal infection, the mortality at the end of the 1st month was 51.9%, and the mortality at the end of the 3rd month was 59.5% in the group with reproduction. The difficulty in this and similar studies, including ours, is that it is not possible to clearly distinguish whether the patients were lost due to malignancy or due to *Candida* infection.

Fungal infections are opportunistic pathogens which rank 4th among hospital-acquired infections according to studies

in the USA. *Candida* spp, which colonizes the oral cavity and gastrointestinal and genitourinary system in healthy people, can cause fatal infection in immunosuppressed conditions. The main immunosuppression conditions can be listed as chemotherapy and radiotherapy treatments, long-term use of corticosteroids and antibiotics, and the presence of malignancy.[8,9] *Candida* spp. is still the most common in ICU and *C. albicans* comes first.[10] However, some of the increasing non-albicans species have serious consequences due to their resistance to azoles and delays that may occur in reaching echinocandins. In our study, the most common fungal agent was *Candida* spp with *C. albicans* coming first and Fungi other than *Candida* spp. reproduced in 2 cases in our study. Li et al.[11] compared 80 patients diagnosed with a malignancy in tertiary ICU patients with patients without malignancy and found that *Candida* spp. found 30% mortality due to infection and highlighted it as a much higher mortality rate compared to patients without malignancy.

The risk factors that increase the frequency of *Candida* infection in our study overlap with the risk factors that have been revealed in many previous studies.[12] *Candida* Risk Score, presence and duration of the CVC, length of stay in ICU and antibiotic, steroid, and other immunosuppressed treatments in the last 1 month were evaluated. *Candida* Risk Score includes 4 criteria and it is accepted that a value over 2.5 increases the risk. A *Candida* score of >2.5 was found to have 81% sensitivity, 74% specificity, 98% negative predictive value and 16% positive predictive value for invasive candidiasis. In the score, 2 points were given for sepsis and 1 point for other risk factors.[13]

When we compared our patient groups with and without *Candida* reproduction in our study; the incidence of multiple fungal colonization, *Candida* risk score, presence of sepsis, presence and duration of the CVC, antibiotic and steroid use in the last 1 month were found to be the factors determining the risk of *Candida* infection. Although it is known that the use of TPN in groups with and without *Candida* growth, having undergone surgery and receiving immunosuppressive therapy in the last 1 month, increased the risk, they did not make a statistically significant difference. Regarding the use of TPN, we think that we may have obtained clarity by the fact that the standard prepared TPN products in our hospital are transported from the hospital pharmacy to our unit with the cold chain, and that no additions are made to the TPN products, and that they are given in a time not exceeding 24 hours by always paying attention to the extremely sterile conditions with the central catheter.

Another controversial issue in this regard is whether prolonged ICU stays cause an increase in the frequency of *Candida* infection. In the design of many studies in the literature, it is seen that the time to increase the risk of *Candida* is considered to be 30 days or more. In a meta-analysis published by Zhang et al.[9] ICU hospitalization for the risk of *Candida* infection was shown as 25.8 days. In our study, the average duration of stay in ICU was 14.22±21.12 days for all patients. The day of hospitalization in the ICU was 35.33±32.09 days in patients with *Candida* reproduction and 7.43±8.79 days in patients without reproduction, and a significant difference was observed. (p=0.001). What we want to emphasize here, regardless of mortality, is the necessity to ensure the rational use of ICUs and to ensure that patients whose ICU indications disappear should be transferred to the necessary services immediately.

At the beginning of our study, the main issue we wanted to achieve was to examine whether *Candida* infections are mortal in malignant ICU patients. As a result of our study, we did not see a difference in mortality, and this result made us think: Wonder if *Candida* spp. in malignant patients does not cause as many frightening results as we think?

Candida spp. reproduction, especially in blood culture, creates a state of anxiety and alarm, especially in physicians. For these patients, the risk factors that can be corrected are reviewed, and it is decided whether to change the CVC, nasogastric tube and urinary catheter and, if TPN is applied, whether to stop it. In patients with candidemia, an ophthalmology consultation is urgently requested for *Candida* opthalmitis. This examination is done at the bedside, and there may be delays in terms of the need for consultation with other branches. Yet, bedside transthoracic ECHO is performed by the cardiologist for the screening of *Candida* endocarditis in patients with candidemia and transaesophageal ECHO is often recommended to the patients. Since this examination cannot be performed at the bedside, the transport of the patient to another block carries risks for both the physicians and the patient due to possible complications and procedure-specific difficulties associated with the transport. Again, in all patients in whom we detected *Candida* spp. infection, consultation from infectious diseases is requested and opinions are taken for the antifungal agent to be selected, and inevitable treatment delays contribute to the increase in mortality.

The number of the cases was one of the limitations of our study. Furthermore, we need more spesific diagnostic tools for candidemia and colonisation.

CONCLUSION

If we summarize our work, *C. albicans* was the most common pathogen. Candidemia and other *Candida* infections can cause an increase in ICU deaths and ICU costs due to *Candida* infections, as well as the severity of the disease and the complications experienced. As ICU physicians, we see that the number of patients who come to the ICU with the diagnosis of malignancy is quite high. We think that we should keep in mind the predisposing factors and risk scoring for *Candida* spp infections in our cancer patients hospitalized in the ICU.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethics Committee of Başakşehir Çam and Sakura City Hospital, with the decree dated 13/01/2022 and numbered 2022.01.13.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Evaluation of alarm fatigue in nurses working in intensive care units

İlkay Ceylan[1], Ebru Karakoç[2]

[1]Department of Anesthesiology and Reanmiation, Bursa Yüksek İhtisas Training and Research Hospital, University of Health Sciences, Bursa, Turkey
[2]Department of Anesthesiology and Reanmiation, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

ABSTRACT

Aims: This study aimed to investigate alarm fatigue, which has a negative impact on nurses working in intensive care units.

Methods: A questionnaire of 20 questions consisting of the alarm fatigue scale in nursing and sociodemographic questions prepared on Google Forms was sent to the nurses working in intensive care units as a social messaging platform and e-mail between 1 January-1 February 2022.

Results: 219 nurses provided feedback. Nurses working in adult intensive care units participated with 70.6%. It was observed that alarm fatigue scores decreased as the duration of working in the intensive care unit and the duration of profession of the nurse increased.

Conclusion: As the age and professional experience of the nurses increase, the fatigue caused by the alarms decreases. Since this situation may pose a danger to the safety of patients who followed by the younger or nurses in the early years of their professions, it would be appropriate to develop nurses' methods of coping with alarms.

Keywords: Alarm, noise level, intensive care nursing, stress

INTRODUCTION

Intensive care units (ICU) are special treatment units with high technological equipment, developed for the follow-up and treatment of life-threatening organ failures seen in the course of both acute diseases and chronic diseases, with a high number of health professionals per patient for close observation and rapid intervention.[1] The existing oxygen-air system, bedside monitor, drug and food infusion devices, mechanical ventilator, patient warming-cooling device and, when necessary, dialysis device, telephone and computers in these units cause the noise level to reach 90 decibels.[2] The addition of medical device alarms, which are detected to ring an average of 170 times per bed, to these sounds further increases the noise problem.[3]

Alarms are an essential detection and warning tool that alerts nurses. Potentially dangerous changes in the patient's clinical condition or equipment failures can threat patient safety. An excessive number of out-of-process and false alarm signals from medical devices produces alarm fatigue. Alarm fatigue is a cognitive state that results in insecure solutions, such as delayed response time to alarms, disabled alarms, turning the alarm volume down to inaudible, limiting parameters set to unsafe values, or turning off the warning message without reason. Alarm fatigue is a patient safety issue.[4] Alarm fatigue is a phenomenon that occurs when nurses work in a clinical environment where alarm sounds are frequently heard. Alarm fatigue can negatively affect nurses' productivity and concentration. In addition, the physical and mental health of employees who are constantly affected by their environment may also be affected.[3]

For this reason, it is crucial to determine and inform nurses about the effects of alarms. For this purpose, the Nurses' Alarm Fatigue Scale (NAFS) was developed and translated into Turkish for validity and reliability.[5]

This study aims to determine the alarm fatigue of nurses working in intensive care units and guide the measures that can be taken in this direction.

METHODS

The study was carried out with the permission of Bursa Yüksek İhtisas Training and Research Hospital Clinical Researches Ethics Committee (Date: 29.12.2021, Decision No: 2011-KAEK-25 2021/12-08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The participant questionnaire and scale form, consisting of 2 sections and a total of 20 questions, prepared with Google Forms, was sent to the nurses working in the different intensive care units in various hospitals in Turkey between January 1, 2022 and February 1, 2022 via e-mail and social

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messaging platform. The questionnaire form used in our study was translated into Turkish and validated in Turkish by Kahraman et al.[5] Permission to use it in the study was obtained from the authors. The sample size of the study, in which the convenience sampling method was used, consisted of volunteer nurses who worked in the intensive care units between January 1, 2022 and February 1, 2022. The first 11-question part of the questionnaire consists of demographic data. The second part is the nurses' alarm fatigue scale consisting of 9 questions.[5] There is no specific cut-off value for the alarm fatigue questionnaire. The participants' alarm fatigue scores were evaluated sequentially based on their answers to the questions in the questionnaire.

Statistical Methods

The Jamovi (The jamovi project (2022). jamovi (Version 2.3)) package program was used for the statistical calculations of the data obtained from the research. Continuous variables were obtained by measurements mean±standard deviation; categorical variables in sociodemographic and clinical data were expressed as percentages and numbers. The data were obtained by Post Hoc Tukey HSD analysis after the analysis of variance was significant and homogeneous distribution was determined after One Way ANOVA analysis, $p<0.05$ was considered statistically significant.

RESULTS

The questionnaires sent were returned by 219 intensive care nurses. The participants' demographic data and their answers to the questionnaire are presented in **Table 1**. 70 % of the participants were women, 68 % of them had graduated from university and half of them were married. More than half of the group was between 25 and 44 years old.

Significant differences in NAFS were found between the age groups of 25-34 and over 45 years (p=0.003), 19-24 and 35-44 (p=0.024); 19-24 to 45 and above (p=0.0001).

According to the duration of the occupation, a significant difference was found between the NAFS scores of the nurses with a working period of 1-5 years and more than 15 years (p=0.008).

In the statistical analysis performed between NAFS (**Table 2**) according to the length of work in the intensive care unit, less than one year and more than 15 years (p=0.002); A significant difference was found in nurses with a working time of 1-5 years and more than 15 years (p=0.034).

Table 2. Nurses' Alarm Fatigue Questionnaire Scores by Age Groups

	NAFS scores (mean±SD)
Age (year)	
19-24	15.81±6.1
25-34	14.79±5.8
35-44	11.88±5.7
45 +	9.94±4.3
Intensive care working length (year)	
< 1	15.87±4.8
1-5	14.41±5.6
6-14	13.14±6.5
15 +	10.24±4.8
Occupational length (year)	
<1	13.06±4.9
1-5	15.69±6.1
6-14	13.97±5.3
15 +	11.52±6.1
Shifts	
Night	11.44±4.9
Day	14.2±5.9
Day/night	13.98±6.1

Table 1. Demographic Data and Alarm Fatigue Evaluation Questionnaire

	n:219 (%)				
Gender	**Male**			**Female**	
	29.7			70.3	
Age	19-24	25-34		35-44	>45
	16.4	49.8		26.5	7.3
Marriage	**Married**			**Single**	
	58.9			41.1	
Degree	**Highschool**	**Pre-degree**		**Degree**	**High-degree**
	11.4	12.3		68.9	7.3
Occupational length(year)	<1	1-5		6-14	>15
	5.5	36.5		30.6	36.5
ICU working length(year)	<1	1-5		6-14	>15
	7.8	52.1		30.6	9.6
Facility	**University**		**State**		**Private**
	25.1		66.2		8.7
Intensive care unit	**General**		**Surgical**	**Medical**	**Child**
	70.6		5	15.1	3.7
Shifts	**Day**		**Night**		**Day-Night**
	8.7		4.1		87.2
Chronic illness	**present**			**Absent**	
	22.4			77.6	
Alarm Fatigue Evaluation (%)					
	Always	**Usually**	**Occasionally**	**Seldom**	**Never**
I turn off alarms at the beginning of every shift	4.6	11	9.1	12.3	63.3
I usually hear a certain amount of noise in the environment/clinic	37.7	43.8	11.4	4.6	3.2
The heavy workload in some shifts prevents my quick response to alarms	9.1	20.5	37	22.8	10.5
when alarms go off again and again, I become insensible	0.5	0.9	12.3	22.4	63.9
Alarm sounds make me angry	7.3	21.9	30.1	25.1	15.5
When I am sad and nervous, I am more sensitive to alarm sounds	14.6	29.7	30.6	14.2	11
When alarms sound repeatedly and continuously, I lose my patience	4.1	16	23.7	30.1	26
Alarm sounds prevent me from focusing on my professional tasks	3.7	16.4	23.3	22.8	33.8
I pay less attention to the alarms of the equipment during visiting hours	1.8	3.7	11	20.5	63

Statistical analysis could not be performed, as a homogeneous distribution could not be achieved between the groups in the NAFS scores (**Table 2**) according to the working hours in the intensive care unit.

DISCUSSION

Intensive care units (ICUs) are hospital departments that are constantly exposed to loud noise. Many factors contribute to the high sound intensity in ICUs. In addition to these, alarms reporting changes in the physiological parameters of patients or faults in machines cause this sound intensity to increase even more. This situation inevitably causes adverse effects on employee health, employee productivity and patient safety.[6]

The alarm fatigue assessment questionnaire was created by Torabizadeh to evaluate the alarm fatigue of nurses.[7] Its validity and reliability were established by Kahraman et al.[5] This questionnaire aims to measure alarm fatigue by evaluating the attitudes and behaviors of nurses working in the intensive care unit towards alarms. No cut-off value is defined for alarm fatigue. However, high values are associated with higher levels of fatigue. Since the purpose of the study was to investigate the alarm fatigue, the answers to the questions were evaluated and reviewed individually. Therefore, the aim is to make corrective suggestions when the causes are uncovered. In assessing alarm fatigue among nurses in our country, it is more important to define under what conditions it increases and how it can be prevented than to state "there is alarm fatigue".

Alarm fatigue occurs when the nurses are desensitized to alarms and lead to negative results in terms of patient safety.[8,9] Depending on alarm fatigue, nurses may try to silence alarms, decrease the volume of the alarm, delay responding to the alarm by judging that the alarm is false, or try to turn off the alarm permanently without evaluating the patient.[9] "When alarms go off, again and again, I become insensible"63.9% of them answered as "never", and the high rate of this is critical and pleasing in terms of patient safety. Along with this question, "I usually hear a certain amount of noise in the environment/clinic," 89.9% of the participants answered that they heard a noise. When alarms are added to the basal sound level in ICUs, it increases to 90-110 decibels. Considering this, the nurses who are constantly in the ICU are exposed to loud noise. In addition to the employees, this situation also negatively affects the patients hospitalized in the ICU. This loudness may cause sleep disturbance and delirium in patients. It is therefore vital to control the volume and alarms.

There was a significant relationship between the age groups and alarm fatigue scores of the nurses participating in our study. Contrary to expectations, it was observed that alarm fatigue scores decreased with age. There was a significant difference between the scores of the groups aged 19-24 and 25-34 years and those over 45 years old. At the same time, a significant difference was found between the 19-24 age group scores and the 35-44 age group. There was a significant difference in alarm fatigue scores between nurses with a 1-5 years working history and nurses working in the intensive care unit for more than 15 years. Age, duration of profession years, duration of work in the intensive care unit and alarm fatigue score showed significant differences. It has been thought that this situation may be due to the increase in experience, knowledge and skill level, and the fact that it is easier to cope with the alarm management process, or it may also be due to occupational desensitization to alarms, which is a more dangerous situation, and it has not been possible to distinguish it. When the answers given to all the questions were evaluated, we concluded that advancing age and increasing professional experience enabled nurses to cope with alarm fatigue more successfully.

To the question "I turn off alarms at the beginning of every shift" in the alarm fatigue survey, 63% of the participants answered that they do not turn them off. This indicates that although alarm fatigue is present, nurses in the intensive care unit still act by alarm management. In the study of Akturan et al.[10] in which they evaluated the alarm fatigue of nurses working in COVID-19 intensive care units, they stated that nurses were more sensitive to the alarms of some patients whose clinical condition worsened and to the alarms of some devices during night shifts (such as being more sensitive to mechanical ventilators than to the sound of the infusion pump). It has also been suggested that nurses who work overtime and are less active on the night shift compared to the day shift may cause them to hear alarms more and react negatively. There was no meaningful difference between the groups since the nurses who answered our questionnaire, who were working night, day, night/day, were not homogeneously distributed among the groups. However, when the alarm fatigue score averages of the groups are examined, the average score of the group working only at night was found to be lower than the group working only during the day and day/night working group. According to the study of Şanlıtürk et al.[11] nurses working on the night shift experienced a significantly higher level of stress. It has been reported that night shift nurses are under more stress as a result of being more sensitive to alarms, and they experience the anxiety that "something can happen to the patient at any moment".[12] Reducing the working hours of night shifts can be effective in reducing this anxiety.

"The heavy workload in some shifts prevents my quick response to alarms" 66.6% of the participants answered this question as heavy workload sometimes-usually-always prevents them from responding to alarms. In the study of Akturan et al.[10] "the necessity to wear personal protective equipment" was determined as a factor that increases alarm fatigue in a process such as a pandemic where workload increases. The international patient safety commission has made some recommendations by setting targets for 'Improving Clinical Alarm Systems. It has been stated that alarm fatigue can be reduced by re-adjusting alarm limits according to the patient's condition before each shift, changing ECG electrodes, and re-adjusting alarms according to the situation when a new patient arrives. For basic monitoring in ICU, pulse rate, respiratory rate, blood pressure, and oxygen saturation (SpO_2) are monitored. According to the study of Eskin et al.[1] SpO_2 alarm is frequently encountered in hospitalized patients. Despite this, it was determined that the alarm settings were the least appropriate parameter according to the patient's clinic. It is thought that the alarm settings may be left in an inappropriately wide range since the saturation probe comes off easily from the finger, is challenging to fix, and more frequent alarms are activated due to other reasons.

It has been revealed that the nurses, who make up a total rate of 84.4% of the question "Alarm sounds make me angry", are angry because of alarms. This may be due to the anxiety created by the alarms, or it may be due to the noise alone. "When I am sad and nervous, I am more sensitive to alarm sounds". Mindfulness training and cognitive-behavioral therapies are recommended to reduce the rate of burnout in nurses.[13] "When alarms sound repeatedly and continuously, I lose my patience" 20.1% of the participants stated that the repeating of alarms often and always causes them to lose their patience. Since it will be difficult for intensive care nurses to develop appropriate behaviors for alarm management, appropriate approaches should be developed to support this team.[10] Improving working hours and conditions in institutions, establishing the alarm management process, inter professional cooperation and timely intervention of the technical support team can reduce this problem. "I pay less attention to the alarms of the equipment during visiting hours" was answered as "never" at a rate of 63%, which can be interpreted as the intensive care nurses continuing the alarm management process despite all their fatigue and ensuring patient safety.

According to the study of Akturan et al.[10] being a university and high school graduate led to significant differences in the alarm fatigue scores of nurses. The university graduate group showed better positive practices to reduce alarm fatigue.[14] In this sense, it is recommended to provide training to explain the conditions and effects of intensive care nursing in the pre-graduation period.[10] Although nurses do not have any suggestions to reduce the effects of alarms in their social lives, social and artistic activities can reduce the effects of alarms by diverting their attention. In addition, institutions should consider how they organize social and artistic events. On the contrary, manufacturers can develop solutions to monitor and track by specifying a different sound for each device. As it is known, the shortage of nurses is a significant problem worldwide. Salary improvements and rewards are among the things that need to be done to reduce the effects of this situation.[14] For the same purpose, economic improvements and social support for children and families are practices that managers should do.[10]

It is urgently necessary for patient safety and employee satisfaction to reduce the rate of respondents who answered the question "Alarm sounds prevent me from focusing on my professional duties" as always-usually.[15] Alarm management is a complex issue that can reduce alarm fatigue and positively impact the clinical aspect of patient safety.[16] Recognizing and preventing the deterioration in the patient's condition is also the nurse's responsibility.[17] For this purpose, nurses should be aware of the risks of inappropriate alarm settings and should be equipped to respond appropriately.[18] Effective alarm management is a challenging issue for nurses that requires knowledge and practice skills in alarm safety.[19] Studies indicate that personnel training is essential to increase alarm awareness for this purpose.[20]

CONCLUSION

Nurses are the health workers who work at the patient's bedside for the longest time. For this reason, they are the healthcare workers who are most exposed to alarms, although many of them are false. Establishing alarm management protocols to avoid alarm fatigue, establishing a multidisciplinary team including the medical device manufacturer, arranging alarm settings according to the patient, and developing appropriate strategies to avoid alarm fatigue will help increase the quality and safety of patient care by reducing stress exposure and fatigue of nurses.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bursa Yüksek İhtisas Training and Research Hospital Clinical Researches Ethics Committee (Date: 29.12.2021, Decision No: 2011-KAEK-25 2021/12-08).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Relationship between nutritional scores and 28-day mortality in critical patients who received mechanical ventilator support for non-surgical reasons

Öztürk Taşkın, Özgür Yılmaz

[1]Department of Anesthesiology and Reanimation, Faculty of Medicine, Kastamonu University, Kastamonu, Turkey
[2]Department of Anesthesiology and Reanimation, Kastamonu Training and Research Hospital, Kastamonu, Turkey

ABSTRACT

Aims: Malnutrition may cause an increase in morbidity and mortality in intensive care patients. In this study, we aimed to investigate the relationship between nutritional scores and 28-day mortality in critically ill patients followed on a mechanical ventilator for non-surgical reasons.

Methods: 91 patients admitted to the intensive care unit for non-surgical reasons, followed up on mechanical ventilators, and whose data were available were included. The prognostic nutrition index (PNI), geriatric nutrition risk index (GNRI), nutritional risk index (NRI), and controlling nutritional status (CONUT) score were calculated from the data of the patients. Patients were divided into two groups survival and non-survival.

Results: NRI, PNI, and GNRI scores were statistically significantly higher in the Survivor group. Neutrophil lymphocyte ratio, LDH albumin ratio, CONUT, APACHE, and SAPS scores were statistically higher in the nonsurvivor group. In logistic regression analysis for nutritional scores, CONUT was found to be an independent risk factor for mortality. In the ROC analysis, the AUC value for CONUT was 0.925. The cut-off value for CONUT was 7.5, the sensitivity was 86.4%, and the specificity was 87.0%.

Conclusion: The CONUT nutrition score, which can be easily calculated from routine parameters and does not cause extra costs, can be used as an independent evaluation tool in determining the 28-day mortality of intensive care patients.

Keywords: Critical Patients, prognostic nutrition index, geriatric nutrition risk index, nutritional risk index, controlling nutritional status

INTRODUCTION

Malnutrition is defined as a nutrient deficiency resulting from inadequate food intake or inability to use and absorbed digested food.[1-3] It is essential to the treatment of patients. Malnutrition can lead to the deterioration or delay in wound healing, suppression of the immune system, regression in cognitive functions, and decreased functional capacities in general, resulting in severe clinical conditions.[4]

It has been reported that patients with malnutrition have a higher mortality and morbidity rate, more extended hospital stay, and more drug use than patients without malnutrition.[5] A study reported that malnutrition is an important problem in critical care units, with a rate of 78.1% in developing countries and 50.8% in developed countries.[6] In the study of Giner et al.[7] malnutrition was found in 42% of the patients in intensive care units. Another study found that 38% of patients receiving ventilator support had malnutrition.[8] In a study that included intensive care patients receiving mechanical ventilator support, malnutrition was found in all patients.[9] The most important point here is to determine intensive care patients' nutritional status early and start appropriate nutritional support. Studies report that mechanical ventilator dependence, length of stay, and mortality of intensive care patients will decrease. Conversely, malnutrition may cause complications such as infection and multi-organ failure in intensive care patients, resulting in a more extended stay in the intensive care unit and increased morbidity and mortality.[10] Many nutritional indices are used to evaluate malnutrition.[11] The prognostic nutritional index (PNI) is a simple, immuno-nutritional parameter calculated from serum albumin and total lymphocytes.[12] Geriatric nutrition risk index (GNRI), Body Mass Index (BMI), and serum albumin values are used for the same purpose, Nutritional risk index (NRI), body weight and serum albumin values, Controlling nutritional status (CONUT) score from serum albumin , total cholesterol, and serum albumin values calculated using total lymphocyte values.[13-15]

Corresponding Author: Öztürk Taşkın, drozturk275@hotmail.com

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In this study, we aimed to investigate the relationship between nutritional scores and 28-day mortality in critically ill patients who received mechanical ventilator support for non-surgical reasons.

METHODS

The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 14.02.20222, Decision No: 2022-KAEK-137). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with a history of leukemia/lymphoma or a diagnosis of malignancy, a history of major surgery in the last six months, a history of drug use that may cause bone marrow depression, a history of cirrhosis, pregnancy status, and renal failure were excluded from the study.

Demographic characteristics such as age, comorbidity, gender and 28-day mortality, Acute Physiology, and Chronic Health Evaluation (APACHE II) scores, The Simplified Acute Physiology Score (SAPS) scores, leukocytes, hemoglobin, thrombocyte, neutrophil-lymphocyte, C- reactive protein (CRP), albumin, creatine, urea, alanine transaminase (ALT), aspartate aminotransferase (AST), prealbumin, lactate dehydrogenase (LDH) values were recorded from the hospital information management system and patient file data. In addition, prognostic nutrition index (PNI), geriatric nutrition risk index (GNRI), nutritional risk index (NRI), and controlling nutritional status (CONUT) score calculations were made from the data of the patients. Patients were divided into two groups survival and non-survival.

Calculation of Malnutrition Scores

Calculation of the nutritional risk index: NRI= [1.519×serum albumin g/dL)+(41.7×body weight (kg)/ideal body weight (kg)]

NRI<83.5; major risk, 83.5–97.5; moderate risk, 97.5–100; mild risk, NRI >100; no risk.[14]

The PNI was calculated by a formula as follows. PNI Score: Serum albumin (g/dL)× 10+ total lymphocyte count (mm³) ×0.005.

The patients were evaluated in three groups. PNI > 38: normal, PNI of 35–38: Moderate, PNI < 35: Severe risk of malnutrition.[12]

The GNRI was calculated by a formula as follows. GNRI = Serum albumin (g/dL)× 14.89+ 41.7 × (body weight (kg)/ideal body weight (kg)).

GNRI threshold values were calculated as 4 degrees depending on nutrition: GNRI:< 82: Major risk, GNRI: 82 to <92: Moderate risk, GNRI: 92 to ≤98: Low risk, GNRI: >98: No risk.[13]

Body Mass Index (BMI) was calculated according to the following formula: BMI=weight (kg)/height² (m²).[16] The ideal body weight of the patients was calculated using the Lorentz formula.[13]

The calculation of the CONUT score is shown in **Table 1.**[17]

Table 1: CONUT scores

Parameters	Degree Of Malnutrition			
	Normal	Mild	Moderate	Severe
Serum Albumin (G/Dl)	≥3.5	3.0–3.49	2.5–2.99	<2.5
Point	0	2	4	6
Total Lymphocytes (103/Ul)	≥1600	1200–1599	800–1199	<800
Point	0	1	2	3
Total Cholesterol (Mg/Dl)	≥180	140–179	100–139	<100
Point	0	1	2	3
Total CONUT Scores	0-1	2-4	5-8	9–12

Statistical Analysis

Statistical analyzes were performed using SPSS 26.00 (SPSS Inc, Chicago, USA). The normal distribution of the data was checked with the Kolmogorov Smirnov test. Independent samples t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Analysis of categorical data was done with the Pearson Chi-square test. Logistic regression analysis was applied for the nutritional scores that were found to be significant. ROC analysis was performed to determine the mortality status of the patients at the end of 28 days and the Area Under Curve (AUC), cut-off, sensitivity, and specificity values for Nutrition scores. The results were evaluated at the 95% confidence interval and the significance level of p<0.05.

RESULTS

A total of 91 patients were included in our study. The mean age of the patients was 70.44 (26.0-95.0) years, and 47 (51.6%) of all patients were women. While there was a statistically significant difference in age and BMI values between the survivor and non-survivor groups, there was no statistical difference between the two groups regarding gender, hospitalization diagnoses, and comorbidities (**Table 2**).

Table 2. Demographic characteristics of the patients.

Variables	Total N=91	Group Survival n= 69 (75.8%)	Group Non- Survival n= 22 (24.2%)	P
Age(Years)	70.44 (26.0-95.0)	67.67 (29.0-90.0)	79.14 (63,0-95,0)	<0.001
Gender				0.673
Female	47 (51.6%)	37 (53.6%)	10 (45.5%)	
Male	44 (48.4%)	32 (46.4%)	12 (54.5%)	
Hospitalization Diagnosis				0.498
Pneumonia	33 (36.3%)	23 (33.4%)	10 (45.5%)	
Asthma	2 (2.2%)	2 (2.9%)	0	
Chronic Obstructive Pulmonary Disease	11 (12.1%)	9 (13.1%)	2 (9.1%)	
İnfarct	20 (22.0%)	13 (18.8%)	7 (31.8%)	
Intra Cranial Hemorrhage	13 (14.3%)	11 (15.9%)	2 (9.1%)	
Epilepsy	3 (3.3%)	2 (2.9%)	1 (4.5%)	
Diabetic Ketoacidosis	5 (5.5%)	5 (7.2%)	0	
Hepatic Encephalopathy	4 (4.3%)	4 (5.8%)	0	
Additional Disease				0.567
None	11 (12.1%)	9 (13.1%)	2 (9.1%)	
Diabetes Mellitus	12 (13.2%)	10 (14.5%)	2 (9.1%)	
Hypertension	26 (28.6%)	21 (30.4%)	5 (22.7%)	
Neurological Disease	23 (25.3%)	14 (20.3%)	9 (40.9%)	
Respiratory Disease	15 (16.5%)	12 (17.4%)	3 (13.7%)	
Cardiac Disease	4 (4.3%)	3 (4.3%)	1 (4.5%)	
BMI	21.15 (16.2-30.7)	22.21 (16.8-30.7)	17.82 (16.2-20.1)	<0.001

When the hospitalization laboratory values, NRI, GNRI, PNI, CONUT, APACHE II, and SAPS scores of the two groups were compared, lymphocyte, platelet, creatine, albumin, prealbumin, triglyceride, total cholesterol, total bilirubin, NRI, PNI, and GNRI scores were statistically significant in the Survival group. Neutrophil lymphocyte ratio, LDH albumin ratio, CONUT, APACHE, and SAPS scores were statistically higher in the non-survival group (Table 3).

When the subgroups of nutritional scoring were compared, the most common NRI, PNI, and GNRI subtypes in the Survival group were Absent, while in the Non--Survival, it was the severe type. The most common CONUT subtypes were Absent and Modarate in the Survival group, while Modarate and Severe types were in the Non-Survival group. When the four nutrition scores subtypes were examined, there was a statistically significant difference between the two groups (Table 4).

Table 4. Nutrition scores; NRI, PNI, GNRI, CONUT.

Variables	Total, n=91	Group Survival, n=69 (75.8%) n (%)	Group Non -Survival, n=22 (24.2%) n (%)	p
NRI				<0.001
1 Absent	27 (29.7%)	27 (39.1%)	0	
2 Mild	18 (19.8%)	18 (26.1%)	0	
3 Moderate	26 (28.6%)	17 (24.6%)	9 (40.9%)	
4 Severe	20 (21.9%)	7 (10.2%)	13 (59.1%)	
PNI				<0.001
1 Absent	39 (42.9%)	39 (56.5%)	0	
2 Moderate	22 (24.2%)	17 (24.6%)	5 (22.7%)	
3 Severe	30 (32.9%)	13 (18.9%)	17 (77.3%)	
GNRI				<0.001
1 Absent	29 (31.9%)	29 (42.0%)	0	
2 Mild	18 (19.8%)	18 (26.1%)	0	
3 Moderate	21 (23.1%)	13 (18.8%)	8 (36.4%)	
4 Severe	23 (25.2%)	9 (13.1%)	14 (%63.6)	
CONUT				<0.001
1 Absent	26 (28.6%)	26 (37.7%)	0	
2 Mild	22 (24.2%)	22 (31.9%)	0	
3 Moderate	26 (28.6%)	15 (21.7%)	11 (50.0%)	
4 Severe	17 (18.6%)	6 (8.7%)	11 (50.0%)	

In the logistic regression analysis for nutritional scores, CONUT was found to be an independent risk factor for mortality (Table 5). In the ROC analysis, the AUC value for CONUT was 0.925. The cut-off value for CONUT was 7.5, the sensitivity was 86.4%, and the specificity was 87.0% (Figure 1).

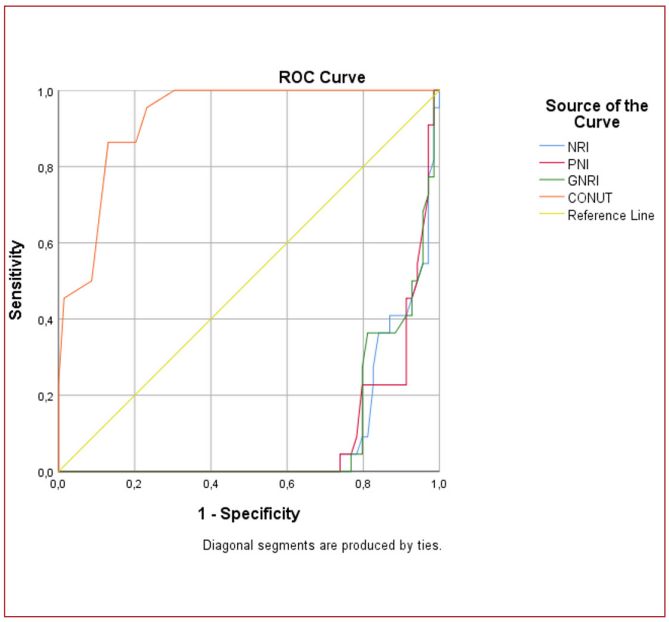

Figure 1. Roc curve

Table 5. Logistic regression analysis.

Variables	β	SE	P	OR	95% CI for OR	
					Lower	Upper
Constant	9.188	11.893	0.440	9779,709		
NRI	-0,056	0.237	0.813	0.946	0.595	1.503
PNI	0.127	0.409	0.756	1.135	0.5100	2.528
GNRI	-0.159	0.213	0.445	0.853	0.562	1.295
CONUT	0.526	0.242	0.030	1.691	1.052	2.720

Table 3. Laboratory, APACHE II, and SAPS Nutrition scores of the groups

Variables	Total n=91	Group survival n= 69 (75.8%)	Group Non-Survival n= 22 (24.2%)	p
WBC(103/ul)	11.40 (7.10-21.30)	11.29 (7.1-20.1)	11.74 (7.4-21.3)	0.597
Neutrophil(103/ul)	7.6 (3.1-15.6)	7.41 (3.1-15.6)	8.21 (3.3-15.6)	0.270
Lymphocyte(103/ul)	0.98 (0.6-1.3)	1.02 (0.6-1.3)	0.87 (0.6-1.3)	0.001
Platelets(103/ul)	246.08 (60.0-449.0)	259.58 (89.0-449.0)	203.73 (60.0-334.0)	0.040
N/L	8.19 (3.15-22.29)	7.63 (3.15-22.29)	9.92 (4.72-19.5)	0.029
P/L	254.99 (75.0-637.14)	261.17 (83.08-3637.14)	235.59 (75.0-383.78)	0.425
Creatinine (mg/dL)	0.67 (0.12-1.9)	0.77 (0.22-1.9)	0.37 (0.12-0.87)	<0.001
ALT(U/L)	14.12 (3.0-80.0)	13.75 (3.0-45.0)	15.27 (3.0-80.0)	0.233
AST(U/L)	14.81 (3.0-62.0)	14.54 (3.0-53.0)	15.68 (4.0-62.0)	0.320
CRP (mg/L)	36.63 (3.5-126.9)	35.21 (5.3-126.9)	41.1 (3.5-102.6)	0.673
Albumin(g/dL)	3.03 (2.3-3.86)	3.18 (2.3-3.86)	2.56 (2.3-3.2)	<0.001
C/A	12.64 (1.46-41.20)	11.44 (1.49-36.01)	16.39 (1.46-41.2)	0.211
Total Cholesterol (mg/dL)	152.88 (94.6-214.0)	160.12 (94.6-1241.0)	130.2 (98.0-168.0)	<0.001
Triglyceride(mg/dL)	123.65 (80.6-243.0)	131.99 (95.8-1243.0)	97.48 (80.6-134.0)	<0.001
Urea (mg/dL)	39.3 (10.3-133.0)	40.08 (10.3-133.0)	36.88 (11.6-65.2)	0.864
Total Bilirubin (mg/dL)	0.60 (0.12-1.4)	0.64 (0.12-1.4)	0.5 (0.2-1.2)	0.049
Prealbumin (mg/dL)	20.0 (6.5-28.7)	20.77 (6.5-28.7)	17.55 (16.2-21.3)	<0.001
LDH(U/L)	281.93 (146.0-789.0)	284.77 (159.0-489.0)	273.05 (2146.0-442.0)	0.475
LDH/Albumin	94.10 (51.22-172.66)	90.1 (51.22-154.0)	106.65 (52.52-172.66)	0.023
Sodium(mEq/L)	142.14 (124.0-159.0)	141.48 (130.0-159.0)	144.23 (124.0-155.0)	0.054
Potassium(mEq/L)	4.27 (3.1-5.6)	4.24 (3.1-5.6)	4.35 (3.1-5.6)	0.474
Procalcitonin	1.1 (0.05-12.9)	0.78 (0.05-5.6)	02.08 (0.05-12.9)	0.079
Lactate(mmol/L)	2.21 (0.4-7.9)	2.06 (0.4-7.9)	2.68 (0.8-5.4)	0.054
NRI	92.74 (79.5-105.5)	95.92 (80.0-105.5)	82.77 (79.5-87.9)	<0.001
PNI	37.12 (31.0-43.9)	38.16 (31.0-43.9)	33.87 (32.0-36.6)	<0.001
GNRI	90.95 (74.0-104.5)	94.12 (74.0-104.5)	81.01 (75.0-84.6)	<0.001
CONUT	4.63 (0-11.0)	3.28 (0-10)	8.86 (5.0-11.0)	<0.001
APACHE II	23.20 (12.0-42.0)	21.20 (12.0-32.0)	29.5 (15.0-42.0)	<0.001
SAPS	36.58 (20.0-58.0)	33.88 (20.0-58.0)	45.04 (29.0-58.0)	<0.001

DISCUSSION

Ninety-one intensive care patients with mechanical ventilator support for non-surgical reasons were included in our study. In addition, the relationship between nutrition scores and 28-day mortality during hospitalization in the intensive care unit was investigated. It was found that there was a statistical difference between the two groups in terms of nutritional scores, and CONUT was an independent risk factor for 28-day mortality.

It has been reported that patients with malnutrition have a higher mortality and morbidity rate, more extended hospital stay, and more drug use than patients without malnutrition.[5] Malnutrition rates in hospitalized patients vary between 15% and 60%, depending on the type of hospital, the region of the hospital, and the population of the study.[18-20] Patients may be malnourished when admitted to the intensive care unit (ICU), or malnutrition may develop due to critical illness after admission. The prevalence of malnutrition in ICU patients varies between 30% and 50%.[7,10] Hill et al.[21] reported that 50% of patients undergoing major surgery had impaired nutritional status. In another study, malnutrition was found in 38% of patients receiving ventilator support.[8] In the study of Giner et al.[7] malnutrition was found in 42% of the patients in the ICU. Yi-Chia Huang et al.[9] detected malnutrition in all patients followed in the ICU with a mechanical ventilator. In our study, similar to the literature, there was 73% malnutrition according to NRI scoring, 61% according to PNI scoring, 71% according to GNRI scoring, and 74% according to CONUT scoring.

Malnutrition can lead to complications such as infection and multiple organ failure, prolonged stay in the intensive care unit, and increased morbidity and mortality in intensive care patients.[22] Most such complications can be evaluated with bedside ultrasonography.[23] Barr et al.'s[24] study stated that malnutrition was associated with increased mortality and morbidity in intensive care. Although malnutrition affects all ICU patients, its adverse effects are more dangerous, especially in patients with sepsis, trauma, and burn patients.[25] A multicenter study that included 2887 ICU patients found that increased energy and protein intake were associated with improved clinical outcomes in critically ill patients.[26] A prospective study including 48 critically ill patients showed that energy deficit one week after admission to the ICU was associated with infectious and other complications.[27] Another study reported a strong relationship between increased energy deficit and complications such as acute respiratory distress syndrome (ARDS), renal failure, need for surgery, and pressure sores.[28] In our study, the mortality rate was higher in patients with malnutrition, similar to the literature.

The Nutritional Risk Index (NRI), developed to evaluate patients' nutritional status in a practical way using objective parameters, is calculated by body weight and serum albumin level. NRI, used in many patient groups, has also been effective in patients with heart failure.[29,30] In addition to determining the nutritional status, the correlation between NRI score and poor disease outcomes suggests that the index may also guide the treatment planning of the disease. For example, according to NRI, the study of Aziz et al.[14] emphasized that the prognosis might be poor in patients with a high risk of malnutrition. Similarly, in our study, the mortality rate was increased in patients with a high risk of malnutrition, according to NRI.

Geriatric nutritional risk index (GNRI), is calculated by BMI and serum albumin value. The index was first used by Bouillanne et al.[13] to determine the relationship between malnutrition and mortality in hospitalized elderly patients. Then, in the study of Kinugasa et al.[31] it was found that there is a relationship between GNRI and mortality in patients with heart failure. The survey of Sze et al. showed that GNRI is an important marker in determining mortality. Similarly, in our research, GNRI values were lower in the group with a mortal course.

The parenteral nutrition index (PNI) is calculated from serum albumin and lymphocyte values and evaluating nutritional and infection conditions together.[12] In their study, Huang et al.[9] emphasized that low PNI values are associated with poor outcomes. In this study, PNI values were lower in the group with a mortal course.

Control of Nutritional Status (CONUT) screening tools that evaluate nutritional status using biochemical findings of patients are practical and easy to use in hospitalized patients. The first validity study of this scoring method was conducted in 2005, showing that it gave results compatible with proven ways.[32] In their study, Iwakami et al.[33] showed that CONUT is an independent assessment tool, especially for long-term mortality. Similarly, in our research, the CONUT score was significantly higher in the mortal group and CONUT was found to be an independent assessment tool for 28-day mortality in this patient group.

Limitations

The limitations of our study include the fact that it was a single-center study, different hospitalization diagnoses of the included patients, various comorbidities of the patients, and the limited number of patients.

CONCLUSION

The CONUT nutrition score, which can be easily calculated from routine parameters and does not cause extra costs, can be used as an independent evaluation tool in determining the 28-day mortality of intensive care patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 14.02.20222, Decision No: 2022-KAEK-137).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Evaluation of patients diagnosed with intermediate -high risk pulmonary thromboembolism

Sedat Çiçek, Fatih Üzer, Tülay Özdemir

Department of Chest Diseases, Faculty of Medicine, Akdeniz University, Antalya, Türkiye

ABSTRACT

Aims: In this study we aimed to share our treatment approach in patients with intermediate -high risk pulmonary embolism (PE).

Methods: This is a single center retrospective observational study. Patients diagnosed with PE at Akdeniz University Hospital between January 1, 2015, and January 1, 2021, were retrospectively analyzed. Patients whose diagnosis of PE was confirmed by computed tomography angiography (CTA) or perfusion/ventilation scintigraphy were considered to have PE. Patients with intermediate-high risk were included in the study. Patients with a diagnosis of low-risk, low-intermediate risk, high-risk PE, patients younger than 18 years of age, and pregnant were excluded from the study.

Results: A total of 150 patients, 64 (42.7%) male and 86 (57.3%) female, with a mean age of 62.2±16.2 years, who met the criteria of these patients were included. 22.7% (34) of the patients received thrombolytic therapy. While 67.7% (23) of the patients who received thrombolytic therapy received half-dose (50mg rt-PA) thrombolytic therapy, 32.3% (11) received full-dose (100 mg rt-PA) thrombolytic therapy. Major hemorrhage (3 intracranial hemorrhages, 1 femoral hemorrhage) was detected in 11.7% (4) of the patients who received thrombolytic therapy.

Conclusion: No significant effect of thrombolytic therapy or full or half dose on mortality was found in the intermediate -high risk group.

Keywords: Pulmonary embolism, thrombolytic, intermediate-high risk

INTRODUCTION

Pulmonary thromboembolism (PE) is a common cause of cardiovascular mortality nowadays, with an increasing incidence and decreasing mortality rate. It usually occurs as a complication of deep vein thrombosis (DVT).[1] In PE, a series of pathophysiological events are triggered by the placement of the thrombus in the lungs. The number and diameter of occluded vessels, the size of the embolism, the patient's cardiopulmonary reserve, reflex vasoconstriction due to pulmonary artery dilatation, inflammatory mediators, serotonin released from platelets, thromboxane, and vasoconstriction due to fibrinogen degradation product fibrinopeptid B trigger a series of pathophysiological events in PE. These pathophysiological events present three different tables to us in the clinic; massive (high risk), sub-massive (intermediate risk), and non-massive (low risk). In the guideline published by the European Society of Cardiology (ESC) in 2019, the intermediate-risk group is divided into high-intermediate risk and low-intermediate risk.[1] High-risk PE has acute right ventricular failure accompanied by hypotension, shock, or cardiopulmonary arrest. Patients with syncope, severe hypoxemia, cardiac arrest, or who are undergoing cardiopulmonary resuscitation should be evaluated for high-risk PE. In patients with intermediate -risk PE, there are signs of right ventricular dysfunction (dilatation and hypokinesia) detected on echocardiography despite normal systemic blood pressure. In low-risk PE, systemic blood pressure and right ventricular functions are found to be normal. This classification is important in terms of complicated clinical course, mortality risk, and determination of treatment approach.

According to the prognostic assessment strategy, patients who are hemodynamically unstable due to shock or hypotension go directly into the high-risk group. When PE is proven, direct reperfusion therapy is administered. Further risk assessment should be performed after diagnosis in patients without hypotension or shock. Low and intermediate-risk patients are identified with PESI or sPESI tests. Patients with PESI Class I-II or sPESI=0 are considered low risk, and patients with PESI Class III-IV or sPESI ≥ 1 are considered intermediate risk. Among intermediate -risk patients, those with right ventricular dysfunction and positive cardiac biomarkers are in the high-risk group. It is recommended that this group, which has a

Corresponding Author: Fatih Üzer, uzerfatih@gmail.com

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intermediate-high risk for an early poor prognosis, be closely monitored under anticoagulants, and rescue reperfusion therapy should be applied when signs of hemodynamic impairment are detected. We do not have sufficient studies on the effect of full-dose or half-dose thrombolytic therapy on mortality and morbidity in the intermediate -high-risk group. In the largest study on this subject, it was stated that the application of thrombolytic therapy in the intermediate -high risk group prevented hemodynamic decompensation but increased intracranial hemorrhage.[2] Clinicians may hesitate to apply full-dose thrombolytic therapy due to the fear of major bleeding risk and seek alternative treatments to reduce bleeding risk.[3] Our study was carried out to share our treatment approach with intermediate -high risk PE patients who have question marks in terms of treatment.

METHODS

This study was approved by the Ethics Committee of the Akdeniz University School of Medicine (Date: 09.11.2022, Decision No: KAEK-665). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This is a single center retrospective observational study. Patients diagnosed with PE at Akdeniz University Hospital between January 1, 2015, and January 1, 2021, were retrospectively analyzed. I26, I26.0, and I26.9 ICD codes were scanned from the hospital automation system, and patients who were examined for PE were identified. Patients whose diagnosis of PE was confirmed by computed tomography angiography (CTA) or perfusion/ventilation scintigraphy were considered to have PE. Patients with intermediate-high risk (PESI (Pulmonary Embolism Severity Index) Class III-IV or sPESI (simplified PESI) ≥1 according to the 2019 European Society of Cardiology Guidelines and those with positive right ventricular dysfunction and cardiac biomarkers) were included in the study.[1] Patients with a diagnosis of low-risk, low-intermediate risk, high-risk PE, patients younger than 18 years of age, and pregnant were excluded from the study.

Symptoms, sociodemographic data, comorbidities, and radiological findings leading to the diagnosis of PE were recorded in the data form. Echocardiographic findings performed in the emergency room or as soon as possible after hospitalization were noted. The unit where the patients were hospitalized (chest disease service or intensive care), the treatments they received for pulmonary embolism, the number of days they spent in the hospital, and their in-hospital mortality were examined. Thrombolytic treatment was administered as a full dose (100 mg/2 hour TPA) or half dose (50 mg/2 hour TPA).

Statistical Analysis

Statistical analyzes of the data were run using the SPSS 19.0 program. Categorical variables were defined as frequency and percentage, and continuous variables as mean and standard deviation. The conformity of the data to the normal distributions was evaluated with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare the medians of the paired groups that did not fit the normal distribution, and the chi-square significance test was used for the analysis of categorical variables. The relationship of continuous variables with each other was evaluated with the Spearman Correlation test. The statistical significance level was accepted as 0.05 in the study.

RESULTS

A total of 13100 patients were examined with a preliminary diagnosis of PE at Akdeniz University during the study. A total of 150 patients, 64 (42.7%) male and 86 (57.3%) female, with a mean age of 62.2±16.2 years, who met the criteria of these patients were included. 22.7% (34) of the patients received thrombolytic therapy. While 67.7% (23) of the patients who received thrombolytic therapy received half-dose (50 mg rt-PA) thrombolytic therapy, 32.3% (11) received full-dose (100 mg rt-PA) thrombolytic therapy. Major hemorrhage (3 intracranial hemorrhages, 1 femoral hemorrhage) was observed in 11.7% (4) of the patients who received thrombolytic therapy. The most common comorbid disease was hypertension (n=43, 28.7%), while 21.3% (32) of the patients had a history of malignancy. The basic characteristics of the patients are given in Table 1.

Table 1. General features of the patients

Feature	n (%)
Gender	
Female	86 (57.3)
Male	64 42.7)
Treatment	
Thrombolytic	34 (22.7)
LMWH	116 (77.3)
Comorbidity	
Hypertension	43 (28.7)
Diabetes mellitus	33 (22.0)
Coronary artery disease	10 (6.7)
Malignancy	32 (21.3)
Chronic lung disease	16 (10.7)
Atrial fibrillation	6 (4.0)
PE risk factor +	46 (30.7)
Immobilization	9 (6.0)
PE history	6 (4.0)
Symptom	
Shortness of breath	82 (54.7)
Chest Pain	30 (20.0)
Syncope	32 (21.3)
Other	6 (4.0)
Mortality	
30 day	28 (18.7)
Need for intensive care	
Need for intensive care	71 (47.3)

PE: pulmonary embolism, LMWH: low molecular weight heparin

Right heart cavities were found to be wide in all of the patients who received thrombolytic therapy, and the mean pulmonary artery pressure (PAP) was 57.7±10.1 in these patients. Transthoracic echocardiography (TTE) findings of patients receiving thrombolytic therapy before and after thrombolytic therapy are given in Table 2.

Table 2. Echocardiography findings

	Pre- treatment		Pos-treatment	
	Half-dose thrombolytic	Full-dose thrombolytic	Half-dose thrombolytic	Full-dose thrombolytic
Right gap width	23 (100)	11 (100)	2 (11.1)	1 (14.3)
D-septum	9 (39.1)	9 (81.8)	n.d.	n.d.
PAP	57.7±10.1	n.d.	39.5±12.8	38.7±8.5
TV velocity	3.5±0.3	3.6±0.4	2.6±0.5	2.6±0.4

PAP: pulmonary artery pressure, TV: Tricuspid regurgitation, n.d.: no data

When the full thrombolytic treatment dose (100 mg tPA) and half dose (50 mg tPA) were compared, the probability of D-septum before the treatment was found to be statistically significantly higher in the group that received the full dose of thrombolytics (p:0.030). There was no statistically significant difference between the groups in terms of other clinical and prognostic factors. The comparison of patients receiving full-dose thrombolytic therapy with patients receiving half-dose thrombolytic therapy is given in **Table 3**. According to the results of logistic regression test, after controlling the age and gender of the patients, taking thrombolytic therapy was not found to be a factor in increasing the chance of survival within 30 days (p=0.82). Thrombolytic therapy had no significant effect on TTE findings in subjects with wide right cavities at the beginning of treatment (p=0.24). When the patients who received thrombolytic (full dose+half dose) treatment compared with low molecular weight heparin (LMWH), the incidence of D-septum (p: 0.006) and intensive care unit admission rate (p <0.001) were significantly higher in the group receiving thrombolytic therapy. Moreover, the duration of hospitalization in the intensive care unit (p<0.001) was higher in the group receiving LMWH. A detailed comparison of patients receiving LMWH and patients receiving thrombolytic therapy is given in **Table 4**.

DISCUSSION

In this study, in which we investigated the efficacy of thrombolytic therapy in patients with intermediate-high risk pulmonary embolism, no statistically significant difference was found in the mortality, length of stay in the intensive care unit, and cardiac decompensation effects of full-dose and half-dose r-tPA administration. When the patients who received LMWH treatment and those who received thrombolytic treatment were compared, it was found that the group that received thrombolytic treatment had a higher rate of hospitalization in the intensive care unit, while the group that received LMWH treatment stayed in the intensive care unit longer.

Hospital mortality due to PE has been reported at 7%, and hemodynamically unstable patients at 33%.[4] Systemic thrombolytic therapy has been shown to prevent hemodynamic collapse and reduce mortality due to progressive right heart failure in patients with moderate to high risk.[5] In the PEITHO study,[2] systemic fibrinolytic therapy was shown to prevent cardiac collapse compared with LMWH. However, an increased risk of intracranial hemorrhage has been demonstrated. In addition, in the TOPCOAT study,[6] in which systemic thrombolytic treatment and LMWH treatment were compared in patients with sub-massive PE, it was found that thrombolytic

Table 3. Comparison of full dose and half dose of thrombolytic therapy

		Half-dose (n=23)	Full-dose (n=11)	p
Gender n(%)	Female	12 (52.2)	7 (63.6)	0.715
Age (mean±ss)		60.7±16.7	64.1±12.9	0.553
Comorbidity n(%)	+	21 (91.3)	9 (81.8)	0.580
PE risk factor n(%)	+	5 (21.7)	4 (36.4)	0.425
Echocardiography (pre treatment)	Right Width n(%)	23 (100)	11 (100)	1.000
	D-septum n(%)	9 (39.1)	9 (81.8)	0.030
	PAP (mean ±ss)	57.7±10.1	-	n.d.
	Tricuspid insufficiency velocity (mean±ss)	3.5±0.3	3.6±0.4	n.d.
Intensive care unite n(%)		20 (87.0)	10 (90.9)	1.000
Major bleeding		1 (4.4)	2 (18.2)	n.d.
Mortality n(%)		4 (17.4)	2 (18.2)	n.d.
Echocardiography (post- treatment)	Right gap width n (%)	2 (11.1)	1 (14.3)	n.d.
	PAP (mean ±ss)	39.5±12.8	38.7±8.5	0.945
	Tricuspid insufficiency velocity (mean±ss)	2.6±0.5	2.6±0.4	0.872
Intensive care hospital stay/day (mean±ss)		2.8 ±2.4	2.6±1.4	0.795

i.d: insufficient data, PAP: pulmonary artery pressure

Table 4. Comparison of low molecular weight heparin and systemic thrombolytic therapies

		LMWH (n=116)	Thrombolytic (n=34)	p
Gender n(%)	Female	67 (57.8)	19 (55.9)	0.847
Age (mean ±ss)		62.3±16.5	61.8±15.4	0.866
Comorbidity n(%)	+	104 (89.7)	30 (88.2)	0.760
PE risk factor n(%)	+	37 (31.9)	9 (26.5)	0.673
Echocardiography (pre treatment)	Right width n(%)	108 (93.1)	34 (100)	0.199
	D-septum n(%)	30 (25.9)	18 (52.9)	0.006
	PAP (mean ±ss)	51.6±23.5	57.7±10.1	0.588
	Tricuspid insufficiency velocity (mean±ss)	3.3±0.6	3.5±0.3	0.384
Troponin n(%)	Positive	107 (92.2)	34(100)	0.210
Intensive care hospitalization n(%)		41 (35.3)	30 (88.2)	<0.001
Mortality n(%)		22 (19.1)	6 (17.6)	1.000
Echocardiography (post- treatment)	Right gap width	17 (21.3)	3 (12.0)	0.391
	D-septum	8 (10.0)	0	-
	PAP (mean±ss)	42.4±14.1	39.3±11.6	0.323
	Tricuspid insufficiency velocity (mean±ss)	2.7±0.5	2.6±0.4	0.316
Intensive care hospital stay/day (mean±ss)		6.2 ±4.0	2.8±2.1	<0.001

PAP: pulmonary artery pressure

treatment had a positive effect on 3-month cardiac outcomes, reduced dyspnea, but its effect on mortality was not different from LMWH treatment. In our study, 22.7% of the patients diagnosed with intermediate-high risk PE were treated with thrombolytic therapy. Early mortality was found to be 18.7%. Compared with LMWH, the effect of thrombolytic therapy on 30-day mortality was not different from the LMWH-treated group, but the duration of stay in the ICU was higher in the LMWH-treated group.

The role of full-dose thrombolytic therapy in high-risk patients has been well defined in many studies and emphasized in many guidelines. However, there is insufficient evidence for half-dose thrombolytic therapy.[7] In the study by Kiser et al.[8] 50 mg r-tPA treatment was compared with 100 mg r-tPA treatment, and 50 mg r-tPA was associated with treatment escalation, but no significant difference was found between treatments in terms of mortality and major bleeding risk. In another study comparing full-dose and half-dose thrombolytic therapy given with the aid of ultrasound-guided catheter in sub-massive and massive PE, it was shown that half-dose therapy improved right ventricular functions, decreased pulmonary artery pressure, and did not cause intracranial bleeding.[3] In our study, although we did not have enough patients to evaluate mortality and major bleeding between doses, no statistically significant difference was found between the treatment doses in the time spent in the intensive care unit.

If the patients diagnosed with PE are in the high-risk group, it is recommended to be monitored in the intensive care unit. It is recommended to decide where to follow the patients in the intermediate-high risk group according to the patient's clinic. It has been stated that if the patient has hypotension, tachycardia, tachypnea, and increased oxygen demand, intensive care monitoring may be necessary.[9] In our study, 47.3% of the patients were monitored in the intensive care unit. As LMWH and patients who were started on thrombolytic therapy were compared, the patients having thrombolytic therapy were admitted to the intensive care unit at a higher rate, and the full dose or half dose of thrombolytic therapy did not affect the length of stay in the intensive care unit.

Our study has some limitations. These can be regarded as the small number of patients, the single-center study, and the absence of monitoring echocardiograms of all patients after treatment.

CONCLUSION

No significant effect of thrombolytic therapy or full or half dose on mortality and long-term TTE findings was found in the intermediate -high risk group. In addition, no significant difference was found between the treatments in terms of major side effects.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ethics Committee of the Akdeniz University School of Medicine (Date: 09.11.2022, Decision No: KAEK-665).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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KASTAMONU MEDICAL JOURNAL

Original Article

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Our early results of carotis endarterectomy with no shunt and primary closure method

Burak Tamtekin[1], Güler Gülşen Ersoy[1], İsmail Dal[2]

[1]Department of Cardiovascular Surgery, Kastamonu University, Kastamonu, Turkey
[2]Department of Thoracic Surgery, Kastamonu Training and Research Hospital, Kastamonu, Turkey

ABSTRACT

Aims: Carotid artery disease is one of the most important causes of stroke. If left untreated, it causes serious mortality and morbidity. The gold standard treatment for carotid artery stenosis is carotid endarterectomy. The use of shunt, primary or patch closure of the arteriotomy varies according to clinical experience. In this article, we present the results of carotid endarterectomy performed with no shunt and primary closure method.

Methods: Thirty cases who underwent carotid endarterectomy in our clinic between April 2021 and April 2022 were analyzed retrospectively. All patients underwent selective carotid surgery. All surgeries were performed with the same technique and under general anesthesia. The patients were evaluated in terms of demographic characteristics, operation time, cross-clamp time, mortality, morbidity, and hospital stay.

Results: The clinical data of the early follow-up in the first month postoperatively were evaluated. Six (20%) of the patients were female and 24 (80%) were male. All of the males were active smokers. The mean age was 71.1 (min:65-max:82). Twenty five patients had a history of coronary artery disease. The mean cross-clamp time was 9.1 (±0.8) minutes. All surgeries were performed without using shunts. In all patients, primary closure was performed without the use of arterotomy grafts.

Conclusion: As an early morbidity, dysphagia was detected in 1 patient. This symptom disappeared at follow-up at 1 month. No early mortality was observed in any patient at 1-month follow-up. With increasing experience, carotid endarterectomy operations can be performed safely with no shunt and primary closure method. Our early surgical results are consistent with the literature.

Keywords: Carotid endarterectomy, primary closure, shunt

INTRODUCTION

Stroke is a very tiring and socioeconomic burden for patients and their relatives all over the world. Carotid artery occlusion is one of the most important causes of stroke.[1] These occlusions are the second cause of cardiovascular death after coronary artery diseases. Despite advancing technology and interventional techniques, open carotid endarterectomy still remains the gold standard in the treatment of this disease.[2]

In this study, we aimed to present the characteristics, surgical technique and early results of the patients we operated for carotid artery stenosis.

METHODS

Thirty cases who underwent carotid endarterectomy in our clinic between April 2021 and April 2022 were analyzed retrospectively. Demographic data, morbidity and mortality data of the patients were obtained from the hospital database. Patients over the age of 85, pregnant women and patients with covid infection were excluded from the study.

Before the start of the study, permission was obtained from the Ethics Committee of Kastamonu University with the approval number 2022-KAEK-42.

Diagnosis was often made by Doppler USG in neurology clinics or outpatient clinics. Consultation was requested by us for patients with a stenosis of more than 70% in Doppler USG. A definitive diagnosis was made with Computed Tomography (CT) angiography and the location of the lesions was determined in detail.

Surgical indication decision was made in patients with stenosis of 70% or more in CT angio. The surgical procedure was performed in the standard way and under general anesthesia in all patients. The carotid artery was reached with the classical carotid approach. Common, external and internal carotid arteries were found and turned with nylon tapes. Clamps were placed after 5000 units of heparinization. Endarterectomy was performed by longitudinal arterotomy from the common carotid artery to the internal carotid artery (**Figure 1**).

Corresponding Author: Ismail Dal, drismaildal@gmail.com

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No shunt was used in any patient. All arterotomies were closed primary with 6/0 polyprolene. Low molecular weight heparin was given postoperatively. After oral intake was started, oral antiaggregant treatment was started.

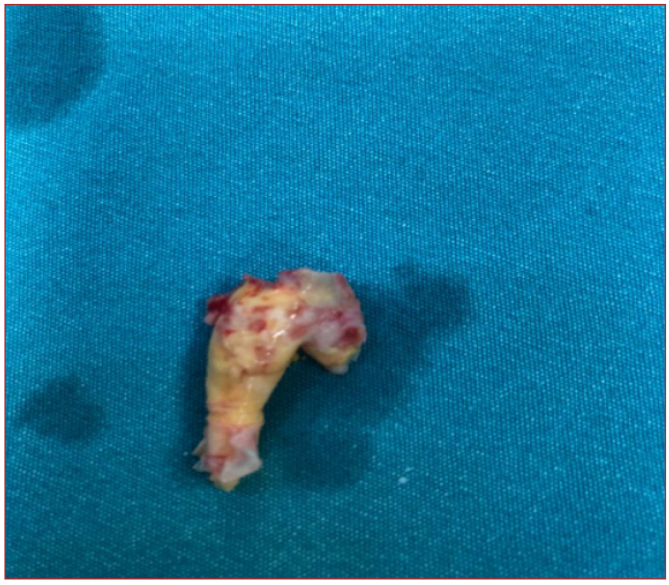

Figure 1. Completely removed plaque.

All patients were brought to the intensive care unit intubated. After about 1 hour, they were stabilized in terms of neurological, respiratory, cardiac and metabolic parameters and were extubated. Hypertension, the most common intensive care problem, was controlled with intravenous antihypertensives. Intensive care follow-up was performed on the 1st postoperative day. Oral anticoagulants and oral antihypertensives were administered during clinical follow-ups. After 2 more days of clinical follow-up, the patients were routinely discharged on the 3rd postoperative day.

SSPS v24.0 (SSPS Inc, Chicago, IL) was used to analyze the data. Categorical variables were evaluated as numbers and percentages. Mean and standard deviation values were calculated for continuous variables.

RESULTS

In our study, 30 cases who underwent carotid endarterketomy in our clinic were evaluated. The mean age of the patients was 71.1 (min:65-max:82). Twenty-four of the patients were male (80%), and 6 of them were female (20%). Demographic characteristics of the patients are shown in **Table 1**.

Table 1: Demographic characteristics of the patients

	n	%
Gender		
Male	24	80
Female	6	20
Smoking history	24	80
Diabetes	12	40
Hypertension	27	90
Coronary artery disease	20	66
Cerebrovascular event	30	100

CT angiography revealed unilateral severe stenosis in 17 patients (57%), and bilateral severe stenosis in 13 patients (43%). Unilateral complete occlusion of the internal carotid artery was detected in 2 patients (7%) (**Table 2**).

Table 2: Carotid lesions on CT angiography

	n	%
Unilateral severe stenosis	17	57
Bilateral severe stenosis	13	43
Unilateral complete occlusion	2	7

Isolated carotid endarterectomy was performed in all cases. The mean cross-clamp time was 9.1 (±0.8) minutes. First, carotid endarterectomy was performed in a patient with coronary artery disease. 15 days later, coronary artery bypass surgery was performed on the same patient. Dysphagia was detected in 1 patient. In this patient's follow-up one month later, there was a decrease in his complaint. Postoperative complications are shown in **Table 3**. All patients were discharged on the 3rd postoperative day. No mortality was observed in any patient.

Table 3. Postoperative complications

	n	%
Early mortality	0	0
Hypertension	20	66
Bleeding, hematoma	0	0
Reoperation	0	0
Minor neurological deficit (difficulty swallowing)	1	3.3
Major neurological deficit	0	0

DISCUSSION

Carotid artery disease can cause stroke and death.[3] Since the carotid endarterectomy surgery performed for the first time by De Bakey in 1953, this technique still maintains its place as the safest surgical method.[4]

Carotid endarterectomy operations can be performed with general, local and regional anesthesia techniques. The superiority of these anesthesia methods to each other has not been determined yet.[5] General anesthesia seems to be a more comfortable method since surgery is performed in a critical area.[6] We preferred to perform all carotid endarterectomy operations under general anesthesia.

There are many articles about the use of shunts during surgery. Shunt use has possible side effects such as stroke and carotid wall damage. Some authors reported that shunt use carries a 3% risk of embolism and dissection. In addition, shunt placement prolongs the operation time.[7,8] For these reasons, we did not use shunts in carotid endarterectomy operations. The operations were completed with the shortest cross-clamp time with the least manipulation possible.

Primary closure of the arterotomy causes less endothelial damage because it is a native vessel repair. There are articles in the literature reporting that there is no statistically significant difference between closure of the artery with a patch or primary closure.[9,10] In this study, all cases were closed primarily. Thrombosis was not observed in any of the patients, thanks to the low molecular weight heparin used in the early period and the oral antiaggregant used afterwards.

In our clinic, 30 cases of carotid stenosis were operated and discharged within 1 year without any problems. No early mortality was observed in any patient. In the follow-ups 1 month later, 100% survival was detected. It was thought that the transient dysphagia seen in 1 patient was due to traction of the hypogloss nerve. Our early surgical results are consistent with the current literature. Performing these surgeries with the least manipulation and the shortest cross-clamp time yields the best clinical results.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Researches Ethics Committee (Date: 11.05.2022, Decision No: 2022-KAEK-42).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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KASTAMONU MEDICAL JOURNAL

Original Article

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Efficacy of erector spina plane blocks and paravertebral blocks in kyphoplasty surgery

Tuğba Onur, Anıl Onur, Asiye Demirel, Şeyda Efsun Özgünay, Ümran Karaca, Osman Sıla Aydın

Department of Anesthesiology and Reanimation, Bursa Yüksek İhtisas Training and Research Hospital, University of Health Sciences, Bursa, Turkey

ABSTRACT

Aims: Kyphoplasty (KP) surgeries are commonly performed under local, general and regional anesthesia. The purpose of our study was to compare the perioperative and postoperative effects of ultrasound (USG) guided erector spinae plane blocks (ESPB) and paravertebral blocks (PVB) in patients with KP.

Methods: Forty patients who underwent kyphoplasty were evaluated retrospective as Group 1 (ESPB, n=20) and Group 2 (PVB, n=20). Perioperative additional opioid, hemodynamic parameters, complications, postoperative analgesia requirement, pain with visual analog scale (VAS) at specified times, amount of analgesic used within 24 hours, first mobilization and discharge time, and complications were compared.

Results: There was no difference between the study groups regarding demographic data, ASA, preoperative analgesic use, mean arterial pressure (MAP), heart rate (HR), SpO_2, additional opioid requirement, perioperative complication rates, VAS and surgical level. A significant difference was observed between Group 1 and Group 2 regarding the VAS score and paracetamol dose at 6 hours postoperatively (p:0.023 and p:0.006, respectively). There was no statistical difference between the groups first mobilization and discharge time, postoperative complications, postoperative intensive care needs (PICU), and tramadol dose rates used (p>0.05).

Conclusion: The USG-guided ESPB and PVB did not appear superior to one another in kyphoplasty procedures regarding 12 and 24-hour VAS scores, first mobilization and discharge time, postoperative complications, PICU needs and tramadol dose. The analgesic effect of ESPB in KP surgery was superior to that of PVB, 6 hours postoperatively. Therefore, it is possible to consider them a safe and alternative method of anesthesia and analgesia.

Keywords: Anesthesia, analgesia, erector spina plane block, paravertebral nerve block, ultrasound, percutaneous kyphoplasty, postoperative pain.

INTRODUCTION

Vertebral compression fractures results morbidity and mortality in osteoporotic patients. Symptomatic with significant pain, dysfunction and majorly impact public health.[1] A multimodal approach to management consists of analgesics, osteoporosis medication, and physical therapy. The patients resistant to conservative management are eligible for vertebroplasty or kyphoplasty (KP).[2] As an alternative to stabilization surgery, KP is preferred because of its less invasive nature, its ability to restore the anterior and middle vertebral columns, its ability to alleviate symptoms quickly, and its ability to bring a patient back into society rapidly. Trocar placement, balloon dilation, and cement injection are painful procedures in KP surgery. Pain management in the elderly population involves many different anesthetic techniques, all of which have limitations. General anesthesia application is risky for the older adults of KP patients with comorbidities. It may also prevent clinical evaluation of bone cement leakage.[3,4] As patients are awake during local anesthesia, surgeons can detect early neurological symptoms and prevent nerve damage. Additionally, anxiety, agitation, and the possibility of a painful reaction from the patient may result in patient and surgeon dissatisfaction during local anesthesia.[4] Although sedative analgesia is an alternative, safe and feasible method, here, we have a potential risk of respiratory depression due to systemic opioid administration.[5]

Recently, there have been thoracic paravertebral block, central and fascial plan block approaches have been described. Most PVBs and ESPB are interfacial plane blocks that create sensory blockades of local anesthetics' spinal nerve dorsal roots as part of multimodal analgesia.[6] ESPB is a representative method of indirect thoracic PVB, first described in 2016.[6] It is preferred safely because it does not affect hemodynamics, does not cause respiratory depression, is easy to apply and has low complication risks. So, it has been used as an analgesic option for many surgeries.[7]

Corresponding Author: Tuğba Onur, doktor-t@hotmail.com

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Our study aimed to compare perioperative and postoperative affects of USG-guided ESPB and PVB methods KP patients in our clinic.

METHODS

Study Design

A retrospective study was conducted on patients who underwent USG-guided ESPB and PVB procedures for kyphoplasty surgery between January 15 and December 31, 2021. Written consent was obtained for each patient. Local ethics committee approval was obtained with the protocol date and the number of 2011- KAEK-25 2022/04-10 from Bursa High Specialized and Education Hospital.

Recruitment and Data Collection

Forty adult patients with pathological vertebral fractures who applied to the hospital due to symptoms and did not benefit from previous conservative treatments were included in our research. Patients with an inability to communicate, the presence of neurological symptoms and disease, diagnosis of a metastatic bone tumor or multiple myeloma, asymptomatic fractures, systemic or local infections, and patients with coagulation disorders were excluded from the study. Demographic characteristics of the patients (age, gender, Body mass index (BMI), The American Society of Anesthesiologists (ASA) classification scores), preoperative analgesic use and mobilization level, preoperative pain values, hemodynamic parameters, and level surgery were recorded. Mean arterial pressure (MAB), Heart rate (HR), peripheral oxygen saturation (SpO_2); T1: the beginning of surgery; T2: 15th minute during surgery; T3: 30th minute during surgery; T4: 45th minute during surgery; and T5: end of the surgery, the dose and type of sedation, the need for additional opioids, complications (such as arrhythmia, respiratory depression, total spinal block, hypotension), the duration of anesthesia and surgery were determined. As a anesthesia technique, the patients were seperated to Group 1 (ESPB) and Group 2 (PVB). In the postoperative period, VAS values at 2, 6, 12, and 24 hours (as a routine procedure of patients who has one of the block technique for analgesia in the postoperative period), the time of first analgesic administration, dose of the analgesic administered within 24 hours, first mobilization and the discharge time, postoperative intensive care need (PICU), and complications were recorded. For all patients postoperative rescue analgesia procedure was 1 mg/kg of tramadol and 1gr of paracetamol intravenously at any time if the patient declares VAS score over 4 and 2, respectively.

Sedoanalgesia

All patients were administered 1 mg midazolam iv after routine monitoring (MAB, HR, SpO_2) in the operating room. Hemodynamically stable patients were placed in the prone position and the fascial plane block method chosen by the blind anesthesiologist for multimodal analgesia and anesthesia was applied to the study.

The Ultrasound-guided Erector Spinae Blane block Technique

After infiltration of 1 mL of 2% prilocaine into the subcutaneous tissue, 40 mL of local anesthetics (combination of 25 mL 0.25% bupivacaine+10 mL 2% lidocaine+5 mL saline) was applied from the vertebral level one below the surgical level. The 22-gauge, 50 mm peripheral block needle (Stimuplex A®; B Braun, Melsungen, Germany) placement was applied via low frequency (2-5MHz) USG linear probe (GE Healthcare Logiq P5, USA) at 3 cm lateral, longitudinal, and parasagittal to the vertebrae.

The Ultrasound-guided Paravertebral Nerve Block Technique

After infiltration, 1 mL of 2% prilocaine into the subcutaneous tissue 2–2.5 cm lateral to the spinous processes, 40 mL local anesthetics (combination of 25 mL 0.25% bupivacaine+10 mL 2% lidocaine+5 mL saline) injected bilaterally from the vertebral level one below the surgical level. The 22-gauge, 50 mm peripheral block needle (Stimuplex A®; B Braun, Melsungen, Germany) was used for the PVB, and placement was applied via high frequency (5-13 MHz) USG linear probe (GE Healthcare Logiq P5, USA) placed longitudinally to the lower vertebral level of the selected surgical level. The needle was moved into the selected paravertebral area by passing the trapezius, rhomboids, erector spinal muscles, and superior costotransverse ligament. In each procedure, downward displacement of the parietal pleura was observed.

Statistical Analysis

Descriptive data are presented in numbers and percentages, while measurement data are presented in the mean±standard deviation and median (minimum-maximum) values. Chi-square and Fisher tests were used to compare categorical data. The normality distribution of measurements was evaluated using the Shapiro-Wilk test and histogram graphs. Student-T Test was used to compare normally distributed measurements in independent groups, and the Mann-Whitney U test was used to compare non-normally distributed measurements. $P<0.05$ was accepted for statistical significance. All analyzes were analyzed with the SPSS 20 for the mac version program.

RESULTS

Forty patients who underwent ESPB (n=20) and PVB (n=20) as the anesthesia method were evaluated. Of the patients, 19 were female, and 21 were male. There was no statistical difference between the groups regarding age, gender, smoking, ASA, surgical level, analgesic use, chronic diseases (hypertension, diabetes mellitus, presence of coronary artery disease), and preoperative VAS scores. The rate of obesity was significantly higher in Group 1 compared to Group 2 (p=0.041). The general features of the study patients are presented in **Table 1** in detail.

Table 1. Distribution of the general demographic data of the patients

	Group 1	Group2	P
Gender			0.527[c]
Female	8 (40.0)	11 (55.0)	
Male	12 (60.0)	9 (45.0)	
Age (median(min-max)	71.0 (66.0-82.0)	70.5 (64.0-81.0)	0.738[m]
ASA (median(min-max)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	0.841[m]
Level			1,000[c]
Thoracic, n (%)	9 (45.0)	8 (40.0)	
Lumbar, n (%)	11 (55.0)	12 (60.0)	
HT, n (%)	8 (40.0)	11 (55.0)	0.527[c]
DM, n (%)	10 (50.0)	11 (55.0)	1,000[c]
CAD, n (%)	12 (60.0)	12 (60.0)	1,000[c]
Obesity, n (%)	10 (50.0)	3 (15.0)	0.041[c]
Smoking, n (%)	5 (25.0)	8 (40.0)	0.501[c]
Other, n (%)	8 (40.0)	10 (50.0)	0.751[c]
VAS0 (median(min-max)	7.5 (6.0-9.0)	7.0 (6.0-9.0)	0.108[m]
Preoperative analgesic used, n (%)	13 (65.0)	9 (45.0)	0.341[c]

m: Mann Whitney U test, c: Chi-square test, HT: Hypertension, DM: Diabetes Mellitus, CAD: Coronary Artery Disease VAS 0: Preop erative visual analog scale pain severity score.

Other: Rheumatological diseases, Goiter, Hiperlipidemi

There was no statistical difference between the groups regarding MAP, SpO_2 values, additional opioid need, and perioperative complication rates at the specified times during surgery (p>0.05). The perioperative conditions of the study patients are given in **Table 2** in detail.

Table 2. Analyzing perioperative data according to study groups

	Group 1	Group 2	P
	Mean±Std. Deflection	Mean±Std. Deflection	
MAP1	75.6±14.4	81.6±14.4	0.190[t]
MAP2	71.3±12.1	79±13.7	0.064[t]
MAP3	67.7±11.2	73.9±12.3	0.099[t]
MAP4 (median(min-max)	62.5 (52.0-87.0)	76.0 (55.0-87.0)	0.102[m]
HR1	81.3±9.8	78.4±9.6	0.351[t]
HR2	81.3±9.3	79.6±9.0	0.573[t]
HR3 (median(min-max)	77.5 (61.0-112.0)	79.0 (65.0-92.0)	0.862[m]
HR4 (median(min-max)	78.5 (57.0-109.0)	75.0 (67.0-98.0)	0.327[m]
SpO_2-1 (median(min-max)	96.0 (94.0-98.0)	96.0 (94.0-98.0)	0.901[m]
SpO_2-2 (median(min-max)	97.0 (94.0-98.0)	96.5 (95.0-98.0)	0.602[m]
SpO_2-3 (median(min-max)	96.5 (92.0-98.0)	96.5 (86.0-98.0)	0.968[m]
SpO_2-4 (median(min-max)	96.5 (94.0-98.0)	96.5 (92.0-98.0)	0.968[m]
Need for additional opioids n (%)	4 (20.0)	6 (30.0)	0.716[c]
Operation time (min) (median (min-max)	50.0 (35.0-65.0)	60.0 (40.0-70.0)	0.009[m]
Peroperative complication n (%)	6 (30.0)	5 (25.0)	1,000[c]

I: Independent T test in groups m Mann Whitney U test , c Chi- square test min: Minute
MAP1: mean arterial pressure at 15th minute of surgery, MAP2: mean arterial pressure at 30th minute of surgery, MAP3: mean arterial pressure at 45th minute of surgery, MAP4: mean arterial pressure at 60th minute of surgery, HR1: Heart rate at 15th minute of surgery HR, HR2: Heart rate at 30th minute of surgery HR, HR3: Heart rate at 45th minute HR of surgery, HR4: Heart rate at 60th minute of surgery HR, SpO_2-1: 15th minute of surgery SpO_2, SpO_2-2: 30th minute of surgery SpO_2, SpO_2-3: 45th minute of surgery SpO_2, SpO_2-4: 60.min SpO_2 of surgery

Postoperative 6th-hour VAS scores and median paracetamol doses used in Group 1 patients were significantly lower compared to Group 2 patients (p=0.023 and p=0.006, respectively). There was no statistical difference between the groups regarding VAS scores, first mobilization time, time to discharge, postoperative complications, PICU needs and the dose of tramadol after surgery (p>0.05). Postoperative characteristics of the study patients are detailed in **Table 3**.

Table 3. Analyzing postoperative data according to study groups

	Group 1	Group 2	p
	Median (Min-Max)	Median (Min-Max)	
VAS1	1.5 (0.0-3.0)	2.0 (0.0-4.0)	0.068[m]
VAS2	1.5 (0.0-4.0)	2.0 (0.0-4.0)	0.023[m]
VAS3	1.0 (0.0-3.0)	2.0 (0.0-4.0)	0.355[m]
VAS4	1.0 (0.0-2.0)	1.0 (0.0-4.0)	0.211[m]
Mobilization time (h)	6.0 (5.0-10.0)	7.0 (6.0-10.0)	0.102[m]
Discharge time (h)	20.0 (12.0-48.0)	30.0 (12.0-56.0)	0.142[m]
Complication n (%)	3 (15.0)	3 (15.0)	0.669f
PICU n (%)	5 (25.0)	7 (35.0)	0.731[c]
Paracetamol dose (mg)	0.0 (0.0-3000.0)	1000.0 (0.0-3000.0)	0.006[m]
Tramadol dose (mg)	0.0 (0.0-100.0)	0.0 (0.0-200.0)	0.102[m]

M: Mann Whitney U test, c Chi- square test , f Fisher test
PICU: postoperative need for intensive care unite. h : Hour , mg: Milligram
VAS1: Postop 2nd hour visual analog scale pain severity score, VAS2: Postop 6th hour visual analog scale pain severity score, VAS3: Postop 12th hour visual analog scale pain severity score, VAS4: Postop 24th hour visual analog scale pain severity score.

DISCUSSION

This is the first study to compare ESPB and PVB techniques in anesthesia and analgesia of KP surgery according to us. The primary outcome of this research: The postoperative 6th-hour VAS score and the paracetamol doses used were lower in Group 1. At all other times, hemodynamic parameters during the perioperative period, the dosage of opioids used, the postoperative VAS scores, the first mobilization and discharge times, the need for the intensive care unit, the amount of analgesic used, and complications were similar in groups.

Compression fractures in the thoracolumbar region, osteoporotic fractures, and accompanying chronic pain are the most critical indications of kyphoplasty.[8] In anesthesia techniques, there are options for using local or general anesthesia, depending on the patient's ability to the prone position. In patients undergoing kyphoplasty, a high rate of symptomatic improvement and early discharge in the first days after the procedure are significant advantages, especially for elderly patients. A relatively new technique is restoring vertebral height by applying inflatable balloon pads to the collapsed vertebra in KP and injecting cement with low pressure into the volume created by the balloon.[9] The fact that kyphoplasty is minimally invasive and can be performed under local anesthesia, the duration of the procedure is significantly short even when general anesthesia is applied, and the risks of surgery and pain experienced by elderly patients in stabilization surgery are significantly reduced, increasing the frequency of application.[10] Although local sedation and general anesthesia are often used together, the expectations of patients and surgeons and the search for safer anesthesia techniques have increased the use of other anesthesia methods.

A central block, such as spinal anesthesia or epidural anesthesia, is frequently used in kyphoplasty surgeries. Still, it is associated with severe complications such as epidural leakage, spinal hematoma, infection, hypotension, and urinary retention.[11,12] The undesirable side effects of central block methods have made fascial area blocks considered. The distribution of local anesthetics in PVB includes both ventral and dorsal spinal branches, according to a review of anatomical research. In contrast, regional anesthetic distribution in ESPB is limited (it cannot block dorsal and intercostal nerves), which makes it less effective.[13]

USG-guided PVB and local anesthesia applications have been studied for their effects on postoperative opioid use, pain scores, and opioid-related side effects following kyphoplasty surgery. This technique is considered an effective anesthesia method.[14,15] Based on a meta-analysis, PVB has been shown successful pain control and less side effects when administered with or without general anesthesia. Compared with the general anesthesia groups administered by other analgesic modalities, PVB has been shown to be better and more effective.[16] As an outcome of our study, we reported a significant reduction in VAS scores postoperatively, with fewer side effects, especially those associated with analgesics and opioids. In association with pain reduction, early mobilization and early discharge were observed. Various complications have been related to paravertebral blockages, such as pneumothorax, intrathecal injection or hemothorax, ipsilateral brachial plexus block, and hemidiaphragmatic paresis.[17] The outcome of our study did not reveal any PVB-related complications.

Perioperative thoracic ESPB has been shown to provide good analgesia and reduce postoperative nausea, vomiting, and pain scores in patients following lumbosacral spinal surgery.[18,19] A decrease in perioperative and postoperative opioid consumption, early patient mobilization and chest tube removal has been observed, particularly in cardiac surgery.[20] There is consensus among most authors that ESPB has certain advantages over central blocks. An increase in the use of ESPB in perioperative pain control has been noted among patients undergoing kyphoplasty.[21,22] Two critical complications related to ESPB were reported in the literature; The first is iatrogenic pneumothorax, and the other is motor weakness after cesarean section.[23] According to our study, ESPB is associated with reduced opioid consumption during surgery, reduced postoperative pain scores, and reduced analgesic use. We did not observe any ESPB-related complications during the course of our study. PVB is an advanced difficulty technique compared to ESPB.[24] Since the needle tip in ESPB is located at a superficial position than PVB technique, ultrasonography provides more precise visualization of the needle than in PVB. Therefore, ESPB is preferred in obese patients. A similar trend was observed in our study, where obese patients were more likely to undergo ESPB.

Several randomized studies comparing PVB and ESPB in thoracic and breast surgery patients found a significant reduction in postoperative pain scores, opioid usage, and additional analgesic usage following PVB.[25] PVB and ESPB had similar effects on pain scores and analgesic consumption following breast surgery. PVB and ESPB provided different analgesic effects postoperatively depending on the surgical site. According to another study comparing ESPB and PVB in patients for video-assisted thoracic surgery (VATS), the pain scores were similar between the two groups when moving, and the pain scores were lower in the PVB group at rest.[26] As part of our study, we compared VAS scores during movement between ESPB and PVB in patients with KP; 6 hours postoperatively, ESPB provided a superior analgesic effect to PVB. According to our hypothesis, the ESPB group's lower postoperative 6th-hour VAS values may be related to a quicker distribution of local anesthetic and a faster decrease in its effect because of its richer vascularity of paravertebral space in PVB group. A study in the VATS patients showed that combination of PVB and ESPB had superior analgesia to ESPB.[27] Even though the general VAS values were similar between the ESPB and PVB groups in our study, we are considering the possibility of combining the two techniques for better anesthesia management and early analgesia.

Study Limitations

Although our study is the first in the literature to compare the efficacy of ESPB and PVB techniques in anesthesia and analgesia of KP surgery, it does have some limitations. One of the most important limitations of our study is the small sample size. Our other limitations include the lack of prospective long-term follow-up of the patient and the absence of ongoing pain evaluations. Another limitation of our study was the inability to assess VAS separately at rest and in motion.

CONCLUSION

The ESPB and PVB techniques provided adequate postoperative analgesia in KP surgery, early mobilization, and discharge, reducing perioperative opioid requirements and associated side effects. Additionally, the ESPB technique's postoperative VAS score at 6 hours was lower than the PVB technique, and paracetamol use after ESPB was lower than following PVB. We suggest more likely use ESPBs and PVBs as safer alternatives for KP surgeries in geriatrics and fragile groups, which generally have limited or difficult access to general anesthesia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (Decision No: 2011-KAEK-25 2022/04-10).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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KASTAMONU MEDICAL JOURNAL

Case Report

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An unusual cause of ascites: eosinophilic gastroenteritis

İdris Kurt, Ezgi Bulut

[1]Department of Gastroenterology, Kastamonu Training and Research Hospital, Kastamonu, Turkey
[2]Department of Internal Medicine, Faculty of Medicine, Trakya University, Edirne, Turkey

ABSTRACT

Eosinophilic gastroenteritis is a rare disease, characterized by eosinophilic infiltrates in the intestinal layers. Its etiology is not well known. Biopsy is mandatory for accurate diagnosis. Clinical presentationis variable and can be seen in numerous diseases. There are no patognomonic findings. Serosal type involvement is the rarestand usually is associatedwith ascites. In this case, we report a 21-year-old femalepatient presented with abdominal pain, diarrhea, vomiting and ascites.Diagnosis of eosinophilic gastroenteritis was made after eliminatingbroad-spectrummimicking causes of tissue eosinophilia.The patient recovered completely after treatment with steroids.

Keywords: Corticosteroids, eosinophilic gastroenteritis, ascites

INTRODUCTION

Eosinophilic gastroenteritis (EGE) despite its infrequent occurrence is one of the most significant primary eosinophilic gastrointestinal disorders. Most common symptom is abdominal pain. All levels of the gastrointestinal tract (GI) from the esophagus to the rectum may be affected.[1] There is a little data about the epidemiology of EGE. The prevalence of EGE in the United States is estimated to be 5.1 per 100,000 based on prior survey data.[2] EGE is well known to be more common among the pediatric population. Although it can affect all ages, the majority of cases in adults ocur from third to the fifth decades of life.[3] Three criteria are required for the diagnosis of EGE: GI symptoms, histological evidence of eosinophilic infiltration of the GI tract and exclusion of secondary tissue eosinophilia causes.[4] We report a case of EGE, that presented with abdominal pain, vomiting, diarhea and ascites.

CASE

A 21-year-old woman was admitted to the emergency room with complaints of abdominal swelling, diarrhea (stool frequency 5-6 times/day) started twenty days ago, and recently appeared epigastric pain and vomiting. İnprevious history it was learned that she was followed up by dermatology with the diagnosis of atopic dermatitis in childhood and adolescence periods. She has not recently traveled to a different place orchange her routinefood consumption. In addition she has no history of abdominal surgery or food sensitivity. On physical examination, her body temprature, blood pressure were normal, pulse rate was 95/ min and respiratory rate 21/min. Chest auscultation demonstrated bilaterally normal breath sounds. Her abdomen was distended, without rijidity and rebound, bowel sounds were evaluated as hyperactive. There was tenderness with dullnessin lower quadrants.

The laboratory tests were monitored as follows: hemoglobin 12,4 g/dL, leukocytes 15,1 10^3/uL (eosinophils 7.9 10^3/uL), platelet count of 359 10^3/uL. Electrolytes level were normal. The serum protein level was 7,5 g/dL; albumin 3,8 g/dL; blood urea nitrogen 14 mg/dL; creatinin 0,5 mg/dL; ALT 140 U/L; AST 288 U/L; LDH 576 U/L; C- reactive protein 0,79 mg/dL; total Ig E 203 IU/mL (upper limit 100 IU/mL), eriytrocyte sedimentation rate (ESR)16mm/hr. Coagulation parameters were normal. Her stool tests were negative for occult blood and enteric pathogens (bacteria, parasites).

A simple chest and abdominal radiograph was normal. A significant amount of ascites was observed in the abdominal ultrasound. Computed tomography (CT) showed free fluid in the perihepatic, perisplenic and pelvic regions (**Figure 1**).

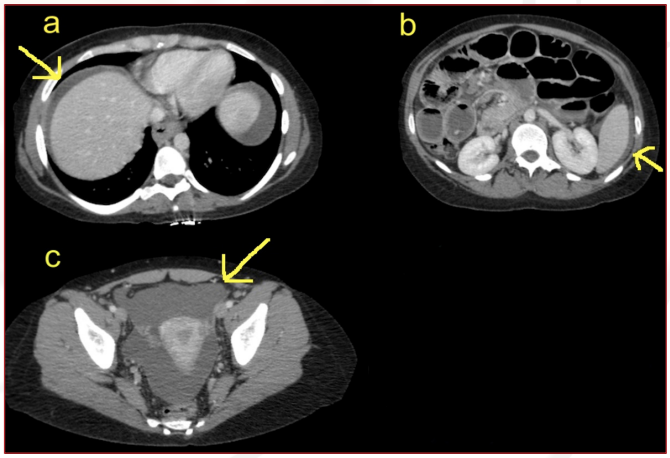

Figure 1. Perihepatic (a), perisplenic (b), and pelvic (c) peritoneal free fluid

Corresponding Author: İdris Kurt, idrisk8607055022@gmail.com

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Paracentesis was performed from the ascitic fluid for biochemical, microbiological and cytological analysis. Acid fluid tests were monitored as follows: total protein 5.6 g/L, albumin level 3 g/dL, and caculated serum ascites albumin gradient 0.8 g/dL (<1.1, non-cirrhotic). In addition, ascitic fluid contained 24,000 cells/mm³ cells, 80% of which was eosinophil predominant leukocytes. The glucose level, lactate dehydrogenase (LDH), and adenosine deaminase (ADA) were measured as 74 mg/dL(normal), 241 U/L (normal) and 15 U/L (normal), respectively. The cultures for bacteria, parasites and Tuberculosis were negative. Malignant cells were not observed.

The gynecological examination performed to exclude malignancy was normal. Hematology consultation was made to rull-out hematological causes. Peripheral blood smear was consistent with complete blood count and no atypical cells were found. BCR-ABL, PDGFR Alpha , Flip 1-like 1 gene mutations which are seen in hematological diseases like hypereosinophilic syndrome or chronic myeloproliferative neoplasms were negative. Rheumatologic tests to exclude Celiac, collagen and vasculardiseases that may show similar clinical features were also negative (Anti- tissue transglutaminase, Antinuclear antibodies, ANCA).

Endoscopy and colonoscopy was performed. Gastroscopy showed slightly hyperemic and edematous mucosa in the antrum and duodenum, pylor was slightly deformed. Random biopsies were taken from esophagus and stomach. The histopatology showed focal chronic esophagitis with prominent eosinophilic infiltration (70 eosinophils per HPF, **Figure 2**), chronic gastritis and superficial erosions at the postbulber area.

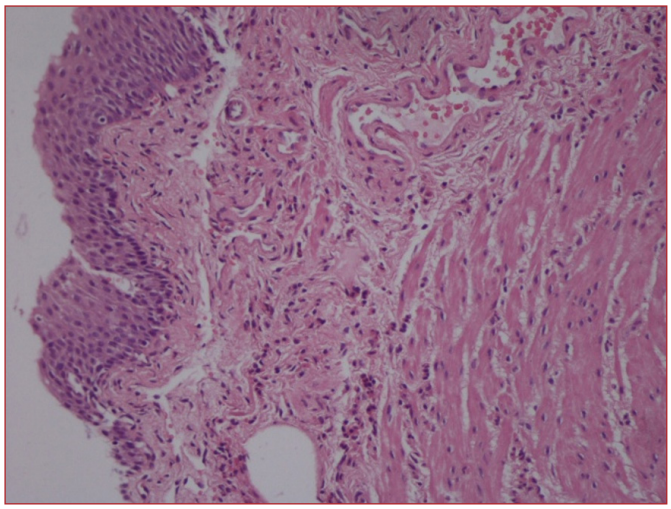

Figure 2. Microscopic image showing70 eosinophils/high power field (HPF) inesophagus(HE, 200x).

Helicobacter Pylori was negative. Endoscopic view in colonoscopy was normal, but randomly taken mucosal biopsies revealed synchronously eosinophilic infiltration of the terminal ileum (≥100 eosinophils/HPF) and ascending colon (≥20 eosinophils/HPF) (**Figure 3**). Accompanied by all these findings and no extraintestinal manifestation, diagnosis of Eosinophilic Gastrpoenteritis was made. 40 mg prednisolone per day was started. As a result vomiting, diarrhea and pain regressed at the third day of therapy. Control laboratory findings and abdominal ultrasound imaging return to normal. The steroid dose was gradually tapered and discontunied in eight weeks. She remained symptom free on a 12-month follow up.

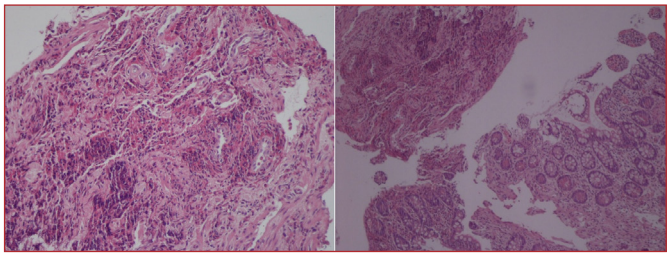

Figure 1. Microscopic image showing increased numbers of eosinophils in ileum. [More than 100 eosinophils / high power field (HPF) Hematoxylin-eosin stain (HE), 200x]

DISCUSSION

İmmunoglobulin E dependent and delayed TH2 cell mediated allergic mechanisms have been showed to be involved in the physiopathology of EGE. Interleukin 5 has also been demonstrated to play asignificant role in the expansion of eosinophils and their accumulation in GI. Chemokines like eotaxin 1, α4β7 integrin also contribute to aggregation of eosinophils in the intestinal wall. Other mediators particularly Interleukin 3,4,13, Leukotrienes and Tumor Necrosis Factor Alpha help to increase eosinophilic trafficking and prolong their activity together with lymphocytes. About %45 to %65 of patients has synchronously allergic diseases like asthma, allergic rinitis, eczema, drug and food intolerance.[5] In previous history of our patient, there was atopic dermatitis in childhood and adolescence periods, consistent with the literature.

As is mentioned above diagnosis is established with combination of clinical , pathological findings and exclusion of secondary tissue eosinophilia causes.[4]

The clinical features of EGE are related not just to the affected segment as well as the affected layer of the gastrointestinal wall. According to Klein's diagnostic classification from 1970, the infiltration may be predominantly at the mucosal, muscular or subserosal layer6[4]

Mucosal eosinophilic gastroenteritis is the most common type and the main affected areas are stomach and duodenum. Patients present with symptoms such as abdominal pain, weight loss, nausea, vomiting,and findings of iron deficiency, malabsorption, protein-losing enteropathy. Common endoscopic appearances are mucosal hyperemia, aphthae and ulcerations. In muscular type, wall thickening occurs and the patient presents with nausea, vomiting, abdominal distension as a result of impaired motility, stricture formation, and rigidity. Serosal type involvement is the rarest form and is seen with signs of eosinophilic ascites, intense peripheral eosinophilia and peritonitis.[7]

There is no established cut-off eosinophilic density on pathology. Along with the pathological findings (altered behavior and distribution of eosinophils, epitelial changes) the proposed numbers of eosinophils based on reported literature are: ≥15 per high-power field (HPF) in the esophagus, ≥30 per HPF in 5 HPF in the stomach, ≥30 per HPF in the duodenum, >56 per HPF in the ileum, >100 per HPF in right colon, >84 per HPF in transverse and descending colon, >64 per HPF in the rectosigmoid colon.[8]

Our case applied with the complaints of nausea, vomiting, diarrhea, abdominal distension and detected eosinophil predominant ascitic fluid. Peripheral eosinophilia occured at laboratory tests. Endoscopic biopsies were taken for differantial diagnosis. Histopathology revealed prominent eosinophilic infiltration and pathological changes in the

structure of mucosal layer. Number of eosinophils were highly above from proposed cut-offs.With all these data, EGE was confirmed after exclusion of parasitic diseases, drug or food allergy, reumatological diseases, hematological malignancies, inflammatory bowel, and celiac diseases. The presence of nause, vomiting, peripheral eosinophilia, eosinophil infiltration of mucosa and eosinophilic ascites indicate mucosal and serosal type of EGE, synhronously.

In the treatment of patients, the relationship of diet with symptoms should be questioned. In some cases there are patients treated with diet but empirical food elimination requires further study for long-term outcomes and efficacy in adults.[9,10]

In a study by Guıllaume Pıneton de Chambrun et al.[11] avoidance of culprit allergens was insufficient to resolve symptoms.The most commonly used treatment was oral corticosteroid therapy in 74% of patients. Corticosteroids were administered orally at a dose of 40-60 mg/day for a short period of time (1 week to 4 months), and subsequently reduced rapidly. Corticosteroid therapy appeared to be effective in 95% of patients. Based on case reports, other treatments include: Leukotriene inhibitors (montelukast), mast cell stabilizers (oral cromolyn), Interleukin-5 inhibitors, Ketotifen, immunosuppressive drugs, biologic agents like Vedolizumab, Mepolizumab (anti-IL 5 antibodiy) and Omalizumab (anti-IgE monoclonal antibody).[12,13]

In our patient symptomes and pathological findings regresed totally after eight weeks course of corticosteroids.

CONCLUSION

Eosinophilic gastrointestinal disorders are among the rare diseases. Its etiology has not been fully elucidated. Symptoms and signs are similar to many other diseases. Diagnosis requires high suspicion and exclusion of various disorders associated with peripheral and tissue eosinophilia. The disease course is variable. Corticosteroids have been used successfully to treat eosinophilic gastrointestinal disorders.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Transanal protrusion ventriculoperitoneal shunt migration in hydrocephalus patients

Tommy Alfandy Nazwar[1], Farhad Bal'afif[1], Donny Wisnu Wardhana[1], Sabrinadia Hanareta Hantoko[2], Mustofa Mustofa[1]

[1]Division of Neurosurgery, Department of Surgery, Saiful Anwar Hospital, Brawijaya University, Malang East Java, Indonesia
[2]Department of Surgery, Saiful Anwar Hospital Malang, Brawijaya University, East Java, Indonesia

ABSTRACT

Perforation of the abdominal viscera and protrusion of the distal end of the ventriculoperitoneal shunt are uncommon but serious complications of pediatric surgery. We report a case of distal ventriculoperitoneal shunt protrusion into the appendix by transanal access in a patient who did not exhibit typical appendicitis symptoms. We report the case of a 2-year-old male with anal extrusion and assess his condition.

Keywords: Transanal protrusion, pediatric, ventriculoperitoneal shunt, hydrocephalus

INTRODUCTION

The cerebrospinal fluid (CSF) hemodynamic disorder known as hydrocephalus is caused by an imbalance in the production, circulation, and absorption of cerebrospinal fluid. This results in increased intracranial pressure, ventricular dilatation, and crowding of the brain tissue in the surrounding area. Hydrocephalus can affect people of any age, but it most frequently affects young children and newborns. Because the fontanel is still open in newborns, the accumulation of cerebrospinal fluid can be compensated for by broadening the bones of the skull. As a result, the clinical signs of hydrocephalus in infants are more obvious than in older children and adults.[1-3]

There are a significant number of people living with hydrocephalus across the globe. The incidence of hydrocephalus in Japan is approximately 0.2 per 1000 births, which is significantly lower than the incidence of hydrocephalus in the United States, which is approximately 0.5-4 per 1000 live births. Just in Indonesia, there are roughly 2 occurrences of hydrocephalus for every 1000 babies that are born. Approximately 46% of infantile hydrocephalus can be attributed to defects in brain development, 50% can be attributed to subarachnoid hemorrhage and meningitis, and fewer than 4% can be attributed to tumors in the posterior fossa.[4]

The ventriculoperitoneal shunt is one of the most frequently performed surgical therapies by 30% because it has a major impact on the management of hydrocephalus patients, the shunt consists of two valves connected to a catheter from the intraventricular to the peritoneal cavity, and it is one of the most common surgical treatments for hydrocephalus.[5] This therapy, on the other hand, might result in a number of consequences, such as infection, blockage, the creation of a pseudocyst, perforation, and migration of the ventriculoperitoneal shunt.[6] Migration from the ventriculoperitoneal shunt is the most difficult complication because it can enter other organs such as the mouth, thorax, diaphragm, heart, pulmonary artery, breast, abdomen, bile, liver, umbilicus, colon, inguinal, urinary bladder, vagina, anus, and scrotum, which adds to the complexity of the management. This is the most difficult complication because it can enter other organs.[7,8] We present a case report of ventriculoperitoneal shunt migration; hence, research on ventriculoperitoneal shunt migration in patients with hydrocephalus is required.

CASE

A 2-year-old boy came to the RSSA Malang emergency room with complaints of a ventriculoperitoneal shunt tube coming out of the anus in the last 1 day of before hospital admission. The tube comes out when the patient is defecating but the tube also goes in by itself. When he was taken to the hospital, the tube did not appear to come out of the anus. There was no previous history of bowel obstruction. In the local area of the anus, a shunt tube can be seen coming out through the anus in a tied position. Patients underwent a total of 4 operations in 2020 namely; ventriculoperitoneal shunt kocher D shunt surgery in June, meningocele surgery in September, wound descence surgery in October. Then the following year Debridement surgery + abscess drainage + reinsertion of VP Kocher D shunt in November 2021.

Corresponding Author: Tommy Alfandy Nazwar, nsubtommy@gmail.com

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Physical examination in September 2022 showed no abdominal dilatation or free intra-abdominal air. The ventriculoperitoneal shunt tube with an intraperitoneal impression tip and intestinal air distribution to the pelvic cavity with visible fecal material is seen. The patient was diagnosed with Transanal Protrusion of ventriculoperitoneal shunt.

The treatment plan for this patient is: Head up 30°, IVFD C1:2 1,000 cc/24 hours, Inj. Omeprazole 1×10mg and Inj. Metamizole 3×100mg for pain. The action plan that will be carried out is "Urgent Aff Shunt D + Analysis + Culture of LCS and Consulting Pediatric Surgeon for evaluation of acute abdomen and evaluation of durante surgery. Monitoring is carried out on the parameters of vital signs (general impression), heart rate (HR), Respiration rate (RR), Tax, Neurological status, signs of increased intracranial pressure, signs of acute abdomen, B1-B6 function and response to therapy.

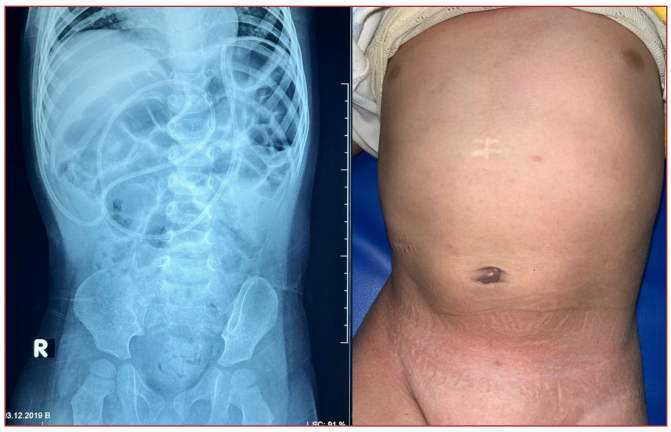

Figure 1. X-ray imaging on distal peritoneal catheter coiled at lower

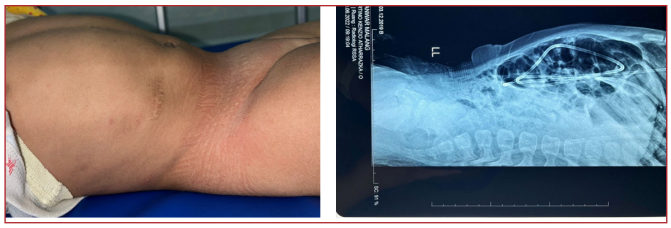

Figure 2. Side X-ray abdomen shunt tubbing

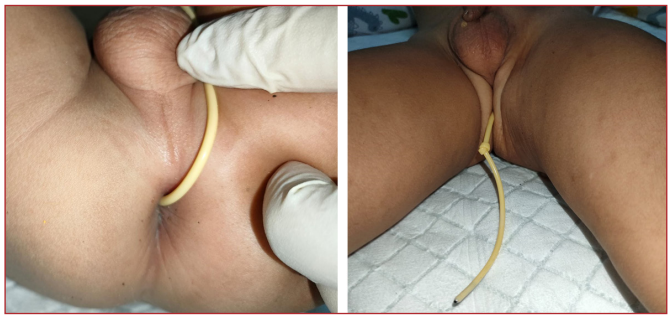

Figure 3. Images of protruding the distal catheter end.

DISCUSSION

The ventriculoperitoneal shunt is the most prevalent and globally acknowledged surgical treatment for hydrocephalus in children. Wilson and Bertan reported the first case of distal ventriculoperitoneal shunt anal extrusion in 1966.[9] The period between shunt surgery and intestinal perforation in babies was shown to be brief and age-related. The longevity was greater in the older group. The time between shunt placement and catheter protrusion from the anus ranged from 2 to 20 months, with an average of 6.1 months.[11] In pediatric patients, foreign body reaction, rigid shunt tip, and thin gut wall are factors related with intestinal perforation,[11,12] abdominal infection, silicone allergy,[13] use of trocar for peritoneal tip insertion.[14] Patients with an extruding anal shunt may exhibit abdominal peritonitis. The fibrous tracts that grow at the site of the perforation typically close the perforation and prevent feces from spilling into the peritoneum and causing peritonitis in the majority of cases.[15]

Therefore, the diagnosis is incomplete until the gram-negative organism has been investigated. The process of shunt extrusion is poorly understood, but the most plausible explanation is that the shunt tube is expelled by consecutive intestinal peristalsis once bowel perforation is identified. Early diagnosis, thorough clinical, radiographic, and biochemical exams, and rapid treatment are essential for treatment success. Standard treatment involves removing the extruded shunt system, managing infection, and improving the patient's health, followed by CSF diversion surgery. Laparotomy with revision of the peritoneal shunt tip, conventional exploratory laparotomy and repair of bowel perforation, endoscopic localization of the enterotomy site and removal of the shunt, removal of the shunt, external CSF diversion and use of antibiotics, and subsequent ventriculoperitoneal shunt replacement when there are no signs of infection are the various treatment options. which is accessible In situations of uncomplicated shunt extrusion, the shunt tube can be drawn through the extrusion orifice, and bowel perforation can be treated conservatively; nevertheless, laparotomy is necessary for shunt removal in difficult cases. Appendicitis following a ventriculoperitoneal shunt is a known complication; however, shunt extrusion through an appendicular perforation has not been recorded in the medical literature to the best of our knowledge. In these kinds of circumstances, extracting the shunt through the extrusion orifice can prove to be a difficult task. The presence of appendicitis, in conjunction with the removal of the shunt through the orifice that has been extruded, has the potential to result in the formation of peritonitis or an appendicular abscess. In these kinds of situations, management needs to be resolute in order to reach a sensible conclusion. As a result, patients who have difficulties coping with other patients, regardless of whether or not they can, should be placed in a different group, and the shunt should be removed via laparotomy, followed by prophylactic appendectomy.

CONCLUSION

Suspicious complications of bowel perforation in ventriculoperitoneal shunt should be considered as a malfunctioning shunt with various signs and symptoms. These signs and symptoms include cellulitis of the shunt tract or infection of the shunt, meningitis or cerebral abscess, and abdominal symptoms. A thin bowel wall in children, a sharp and stiff end of ventriculoperitoneal shunt, distal tip of ventricularperitoneal catheter placement with trocar, long peritoneal catheters, chronic irritation caused by shunt, previous surgery, infection, and silicone allergy are some of the contributing factors that affect the complications in the anal extrusion of the peritoneal catheter.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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