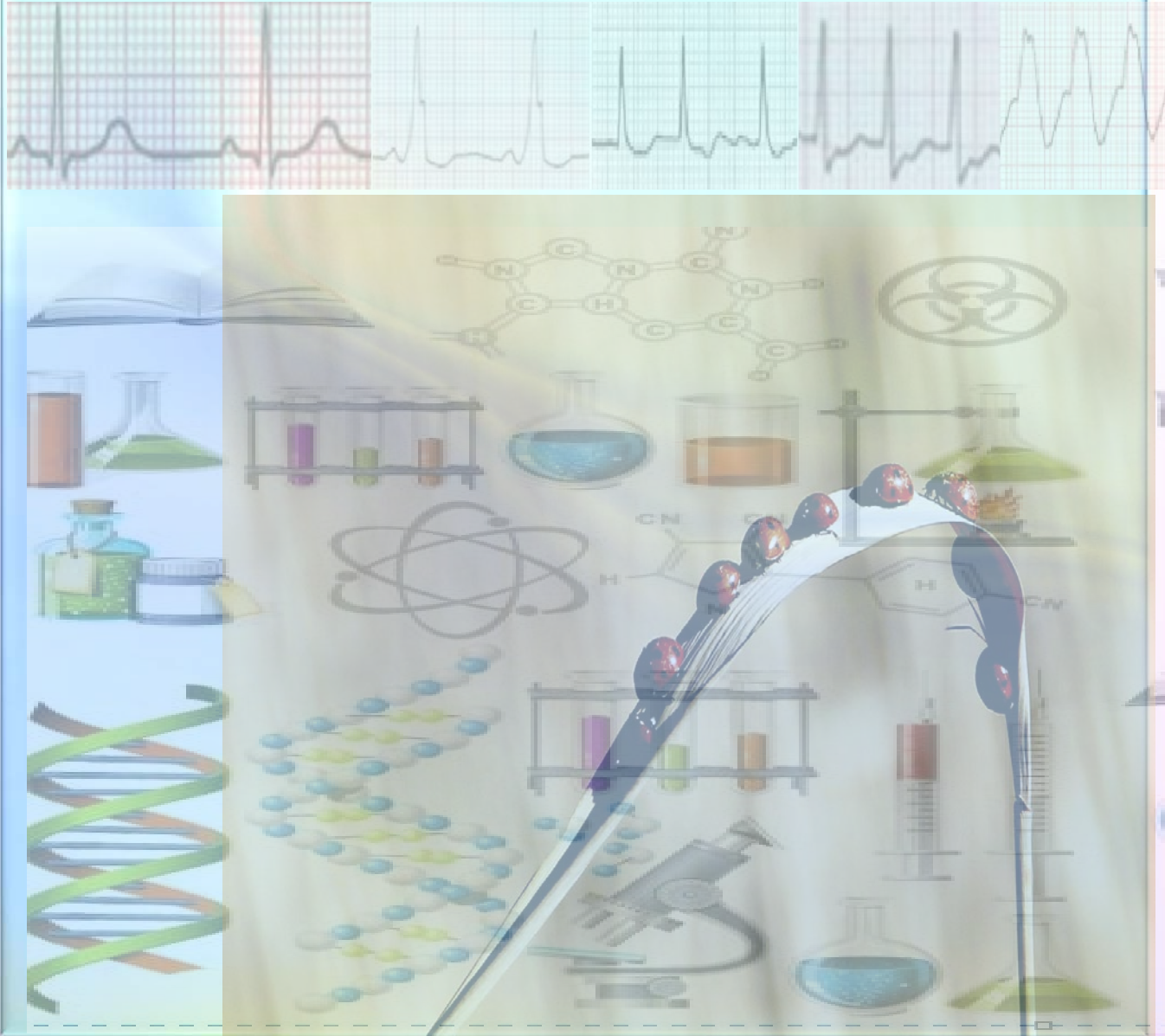


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Books; 1. Wagner G. S. Marriott's Practical electrocardiography, Tenth ed. Lippincott Williams Publisher, 2000: 124-129

Web article: Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. *Am J Nurs* [serial on the Internet] 2002 [cited 12 Aug 2002]. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website; Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 July 2002]. Available from: www.cancer-pain.org

Thesis; Gezer R: Morphological Characteristics and Individual Differences of Rugae Palatines. Master Thesis, Şanlıurfa: Harran University Institute of Health Sciences, 2016.

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EFFECTS OF COVID-19 PANDEMIC ON PREGNANT PSYCHOLOGY

COVID-19 PANDEMİSİNİN GEBE PSİKOLOJİSİ ÜZERİNE ETKİLERİ

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Abstract

Background: Coronavirus Disease 2019 (COVID-19) pandemic has affected many countries from different aspects since December 2019. The present study aims to determine the frequency of prenatal depression risk and anxiety and associated risk factors in pregnant women as a vulnerable group in the COVID-19 Pandemic. **Materials and Methods:** This cross-sectional study included 234 pregnant women selected by cluster sampling method from all Primary Care Outpatient Clinics in Nigde. After ethics committee approval and institution permission was obtained, the data were collected online using the "Edinburgh Postpartum Depression Scale", "State and Trait Anxiety Index (STAI)" and a sociodemographic questionnaire. **Results:** In the present study, the frequency of prenatal depression risk was 24.4%. The median value of the STAI trait score was 41 (23-74), and the median value of the STAI state was 34 (20-80). Prenatal depression risk was associated with job loss (OR: 2.68), multiple pregnancies (OR: 15.31), high COVID-19 perceived risk score (OR: 1.14), and high STAI state score (OR: 1.10) ($p < 0.05$). Prenatal anxiety was associated with being a healthcare worker (OR: 11.66), smoking (OR: 17.21), having health problems during last pregnancy (OR: 3.74), thought of the people living with her at risk (OR: 2.48), and being depressed (OR: 4.73) ($p < 0.05$). **Conclusion:** The COVID-19 Pandemic has been increasing the prevalence of depression risk and anxiety in pregnant women. It is essential to continue routine visits to healthcare centers taking necessary preventive measures and providing psychosocial support to pregnant women.

Keywords: COVID-19, prenatal depression, prenatal anxiety, Turkey

ÖZ

Amaç: Koronavirüs hastalığı 2019 (COVID-19) pandemisi Aralık 2019'dan bu yana birçok ülkeyi farklı açılardan etkilemektedir. Bu çalışmanın amacı COVID-19 pandemisinde kırılgan bir grup olan gebelerde perinatal depresyon ve anksiyete sıklığının ve ilişkili risk faktörlerinin belirlenmesidir. **Gereç ve Yöntem:** Kesitsel tipteki çalışmamıza Niğde'deki tüm Aile Sağlığı Merkezleri'nden küme örnekleme yöntemi ile seçilen 234 gebe dahil edilmiştir. Etik kurul ve kurum izinleri alındıktan sonra veri 'Edinburgh Postpartum Depresyon Ölçeği', 'State and Trait Anxiety Index (STAI)' ve sosyodemografik soru formu ile online olarak toplanmıştır. **Bulgular:** Bu çalışmada perinatal depresyon sıklığı %24.4 olarak tespit edilmiştir. STAI sürekli anksiyete puan ortanca değeri 41 (23-74), durumluk anksiyete ortanca değeri 34 (20-80) olarak bulunmuştur. Perinatal depresyon, kendisinin ve/veya eşinin iş kaybı yaşaması (OR:2.68), çoğul gebeliğe sahip olma (OR:15.31), COVID-19 algılanan risk puanının yüksek olması (OR:1.14) ve durumluk anksiyete puanının yüksek olması (OR:1.10) ile ilişkili bulunmuştur ($p < 0.05$). Perinatal anksiyetenin ise sağlık çalışanı olma (OR:11.66), sigara kullanımı (OR:17.21), gebelikte sağlık problemi yaşama (OR:3.74), beraber yaşadığı kişilerin risk altında olduğunu düşünme (OR:2.48) ve depresif olma (OR:4.73) ile ilişkili olduğu gösterilmiştir ($p < 0.05$). **Sonuç:** COVID-19 pandemisinin gebelerde depresyon ve anksiyete sıklığını artırdığı gösterilmiş olup, gebelere bu dönemde gerekli koruyucu önlemlerin alınarak rutin sağlık kontrollerinin devamı ve psikososyal desteğin sağlanması önem arz etmektedir.

Anahtar kelimeler: COVID-19, perinatal depresyon, perinatal anksiyete

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Introduction

Coronavirus disease 2019 (COVID-19) emerged in China with the reporting of cases of pneumonia with unknown etiology since December 2019, and World Health Organization (WHO) declared this outbreak as an international emergency public health problem.(1) SARS-CoV-2 spread all over the world rapidly and this situation accepted as a pandemic in March 2020,. Turkey is the 9th country where the COVID-19 cases were most commonly seen as of May 2021 (2).

Pregnants are one of the vulnerable groups of epidemics. Pregnancy during Swine Flu (H1N1) (3) and Severe Acute Respiratory Syndrome (SARS) (4) pandemics were associated with increased mortality. Therefore, with the many questions about the COVID-19 infection, clinical studies primarily focused on the effects of the virus on pregnancy and fetus (5). However, it is essential to address the psychosocial impacts of the pandemic as well as the clinical course and prevention methods of the disease in both the general population and pregnant women. The fact that the COVID-19 disease is novel, highly contagious from person to person, and has a high fatality rate, the long-term consequences of the disease are unknown, (6) quarantine and social isolation (7) are the main factors that could explain the increased psychological impact on pregnants.

Pregnants have physiological and anatomical changes, worry both for themselves and their babies. In addition, prenatal stress increases with the limited access to routine health services due to the concern of being infected, lack of social support due to isolation during the Pandemic (8).

Worsening of psychosocial functions (9) nausea/vomiting, preeclampsia, a cesarean delivery (10), preterm birth (11), low birth weight (12), low APGAR score, impairment in emotional and neuropsychiatric development in the baby (13) can be observed with perinatal mental problems.

In a systematic review conducted by WHO before the COVID-19 Pandemic, the prevalence of prenatal psychological disorders was approximately 16% (14). In meta-analysis studies conducted during the COVID-19 Pandemic, the frequency of prenatal depression was 25-32%, and the frequency of prenatal anxiety was 37-43% (15–17). In the prenatal period, it is important to reveal the effects of stress factors brought about by the Pandemic to develop effective and specific interventions. Unfortunately, there are a limited number of studies on this subject in Turkey (18–21). The present study aims to determine the prenatal depression risk and anxiety status and affecting factors during the COVID-19 Pandemic.

Materials and Methods

Study Design and Participants

The study was conducted in Nigde, a province in Central Anatolian Region of Turkey (Figure 1). The universe of this cross-sectional study consists of 1386 pregnant women registered to Primary Care Outpatient Clinics (PCOC) in the province. There are 120 PCOCs in Nigde, and six PCOCs were not included in the study since they did not have a documented pregnant woman. Using the Open-epi program, the sample size was calculated as 346 (event frequency 25%, the margin of error 5%, design effect 1.2, confidence interval 95%). Inclusion criteria were determined as being pregnant, literate, speaking and understanding Turkish, and agreeing to participate in the study. The women whose pregnancy terminated at the time of the study were excluded from the study. The sample was selected according to the cluster sampling method as each PCOC was accepted as a cluster. The list of pregnant women registered to PCOCs was obtained from the relevant unit of the Provincial Health Directorate. The pregnant women were selected according to the pregnancy trimester and pregnant number registered in the PCOCs. Family physicians were informed about the study, and an online informed consent and questionnaire were applied to the selected pregnant women by reaching them through family physicians. Two hundred thirty-four pregnant women were included in the study (67% of the minimum sample number).



Figure 1. Nigde Province Location in Turkey map (taken from Google Earth software)

Data Collection

The data was collected between 11.06.2020-08.07.2020 using the online survey method by the Google forms application. Before the survey, informed consent was obtained online. Then, sociodemographic forms, 'Edinburgh Postpartum Depression Scale' and 'State-Trait Anxiety Scale (STAI)' were applied. Self-score about COVID-19 risk and family communication scores were determined by asking participants to give a score between 1 (no risk) and 10 (high risk).

Edinburgh Postpartum Depression Scale (EPDS): EPDS can be used for screening both pregnant and postpartum women (22). EPDS is a 10-question scale with four options used for evaluating how mothers felt in the last week. The total score is obtained by giving points of 0,1,2,3 to each question. There are direct and reverse coded statements on the scale. The EPDS Turkish validation study was conducted by Engindeniz et al., and EPDS has a sensitivity of 84% and a specificity of 88% in the Turkish population (23). Cronbach alpha coefficient was reported as 0.79 by Engindeniz et al. (23). In the present study, the EPDS Cronbach alpha-coefficient was calculated as 0.88. The cut-off value was accepted as 13 for depressive symptoms in the present study.

State-Trait Anxiety Scale (STAI): STAI is a four-option Likert-type scale that separately measures state and trait anxiety levels with 20 questions. The total score for both scales varies between 20-80. A high score indicates high anxiety. There are direct and reverse statements. A predetermined constant value is added to the difference between the total scores of the direct and reverse statements. This constant value is 50 for State Anxiety Inventory and 35 for the Trait Anxiety Inventory. The last value obtained is the individual's anxiety score (24,25). Reliability coefficients determined by the alpha correlations of the STAI; 0.83 to 0.87 for the STAI-Trait subscale, 0.94 and 0.96 for the STAI-State (25). In the present study, the Cronbach alpha-coefficient was calculated as 0.93 for the STAI-State subscale and 0.87 for the STAI-Trait subscale presenting very high reliability.

Data Analysis

Frequency, percentage, median, minimum and maximum values for descriptive statistics; Chi-Square Test and Fisher's Exact Test for categorical variable analysis; Mann Whitney U Test and Kruskal Wallis test for continuous variable analysis; Binary Logistic Regression for multivariate analysis were used. STAI-State and STAI-Trait scores were transformed into categorical variables with the "median split" method, and multivariate analysis was applied.

Ethical Approval

Before data collection, permission from the ethics committee (Decision number: 2020 / 05-15) and institutional approval from Provincial Health Directorate were obtained.

Results

Sociodemographic Features

Two hundred thirty-four pregnant women were included in the present study, and the median age is 26 (17-42). Eleven (4.7%) of the participants are healthcare workers. 23.1% of the participants are in the first trimester, 41.0% are in the second, and 35.9% are in the third trimester. 81 (34.6%) of the participants have their first pregnancies. A previous pregnancy loss exists among 28.2% of the participants.

The rate of having pregnancy controls in a PCOC is 24.8%, in a private hospital/clinic is 32.5%, and in a state hospital/university hospital/training and research hospital is 42.7%. Only one participant stated a family member developed COVID-19 infection living at the same home. Of the participants, 75.2% regularly follow the statistical data about the COVID-19 Pandemic, and 80.3% learn about COVID-19 infection from healthcare workers/Ministry of Health. Some sociodemographic, obstetric, and COVID-19 characteristics of the participants are shown in Table 1 and Table 2.

Depression risk and Related Factors

The frequency of prenatal depression risk in the present study is 24.4%, as the cut-off point is 13, and 29.9% as the cut-off point is 12. The depression risk was lower in those with private health insurance (20%) than those without (33.8%) ($p=0.022$). According to working status, the highest depression risk was found among the pregnant women on maternity leave (71.4%) and the lowest in the pregnant women working flexible hours (20.0%) ($p=0.036$). The rate of depression risk is higher in the pregnant women (35.7%) who/whose spouses lost their work compared to who/whose spouses did not (16.2%) ($p=0.001$).

The factors affecting prenatal depression risk as the results of univariate analysis are shown in Table 3.

Age, income level, educational status, being a healthcare worker, family type, home type, physical exercise, gestational week, parity, previous pregnancy loss, plan of the present pregnancy, and family communication score were not associated with prenatal depression risk ($p > 0.05$). According to the result of multivariate analysis, those who/whose spouse lost their work ($OR=2.68$), having multiple pregnancies ($OR=15.31$), giving a high self-score about COVID-19 risk ($OR=1.14$), and having higher state anxiety scores ($OR=1.10$) were found to be more depressive ($p > 0.05$) (Table 4).

Trait Anxiety and Related Factors

The median score of STAI-Trait is 41 (23-74). The frequency of trait anxiety is 67.9%, as the cut-off point is 40. Married participants, those who/whose spouses lost their works during the COVID-19 Pandemic, occasional smokers, those having health problems during the present pregnancy, those who have not yet planned about the birth process, those having multiple pregnancies, those thinking she/family members living with her/ friends and relatives had a high COVID-19 risk, those who did not know who was at risk in the society were found to have higher STAI-Trait anxiety score ($p < 0.05$) (Table 5).

Additionally, trait anxiety score was found to have low positive correlation with income level ($r = 0.138$) and with the self-score for COVID-19 risk ($r = 0.200$); low negative correlation with daily sleep time ($r = -0.144$) and family communication score ($r = -0.264$); moderate positive correlation with the STAI-State anxiety score ($r = 0.693$) ($p < 0.05$).

State Anxiety and Related Factors

The median score of STAI-State anxiety of participants is 34 (20-80). The frequency of state anxiety is 32.1%, as the cut-off point is 40. Married participants, healthcare workers, occasional smokers, those not exercising regularly, those having planned pregnancy, those having health problems during the present pregnancy, those having a plan about the birth process, those having multiple pregnancies, those thinking she/family members living with her had high COVID-19 risk were found to have higher STAI-State anxiety score ($p < 0.05$) (Table 5). Additionally, state anxiety score was found to have low positive correlation with income level ($r = 0.173$) and the self-score about COVID-19 risk ($r = 0.196$); low negative correlation with the last child age ($r = -0.170$); moderate negative correlation with family communication score ($r = -0.348$); moderate positive

correlation with the STAI-Trait anxiety score ($r = 0.693$) ($p < 0.05$). According to multivariate analysis, those who/whose spouses lost their works (OR = 2.32), occasional smokers (OR = 26.11), those thinking themselves had high-risk COVID-19 (OR = 7.88), and those having depression risk (OR = 12.98) have higher trait anxiety; healthcare workers (OR = 11.66), occasional smokers (OR = 17.21), those having health problems during the present pregnancy (OR = 3.74), those thinking family members living with themselves had high COVID-19 risk (OR = 2.48) and those having depression risk (OR = 4.73), have higher state anxiety (Table 6).

Table 1. Sociodemographic Characteristics of Participants (n=234)

Education level, (%)*	Secondary school or lower	117 (50.0)
	High school or higher	117 (50.0)
Marital Status, (%)*	Single	4 (1.7)
	Married	230 (98.3)
Having private health insurance, (%)*	Yes	160 (68.4)
	No	74 (31.6)
Working status, (%)*	Not working	188 (80.3)
	Yes/Full time	17 (7.3)
	Yes/Flexible hours	10 (4.3)
	Administrative leave/Maternity leave	19 (8.1)
Having extended family, (%)*	Yes	37 (15.8)
	No	197 (84.2)
Having a house with garden, (%)*	Yes	95 (40.6)
	No	39 (59.4)
Having chronic disease, (%)*	Yes	16 (6.8)
	No	218 (93.2)
Smoking, (%)*	Yes/Everyday smoker	9 (3.8)
	No/Ex smoker	21 (9.0)
	Never smoked	190 (81.2)
	Yes/Occasional smoker	14 (6.0)
Physical exercise, (%)*	Never exercise	122 (52.1)
	Occasional exercise	81 (34.6)
	Regular exercise	31 (13.2)
Age, years, median (min-max)		26 (17-42)
Monthly income level (TL), median (min-max)		2500 (250-15000)
Daily sleep hours, median (min-max)		8(1-15)
*Indicates column percentages		

Table 2. Obstetric and COVID-19 Characteristics of Participants (n=234)

Multiple pregnancies, (%)*	Yes	7 (3.0)
	No	227 (97.0)
Having health problems during the present pregnancy, (%)*	Yes	28 (12.0)
	No	206 (88.0)
Having a plan for the birth process, (%)*	Yes	167 (71.4)
	No	67 (28.6)
Thinking she had a high COVID-19 risk, (%)*	Yes	100 (42.9)
	No	134 (57.1)
Thinking the people living with her had a high COVID-19 risk, (%)*	Yes	51 (21.9)
	No	183 (78.1)
Thinking her relatives and friends had high COVID-19 risk, (%)*	Yes	33 (14.2)
	No	201 (85.8)
Not knowing who had high COVID-19 risk in the community, (%)*	Yes	142 (60.9)
	No	92 (39.1)
Self-score about COVID-19 risk, median (min-max)		4 (1-10)
Family communication score, median (min-max)		10 (1-10)

*Indicates column percentages

Table 3. Factors Affecting Prenatal Depression during COVID-19 Pandemic (n=234)

		Non-depressive, (%) *	Depressive, (%) *	P
Private health insurance	Yes	128 (80.0)	32 (20.0)	0.022**
	No	49 (66.2)	25 (33.8)	
Working status	Not working	147 (78.2)	41 (21.8)	0.036**
	Yes/Full time	11 (64.7)	6 (35.3)	
	Yes/Flexible hours	8 (80.0)	2 (20.0)	
	Administrative leave	9 (75.0)	3 (25.0)	
	Maternity leave	2 (28.6)	5 (71.4)	
Work loss of herself or her spouse	Yes	63 (64.3)	35 (35.7)	0.001**
	No	114 (83.8)	22 (16.2)	
Smoking	Yes/Everyday smoker	7 (77.8)	2 (22.2)	0.002**
	No/Ex smoker	19 (90.5)	2 (9.5)	
	Never smoked	146 (76.8)	44 (23.2)	
	Yes/Occasional smoker	5 (35.7)	9 (64.3)	
Daily sleep hours median (min-max)		8 (2-15)	8 (1-13)	0.052 [§]

* Indicates row percentages, ** Chi-Square Test, [§] Mann Whitney U Test, [¥]Fisher's Exact Test

Table 3. Factors Affecting Prenatal Depression during COVID-19 Pandemic (continued)

		Non-depressive, (%) *	Depressive, (%) *	P
Trimester	1 st Trimester	39 (72.2)	15 (27.8)	0.753**
	2 st Trimester	74 (77.1)	22 (22.9)	
	3 st Trimester	64 (76.2)	20 (23.8)	
First pregnancy	Yes	67 (82.7)	14 (17.3)	0.067**
	No	110 (71.9)	43 (28.1)	
Planned pregnancy	Yes	139 (78.1)	39 (21.9)	0.120**
	No	38 (67.9)	18 (32.1)	
Pregnancy type	Singleton	176 (77.5)	51 (22.5)	0.001 [¥]
	Multiple	1 (14.3)	6 (85.7)	
Having health problem during the present pregnancy	Yes	16 (57.1)	12 (42.9)	0.015**
	No	161 (78.2)	45 (21.8)	
Having a plan about the birth process	Yes	131 (78.4)	36 (21.6)	0.115**
	No	46 (68.7)	21 (31.3)	
Thinking themselves had high COVID-19 risk	Yes	69 (69.0)	31 (31.0)	0.044**
	No	107 (80.5)	26 (19.5)	
Self-score about COVID-19 risk median (min-max)		3 (1-10)	6 (1-10)	0.012 [§]
STAI trait anxiety score median (min-max)		38 (23-61)	48 (37-74)	<0.001 [§]
STAI state anxiety score median (min-max)		31 (20-55)	43 (20-80)	<0.001 [§]

* Indicates row percentages, ** Chi-Square Test, [§] Mann Whitney U Test, [¥]Fisher's Exact Test

Table 4. Multivariate Analysis of Factors Associated with Prenatal Depression during COVID-19 Pandemic (n=234)

	OR (95% CI)	P*
Work loss of herself or her spouse	2.68 (1.30-5.51)	0.007
Having multiple pregnancy	15.31 (1.44-162.03)	0.023
Self-score about COVID-19 risk	1.14 (1.01-1.28)	0.029
STAI-State anxiety score	1.10 (1.06-1.14)	<0.001

* Binary logistic regression (age, private health insurance, thinking she had a high COVID-19 risk, working status, loss of work for herself or her spouse, smoking, daily sleep time, having health problem in the present pregnancy, pregnancy type, STAI-state score, self-score about COVID-19 risk were entered into the model)

Table 5. Factors Affecting Prenatal Anxiety during COVID-19 Pandemic (n=234)

		STAI Trait anxiety score median (min-max)	P	STAI State anxiety score median (min-max)	P
Marital status	Single	27 (27-33)	0.003*	21 (21-29)	0.008*
	Married	41 (23-74)		34 (20-80)	
Healthcare worker	Yes	45 (35-62)	0.106*	44 (29-80)	0.004*
	No	41 (23-74)		33 (20-71)	
Working status	Not working	41 (23-74)	0.234**	33 (20-71)	0.126**
	Yes/Full time	39 (35-62)		35 (22-80)	
	Yes/Flexible hours	39 (31-57)		34 (21-53)	
	Administrative leave	41 (32-54)		40 (22-51)	
	Maternity leave	50 (29-73)		45 (29-63)	
Work loss of herself or her spouse	Yes	45 (23-74)	0.007*	37 (20-80)	0.128*
	No	39 (25-70)		32 (20-55)	
Smoking	Yes/Every day smoker	36 (27-70)	<0.001**	22 (21-54)	0.008**
	No/Ex smoker	38 (28-49)		35 (20-51)	
	Never smoked	41 (23-74)		33 (20-80)	
	Yes/Occasional smoker	49 (39-57)		40 (27-69)	
Physical exercise	Never exercise	43 (26-74)	0.049**	35 (20-80)	0.027**
	Occasional exercise	40 (23-70)		34 (20-54)	
	Regular exercise	38 (27-52)		30 (20-64)	

*Mann Whitney U Test, **Kruskal Wallis Test

Table 5. Factors Affecting Prenatal Anxiety during COVID-19 Pandemic (continued)

		STAI Trait anxiety score median (min-max)	P	STAI State anxiety score median (min-max)	P
Planned pregnancy	Yes	40 (23-74)	0.062*	33 (20-80)	0.017*
	No	43 (29-61)		37 (20-69)	
Having health problem during the present pregnancy	Yes	47 (26-70)	0.020*	41 (20-80)	0.002*
	No	40 (23-74)		32 (20-71)	
Having a plan about the birth process	Yes	40 (23-74)	0.021*	32 (20-71)	0.012*
	No	43 (25-73)		37 (20-80)	
Pregnancy type	Singleton	40 (23-74)	0.005*	33 (20-80)	0.002*
	Multiple	51 (42-57)		49 (35-49)	
Thinking themselves had high COVID-19 risk	Yes	44 (23-70)	<0.001*	38 (20-80)	0.003*
	No	39 (25-74)		32 (20-71)	
Thinking the people living	Yes	48 (29-73)	<0.001*	40 (20-80)	<0.001*

Table 5. Factors Affecting Prenatal Anxiety during COVID-19 Pandemic (n=234)

		STAI Trait anxiety score median (min-max)	P	STAI State anxiety score median (min-max)	P
Marital status	Single	27 (27-33)	0.003*	21 (21-29)	0.008*
	Married	41 (23-74)		34 (20-80)	
Healthcare worker	Yes	45 (35-62)	0.106*	44 (29-80)	0.004*
	No	41 (23-74)		33 (20-71)	
Working status	Not working	41 (23-74)	0.234**	33 (20-71)	0.126**
	Yes/Full time	39 (35-62)		35 (22-80)	
	Yes/Flexible hours	39 (31-57)		34 (21-53)	
	Administrative leave	41 (32-54)		40 (22-51)	
	Maternity leave	50 (29-73)		45 (29-63)	
Work loss of herself or her spouse	Yes	45 (23-74)	0.007*	37 (20-80)	0.128*
	No	39 (25-70)		32 (20-55)	
Smoking	Yes/Every day smoker	36 (27-70)	<0.001**	22 (21-54)	0.008**
	No/Ex smoker	38 (28-49)		35 (20-51)	
	Never smoked	41 (23-74)		33 (20-80)	
	Yes/Occasional smoker	49 (39-57)		40 (27-69)	
Physical exercise	Never exercise	43 (26-74)	0.049**	35 (20-80)	0.027**
	Occasional exercise	40 (23-70)		34 (20-54)	
	Regular exercise	38 (27-52)		30 (20-64)	
with her had high COVID-19 risk	No	39 (23-74)		32 (20-71)	
Thinking her relatives and friends had high COVID-19 risk	Yes	47 (29-62)	0.041*	39 (20-80)	0.117*
	No	40 (23-74)		34 (20-71)	
Not knowing who had high COVID-19 risk in the community	Yes	40 (25-74)	0.006*	33 (20-80)	0.087*
	No	43 (23-73)		37 (20-69)	
Depression (EPDS \geq 13)	Non-depressive	38 (23-61)	<0.001*	31 (20-55)	<0.001*
	depressive	48 (37-74)		43 (20-80)	

*Mann Whitney U Test, **Kruskal Wallis Test

Table 6. Multivariate Analysis of Factors Associated with Trait and State Anxiety during COVID- 19 Pandemic (n=234)

	STAI Trait Anxiety		STAI State Anxiety	
	OR (95% CI)	P *	OR (95% CI)	P **
Being healthcare worker	-	-	11.66 (1.25-108.65)	0.031
Work loss of herself or her spouse	2.32 (1.18-4.55)	0.015	-	-
Being occasional smoker (compared to everyday smoker)	26.11 (1.54-440.54)	0.024	17.21 (1.47-258.35)	0.039
Having health problem during the present pregnancy	-	-	3.74 (1.26-11.12)	0.017
Thinking the people living with her had high COVID-19 risk	7.88 (3.40-18.29)	<0.001	2.48 (1.18-5.21)	0.016
Being depressive (EPDS \geq 13)	12.98 (4.81-35.00)	<0.001	4.73 (2.16-10.34)	<0.001

* Binary logistic regression (age, marital status, work loss of herself or her spouse, thinking she had a high COVID-19 risk, smoking, having a health problem during the present pregnancy, pregnancy type, physical exercise, being depressed (EPDS \geq 13) were entered into the model.) ** Binary logistic regression (age, marital status, risk, smoking, having health problems during the present pregnancy, pregnancy type, being a healthcare worker, physical exercise, planned pregnancy, thinking she had a high COVID-19 risk, being depressed (EPDS \geq 13) were entered into the model.)

DISCUSSION

In this population-based study, the frequency of prenatal depression risk is 24.4%. Prenatal depression prevalence during the COVID-19 Pandemic, which was about 16% before the COVID-19 Pandemic, (14) has been found as over 30% all over the world.(15) In a study from Turkey, prenatal depression frequency was 35.4% (19). In the present study, since the participation rate of pregnant women with depressive symptoms may be low, the frequency of depression risk may be found as lower than exists, but the increase in the prenatal depression risk compared to the pre-pandemic period is obvious. In the present study, the median score for trait anxiety is 41 (23-74), and for the state anxiety is 34 (20-80). In the study of Yassa et al., the STAI trait and state anxiety mean scores were 43.16 and 41.96, respectively (26). In the present study, the state anxiety score was lower than the trait anxiety score. This result may be due to maternity leave for pregnant women with 24th gestational week in Turkey decreasing the social contact and anxiety of being infected. In addition, since the study was conducted in Nigde, a small Anatolian city, the state anxiety score might be found relatively low.

In the present study, the frequency of state anxiety is 32.1%, as the cut-off point is 40. In a meta-analysis study including 23 studies, the frequency of anxiety was 37% (16). Although using different screening scales shows different rates. It is obvious that the Pandemic causes an increase in prenatal anxiety. Since a comprehensive review in 2017, the frequency of prenatal anxiety was found to be 15.2% (27).

Working status is another factor increasing prenatal depression and anxiety during the COVID-19 Pandemic. While actively working can be protective, creating a social environment can increase anxiety by increasing viral exposure. In the study of Durankus, depression level among actively working women was significantly higher than non-working women (19). Diversely, there are studies in which actively working was shown to be protective against prenatal depressive symptoms (21,28,29). In the present study, in accordance with the literature, the highest rate of depression risk is among the women on maternity leave, and the lowest depression risk rate was among the women working flexible hours. In this context, it can be concluded that working flexible provides some protection creating a social environment.

Being a healthcare worker can protect psychological problems due to better health-related knowledge and practices and increase the anxiety of being infected due to increased risk of viral exposure. According to the literature, being a healthcare worker does not affect depression and anxiety scores (28,30). However, in the present study, the state anxiety is 11.66 times higher in healthcare workers than those who are not healthcare workers, while there was no significant relation in terms of depression risk. A higher rate of full-time work during the Pandemic and increased risk of viral exposure among healthcare workers may have increased the anxiety. Additionally, evaluating the risk of COVID-19

exposure in the department where the healthcare worker has been working would explain the difference with the literature.

The Pandemic has had a considerable impact on the economy, with many people being laid off or closing their shops during strict restrictions. 18.3% of the participants in the study of Lebel et al. (31) and 63.7% of the participants in the study of Moyer et al. (30) were found to be lost their work. While there was no relationship between work loss and depression or anxiety in Lebel's study (31), work loss was associated with increased anxiety in the study of Moyer et al. (30). In the present study, 41.9% of the participants have had a work loss themselves/their spouses during the COVID-19 Pandemic. It has been shown that this work loss increased the risk of depression risk 2.68 times and the risk of anxiety 2.32 times.

Smoking, which is one of the high-risk health behaviors, can either be a cause of the stress by the Pandemic or be evaluated as a result. In the study conducted by Dagkalis et al., smoking was found to be increased prenatal stress 3.81 times (32). In the study of Sut et al., anxiety and depression scores were higher in smokers during pregnancy than non-smokers (21). In the present study, the most high-risk group in terms of depression risk and anxiety was occasional smokers. Occasional smoking was shown to alleviate anxiety symptoms (33). Therefore, this group may be smoking to suppress their anxiety symptoms. Ex-smokers were found to have the least prenatal depression risk. This result may be because the women who could quit smoking had a stronger will and coped better with stress during the Pandemic. Nevertheless, the results should be interpreted by considering possible confounding and shared risk factors in terms of causality. During pandemics, avoiding high-risk behaviors as well as improving protective behaviors is a part of stress management.

Physical activity is associated with decreased depression and anxiety during pregnancy (21,31,34). In the present study, one out of every two participants stated that they did not exercise at all. The lowest trait and state anxiety scores were found in those exercising regularly. Physical inactivity has become a significant problem in the general population with home confinement during the COVID-19 Pandemic. This condition may be the target of intervention programs as it is a modifiable risk factor for prenatal psychiatric diseases.

Parity is one of the obstetric determinants of prenatal anxiety. A higher anxiety rate among the women with their first pregnancy was demonstrated through a pre-pandemic study (35). There are different findings during the COVID-19 Pandemic. In the study of Chaves et al., the depression score was the lowest among the women with their first pregnancy (28). In a study from Iranian, it was shown that women with their first pregnancy had two times less anxiety compared to those with third or more pregnancies (36). In the study of Durankus, the highest depression rate was among the women with their first pregnancy (19). In the present study, the depression risk rate was lower in the women with their first pregnancy, but this difference was not significant. The child number did not affect anxiety scores.

Health problems during pregnancy are another factor affecting prenatal psychology, with the anxiety about the present health problem and the anxiety of being infected as a result of increased hospital admissions. In the study of Wu et al., pregnant women with placenta previa were 1.6 times more depressed (29). In the present study, both the rate of depression risk and anxiety scores were higher in the women having health problems during the present pregnancy. Multiple pregnancies, which is described as a high-risk pregnancy, were also evaluated in the present study. It was shown to increase the depression risk rate 15.31 times and increase the anxiety scores. The fact that routine hospital visits, which should be at shorter intervals in high-risk pregnancies, are less due to the viral exposure risk increases prenatal anxiety. Another issue is planning the birth process. In the study of Moyer et al., the number of women planning to give birth in a hospital decreased significantly in the Pandemic compared to the pre-pandemic period. However, the rate of planning to give birth at home and not knowing where to give birth increased (30). In the present study, one out of every three participants has not made a plan about where and how the delivery will occur, which significantly increases the anxiety scores.

A major determinant of prenatal psychology during the COVID-19 Pandemic is the fear of being infected and lack of knowledge about the disease prognosis and how their babies would be affected by the infection. During the pandemics, the health concerns related to the infections were shown to increase prenatal depression and anxiety (19,31,37,38). In the

present study, the rate of prenatal depression risk and anxiety scores are higher in those thinking themselves had high COVID-19 risk.

Study Limitations and Strengths

The present study has some limitations and strengths. The cross-sectional design of the present study does not allow us to compare the pre-pandemic and Pandemic periods. In addition, it is difficult to evaluate the causality between prenatal psychological problems and some risk factors since the bidirectional relationship. Prenatal depression and anxiety were not evaluated with a clinical interview. In the present study, reaching the minimum sample size is 67%. Therefore, the characteristics of the pregnant women who did not participate in the study are important. Lastly, the relatively low sample size may have prevented the finding of some significant relationships. Few studies are evaluating psychological effects in pregnant women during the COVID-19 Pandemic. The present study will make an essential contribution to the literature.

CONCLUSION

In the present study, it was shown that the COVID-19 Pandemic increased prenatal depression risk and anxiety. Smoking, physical inactivity, not working actively, being a healthcare worker, work loss, multiple pregnancies, health problems during the present pregnancy, unplanned pregnancy, not having a plan for the birth process, and high-risk perceptions about COVID-19 were found to increase prenatal depression risk or anxiety. Pregnant women should be informed about COVID-19 infection and preventive measures, especially in primary health care centers, and they should be encouraged to continue their routine controls by family physicians, midwives, and nurses working at PCOCs. Primary health care workers are often more aware of the family structure, existing chronic diseases, and psychosocial problems of pregnant women than the health care providers in secondary and tertiary healthcare institutions. Therefore, it is more convenient and applicable to support pregnant women in primary health care institutions. Furthermore, methods of coping with stress should be taught by psychosocial counseling. It should be built on an active pregnancy by providing a suitable outdoor environment for physical exercise. Pregnant healthcare workers should be employed in departments with the least risk of COVID-19 infection.

Ethical Approval: *The Ethics Committee of Nigde University (Decision number: 2020 / 05-15) approved the study.*

Author Contributions: *Concept: N.Y., N.T. Literature Review: N.Y., N.T Design : N.Y.Data acquisition: N.Y., N.T.*

Analysis and interpretation: N.Y. Writing manuscript: N.Y., N.T. Critical revision of manuscript: N.Y., N.T.

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Original Article

Perioperative And Postoperative Comparison of Groups with Uterine Artery and Ovarian Artery Ligation and Groups without Artery Ligation in Laparoscopic Myomectomy

Laparoskopik Myomektomide Uterin Arter Ve Overyan Arter Ligasyonu Yapılanlarla Arter Ligasyonu Yapılmayan Grupların Perioperatif ve Postoperatif Karşılaştırılması

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Abstract

Background: In this prospective study, we aimed to compare the intraoperative complication rates, operation time, preoperative-postoperative AMH and hemoglobin values, and the length of hospital stay for the patients undergoing elective laparoscopic myomectomy made or not made with uterine artery and ovarian artery ligation. **Methods:** In this prospective clinical study, 32 patients undergoing elective laparoscopic myomectomy were divided in two groups as ligated and non-ligated. Primer outcome was determined according to different preoperative-postoperative haemoglobin to determine blood loss in patients. Secunder outcomes were determined as intraoperative complication rates, operation time, preoperative-postoperative AMH and the length of hospital stay. **Results:** Similar demographic characteristics were found for both groups (ligated and non-ligated). Additionally, myoma localization, age (39±5 vs 41.2±3.8), preop haemoglobin (12.7±0.9 vs 12.6 ±1.3), preop and postop AMH (1.9 ±2.2 and 2 ±2.1 vs 1.1 ±1.7 and 1.1 ±1.3) and operation time (69 ±17 vs 75.3 ± 19) were similar, while postoperative haemoglobin values (10.4±1.1 vs 11.4±1.3) were significantly higher for ligated group than non-ligated when compared. **Conclusions:** It was observed that the loss of perioperative and postoperative hemoglobin value is decreased by ligation of uterine and ovarian arteries during and after the laparoscopic myomectomy without causing any important change of the operation time and AMH values.

Key words: Laparoscopy, myomectomy, artery ligation

Öz

Amaç: Bu prospektif çalışmada, elektif laparoskopik myomektomi yapılanlarda uterin arter ve overyan arter ligasyonu yapılan ve yapılmayan hastaların intraoperatif komplikasyon oranları, operasyon süresi, preoperatif-postoperatif AMH ve hemoglobin değerleri ile hastanede kalış sürelerini karşılaştırmayı amaçladık. **Gereç ve Yöntem:** Bu prospektif klinik çalışmada elektif laparoskopik myomektomi yapılan 32 hasta uterin ve overyan arter ligasyonu yapılan ve yapılmayan olarak iki gruba ayrıldı. Primer sonuç, hastalarda kan kaybını belirlemek için preoperatif-postoperatif hemoglobine göre belirlendi. İkincil sonuçlar ise intraoperatif komplikasyon oranları, operasyon süresi, preoperatif-postoperatif AMH ve hastanede kalış süresi olarak belirlendi. **Bulgular:** Her iki grup için (ligasyon yapılan ve yapılmayan) benzer demografik özellikler bulundu. Ayrıca myom lokalizasyonu, yaş (39±5 vs 41,2±3.8), preop hemoglobin (12.7±0.9 vs 12.6 ±1.3), preop ve postop AMH (1.9 ±2.2 ve 2 ±2.1 vs 1.1 ±1.7 ve 1.1 ±1.3) ve operasyon süresi (69 ±17 vs 75.3 ± 19) benzer iken, postoperatif hemoglobin değerleri (10.4±1) (11.4±1.3) karşılaştırıldığında, bağlı grup için bağlanmayan gruba göre anlamlı olarak daha yüksekti.

Sonuç: Laparoskopik myomektomi sırasında ve sonrasında uterin ve over arterlerinin ligasyonu ile operasyon süresi ve AMH değerlerinde önemli bir değişikliğe neden olmadan perioperatif ve postoperatif hemoglobin değer kaybının azaldığı gözlemlendi.

Anahtar kelimeler: Laparoskopik, myomektomi, arter ligasyonu

Introduction

Uterine leiomyomas are the most common pelvic tumor in women (1,2). The reported incidence in reproductive women is 20-25% (3). The rate of diagnosis of these tumors increases with advancing age in the reproductive years (4,5). Rate appears to decrease in postmenopausal women (5). Leiomyoma is the cause of one-third of patients admitted to the gynecology clinic (6). On the other hand, histopathological examination of the uterus revealed that the prevalence of leiomyoma rose above 70% (7). This finding indicates that many women with leiomyomas are asymptomatic. Leiomyomas are clinically important pathologies because they are the most common cause of abnormal uterine bleeding and hysterectomies (8). Leiomyomas can be detected during routine pelvic examinations. Camer and Patel they give the rate of leiomyoma as 74% in premenopausal women and 84% in postmenopausal women in serial sections. Only 20-50% of cases have symptoms directly attributed to leiomyomas (3,9,10). The incidence and severity of symptoms are directly proportional to the size, number and localization of the leiomyoma.

Leiomyoma often causes symptoms of abnormal uterine bleeding, reproductive dysfunction, infertility, spontaneous abortion, pain and compression. Transvaginal USG is the first step in most cases with suspected leiomyoma. It is an adequate diagnostic method. However, USG can be found in some highly enlarged uteruses. may be insufficient, however, with MRI (magnetic resonance imaging) uterus and leiomyoma volume can be measured with full accuracy, as well as ovarian anatomy and It is also possible to distinguish leiomyomas from adenomyosis with full accuracy. Asymptomatic leiomyomas can be followed, when they are symptomatic, the treatment method is determined by looking at the patient's age, fertility status, desire to protect the uterus, the size of the myoma, the location of the myoma, the severity of the patient's symptoms, and whether he has been treated before. (8,17). Most of the leiomyomas are asymptomatic and grow slowly. Small and medium-sized and asymptomatic leiomyomas can be followed by pelvic examination and TV-USG performed every 6-12 months. Surgery is the main step in the treatment of leiomyoma. Hysterectomy while it is a definitive procedure, different techniques such as myomectomy, endometrial ablation, uterine artery embolization (UAE), magnetic resonance focused ultrasonography (MRgFUS) and myolysis are alternative methods. Abnormal uterine bleeding, compression symptoms, if there is infertility, recurrent pregnancy loss, surgical treatment is applied. The most common form of treatment for symptomatic leiomyoma worldwide is hysterectomy (18,19). Myomectomy can be performed in cases of fertility desire, desire to protect the uterus, leiomyoma secondary infertility, recurrent pregnancy loss, pedicled subserous or submucous leiomyoma, submucous leiomyoma with menorrhagia, rapidly growing leiomyoma. In myomectomies, the incidence of febrile morbidity decreases following surgery (19,20). One of the biggest risks in myomectomies is blood loss. By placing a tourniquet on the uterine arteries or using local vasopressin, blood loss can be minimized and therefore less blood transfusion is required (19,21). The risk of blood transfusion during or immediately following myomectomy has been calculated as approximately 15% (8). However, intraoperative blood loss was found in both hysterectomy and myomectomy groups; It should not be overlooked that it correlates with the size of the uterus, the duration of the surgery, and the number of leiomyomas removed in the myomectomy group (21). Following myomectomy, symptoms including menorrhagia and pelvic pressure were found to regress at a rate of 81%. The disadvantage of this procedure is a greater risk of developing leiomyomas from new clones of abnormal myocytes. Until recently, the traditional approach to myomectomies was laparotomy. However, today this situation tends to change in favor of laparoscopic intervention. The first laparoscopic myomectomy was reported in 1979 by Semm K (22). The biggest obstacle in laparoscopic myomectomies is the difficulty of suturing the uterus. In addition, it should not be forgotten that the long operation time increases the risk of pulmonary and thromboembolic complications.

Among the difficulties of laparoscopic myomectomy; bleeding, difficulty in closing the defect, difficulty in intraoperative technique, and difficulty in removing the fibroid from the abdomen. Advantages of laparoscopic myomectomy; less blood loss, less hospital stay, less adhesion, cosmetic scar advantage, less postoperative

morbidity, less operative trauma. After the 1980s, laparoscopy quickly gained a place in surgical practice due to its advantages over conventional open surgery in terms of less postoperative pain, better cosmetic results, and a shorter and uncomplicated recovery. There is a significant suppression of the immune system in the postoperative period in proportion to the size of the surgical procedure (24). Since less tissue dissection is performed during laparoscopic surgery, the neuroendocrine and metabolic responses of the organism to stress and immune suppression in the postoperative period remain at a lower level (25). As a result, the severity of the response to stress and the decrease in the need for analgesics allow for a quicker and uncomplicated recovery and thus an earlier return to daily life.

Anti-Müllerian Hormone (AMH): AMH is produced in Sertoli cells in the testis in men and granulosa cells in the ovary in women (26). Serum AMH levels in women are lower than in men. When the menstrual cycle starts after puberty, the circulating AMH level gradually decreases and cannot be detected at menopause (27). Basic studies have shown that AMH is effective in follicular hormone production. Studies in animals have shown that AMH increases aromatase activity and decreases the number of LH receptors stimulated by FSH in granulosa cells. It reduces testosterone production in theca cells. AMH indicates a primordial follicle pool and has been shown to be released from preantral and early antral follicles by <8 mm during follicular growth. Has a regulatory effect on ovarian activity

Materials and Methods

This study was conducted with the approval of the ethics committee of Şişli Hamidiye Training and Research Hospital, on 30/06/2015, with issue number 456.

This study is an invasive, randomized, controlled prospective study involving 32 patients who underwent laparoscopic myomectomy at Şişli Hamidiye Etfal Training and Research Hospital, Gynecology and Obstetrics Clinic between 23.03.2014 and 20.07.2016. A total of 32 female patients, 16 of whom were clipped uterine and ovarian arteries, and 16 of whom were not clipped, were included in the study. Patients aged between 16 and 45 years, with subserous or intramural uterine subserous or intramural less than 10 cm, uterine bleeding and/or pelvic pain and/or infertility symptoms were included in the study.

In our study, in patients who underwent laparoscopic myomectomy, ovarian and uterine arteries were clipped and not clipped; Preoperative and postoperative hemoglobin values, preoperative and postoperative Anti-Müllerian Hormone values, hospital stay of the patients in the groups, perioperative postoperative complications and operation times were compared.

For uterine artery ligation, the uterine artery was dissected by opening the peritoneum by approximately 2 cm with the help of bipolar scissors and clipped over the ureter from the point where the angle between the external iliac artery and the internal iliac artery coincided with the umbilical artery, and clipped with the number 5 clip. In the ovarian artery ligation, after the ovary was lifted towards the anterior abdominal wall with the help of an atraumatic grasper, the ureteral reflex was observed and clipped with the number 5 clip over the infundibulopelvic ligament.

After the myomectomy procedure and suturing, the clips were removed from where they were.

Criteria for exclusion from the laparoscopic myomectomy study

- Over 45 years old or under 16 years old
- Having fibroids larger than 10 cm
- With multiple myomas in the uterus
- with submycose myoma
- Refusal to work

A detailed anamnesis was obtained from all patients included in the study. General gynecological examination and gynecological ultrasonography were performed. Smears were taken from those who did not have a smear test in the last 1 year. In addition, informed consent was obtained from each patient.

Complete blood count was requested on the 1st day preoperatively and postoperatively from all patients included in the study.

All of the patients included in the study were called preoperatively and after the 20th postoperative day. Anti Müllerian Hormone was requested.

The data were collected and statistical analyzes were made using the SPSS 18.0 for windows software program from the computer environment. While evaluating the study data, descriptive statistical methods (mean, median, standard deviation) as well as the Mann-Whitney U test were used to compare quantitative data. It was accepted when there was statistical significance ($p < 0.05$).

Results

In our study, the results of the preoperative, perioperative and postoperative results in women aged 16-45 years who came to our clinic with treatment-resistant menometrorrhagia and/or pelvic pain and/or infertility complaints between 2014 and 2016 were evaluated in patients who underwent uterine artery and ovarian artery ligation in laparoscopic myomectomy and those who did not. comparison has been made.

As shown in Table 1, when the location of myoma in the uterus was examined in the preoperative examinations of the patients, 8 patients (50%) with myoma in the anterior uterus, 4 patients (25%) with the uterus in the fundus, and 4 patients (25%) with the uterus posterior. In the case group, 6 patients (37.5%) with myoma in the anterior uterus, 5 patients (31.2%) with the uterus in the fundus, and 5 patients (31.2%) with the uterus posterior. In the comparison, there was no significant difference between the groups in terms of localization of myoma, since the p value was above 0.05.

Among the groups; Age, preop hgb, postop hgb, preop AMH, postop AMH, myoma size and parity were compared. Group numbers, means, standard deviations and p values of the compared parameters are shown in Table 2. In the age distribution between those who underwent uterine and ovarian artery ligation and those who did not have arterial ligation, the age of the ligated group was 41.2 ± 3.8 years, while the age of the non-ligamented group was 39 ± 5 years, and there was a significant difference between the ages, since the p value was greater than 0.05. not detected.

In terms of preoperative hemoglobin results between those who underwent uterine and ovarian artery ligation and those who did not have arterial ligation, the preoperative hemoglobin value of the ligated group was 12.6 ± 1.3 , while the preoperative hemoglobin value of the group without ligation was 12.7 ± 0.9 . There was no significant difference between the hemoglobin results as $p > 0.05$.

In terms of postoperative hemoglobin results between those who underwent uterine and ovarian artery ligation and those who did not have arterial ligation, the postoperative hemoglobin value of the ligated group was 11.4 ± 1.3 , while the postoperative hemoglobin value of the group without ligation was 10.4 ± 1.1 . A significant difference was found between the hemoglobin results as $p < 0.05$.

In terms of preoperative Anti-Müllerian Hormone results between the groups who underwent uterine and ovarian artery ligation and those who did not have arterial ligation, the preoperative Anti-Müllerian Hormone value of the ligated group was 1.1 ± 1.7 , while the preoperative Anti-Müllerian Hormone value of the non-ligation group was 1.9 ± 2.2 and there was no significant difference between the preoperative Anti-Müllerian Hormone results as $p > 0.05$.

In terms of postoperative Anti-Müllerian Hormone results between those who underwent uterine and ovarian artery ligation and those who did not have arterial ligation, the postoperative Anti-Müllerian Hormone value of the ligated group was 1.1 ± 1.3 , while the postoperative Anti-Müllerian Hormone value of the non-ligation group was 2 ± 2 It was determined as ,1, and there was no significant difference between postoperative Anti-Müllerian Hormone results as $p > 0.05$.

In the distribution of myoma size between those who underwent uterine and ovarian artery ligation and those who did not have arterial ligation, the size of myoma in the ligated group was 5.3 ± 0.7 cm, while the size of myoma

in the group without ligation was determined as 5.8 ± 1.2 , and it was found to be between fibroid sizes. Since $p > 0.05$, no significant difference was detected.

The operation time and hospital stay were compared between the case and control groups. The operation time of the control group was 69 ± 17 minutes, and the operation time of the case group was 75.3 ± 19 minutes, and there was no significant difference between the groups in terms of operation time. In the Table 3, the hospital stay of the control group was 2.3 ± 0.6 days, and the hospitalization period of the case group was 2.3 ± 0.6 days, and no significant difference was observed between the groups in terms of hospital stay.

Table 1. Comparison of the location of myoma

Location of myoma	Control	With artery ligation	P
Anterior, (%)	8 (50)	6 (37.5)	0.776
Fundus, (%)	4(25)	5 (31.2)	
Posterior, (%)	4(25)	5 (31.2)	

Table 2. The parameters we compared in our study

Variables		Mean±SD	P
Age	Control	39 ± 5	0.163
	With artery ligation	41.2 ± 3.8	0.164
Pre-op hgb	Control	12.7 ± 0.9	0.965
	with artery ligation	12.6 ± 1.3	0.965
Post-op hgb	Control	10.4 ± 1.1	0.032
	with artery ligation	11.4 ± 1.3	0.033
Pre-op AMH	Control	1.9 ± 1.2	0.572
	with artery ligation	1.1 ± 1.7	0.574
Post-op AMH	Control	2 ± 1.1	0.478
	with artery ligation	1.1 ± 1.3	0.512
Myoma size	Control	5.8 ± 1.2	0.227
	with artery ligation	5.3 ± 0.7	0.229
Parite	Control	1 ± 0.73	0.629
	with artery ligation	1.1 ± 0.71	0.629

Table 3. Previous operations of patients who underwent laparoscopic myomectomy

Operation	Control	with artery ligation	P
None (%)	13(81.2)	12(75)	0.83
C/S (%)	2 (12.5)	2(12.5)	
Myomectomy (%)	1(6.2)	2(12.5)	

Discussion

Laparoscopic surgery provides many advantages such as reduced postoperative pain, shorter hospitalization and better cosmetic results. Laparoscopic myomectomy may be a better alternative to the abdominal approach in selected patients. In addition, laparoscopic myomectomy may be associated with complications such as bleeding and other organ injuries and increased recurrence rates. In order to reduce these risks, bilateral uterine artery and ovarian artery ligation procedure is on the agenda before myomectomy.

Bae JH et al. performed laparoscopic myomectomy with uterine artery ligation alone in a group of 90 patients in 2011. and compared the postoperative results and short-term recurrence of the two groups to evaluate the efficacy of uterine artery ligation. As a result of the developments and advances in preoperative medications, surgical technique, experience and laparoscopic surgical instruments, the operation time was shortened, complications were minimized, and perioperative blood loss was reduced in cases without uterine artery ligation. There was no significant difference in postoperative hemoglobin values. Preoperative use of GnRH reduces myoma size, facilitates myomectomy and reduces blood loss during laparoscopic myomectomy.

In the study of Rakesh Sinha et al. in 2011 in which they performed laparoscopic myomectomy with only uterine artery ligation, they concluded that bilateral ligation of the uterine arteries from the point of origin from the internal iliac artery reduces the blood loss that may occur during the surgical procedure. It has also been shown to reduce recurrence rates by necrosis of very small fibroids.

In our study, in order to evaluate the effectiveness of arterial ligation, those who had bilateral uterine and ovarian artery ligation and those who did not have ligation were compared as 2 groups, perioperatively and postoperatively. Arterial ligation was found to be beneficial in providing intraoperative hemostasis. Thus, the need for postoperative blood transfusion decreased as the postoperative hemogram values of the patients did not decrease significantly.

It was shown that there was no significant difference between the Anti-Müllerian Hormone results, which were evaluated to evaluate preoperative and postoperative ovarian reserve, between those who underwent uterine and ovarian artery ligation and those who did not. This shows that Laparoscopic myomectomy with uterine and ovarian artery ligation has no negative effect on ovarian reserve in patients with fibroids with infertility.

There was no significant difference between those who underwent uterine and ovarian artery ligation and those who did not undergo uterine and ovarian artery ligation in terms of operation times.

When the length of hospital stay was compared, no significant difference was observed between those who underwent uterine and ovarian artery ligation and those who did not. There is no data on temporary artery ligation in the current literature. Since our study was prospective, the number of patients was relatively limited. Studies with large samples are needed to contribute more to the literature.

Conclusion

In conclusion, this study showed that uterine and ovarian artery ligation performed during laparoscopic myomectomy reduces the need for perioperative and postoperative blood transfusion.

Laparoscopic myomectomy with uterine and ovarian artery ligation has no negative effect on ovarian reserve in patients with fibroids with infertility, according to the Anti-Müllerian Hormone results evaluated to evaluate ovarian reserve.

Ethical Approval: This study was conducted with the permission number 456 of Şişli Hamidiye etfal training and research hospital Local Ethics Committee (date: 30/06/2015).

Author Contributions: Concept: O.T. Literature Review: M.S.Y Design : O.T. Data acquisition: M.S.Y Analysis and interpretation: O.A Writing manuscript: M.S.Y Critical revision of manuscript: O.A.

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

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Investigation of Oxidative Stress Parameters and Prolidase Enzyme Level Change in Mechanically Ventilated Patients in Intensive Care Unit

Yoğun Bakımda Mekanik Ventilasyon Uygulanan Hastalarda Oksidatif Stres Parametreleri ile Prolidaz Enzim Düzeyi Değişiminin Araştırılması

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Abstract

Background: Mechanical ventilation (MV) therapy can increase oxidative stress in the lungs. Oxidative stress can cause damage to collagen, an important component of the extracellular matrix in the lungs. In this study, total oxidative (TOS) and antioxidative (TAS) status in serum and bronchoalveolar lavage (BAL) were determined in patients who underwent MV. Our aim in the study was to determine whether there is a relationship between MV duration and oxidative stress parameters and prolidase, a collagen turn-over marker, in serum and BAL. **Materials and Methods:** The study included 26 adult patients aged 30-70 years, without primary lung pathology, and who were treated with MV for respiratory failure. TOS-TAS and prolidase enzyme activity were studied to determine oxidative stress levels in blood and BAL samples taken from patients on days 1-3-5. The oxidative stress index (OSI) was found by calculating the TOS/TAS ratio.

Results: As the MV treatment period of the patients gets longer, in the serum; It was observed that OSI and prolidase levels increased significantly ($p<0.01$). Also in BAL; It was determined that the TAS decreased significantly, the OSI increased significantly and the prolidase level decreased significantly ($p<0.001$).

Conclusion: Depending on the duration of MV therapy, increased oxidants (and decreased antioxidant capacity) in serum and BAL cause collagen tissue damage in the lungs. Prolidase in serum has also increased as an indicator of collagen damage in the lungs. We think that serum prolidase activity can be used as a viable test in order to detect and control MV-induced lung injury at an earlier stage.

Key Words: Mechanical Ventilation, Lung Damage, Reactive Oxygen Derivatives, Oxidative Stress, Prolidase

Öz

Amaç: Mekanik ventilasyon (MV) tedavisi akciğerlerde oksidatif stresi artırabilir. Oksidatif stres, akciğerlerde ekstraselüler matriksin önemli komponenti olan kollajenin hasarına neden olabilir. Bu çalışmada, MV uygulanan hastalarda, serum ve bronkoalveolar lavajda (BAL) total oksidatif (TOS) ve antioksidatif (TAS) durum belirlendi. Çalışmadaki amacımız, serumda ve BAL'da, MV süresi ile oksidatif stres parametreleri ve bir kollajen turn-over markeri olan prolidaz arasında bir ilişki olup olmadığını tespit edebilmektir. **Gereç ve Yöntem:** Çalışmaya, yaş aralığı 30-70 olan, primer akciğer patolojisi olmayan, solunum yetmezliği tanısıyla MV tedavisi gören, 26 erişkin hasta dahil edildi. Hastalardan 1- 3- 5- 7. günlerde alınan kan ve BAL örneklerinde, oksidatif stres seviyelerinin belirlenmesi için TOS-TAS ve prolidaz enzim aktivitesi çalışıldı. TOS/TAS oranı hesaplanarak, oksidatif stres indeksi (OSİ) bulundu. **Bulgular:** Hastaların yoğun bakımda kalış süreleri ve MV süresi uzadıkça serumda; TAS'ın anlamlı olarak ($p<0,001$) azaldığı, TOS ve OSİ'nin anlamlı şekilde ($p<0,01$) arttığı, prolidaz seviyesinin anlamlı olarak ($p<0,001$) arttığı görüldü. BAL'da; TAS'ın anlamlı olarak ($p<0,001$) azaldığı, TOS ve OSİ'nin anlamlı olarak ($p<0,001$) arttığı, prolidaz seviyesinin anlamlı olarak ($p<0,001$) azaldığı tespit edildi.

Sonuç; MV tedavisi süresine bağlı olarak, serum ve BAL'da artan oksidanlar (ve azalan antioksidan kapasite) akciğerlerde kollajen doku hasarına neden olmaktadır. Akciğerlerdeki kollajen hasarının göstergesi olarak serumdaki prolidaz da artmaktadır. MV'a bağlı akciğer hasarının, daha erken dönemde belirlenip kontrol altına alınabilmesi açısından, uygulanabilir bir test olarak serum prolidaz enzim aktivitesinden faydalanılabileceği düşüncesindeyiz. Çalışmamızın ileri klinik çalışmalarla desteklenmesi uygun olacaktır.

Anahtar Kelimeler: Mekanik Ventilasyon, Akciğer Hasarı, Reaktif Oksijen Türevleri, Oksidatif Stres, Prolidaz.

Introduction

Mechanical ventilation (MV) therapy, which is inevitable to be applied when necessary, can cause barotrauma and oxygen toxicity in the lungs in correlation with the current state of the patient's lungs and the length of stay in the ventilator (1).

Free radicals can occur during the course of normal metabolic events, as well as the metabolism of some foreign substances, exposure of the organism to external factors such as radiation. It is known that free radicals play a role in the pathophysiology of acute inflammatory conditions, severe sepsis, acute lung injury, emphysema, bronchopulmonary dysplasia, pneumoconiosis, adult respiratory distress syndrome, and multi-organ failure (2). Prolidase is a specific enzyme, which is involved in the metabolic cycle of collagen, which is in the structure of many tissues in the body, and takes an active role in the destruction of collagen and re-participation of proline in the collagen production cycle. Since collagen is a structural component of many organs and tissues, as well as the extracellular matrix, it is affected by the pathology of these structures (3-6).

We also in this study, we aimed to investigate whether changes in oxidative stress parameters and prolidase enzyme levels in serum and bronchoalveolar lavage (BAL) could be used as an early-stage marker of lung injury in intensive care patients undergoing MV.

Material and Method

Local ethics committee approval (12 February 2009, session 02) and informed consent of patients' relatives were obtained before the study. The study was carried out in the General Intensive Care Unit of Harran University Faculty of Medicine (Department of Anesthesiology and Reanimation). The study included 26 adult patients aged 30-70 years who were treated with MV in the intensive care unit and had no primary lung pathology. Demographic data of the patients, hemogram-biochemistry-blood gas values and coma scores on the 1st, 3rd, 5th and 7th days were recorded.

The mechanical ventilator mode was set to Synchronized Intermittent Mandatory Ventilation (SIMV). Fraction of Inspired Oxygen (FiO₂) was started at 100% when the patient was connected to the mechanical ventilator, gradually decreasing according to the blood gas results and fixed to 40% as soon as possible (within the first three hours at the latest). The tidal volume was standardized as 6 milliliter (ml)/kg, positive end expiratory pressure (PEEP) 5 cmH₂O, respiratory rate 10-12/min, Inspiration/Expiration 1:2. Ventilator settings were adjusted in the morning and evening, targeting the values blood gas results (pH: 7.35 – 7.45, PCO₂: 35-45 mmHg, PO₂: 80-100 mmHg, HCO₃: 22-26 mmol/liter [L]).

Enteral nutrition support was started and fluid therapy was arranged for the patients. Hemoglobin level was tried to be kept between 8-12 grams (g)/dl and replacement was done when necessary. BAL samples and blood samples were collected by non-bronchoscopic telescopic method from patients who were connected to mechanical ventilators on days 1-3-5-7. BAL samples were obtained with the help of a non-bronchoscopic telescopic BAL catheter (Combicath, Plastimed, France) after 20 mL of sterile saline was given through the endotracheal tube. The obtained samples were centrifuged at 3000 rpm for 5 minutes and stored in a deep freezer at -80°C until the working time. Hemodynamic and ventilator parameters and arterial blood gas values of the patients were recorded. Prolidase enzyme activity, Total Antioxidant Level (TAS) and Total Oxidant Level (TOS) were measured in serum and BAL samples. The optimized modified Chinard Method (5), which is a colorimetric measurement method for prolidase enzyme activity, and a fully automatic colorimetric method developed by Erel (Rel-Assay commercial kits) were used to measure total antioxidant level and total oxidant level (6). Oxidative Stress Index (OSI); It was calculated by dividing TOS by TAS.

Statistical Assessment: Statistical Package for Social Sciences (SPSS) for Windows 25.0 (SPSS Inc. Chicago USA) program was used for statistical analysis. Repeated Analysis of Variance was used for multiple comparisons between groups and Bonferroni Test was used for within-group comparisons. Results were expressed as mean±standard deviation, and p<0.05 was considered statistically significant.

Results

When the demographic data of the patients were examined; 19 (73.1%) of the patients were male, 7 (26.9%) were female, mean age 64.3 ± 14.13 , mean weight $74.46 \text{ kg} \pm 14.07 \text{ kg}$, mean height was recorded as $167.69 \text{ cm} \pm 6.94 \text{ cm}$. Patients' APACHE II values were 23.7 ± 4.6 on day 1; 3rd day 23.5 ± 4.8 ; 5th day 24.7 ± 5.3 ; Day 7 was 23.7 ± 6.7 , SOFA values were 6.7 ± 2.7 on day 1; 3.day 6.9 ± 2.7 ; 5th day 7.7 ± 3.2 ; It was determined as 7.9 ± 3.1 on the 7th day. When the serum TAS values between the 1st, 3rd, 5th and 7th days of the patients were compared within themselves, a statistically significant difference was found. It was determined that TAS values decreased significantly as the length of stay in the intensive care unit of the patients ($p < 0.001$) (Table 1).

When the serum TOS values of the patients were compared, the TOS values were found to be statistically significantly higher on the 3rd day compared to the 1st day ($p < 0.01$). A statistically insignificant increase ($p > 0.05$) was observed on the fifth day compared to the first day, and a statistically insignificant decrease was observed compared to the third day ($p > 0.05$). The serum TOS values of the patients were found to be significantly increased on the 7th day (compared to the 1-3-5 days) ($p < 0.01$) (Table 1).

The serum OSI values of the patients, such as TOS values, were found to be statistically significantly higher on the 3rd day compared to the 1st day ($p < 0.01$). A statistically insignificant increase ($p > 0.05$) was observed on the fifth day compared to the first day, and a statistically insignificant decrease was observed compared to the third day ($p > 0.05$). The serum OSI values of the patients were found to be significantly increased on the 7th day (compared to the 1-3-5 days) ($p < 0.01$) (Table 1).

Serum prolidase activities were found to be statistically significantly increased on day 3 compared to day 1 ($p < 0.01$). On the fifth day, prolidase levels were found to be statistically significant ($p < 0.01$) compared to the 1st day and insignificantly higher than the 3rd day ($p > 0.05$). The increase in serum prolidase levels on the seventh day was not statistically significant compared to the 5th day ($p > 0.05$), and it was found to be statistically significant compared to the 1st and 3rd days ($p < 0.001$) (Table 1)(Figure 1).

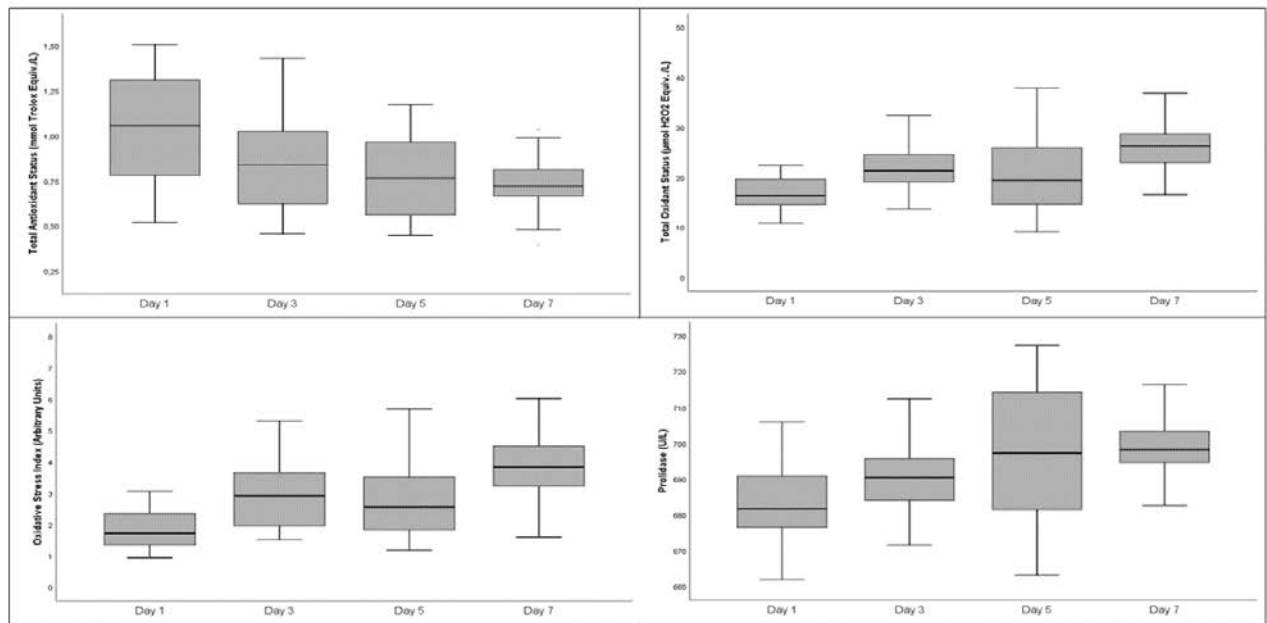
Table 1. Serum prolidase and serum Oxidant/Antioxidant parameters of the patients

	Serum Day1 (n= 26)	Serum Day 3 (n= 26)	Serum Day5 (n= 26)	Serum Day 7 (n= 26)	P
Prolidase (U/L)	682.31 ± 11.73	$691.30 \pm 12.63^{a**}$	$696.20 \pm 18.73^{b**}$	$699.95 \pm 10.48^{c***,e**}$	<0.001
Total Oxidant Level ($\mu\text{mol H}_2\text{O}_2$ Eqv./L)	17.26 ± 3.87	$22.85 \pm 6.45^{a**}$	20.53 ± 7.29	$26.91 \pm 7.01^{c***,e**,f***}$	<0.001
Total Antioxidant Level (mmol Troloks Eqv./L)	1.02 ± 0.31	$0.85 \pm 0.26^{a**}$	$0.76 \pm 0.21^{b***,d**}$	$0.72 \pm 0.16^{c***,e**}$	<0.001
Oxidative Stress Index (AU)	1.81 ± 0.60	$2.89 \pm 1.06^{a***}$	$2.96 \pm 1.50^{b**}$	$3.87 \pm 1.22^{c***,e***,f***}$	<0.001

a: 1 to 3; b: 1 to 5; c: 1 to 7; d: 3 to 5; e: 3 to 7; f: There is a significant difference between the 5th and 7th day. ***: $p \leq 0.001$; **: $p \leq 0.01$; *: $p \leq 0.05$

When the BAL TAS values of the patients were compared, it was determined that the BAL TAS values decreased statistically significantly ($p < 0.05$) on the 3rd day compared to the 1st day. BAL TAS values; on the 5th day; It was found to be statistically significantly higher than the 3rd day ($p < 0.01$), and statistically insignificantly higher than the 1st day ($p > 0.05$). On the 7th day; It was found significantly ($p < 0.01$) and ($p < 0.001$) lower than the 1st and 5th days, and insignificantly ($p > 0.05$) lower than the 3rd day (Table 2)

Figure 1. Serum of the patients on the 1st. 3rd. 5th and 7th days; Difference. distribution and standard deviations between TAS. TOS. OSI. Prolidases



When the BAL TOS values of the patients were compared, we found that the values decreased statistically significantly on the 3rd day compared to the 1st day ($p < 0.001$). BAL TOS values were found to be statistically significantly higher on the 5th day compared to the 1st and 3rd days ($p < 0.01$), ($p < 0.001$). BAL TOS values were found to be increased statistically significantly ($p < 0.001$) on the 7th day compared to the 1st and 3rd days, but in a statistically insignificant way ($p > 0.05$) compared to the 5th day (Table 2).

When the BAL OSI values of the patients were compared, we found that there was a statistically significant decrease on the 3rd day compared to the 1st day ($p < 0.05$). BAL OSI values were found to be increased on the 5th day in a statistically insignificant way ($p > 0.05$) compared to the 1st day, and statistically significantly ($p < 0.01$) compared to the 3rd day. BAL OSI values were found to increase statistically significantly on the 7th day ($p < 0.001$) (Table 2).

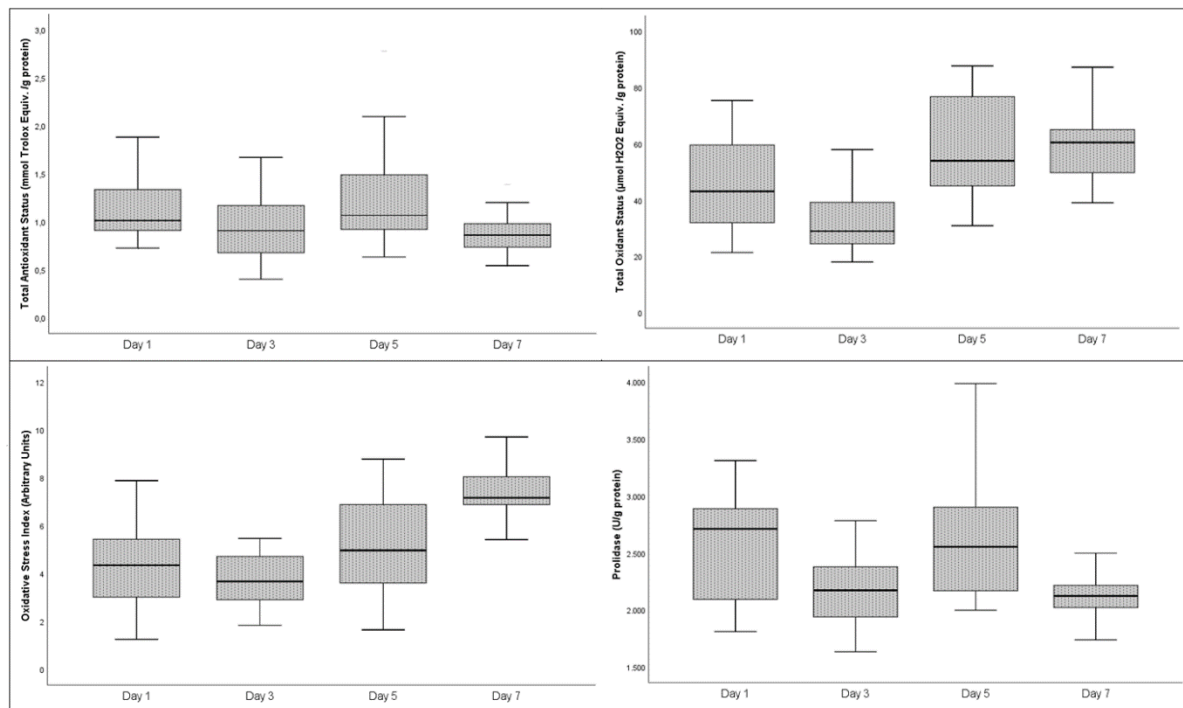
When the BAL prolidase values of the patients were compared, it was found to be statistically significantly lower on the 3rd day compared to the 1st day ($p < 0.05$). On the fifth day, a statistically insignificant ($p > 0.05$) increase was found in the BAL prolidase level compared to the 1st day, and a statistically significant ($p < 0.05$) increase was found compared to the 3rd day. The decrease in BAL prolidase levels on the 7th day was statistically significant compared to the 1st and 7th days ($p < 0.001$), but it was not statistically significant compared to the 3rd day ($p > 0.05$) (Table 2) (Figure 2).

Table 2. BAL prolidase and BAL Oxidant/Antioxidant parameters of the patients

	BAL Day 1 (n= 26)	BAL Day 3 (n= 26)	BAL Day 5 (n= 26)	BAL Day 7 (n= 26)	P
Prolidase (U/L)	2560±434	2203 ± 410 ^{a*}	2590 ± 481 ^{d*}	2122±260 ^{c***,f***}	0.003
Total Oxidant Level (μmol H ₂ O ₂ Eqv./L)	45.84±15.79	32.50 ± 10.99 ^{a***}	57.36 ± 18.08 ^{b**,d***}	60.62±14.93 ^{c***,e***}	<0.001
Total Antioxidant Level (mmol Trolox Eqv./L)	1.14±0.34	0.93 ± 0.30 ^{a*}	1.22 ± 0.45 ^{d**}	0.86±0.19 ^{c**,f***}	0.028
Oxidative Stress Index (AU)	4.25±1.60	3.65 ± 1.04 ^{a*}	5.17 ± 2.06 ^{d**}	7.17±1.55 ^{c***,e***,f***}	<0.001

a: 1 to 3; b: 1 to 5; c: 1 to 7; d: 3 to 5; e: 3 to 7; f: There is a significant difference between the 5th and 7th day. ***: $p \leq 0.001$; **: $p \leq 0.01$; *: $p \leq 0.05$

Figure 2. BAL on the 1st, 3rd, 5th and 7th days of the patients; Difference, distribution and standard deviations between TAS, TOS, OSI, Prolidases



Discussion

Mechanical ventilation therapy can also cause undesirable conditions in the lungs in correlation with the current state of the patient's lungs and the length of stay in the ventilator. Studies show that MV causes oxidative stress in the lung tissue (1,9).

One of the undesirable conditions associated with MV is Ventilator Associated Diaphragm Dysfunction (VIDD). It has been shown that MV-related markers and oxidative stress increase in the diaphragm and there is damage due to oxidation. Mitochondrial abnormalities in the diaphragm during and after MV are seen as evidence of diaphragmatic damage due to ROS (10-18). It is thought that increased lipid peroxidation and protein oxidation cause changes in complexes II, III, IV in the electron transport chain and cause mitochondrial depression and damage (14).

Limited human studies and extensive animal experiments show that MV can cause intradiaphragmatic muscle fiber damage and atrophy, which can cause diaphragmatic failure in many critically ill patients undergoing MV (16,19,20). There are limited studies suggesting that MV-induced oxidative stress in lung tissue may be an indicator of lung injury. In rabbits with iatrogenic hemorrhagic shock; It has been found that in lung damage due to hemorrhagic shock, ischemia during resuscitation, and reperfusion, cytokine levels and ROS levels in BAL increase in a correlated way, and ROS indicate acute lung injury (21,22).

Diaphragm weakness may occur as the duration of mechanical ventilation used in patients with respiratory failure is prolonged. This is thought to cause prolonged weaning (23). It is thought that mechanical ventilation causes diaphragmatic dysfunction by increasing oxidative stress at the diaphragm level, which prolongs the time it takes patients to leave the ventilator. A compilation on these issues was made by Petrof et al. in the compilation; Diaphragm function has been shown to be an important determinant of weaning in mechanically ventilated patients. Although MV is curative in acute lung injury, it can paradoxically increase lung damage (22-26).

In summary, oxidative stress during mechanical ventilation may possibly be a common cause of diaphragmatic dysfunction. Diaphragm dysfunction can also be considered as a cause of prolonged weaning. However, the target in this regard should be to prevent these processes in particular.

In our study; it was investigated how oxidative stress parameters and prolidase (collagen return marker) levels in blood and BAL were affected depending on the duration of MV in intensive care patients without primary lung pathology, and whether this could be used in the early detection of lung damage. Our study; It is important because it is performed in humans and because prolidase is used to show tissue damage due to MV in the lung (3). A fully automatic colorimetric method developed by Erel (many oxidants, total oxidant capacity and many antioxidants were precisely measured) was used (8,9).

The results we found in the serum examinations in our study; shows that patients who started to receive MV therapy were initially affected only locally (lungs) due to intensive care and MV, but were not yet exposed to oxidative damage systemically. Oxidative damage due to MV becomes more evident systemically after the 3rd day. On the 3rd day, we detected that TOS and OSI were highly elevated in the serum, thus oxidative stress was present, and TAS decreased due to excessive consumption in reaction to this and was insufficient against excessive oxidative stress. On the 5th day, the longer the patients stay in the intensive care unit, the significant decrease in TAS, indicating that oxidative stress in the body and thus oxidative damage continues. However, although the increase in OSI on the 5th and 7th days was statistically significant compared to the 1st day, it was not significant compared to the 3rd day. This shows that the consumed antioxidants try to protect the body against oxidative stress, especially on the 3rd day, the oxidative stress, which is very aggravated, is tried to be tolerated by the body and the oxidant / antioxidant balance is maintained. We think that MV therapy also contributed positively to this situation. However, TOS and OSI levels increase very significantly due to the length of stay in the intensive care unit and the prolongation of oxygen exposure at a higher rate than normal (40%) with MV. However, TAS levels decrease significantly due to long-term excessive use. This suggests that the prolonged stay of patients on mechanical ventilators in the intensive care unit leads to an excessive increase in oxidative stress, thus rendering the body's efforts to maintain the oxidant/antioxidant balance insufficient.

The fact that the levels of prolidase, TOS and OSI were statistically significantly increased on the 3rd day compared to the 1st day blood, indicating that an excessive oxidative stress occurred in the patients. This shows that by causing oxidative damage in biomolecules such as lipids and proteins, collagen turnover is accelerated, and as a result, prolidase activity gradually increases. As a matter of fact, on the 5th day, serum prolidase levels were found to be significantly higher, showing that severe oxidative damage continues at the molecular level. However, prolonged stay in intensive care unit causes oxidative stress to increase gradually. A statistically insignificant increase in prolidase level indicated that the acceleration in collagen turnover continued.

In MV therapy, treatment is usually started with 100% oxygen at the beginning, and it is reduced to the lowest oxygen concentration as soon as possible. In the BAL samples of the patients included in the study, TOS and OSI increase on the 1st day due to the excessive oxygen pressure exposed by mechanical ventilation. Accordingly, TAS (due to the sulfhydryl groups it contains) is high, although not excessive. In addition, we can say that prolidase is also high in the 1st day BAL samples, with the destruction of collagen on the bronchoalveolar epithelial surface due to MV. A significant decrease in BAL prolidase level on the 3rd day (compared to the 1st day) indicates that oxidative damage has occurred in the bronchoalveolar surface (lipids and proteins at the molecular level), which is overexposed to oxygen radicals. The increase of prolidase on day 1 in parallel with the accelerated turn-over with collagen damage also confirms our hypothesis. On the 3rd day, the decrease in oxidative stress at the level of bronchoalveolar tissue, decrease in collagen damage (stabilization of collagen turnover) is confirmed by a decrease in prolidase level. The increase in BAL prolidase at day 5 showed collagen degradation on the bronchoalveolar surface (due to mechanical and oxidative damage). On the 7th day, we observed that the BAL prolidase levels were significantly lower than both the 1st day and the 5th day. In this case; We can assume that the prolongation of the patients' dependence on mechanical ventilators in the intensive care unit depletes the total antioxidants of the bronchoalveolar surface (due to both mechanical and severe oxidative damage). However, as the exposure time increases, the protective feature of the mucus

layer covering the surface epithelium may have entered the adaptation process with cellular mechanisms. As a matter of fact, the low prolidase level (compared to the 5th day) indicates that collagen metabolism can be controlled and the turn-over rate can be stabilized.

In the light of these findings, there is a serious oxidative stress that increases with the duration of MV in patients undergoing MV, and this plays a role in the etiopathogenesis and progression of MV-induced lung injury, so a serious oxidative damage occurs and collagen (one of the most affected proteins) is damaged. We can say that in MV-induced lung injury, collagen degradation increases and collagen turnover rate increases, and therefore prolidase enzyme activity in serum increases. Modified Chinard Method, which is a photometric method for demonstrating prolidase enzyme activity, is not yet used as a routine parameter because it is not automated, reliable but not easily applicable. In addition, we think that oxidative stress and oxidative damage occur due to MV in these patients with high oxidative stress markers. The increase in oxidant substances as well as the decrease in antioxidant capacity may contribute to this process by creating collagen tissue damage.

Conclusion

In our study, serum and BAL oxidative stress parameters and prolidase enzyme were found to be associated with MV duration. As the duration of MV treatment increases, prolidase in serum also increases as an indicator of tissue damage in the lungs. We think that serum prolidase enzyme activity can be used to detect and control MV-induced lung damage at an earlier stage. Further studies are needed to support our results at the molecular level in order to reveal the local mechanical effects of MV more comprehensively.

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Ethical Approval: Ethical approval: Harran University Ethics Committee "DATE: 12 February 2009, SESSION NO: 02.

Author Contributions: ED: Study conception and design, interpretation of data, writing manuscript, data acquisition.

ZB: Study conception and design ŞY: Analysis and interpretation of data, literature review

HA: Interpretation of data. HÇ: Statistical analysis of data and critical revision of manuscript

MK: Prepared figures and writing manuscript. NA: Review and interpretation of data

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

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Comparison of Effects of Dexmedetomidine and Thymoquinone on Kidney at Hind Limb Ischemia - Reperfusion Generated Rats

Alt Ekstremitede İskemi-Reperfüzyon Oluşturulan Ratlarda Deksmetomidin ve Thymoquinone'in Böbrek Üzerine Etkilerinin Karşılaştırılması

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Abstract:

Background: In this study it is aimed to compare the effects of Dexmedetomidine (Dex) and Thymoquinone (TQ) on kidney at hind limb ischemia/reperfusion injury generated rats

Materials and Methods: 50 Wistar albino rats were included to the study. Rats were divided into 5 groups (n=10) as Sham, Control, TQ, Dex, and Dex-TQ. After anesthesia was given to the rats, ischemia was performed to left hind limb for 4 hours and then 2 hours reperfusion applied. TQ and Dex were administered intraperitoneally after the end of 4 hours ischemia and 5 minutes before start of reperfusion. At the end of study all rats were sacrificed. Blood and kidney samples were taken to evaluate Total Antioxidant Status (TAS), Total Oxidant Status (TOS) Oxidative Stress Index (OSI) values and histopathological examination.

Results: TAS value was measured that the lowest value in Control Group (0.07±0.01). TAS values of TQ, Dex, Dex-TQ groups were significantly higher than those of Control Group (p<0.05). There was no significant difference between TQ, Dex, Dex-TQ groups regarding to TAS values (p>0.05). TOS values were measured and they were the highest in the Control Group and the lowest in the Sham Group (p<0.05 for all). TOS values of TQ, Dex, Dex-TQ groups significantly lower than those of the Control Group (p<0.05) and significantly higher than those of the Sham Group (p<0.05). There was no significant difference between TQ, Dex, Dex-TQ groups regarding to TOS values (p>0.05). OSI values of TQ, Dex, Dex-TQ groups significantly lower than those of the Control Group (p<0.05) and higher than those of the Sham Group (p<0.05 for all). There was no significant difference between TQ, Dex, Dex-TQ groups regarding to OSI values (p>0.05 for all). The histopathological damage score was the lowest in the Sham group and the highest in the Control group. While there was no significant difference between Sham, TQ, Dex, Dex-TQ groups (p>0.05); It was found to be significantly lower when compared to the control group (p<0.05).

Conclusion: Histopathological changes were observed at kidney in hind limb ischemia/reperfusion due to oxidative stress. TQ and Dex had protective effects on renal tissues at ischemia/reperfusion injury.

Key Words: Ischemia, Reperfusion, Oxidative Stress, Dexmedetomidine, Thymoquinone

Öz

Amaç: Bu çalışmada alt ekstremitede iskemi reperfüzyon hasarı oluşturulan ratlarda Deksmetomidin (Dex) ve Thymoquinone'in (TQ) böbrek üzerine etkilerini karşılaştırılması amaçlandı.

Materyal ve Metod: Çalışmaya 50 adet Wistar albino rat dahil edildi. Sıçanlar Sham, Control, TQ, Dex ve Dex-TQ, olmak üzere 5 gruba (n=10) ayrıldı.

Ratlara anestezi verildikten sonra sol alt ekstremiteye 4 saat iskemi ve 2 saat reperfüzyon uygulandı TQ ve Dex iskemi ardından reperfüzyondan 5 dakika önce intraperitoneal olarak uygulandı. Çalışma bitiminde bütün ratlar sakrifiye edildi ve ratlardan kan ve böbrek numuneleri alınarak histopatolojik değerlendirme yapıldı; Total Antioksidan Seviye (TAS), Total Oksidatif Stres (TOS) ve Oksidatif Stres İndeksi (OSİ) değerleri incelendi.

Bulgular: TAS en düşük kontrol grubunda (0.07±0.01) saptandı. TQ, Dex, Dex-TQ gruplarının TAS değerleri kontrol grubundan yüksek bulundu (p<0.05). TQ, Dex, Dex-TQ grupları arasında TAS açısından anlamlı fark saptanmadı (p>0.05).

TAS en düşük kontrol grubunda (0.07 ± 0.01 , P değeri) saptandı. TQ, Dex, Dex+TQ gruplarının TAS değerleri kontrol grubundan yüksek bulundu ($p < 0.05$). TQ, Dex, Dex-TQ grupları arasında TAS açısından anlamlı fark saptanmadı ($p > 0.05$). TOS en düşük Sham grubunda en yüksek Kontrol grubunda saptandı ($p < 0.05$). TQ, Dex, Dex-TQ gruplarının TOS değerleri Kontrol grubundan anlamlı düşük ($p < 0.05$), Sham grubundan ise anlamlı şekilde yüksek bulundu ($p < 0.05$). TQ, Dex, Dex-TQ Grupları arasında TOS açısından anlamlı fark saptanmadı ($p > 0.05$). TQ, Dex, Dex-TQ gruplarının OSİ değerleri Kontrol grubundan anlamlı düşük ($p < 0.05$), Sham grubundan ise anlamlı şekilde yüksek bulundu ($p < 0.05$). TQ, Dex, Dex-TQ Grupları arasında OSİ açısından anlamlı fark saptanmadı ($p > 0.05$). Histopatolojik hasar skoru en düşük Sham grubunda en yüksek ise Kontrol grubunda görüldü. Sham, TQ, Dex, Dex-TQ grupları arasında anlamlı fark saptanmazken ($p > 0.05$); Kontrol grubuyla karşılaştırıldığında anlamlı olarak düşük tespit edildi ($p < 0.05$).

Sonuç: Alt ekstremitte iskemi-reperfüzyonunda oksidatif stres nedeniyle uzak organlarda belirgin histopatolojik değişiklikler ortaya çıkar. Thymoquinone ve Deksmetomidin, böbrekler üzerinde iskemi-reperfüzyon hasarının önlenmesinde koruyucu etkiye sahiptirler.

Anahtar Kelimeler: İskemi, Reperfüzyon, Oksidatif Stres, Deksmetomidin, Thymoquinone

Introduction

Metabolites formed as a result of anaerobic metabolism in ischemia/reperfusion injury (IRI) are oxidized together with reperfusion and mixed into the circulation and cause distant organ damage (1,2). The body's defense system is activated with antioxidant enzymes against free oxygen radicals (FOR) formed after Ischemia/Reperfusion (IR) (3).

The tourniquet method, which is used in many surgeries, especially orthopedic surgery, is an IR model (4). Kidney damage may occur as a systemic complication of IRI. Anesthetic agents to be used in patient groups with risky kidney functions, in major surgeries that may increase damage to the kidney, and in surgical interventions where kidney functions need to be preserved, such as transplantation, should be chosen carefully considering their effects on the kidney (5,6).

Different agents have been tried for the treatment of IRI, and studies have generally focused on agents with antioxidant properties. The histological effects of agents on distant organs were investigated in various IR models (7,8).

In this study, it was aimed to compare the histopathological and biochemical effects of Dexmedetomidine, which is used for sedation in anesthesia and intensive care practice, and Thymoquinone, which has been shown to have antioxidant properties in various studies, on the kidney in hind limb IRI in rats.

Materials and Methods

Local Ethics Committee approval (approval decision of Harran University Animal Experiments Local Ethics Committee dated 30.04.2012 and numbered B.30.2.HRU.0.05.07.00/270) was obtained before the study. Fifty Wistar-albino female rats (average weight between 180-240 gr) were randomly divided into 5 equal groups ($n = 10$). Rats were kept at room temperature and 12 hours of light and 12 hours of darkness before the study. All rats were fed with tap water and standard rat chow under standard conditions. Feeding of all rats was stopped 8 hours before the intervention.

Ketamine 87 mg/kg was administered intraperitoneally (Ketalar; Parke Davis, Eczacıbasi, Istanbul, Turkey) and Xylazine 13 mg/kg (Rompun; Bayer AG, Leverkusen, Germany) to all rats used in the experiment after 8 hours of fasting. Additional doses were planned, if necessary, once during the experiment. Yassin et al. IR model was taken as an example (9). Left hind limbs of the rats were wrapped with an elastic bandage, and saturation loss and discoloration were achieved. At the end of the procedure, after the histological tissue sample and sufficient blood samples were taken, the rats were decapitated under anesthesia. Total working time was kept equal in all

groups. At the end of the ischemia and reperfusion procedures, laparotomy was performed with a midline incision after the abdomen of the rats was disinfected. Blood samples were taken from the inferior vena cava and sent for biochemical analysis to measure Total Antioxidant Status (TAS) and Total Oxidant Status (TOS) to investigate the relationship between ischemia-reperfusion and oxidative stress. Kidney samples were taken, and histopathological examination was performed.

Preparation of Thymoquinone

Thymoquinone was dissolved using dimethyl sulfoxide (DMSO) and prepared for intraperitoneal injection.

Experimental Groups and Protocol

Rats were divided into 5 groups **Group 1 (Sham, n=10)**: No procedure other than anesthesia was performed throughout the study. Tissue and blood samples were taken at the end of the reperfusion period. **Group 2 (Control, I/R, n=10)**: 4 hours ischemia and 2 hours reperfusion were applied to the left hind limb with tourniquet after anesthesia, no drug was given. **Group 3 (I/R, Thymoquinone, TQ n=10)**: 4 hours ischemia and 2 hours reperfusion were applied to the left hind limb with tourniquet after anesthesia, 20 mg/kg Thymoquinone was administered intraperitoneally (i.p.) 5 minutes before the tourniquet was opened. **Group 4 (I/R, Dexmedetomidine, Dex n=10)**: 4 hours ischemia and 2 hours reperfusion were applied to the left hind limb with tourniquet after anesthesia. 5 minutes before the tourniquet was opened, 25mcg/kg dexmedetomidine, i.p. given **Group 5 (I/R, Dexmedetomidine + Thymoquinone, Dex-TQ n=10)**: 4 hours ischemia with tourniquet and 2 hours reperfusion was applied to the left hind limb after anesthesia, 5 minutes before the tourniquet was opened 25mcg/kg dexmedetomidine and 20 mg/kg Thymoquinone i.p. given. Tissue and blood samples were taken from all rats in the groups at the end of the reperfusion period.

Histopathological Examination of Kidney Tissues: For histopathological examination, kidney tissues were individually fixed in 10% neutral buffered formaldehyde solution. Samples were embedded in paraffin blocks. Sections of 5-micron meters were taken. Stained with hematoxylin-eosin stain. A 20-lens magnification was used.

Histopathological Scoring: the severity of kidney damage was scored with the scoring system used by Solez et al. (10). In preparations for scoring, Tubular necrosis, interstitial edema, loss of brush border, and cast formation of the tubular epithelium from the basement membrane were evaluated as histological parameters. As a scoring score, it was accepted as None: 0 present:1 significant:2. The histological score was determined by summing all parameter scores for each sample.

TAS Measurement: The TAS level of the samples was measured using Rel Assay brand commercial kits. The measurement method is based on the fact that all antioxidant molecules in the sample reduce the colored ABTS cationic radical, and the colored radical decolorizes in proportion to the total concentrations of the antioxidant molecules. Trolox, a water-soluble analogue of vitamin E, is used as the calibrator. Results are expressed as mmol Trolox Equivalent/L (11). TAS results in tissues were expressed as Trolox Equivalent/gram protein.

TOS Measurement: The TOS level of the samples was measured using Rel Assay brand commercial kits. As stated in the working principle of the measurement test, the colorimetric method is used, which is based on the cumulative oxidation of the oxidant molecules contained in the samples to ferrous ion to ferric ion. Results are expressed as $\mu\text{mol H}_2\text{O}_2$ Equivalent/L (11). TOS results in tissues were expressed as $\mu\text{mol H}_2\text{O}_2$ Equivalent/gram protein.

Calculation of Oxidative Stress Index (OSI): When calculating the OSI of the samples, the TAS values are multiplied by 10 to equalize the TOS and the units. The ratio of TOS levels contained in the samples and TAS contained in the samples was stated as OSI (12). Results are expressed as Arbitrary Units (AU).

Statistical Analysis: SPSS package program was used for statistical evaluation. Kruskal Wallis and post hoc Bonferroni tests were used to evaluate the quantitative data between groups. For the Kruskal Wallis test, $p < 0.05$ values were considered statistically significant.

Results

A total of 50 rats were included in this study and were divided into 5 groups with 10 in each group. The study protocol was applied to all rats, and at the end of the study, blood and tissue samples were taken from the rats and the rats were sacrificed. TAS, TOS and OSI parameters were measured in blood samples taken from rats and statistically compared between groups (Table 1).

The scores obtained as a result of the histopathological evaluations made by the specialist pathologist were statistically compared. EM samples of all groups are presented in Figure 1. The histopathological scoring of the groups is shown in Table 1.

Comparison of TAS Values of the Groups

When the mean TAS values were calculated in the blood samples taken, the lowest value was found in the control group (0.07 ± 0.01 mmolTrolox Eqv./L), and the highest value was found in the Sham group (0.33 ± 0.07 mmolTrolox Eqv./L) (Table 1).

When TAS was compared between the groups;

- 1- TAS values of Sham, TQ, Dex, Dex-TQ groups were found to be statistically significantly higher than the control group ($p < 0.05$).
- 2- TAS value in the Sham group was found to be statistically significantly higher than the other groups. ($p < 0.05$).
- 3- TAS values of TQ, DEX, DEX-TQ groups were compared, no statistically significant difference was found ($p > 0.05$)

Comparison of TOS Values of the Groups

When the mean TOS values in the blood samples were calculated, the lowest value was found in the Sham group (18.68 ± 3.41 $\mu\text{molH}_2\text{O}_2\text{Eqv./L}$) and the highest value was found in the Control group (36.97 ± 6.26 $\mu\text{molH}_2\text{O}_2\text{Eqv./L}$) (Table 1).

- 1- TOS values of Sham, TQ, Dex, Dex-TQ groups were found to be statistically significantly lower than the control group ($p < 0.05$).
- 2- The TOS value of the Sham group was found to be statistically significantly lower than the other groups. ($p < 0.05$).
- 3- When the TOS values of the TQ, Dex, Dex-TQ groups were compared between the groups, no statistically significant difference was found ($p > 0.05$)

Comparison of OSI Values of the Groups

When the mean OSI values in the blood samples were calculated, the lowest value was found in the Sham group (5.92 ± 1.89 AU), and the highest value was found in the Control group (54.84 ± 20.67 AU) (Table 1).

When compared between OSI groups;

- 1- OSI values of Sham, TQ, Dex, Dex-TQ groups were found to be statistically significantly lower than the control group ($p < 0.05$).

2- The OSI value of the Sham group was found to be statistically significantly lower than the other groups. ($p < 0.05$).

3- When the OSI values of the TQ, Dex, Dex-TQ groups were compared between the groups, no statistically significant difference was found ($p > 0.05$)

Comparison of Histopathological Damage Scores of the Groups

Histopathological damage scoring was performed on the kidney sample of each rat by a specialist pathologist, and the mean scores of the groups were compared. The lowest value was found in the Sham group (2.60 ± 0.69) and the highest value was found in the control group (4.60 ± 0.69) (Table 1).

When the Histopathological Damage Score was compared between the groups;

1- Sham, TQ, Dex, Dex-TQ Groups Histopathological damage score was found to be statistically significantly lower than the control group ($p < 0.05$) (Figure 1).

2- There was no statistically significant difference between Sham, TQ, Dex, Dex-TQ Groups. ($p > 0.05$).

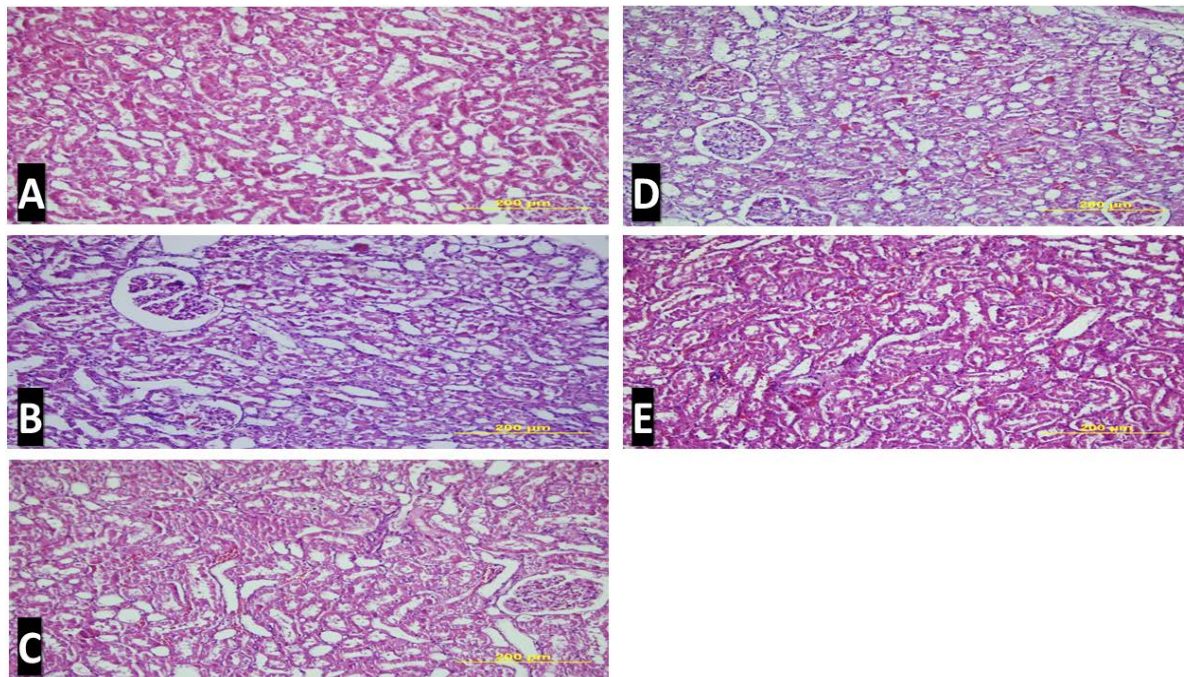


Figure 1. Histopathological examination of kidney samples of the groups (HEx20)

A. Sham Group Kidney; Mild interstitial edema, loss of brush border and tubular cast formation were observed in focal areas. **B. Control Group Kidney;** The findings seen in diffuse tubular damage include tubular dilatation, interstitial edema, tubule epithelial necrosis, and shedding of tubular epithelium into the lumen. **C: Dexmedetomidine Group Kidney;** However, tubular necrosis, which can be distinguished in a few focal areas, was accompanied by mild interstitial edema, brush border loss and focal mild tubular cast formation in focal areas. **D: Dexmedetomidine + Thymoquinone Group Kidney;** However, tubular necrosis, which can be distinguished in a few focal areas, was accompanied by mild interstitial edema, brush border loss and focal mild tubular cast formation in focal areas. **E: Thymoquinone Group Kidney;** However, tubular necrosis, which can be distinguished in a few focal areas, was accompanied by mild interstitial edema, brush border loss and focal mild tubular cast formation in focal areas.

Table 1. Comparison of TAS, TOS, OSI and Histopathological Damage Scores Between Groups

	Sham	Control	Dex	TQ	Dex-TQ	p
TAS	0.33±0.07 ⁺	0.07±0.01 [*]	0.13±0.03 ^{**}	0.14±0.03 ⁺⁺	0.13±0.01 ⁺⁺	<0.05
TOS	18.68±3.41 ⁺	36.97±6.26 [*]	27.46±5.90 ^{**}	27.51±3.73 ^{**}	26.41±5.84 ^{**}	<0.05
OSI	5.92±1.89 ⁺	54.84±20.67 [*]	21.29±7.11 ^{**}	20.11±6.90 ⁺⁺	20.82±6.23 ⁺⁺	<0.05
HDS	2.60±0.69 ⁺	4.60±0.69	3.10±0.87 ⁺	2.80±0.91 ⁺	3.10±1.44 ⁺	<0.05

* Significant value according to sham group $p < 0.05$ + Significant value compared to the control group $p < 0.05$

Dex: Dexmedetomidine; TQ; Thymoquinone; HDS: Histological damage scoring TAS: Total Antioxidant Status; TOS: Total Oxidant Status; OSI: Oxidative Stress Index

Discussion

Our aim in this study is to investigate the effects of Thymoquinone and Dexmedetomidine on the kidneys in IRI caused by IR in the hind limb with tourniquet in rats. As a result, histopathological damage and TAS, TOS, OSI values in TQ, DEX and DEX-TQ groups were found to be significantly more positive in terms of oxidative stress compared to the control group.

IRI occurs after the use of tourniquets in the lower extremities in various surgical operations, especially in orthopedic surgery. IRH has local and systemic effects, and kidney involvement from distant organs affects morbidity and mortality (13,14). Since the tourniquet is widely used in daily surgical practice, the experimental hind limb IR model was taken as an example to see its effects. In studies on this subject, the response of the kidneys of rats was very well determined, and rats were preferred in most of the studies (15). We also used Wistar albino rats in our study.

Many studies have been conducted on antioxidant treatments, since FOR caused by IRH causes undesirable results in many tissues and organs. Since oxidative damage plays a role in the pathogenesis of many pathologic situations such as diabetic nephropathy (16), atrial fibrillation (17), studies have been conducted using antioxidants in the treatment. Antioxidant vitamin E has been shown to reduce the damage in diabetic nephropathy in humans and alpha lipoic acid in rats (18).

Various models were used to generate hind limb IRI in rats. Femoral artery clamping or bandaging methods are used (8,19,20). In our study, Ischemia was provided to the left lower extremities of the rats with an elastic bandage, modeling the method used by Yassin et al. (9). In our study, considering previous studies, a 2-hour reperfusion was performed after 4 hours of ischemia.

The effects of various new agents such as thymoquinone and curcumin are also being investigated for the prevention of cellular damage (21,22). Many chemicals and drugs have been used in experimental models to reduce IRI, but they have not been used in daily practice due to serious side effects or unsuitable use during surgery. Therefore, the effects of sedatives and hypnotics used during anesthesia on IRH have been important (23). In our study, we preferred Dexmedetomidine, an alpha-2 agonist used for sedation in anesthesia and intensive care units, because of its protective effects against IRH (24,25). In studies investigating the effects of dexmedetomidine on the kidney in IR models, histopathological evaluations were made. Parameters such as necrosis in the tubular epithelium, apoptosis, neutrophil infiltration, loss of brush border due to IRH in the kidneys were examined and evaluated with various damage scores. In the study of Koçoğlu et al., the protective effect of dexmedetomidine on the kidneys against IRH was demonstrated histopathologically (19). It has also been shown to be protective in the lung (26) and contralateral kidney (27) in a renal IR model. When the kidney samples taken in the IR model created by mesenteric artery occlusion were examined, histopathologically less damage was observed in the Dexmedetomidine group compared to the control group (24).

In our study, TAS, TOS, and OSI levels were measured. Although there was no significant difference between Dex, TQ and Dex-TQ groups, TAS in these 3 groups was higher than the control group, lower than the Sham group, and TOS and OSI were lower than the control group and higher than the Sham group. (Table 1) ($p < 0.05$).

Thymoquinone is the active ingredient derived from *N. Sativa* and has become popular among medicinal plants due to its proven therapeutic properties. It has anti-inflammatory, anti-neoplastic, gastroprotective, anti-epileptic, anti-histaminic properties. Its most important feature is its antioxidant effect. It acts as an anion scavenger and neutralizes oxygen radicals. Since FOR occurring in IRI plays a role in the pathogenesis of many diseases, Thymoquinone and *N. Sativa* products have been used in many experimental and clinical studies due to their antioxidant properties (28).

The effects of Thymoquinone have been investigated in different IR models. As a result, thymoquinone appears to be a promising agent with its neuroprotective effect in neurodegenerative conditions such as cerebral ischemia, providing protection against oxidative stress (29,30).

In a study in which another renal IR model was applied, *N. Sativa* was found to be effective in reducing urea, creatinine, and tubular necrosis score when the group given *N. Sativa* was compared with the control group. In addition, *N. Sativa*'s TAS was found to be higher and TOS and OSI lower than the control in both blood and kidney samples (31).

In a study investigating the effects of thymoquinone in a hind limb IR model, IR was provided by femoral artery ligation. Again, unlike our study, 2 hours of ischemia and 1 hour of reperfusion were applied. Thymoquinone at different doses (20, 40, 80mg/kg) 1 hour before reperfusion was divided into 3 groups (n:8) and administered i.p. and control and sham groups were formed to compare the results. It was concluded that thymoquinone showed antioxidant properties in the hind limb IR model and prevented the damage caused by oxidative stress on the striated muscle. Based on the EMG results, it was determined that Thymoquinone was protective in both ischemia and reperfusion phases, and the conductivity in neurons that were disrupted in ischemia was also preserved by Thymoquinone (21). In a recent study, it was reported that Thymoquinone and Dexmedetomidine together had a protective effect against erythrocyte deformity in rats treated with hind limb IRH (32).

In the hind limb IR model, we created with a tourniquet, we obtained data similar to this study. TAS in the thymoquinone group was higher than in the control; we found lower TOS and OSI. As demonstrated by the various IR models mentioned above, we also think that Thymoquinone has antioxidant properties. Thymoquinone's antioxidant property has been associated with various mechanisms.

1- The 'quinone' in its structure shows strong redox properties. It can easily pass-through barriers, easily reach the intracellular compartments, and thus scavenge oxygen radicals. Quinone reductase reduces the 2 electrons and prevents the participation of electrons in the cycle, which leads to the formation of FOR, and thus reduces oxidative stress (33).

2- Thymoquinone inhibited iron-dependent microsomal lipid peroxidation in vitro (28).

3- In case of inflammation, oxidants, eicosanoids, cytokines and lytic enzymes are released from inflammatory cells such as macrophages and neutrophils. Thymoquinone inhibits the LO and COX pathways that play a role in inflammation and suppresses oxidative stress with its anti-inflammatory effect (34).

In our study, we aimed to compare the effects of these two antioxidant agents in separate groups and in one group by giving Dexmedetomidine and Thymoquinone together, to compare their superiority over each other. As a result of the data we obtained, we could not find a statistical difference in terms of TAS, TOS, OSI and histopathologically.

Conclusion

As a result, When the data obtained from our study with rats with hind limb IR were evaluated; Thymoquinone and Dexmedetomidine significantly reduce kidney damage due to ischemia-reperfusion. These two agents have no superiority over each other in terms of oxidative stress. In surgical operations where tourniquets are used in the clinic, the kidneys are

affected due to oxidative stress. These effects of Dexmedetomidine should be considered in anesthesia management and intensive care follow-ups in patient groups with poor renal functions such as ARF and CRF or in patients whose renal functions need to be preserved such as transplantation. Thymoquinone has been shown to have antioxidant properties in experimental studies. Further clinical studies are needed to benefit from these features in the clinic.

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Ethical Approval: Ethical Approval was obtained before the study from Harran University Animal Experiments Local Ethics Committee (approval decision: dated 30.04.2012, numbered B.30.2.HRU.0.05.07.00/270).

Author Contributions: Concept: H.A., Ş.Y. Literature Review: E.B., H.A., Ş.Y., M.A.K. Design : H.A., Ş.Y.

Data acquisition: E.B., M.A.K., H.H.Y., A.K. Analysis and interpretation: H.A., N.A., A.T., S.K. Writing manuscript: E.B., H.A., M.A.K. Critical revision of manuscript: E.B., H.A., M.A., Ş.Y.

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











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Original Article

Evaluating Seminal Vesicle Invasion with Multiparametric Magnetic Resonance Imaging in Patients Diagnosed with Prostate Cancer: Is Radiologist Experience Effective?*Prostat Kanseri Tanılı Hastalarda Multiparametrik Manyetik Rezonans Görüntüleme ile Seminal Vezikül İnvazyonunu**Değerlendirme: Radyolog Deneyimi Etkili Mi?***İsmail Evren¹ , Deniz Noyan Özlü^{1*} , Mithat Ekşi² , Ahmet Hacıslamoğlu¹ , Serdar Karadağ¹ , Taner Kargı¹ , Hakan Polat¹ , Yunus Çolakoğlu³ , Ömer Yıldız⁴ , Rüştü Türkay⁵ **¹University of Health Sciences Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, İstanbul, Türkiye²Arnavutköy State Hospital, Department of Urology, İstanbul, Türkiye³Başakşehir Çam & Sakura City Hospital, Department of Urology, İstanbul, Türkiye⁴University of Health Sciences Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Radiology, İstanbul, Türkiye⁵University of Health Sciences Haseki Training and Research Hospital, Department of Radiology, İstanbul, Türkiye**Abstract****Background:** Predicting seminal vesicle invasion (SVI) in patients diagnosed with prostate cancer with multiparametric magnetic (mp) resonance imaging (MRI) provides more accurate local staging and thus more appropriate treatment management. Because mpMRI has a steep learning curve, radiologist experience is crucial. Our study aimed to show the difference that the experience of the urologist would create in the detection rate of mpMRI and SVI by comparing it with radical prostatectomy tissue histopathology.**Materials and Methods:** Patients with positive SVI in radical prostatectomy specimen were included in the study. The group of radiologists less experienced in genitourinary radiology was defined as Observer I, and experienced urologists as Observer II (5 years and more than 2000 MR experience) and Observer III (4 years and more than 1000 MR experience). The groups were compared in terms of accurately predicting SVI positivity.**Results:** Ninety (11.22%) patients were included in the study. All patients were positive for SVI, 80 patients (88.9%) had extraprostatic spread, 21 (23.3%) patients had lymph node (LN) invasion, and 20 (22.2%) patients did not undergo LN dissection. The rates of correctly predicting SVI positivity were 25.9%, 73.8%, 81% for Observer I, II, and III, respectively. The accuracy rate of Observer II and Observer III was significantly ($p < 0.05$) higher than the Observer I group. The accuracy rate did not differ significantly ($p > 0.05$) between Observer II and III groups.**Conclusion:** The ability of mpMRI to detect local factors such as SVI is enhanced by the radiologist's experience, which has the potential to create significant differences in proper staging and treatment plans.**Keywords:** Seminal vesicles, multiparametric magnetic resonance imaging, prostate neoplasms**Öz****Amaç:** Prostat kanseri tanılı hastalarda multiparametrik (mp) manyetik rezonans görüntüleme (MRI) ile seminal vezikül invazyonunu (SVI) öngörme, daha doğru lokal evrelemeyi, böylece daha uygun tedavi yönetimini belirlemeyi sağlamaktadır. mpMRI belirgin bir öğrenme eğrisi gösterdiğinden, radyolog deneyimi önem arz etmektedir. Çalışmamızda, üroradyoloğun deneyiminin mpMRI ile SVI saptama oranında yaratacağı farkı, radikal prostatektomi doku histopatolojisi ile karşılaştırarak göstermeyi hedefledik.**Gereç ve Yöntemler:** Radikal prostatektomi spesmeninde SVI pozitifliği saptanan hastalar çalışmaya dahil edildi. Genitouriner radyolojide daha deneyimsiz radyologlardan oluşan grup Gözlemci I olarak, deneyimli üroradyologlar ise Gözlemci II (5 yıl ve 2000'in üzerinde MR deneyimi) ve Gözlemci III (4 yıl ve 1000'in üzerinde MRI deneyimi) olarak tanımlandı. Gruplar, SVI pozitifliğini doğru tahmin etme açısından karşılaştırıldı.**Bulgular:** Doksan (11,22%) hasta çalışmaya dahil edildi. Tüm hastalar SVI pozitif olup, 80 hasta (88,9%) ekstraprostatik yayılım, 21 (23,3%) hastada lenf nodu (LN) invazyonu mevcut olup, 20 (22,2%) hastaya LN diseksiyonu yapılmamıştır. SVI pozitifliğini doğru tahmin etme oranları sırasıyla Gözlemci I, II ve III için, 25,9%, 73,8%, 81%'dir. Gözlemci II ve Gözlemci III'ün doğruluk oranı Gözlemci I grubundan anlamlı ($p < 0,05$) olarak daha yüksektir. Gözlemci II ve Gözlemci III grupları arasında doğruluk oranı anlamlı ($p > 0,05$) farklılık göstermemiştir.**Sonuç:** Radyoloğun deneyimi, mpMRI'nin SVI gibi lokal faktörleri tespit etme gücünü arttırmakta, bu durum doğru evreleme ve tedavi planında önemli farklar yaratma potansiyeli taşımaktadır.**Anahtar Kelimeler:** Seminal veziküller, multiparametrik manyetik rezonans görüntüleme, prostat neoplazileri***Corresponding author:**

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Introduction

The fundamental goal of prognosis and therapeutic management in prostate cancer (PCa) is to distinguish the localized disease from locally advanced disease. The extraprostatic extension (EPE) and seminal vesicle invasion (SVI) have a worse prognosis due to a higher risk of post-surgical biochemical recurrence (BCR), increased risk of lymph node metastases, and positive surgical margins (1). SVI is directly associated with local recurrence and distant metastasis (2). In these patients, 5-year BCR development rates range from 8% to 68%, with the effect of factors such as Gleason grade, Prostate-specific antigen (PSA) and positive surgical margin (3,4).

Predictive models such as the Kattan nomogram (5) and the Partin tables (6) are used to assess the pre-treatment risk of SVI. Moreover, patients are divided into risk groups based on Gleason grade, clinical T stage and PSA values. In addition to all of these, the widespread use of multiparametric (mp) Magnetic Resonance Imaging (MRI) and the advancement of its techniques have accelerated the process by providing advantages in the diagnostic evaluation of local staging of PCa (7).

When MRI was first employed in prostate cancer in the 1980s, it was limited to T1 and T2-weighted scans, with the primary goal of gaining insight into local staging in patients diagnosed with PCa via biopsy. However, with mpMRI technology, this measurement combined with diffusion-weighted imaging (DWI), diffusion coefficient (ADC) and dynamic contrast-enhanced imaging (DCI) sequences created the possibility of functional and physiological evaluation of the prostate. With the publication of Prostate Imaging and Reporting and Data System (PIRADS) Version 2 in 2014, the evaluation of prostate cancer with MRI has been standardized (8). The precision of MRI in detecting parameters such as SVI and EPE reflects its power in local staging.

The disadvantage of MRI regarding its consistency is due to the interobserver agreement. This problem may be due to the difference in experience among radiologists, as mpMRI shows a marked learning curve (9). Our study aimed to show the difference that the experience of the urologist will create in the detection rate of mpMRI and SVI by comparing it with radical prostatectomy tissue histopathology.

Materials and Methods

Following the ethics committee approval (2020/234), the data of 806 patients who underwent radical prostatectomy for prostate cancer in Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Urology, of from January 2017, when the routine use of mpMRI started in our centre, to December 2020, were retrospectively analyzed. The study was carried out in compliance with the Helsinki Declaration. Patients with unilateral or bilateral SVI in the postoperative pathology specimen (n=99, [12,34%]) were included in the study. Patients with a diagnosis of prostate cancer who received chemotherapy, radiotherapy or hormonal therapy before surgery, patients who did not have preoperative mpMRI and whose mpMRI was found in an external centre, patients who had visual deterioration and artefacts in their mpMRI due to lack of cooperation were excluded. Age, body mass index (BMI), PSA levels and prostate volumes (PV) measured by MRI were recorded. The reference standard for SVI was taken as the histopathological evaluation after radical prostatectomy. Histopathological examination was performed by two experienced urologists unaware with mpMRI interpretations. All specimens were graded according to the International Society of Urological Pathology (ISUP) grade system, and SVI was defined as cancer invasion into the extraprostatic portion of the seminal vesicles (10). Moreover, the presence of EPE, lymph node (LN) invasion, and surgical margin positivity were recorded. Prostate cancer staging was performed according to the 2017 TNM classification with MRI, ISUP grade, and PSA level (11). Patients were classified as low, intermediate, and high risk according to the European Association of Urology (EAU) 2021 Guideline (11). In the interpretation of the patients' MRIs, the observer assignments were random and no special settings were made according to the risk group. Radical prostatectomy procedures were performed using open retropubic, open perineal, laparoscopic, perineoscopic, robot-assisted transperitoneal laparoscopic radical prostatectomy (RARP) or robot-assisted perineal radical prostatectomy (r-PRP) methods. Surgical techniques have been previously mentioned in the literature (12).

MRI technique

The presence of claustrophobia, a pacemaker, or an estimated GFR of ≤ 30 mL/min/1.73 m² were considered as contraindications for MRI. All mpMRI imaging was performed with a 3 Tesla MRI device (Magnetom Verio; Siemens,

Erlanger, Germany) with 16 channel phased array coils. T2 weighted turbo spin echo (TSE) sequence (Slice thickness, 3.5 mm with no intersection gap; TR, 5800 ms; TE, 100 ms; number of signals acquired, 2; resolution, 0.8 mm × 0.8 mm) in 3 planes (axial/ sagittal/ coronal) were obtained. Diffusion-weighted images were acquired as spin echo planar images (Slice thickness, 3.5 mm with no intersection gap; TR 3900/TE 75 ms; number of signals acquired, 1; resolution, 1.4 mm × 1.4 mm; b - factor, 50/ 500 /1000/ 1500 s/mm²). Apparent Diffusion Coefficient (ADC) mapping was performed from the b50, b500, b1000 and b1500 diffusion images using SyngoVia workstation software. T1-weighted high-resolution, fat saturated, isotropic volume imaging was used for dynamic perfusion imaging (Slice thickness, 3 mm; no intersection gap; TR, 5.08/TE 1.77 ms; number of signals acquired, 1; resolution, 1.4 mm × 1.4 mm; contrast injection. The sequence started 24 seconds after initial acquisition; temporal resolution, 8 seconds; number of dynamic time points, 25; total DCE time, 200 seconds). DCE imaging was performed after intravenous injection of 0.1 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Villepinte, France), followed by a 10-ml saline flush, at an injection rate of 3 ml/sec. Endorectal coil (ERC) was not used. SVI was reported as low signal intensity in the seminal vesicles on T2-weighted sequences or a prominent mass on diffusion-weighted and contrast-enhanced sequences confirming findings on T2, as described in PIRADS v2 (8).

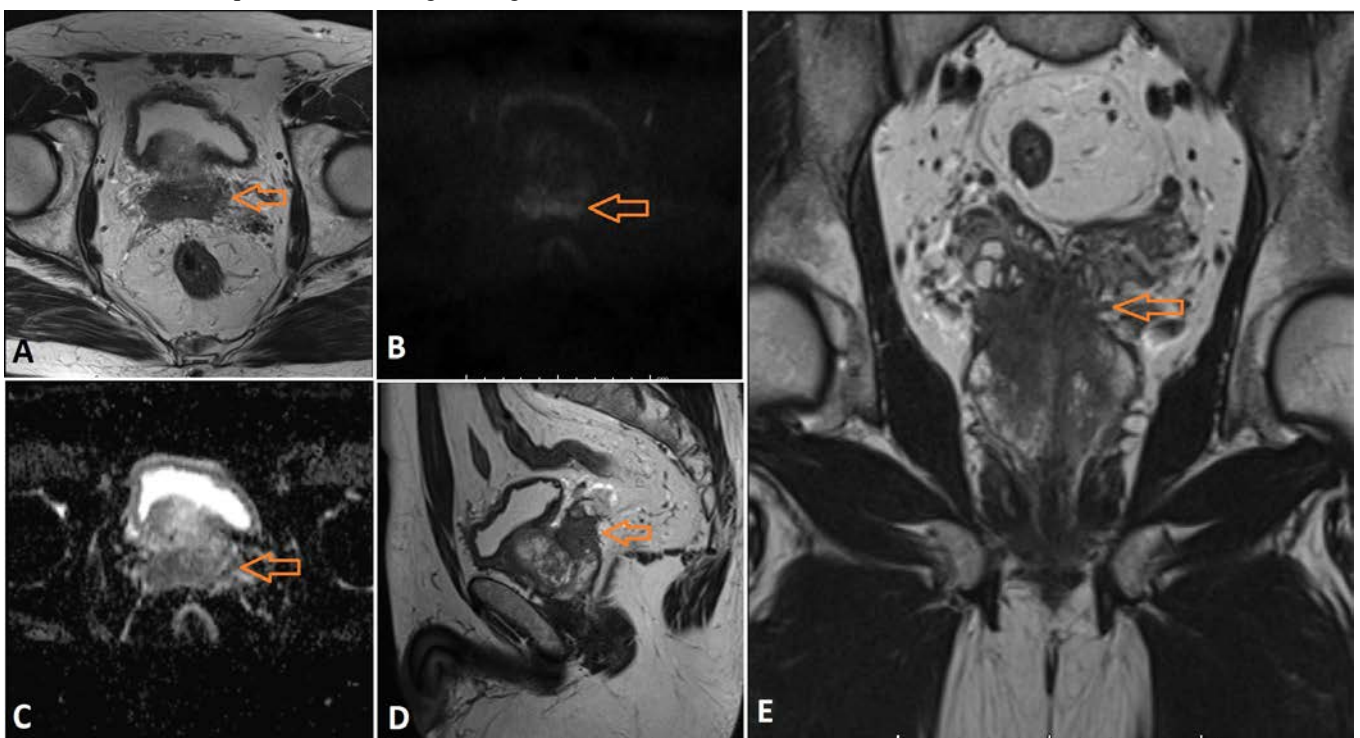


Figure 1. Example of a true positive SVI MRI finding. 68-year-old man with high PSA level (14.8 ng/ml): on mp-MRI which is performed 2 months after positive prostate biopsy (Gleason score was 3+3 on three cores and 3+4 on one core). Axial T2WI (**Fig. 1a**) showing a homogeneous, hypointense mass in bilateral seminal vesicles. Axial DWI (**Fig. 1b**), ADC map (**Fig. 1c**) showing hyperintense signal on high b-value (b 1500) and markedly hypointense mass on ADC map. Sagittal T2WI (**Fig. 1d**) and coronal T2WI (**Fig. 1e**) MRI showing bulging of prostatic capsule, which is a sign of extraprostatic extension, and invasion to bilateral seminal vesicles. Histopathological analysis after radical prostatectomy confirmed bilateral seminal vesicle invasion and extraprostatic extension with Gleason score 4+4.

Both MRI acquisitions made before or after prostate biopsy were considered eligible for inclusion, as in both scenarios, staging information is provided. In patients who had previously undergone transrectal ultrasound-guided biopsy, hyperintense signal on pre-contrast T1-weighted sequences and hypointense areas on T2-weighted sequences were associated with bleeding in the seminal vesicles or prostate (Figure 1). Patients' PSA levels, clinical data, and, if a biopsy was performed before imaging, the histopathological data were all provided to the urologists who conducted the evaluation. The urologists were divided into groups based on their experience. The group of radiologists less experienced in genitourinary radiology was classified as Observer I. The radiologists in this group were those who worked in the field of general radiology and were not dedicated to urology, had no experience with transrectal ultrasound and prostate biopsy, and had less than 500 prostate mpMRI

experience in total. Whereas experienced urologists were defined as Observer II (5 years and more than 2000 MRI experience) and Observer III (4 years and over 1000 MRI experience). The groups were compared in terms of accurately predicting SVI positivity.

Categorical data were given as numbers and percentages. Means and standard deviations were calculated for continuous variables. The frequency of categorical variables was compared using Pearson chi-square, ANOVA and Post-hoc test. The p values of less than 0,05 were regarded as statistically significant. Statistical analysis was performed using Statistical Package of Social Sciences version 21 (IBM SPSS Statistics; IBM Corp., Armonk, NY).

Results

After applying the exclusion criteria, 90 (11.22%) patients with SVI positivity in radical prostatectomy pathology were included in the study. The mean age of the patients was 61.2 ± 6.7 (range: 49-75) years and the mean BMI as 26 ± 2.6 kg/m² (range: 20,5–31,9). Preoperative mean PSA level was 21.7 ± 24.2 ng/dl (range: 4,1-280). In the preoperative evaluation of the whole patient group, 9 (10%) patients are in the low-risk group, 48 (53.3%) patients are in the medium-risk group and 33 (36.7%) patients are in the high-risk group. In postoperative pathology, all patients were positive for SVI, 80 patients (88.9%) had EPE and 45 (50%) had positive surgical margins. There were 21 (23.3%) patients with LN invasion and 20 (22.2%) patients who did not undergo LN dissection. Preoperative demographic data, biopsy, and radical prostatectomy pathologies of the patients are presented in Table 1. The preoperative MRI findings are shown in Table 2. The prostate volume measured by MRI is 35.8 ± 16.8 cc (range: 17-140). In the entire group, 55 (61.1%) patients had a suspicion of SVI by MRI, compared to 41 (45.6%) for suspected EPE and 14 (15,6%) for LN metastasis. The number of patients reported for MRI by Observer I was 27 (30%), the number of Observer II was 42 (46.7%), and Observer III was 21 (23.3%).

The numbers and rates of radiologists reporting the presence of SVI in the MRI report are given in Table 3 and Figure 2. Observer I reported positive SVI in seven patients with a 25.9% accuracy rate, compared to 73.8% for Observer II and 81% for Observer III. The accuracy rate of Observer II and Observer III was significantly ($p < 0.0001$) higher than the Observer I group. The accuracy rate did not differ significantly ($p > 0.05$) between Observer II and III groups.

Table 1: Demographic data of patients, preoperative and postoperative pathology data

Parameters		Mean \pm SD (n; %)
Age		61.2 ± 6.7
BMI		26 ± 2.6
PSA		21.7 ± 24.2
Preoperative Risk	Low-risk	9 (10)
	Intermediate-risk	48 (53.3)
	High-risk	33 (36.7)
PSM	(-)	45 (50)
	(+)	45 (50)
EPE	(-)	10 (11.1)
	(+)	80 (89.9)
SVI	(-)	0 (0)
	(+)	90 (100)
T stage	3b	65 (72.2)
	4	25 (27.8)
LNI	(-)	49 (54.5)
	(+)	21 (23.3)
	Not dissected	20 (22.2)

BMI: Body mass index, PSA: Prostate-specific antigen, PSM: Positive surgical margin, EPE: extraprostatic extension, SVI: seminal vesicle invasion, LNI:

Lymph node invasion

Table 2. MRI data and staging findings

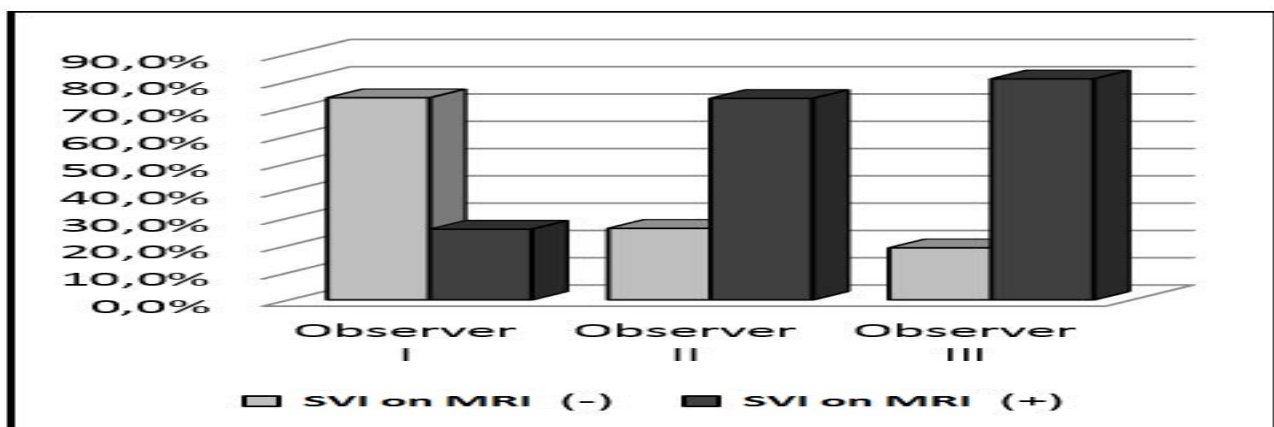
Parameters		Mean \pm SD (n; %)
Prostate volume measured on MRI		35.8 \pm 16.8
SVI on MRI	(-)	35 (38.9)
	(+)	55 (61.1)
EPE on MRI	(-)	49 (54.4)
	(+)	41 (45.6)
LNI on MRI	(-)	76 (84.4)
	(+)	14 (15.6)
Observer I		27 (30)
Observer II		42 (46.7)
Observer III		21 (23.3)

MRI: Magnetic resonance imaging, *SVI*: seminal vesicle invasion, *EPE*: extraprostatic extension, *LNI*: Lymph node invasion

Table 3. Rates of observers accurately predicting SVI with MRI

		Observer I n(%)	Observer II n(%)	Observer III n(%)	P
SVI on MRI	(-)	20 (74.1)	11(26.2)	4(19)	<0.0001 ^{x2} Observer I< Observer 2= Observer 3
	(+)	7(25.9)	31(73.8)	17(81)	

MRI: Magnetic resonance imaging, *SVI*: seminal vesicle invasion ^{x2}Chi-square test

**Figure 2.** Accuracy rates in predicting SVI on MRI among Observers

Discussion

In the case of PCa, staging is crucial in determining treatment options and minimizing risks such as under- or over-treatment. In the classical management of PCa, the decision is made by a combination of parameters such as the histological grade of the tumour obtained by biopsy, PSA level, and rectal examination. However, when using these methods to determine tumour aggressiveness, the risk of under-staging is common, and locally progressed disease can be undetected (13). Suspicion of EPE or SVI in terms of local staging also directly affects the definitive treatment decision, as it brings risks such as insufficient resection in radical prostatectomy and low dosage to seminal vesicles in brachytherapy (7). It will also determine the surgical technique or the dose, template, and adjuvant treatment decisions in radiotherapy, such as defining locally advanced disease, performing extended lymph node dissection, avoiding nerve-sparing surgery to avoid surgical margin positivity (9).

Current patterns in staging PCa are shifting as MRI becomes more widely used in clinical staging. The use of MRI guides definitive treatment and improves surgical, oncological, and functional management (14). In the literature, the sensitivity of

mpMRI in PCa ranges from 53% to 89%, and the specificity ranges from 71% to 90.3% (15,16). When it comes to detecting SVI, sensitivity ranging between 34.9-100% and specificity ranging from 86.1% to 99% have been reported (13, 17-21). A recent meta-analysis showed that even at low sensitivity rates (58%), MRI can detect SVI with high specificity (96%) (13). One factor contributing to the accuracy rates may be the high field strength acquisition of MRI using the 3T system. Ruprecht et al. reported 78% sensitivity and 92.8% specificity in their study using a 1.5 T MRI device (20). However, in the study of Sahin et al., SVI was detected with 85% sensitivity and 96% specificity. The authors attributed this difference to the use of the 3T device and the experience of the urologist (21). In our study, due to its higher magnetic strength, we used a 3T MRI device in all patients, and we aimed to create a more homogeneous patient group by excluding all patients who used ERC.

Gupta et al., in their study comparing mpMRI with the Partin nomogram in organ confined PCa, found the area under the curve (AUC) values to be 0.82 and 0.62, respectively. However, predictive values for SVI were not specifically examined in this study (22). Morlocca et al., in their study in which they compared clinical prediction models such as Partin and CAPRA with mpMRI, discovered that while AUC values were 0.75 and 0.82 in the Partin and Partin + MRI models, respectively, these values were 0.75 and 0.83 in the CAPRA and CAPRA + MRI models (23).

According to guidelines jointly revised by EAU, The European Society for Radiotherapy and Oncology (ESTRO), and The International Society of Geriatric Oncology (SIOG), mpMRI can influence treatment decision by detecting SVI and be used in high-risk or locally advanced PCa (24). Furthermore, MRI also provides excellent soft-tissue separation and is the best approach for preoperative local T staging, according to EAU recommendations (11).

There are also studies stating that mpMRI is still doubtful in making the treatment decision and does not show significant superiority over the clinical parameters used in the Partin tables (9,13,25). More than half of the patients (55%) in Jansen et al.'s study could not be diagnosed with preoperative mpMRI despite being locally advanced (T3-4). Nearly half of these patients did not undergo lymph node dissection and the nerve-sparing surgery approach was chosen. This indicates the potential for undertreatment of false radiological evaluation (9). In our study, although there was locally advanced disease, the rate of patients who did not undergo lymph node dissection was found to be 22.2%. Of course, this low rate cannot be attributed to understaging alone because surgical variables and the operator's perioperative decision will also be influential in the lymph node dissection decision. However, more accurate preoperative staging offers the potential to prevent undertreatment by providing a more effective treatment plan. Again, in the study of Jansen et al., 24% of patients with organ confined PCa gave false positivity in MRI in local further evaluation. The authors concluded that using mpMRI in patients at increased risk of locally advanced disease did not result in a significant improvement in diagnostic accuracy (9).

A strong relationship between SVI and other preoperative clinical characteristics such as EPE has been demonstrated previously. Both conditions can be explained by similar pathological mechanisms that push the tumour to grow invasively (26). The mpMRI has been shown to have good diagnostic accuracy in EPE. Tay et al. showed that radiologists experienced in urology were more likely to predict EPE with mpMRI than inexperienced radiologists, and they found the AUC value as 0.91 and 0.72, respectively (27).

In the study of Popita et al., the interobserver agreement in terms of SVI was examined, and a higher agreement was obtained among the radiologists in the evaluations where mpMRI was taken before the biopsy or without the use of ERC. The authors reported that changes such as post-biopsy haemorrhage may be the cause of this. The accuracy of SVI detection differed according to the use of ERC during mpMRI. While sensitivity and negative predictive value were higher in the group with ERC, higher accuracy rates were achieved with high specificity and positive predictive value in the group without ERC (18). According to a meta-analysis of 75 studies including 9,796 patients, 18 of which were prospective, the use of ERC provided no additional benefit for EPE detection, but slightly improved the sensitivity of SVI detection (13). These examples demonstrate the necessity of MRI technology as well as the radiologist's experience.

There are limited studies in the literature about the learning curve of mpMRI in local staging. A meta-analysis showed that the multiplicity of procedures included had no effect on diagnostic accuracy (13). In another recent study, it is reported that the sensitivity for the locally advanced disease does not improve over the years, despite increasing experience with mpMRI and the increasing number of procedures performed (9). The authors thought that the reason why the accuracy rate did not increase

at the same rate as expected as the number of procedures increased may be the decrease in the time spent by radiologists for evaluation. Given the marked increase in the number of scans, the time available per scan could have been built to possibly offset a potential learning effect. In the patient series of Grivas et al, 72% of the mpMRIs taken were interpreted by radiologists experienced in urology, and higher sensitivity and specificity rates were obtained in the detection of SVI in this group (84.4%, 95.6%, respectively) (7). Ruprecht et al., in their study comparing a urologist with 15 years of experience and an inexperienced radiologist in genitourinary radiology, found a significant difference in local staging efficiency with MRI in favour of an experienced radiologist (86.96% vs. 56.52%). As a result, the interobserver agreement detected a rather weak agreement (20). We also found in our study that the experience of the urologist significantly increased the rate of accurate estimation of SVI with mpMRI. In our patient group with SVI histopathologically verified, the rate of true positive for experienced urologists (Observer II and III) is almost three times higher than those without experience in genitourinary radiology (Observer I) (73.8%, 81% vs. 25.9%, respectively). Although Observer II is more experienced than Observer III, true positive rate was detected with lower accuracy. This may be because the Observer II's MRI reports are older, and the PIRADS scoring system has evolved and become more standardized since then. Of course, this situation can be considered as a limitation of the study. Another reason may be that the distribution of patients according to risk groups is random and not homogeneous. But it should also be noted that the difference between observer II and III is not statistically significant.

The most important limitation of our study is that since the patient group was only SVI positive patients, there was no control group and data such as sensitivity, specificity, false positive, true negative and predictive values could not be given. This situation prevented us from making sensitive and specificity comparisons with the literature. In addition, the radiologists' knowledge of patients' clinical data such as PSA and biopsy is another factor that may affect the results of the study. The fact that the patient distribution was made randomly to the radiologists and the available data were used retrospectively can be presented as another limitation. In addition, mpMRI technology still has limitations. SVI can also occur only microscopically, and low-volume invasion cannot be detected on MRI (7).

Conclusion

The diagnostic accuracy of mpMRI will increase as imaging technology, the PIRADS scoring system, and the experience of radiologists improve. The ability of mpMRI to detect local factors such as SVI is enhanced by the radiologist's experience, which has the potential to create significant differences in proper staging and treatment plans.

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Analysis and interpretation: TK,HP,RT Writing manuscript: İE, DNÖ, ME, ÖY Critical revision of manuscript: ME, AH, SK, TK, HP

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Original Article**Relationship between basal liver function test levels and contrast-induced nephropathy in patients undergoing coronary angiography**

Koroner anjiyografi yapılan hastalarda bazal karaciğer fonksiyon test düzeyleri ile kontrasta bağlı nefropati gelişimi arasındaki ilişki

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Abstract

Background: The purpose of this study was to evaluate the relationship between initial levels of conventional liver function tests (ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: gama glutamil transferase; ALP: alkaline phosphatase) and contrast induced nephropathy (CIN). **Material and methods:** We conducted a retrospective study of 373 subjects with acute coronary syndrome who underwent coronary angiography (CAG). According to the development of CIN, the patients were divided into two groups as those who did not develop contrast nephropathy (Group 1) and those who did (Group 2). Both groups were compared in terms of age, gender, diabetes mellitus, hypertension, estimated glomerular filtration rate (eGFR), laboratory parameters and conventional liver enzymes (ALT, AST, GGT, ALP). The patients were given isotonic solution at a rate of 1 mL/kg/hour as a standard before and after the procedure. CIN is defined as a ≥ 0.5 mg/dL rise in serum creatinine or a 25% increase, assessed within 48-72 hours after administration of contrast medium (CM). **Results:** Overall, CIN developed in 104 patients (group 2 [27.8%]). Age, ALT and AST levels were significantly higher in patients who developed CIN than those without CIN ($p=0.025$, $p<0.001$, $p<0.001$; respectively). In correlation analysis, creatinine increase rate was positively correlated with ALT and AST levels ($r = 0.161$, $p = 0.002$; $r=0.318$, $p<0.001$; respectively). Multivariate logistic regression analysis demonstrated that AST level was an independent predictor of CIN (OR 1.006, 95% CI 1.003–1.009, $p<0.001$). **Conclusions:** According to study; high AST levels may predict CIN in patients who undergoing CAG.

Keywords: Liver function tests, contrast induced nephropathy, coronary angiography

Öz

Amaç: Bu çalışmanın amacı, konvansiyonel karaciğer fonksiyon testlerinin (ALT- Alanin aminotransferaz; AST- Aspartat aminotransferaz; GGT- gama glutamil transferaz; ALP- alkalik fosfataz) başlangıç düzeylerinin kontrast kaynaklı nefropati (KKN) ile arasındaki ilişkiyi değerlendirmektir. **Gereç ve Yöntem:** Koroner anjiyografi (KAG) uygulanan akut koroner sendromlu 373 hastayla retrospektif bir çalışma yürüttük. Hastalar KKN gelişimine göre; kontrast nefropati gelişmeyenler (Grup 1) ve gelişenler (Grup 2) olarak iki gruba ayrıldı. Her iki grup yaş, cinsiyet, diabetes mellitus, hipertansiyon, başlangıç tahmini glomerüler filtrasyon hızı (eGFR), laboratuvar parametreleri ve konvansiyonel karaciğer enzimleri (ALT, AST, GGT, ALP) açısından karşılaştırıldı. Hastalara işlem öncesi ve sonrası standart olarak 1 mL/kg/saat hızında izotonik solüsyon verildi. KKN, kontrast maddenin (KM) uygulanmasından sonraki 48-72 saat içinde değerlendirilen, serum kreatinin düzeyinde $\geq 0,5$ mg/dL'lik bir artış veya %25'lik bir artış olarak tanımlanır. İncelenen parametreler ile KKN oluşumu arasındaki ilişkiyi analiz ettik. **Bulgular:** Toplam olarak 104 hastada kontrast nefropati gelişti (grup 2 [%27.8]). KKN gelişen hastalarda, KKN gelişmeyenlere göre yaş, ALT, AST düzeyleri anlamlı olarak daha yüksekti ($p=0.025$, $p<0.001$, $p<0.001$; sırasıyla). Korelasyon analizinde kreatinin artış oranı, ALT ve AST seviyeleri ile pozitif korelasyon gösterdi (sırasıyla $r = 0.161$, $p = 0.002$; $r=0.318$, $p<0.001$). Çok değişkenli lojistik regresyon analizi, AST seviyesinin KKN'yi bağımsız bir şekilde öngördüğü tespit edildi (OR 1.006, %95 CI 1.003–1.009, $p<0.001$). **Sonuç:** Çalışmamıza göre; yüksek bazal AST seviyeleri, KAG yapılan hastalarda KKN gelişimini öngörebilir.

Anahtar Kelimeler: Karaciğer fonksiyon testleri, kontrast kaynaklı nefropati, koroner anjiyografi

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Introduction

Contrast-induced nephropathy (CIN), which is also called contrast-induced acute kidney injury (CI-AKI), is an iatrogenic disease occurring after the intravascular injection of iodinated radiographic contrast media (1). It accounts for 11–12% of all cases of in-hospital AKI and is also associated with an overall in-hospital mortality rate of 6% (2). CIN can result from intravenous or intraarterial injections of iodine-based contrast medium (CM) during advanced x-ray and computed tomography (CT) imaging studies or coronary artery interventions (3). Of all procedures using CM for diagnostic or therapeutic purposes, coronary angiography and percutaneous coronary intervention (PCI) are associated with the highest rates of CIN (4). More than half of cases are diagnosed after cardiac catheterization; these cases constitute 10-15% of hospitalizations for acute renal failure (5). Although various pathways have been proposed, including contrast-induced tubular toxicity, inadequate renal perfusion, reperfusion injury, inflammation, and apoptosis, the specific mechanisms of CIN are unclear (6). The incidence of CIN may be much higher in patients undergoing coronary angiography if there are underlying conditions such as chronic kidney disease (CKD), diabetes, heart failure or advanced age (7,8). CIN is also associated with longer hospital stay, increased morbidity and mortality, and additional cost (9).

Although many risk factors affecting the development of CIN after coronary angiography have been defined, the relationship between them has not been fully elucidated. There is insufficient data in the literature between routinely measured liver function tests and the development of CIN. The relationship between chronic liver disease and contrast nephropathy has been demonstrated in previous studies (10,11). However, the relationship between liver function tests, which is one of the indicators of acute liver injury, and CIN is not clear. Determining the predictive parameters and risk factors for CIN that may develop in patients undergoing coronary angiography is important in terms of prognosis. In this study, we aimed to elucidate the relationship between routine parameters showing liver function (ALT, AST, GGT, ALP) at the time of admission and CIN in patients who underwent coronary angiography with the diagnosis of acute coronary syndrome.

Materials and Methods

Study population

This study was a retrospective observational study performed at a single center, in which we performed a retrospective review of 373 consecutive cardiac catheterizations because of acute coronary syndrome from June 2021 to December 2021. In terms of population homogeneity, only patients presenting with non-ST-elevation myocardial infarction (NSTEMI) were included in the study. Diagnosis and treatment of acute coronary syndrome was performed according to current guidelines. The exclusion criteria were as follows: chronic liver disease, active hepatitis, acute and chronic biliary system disease, active infection, chronic inflammatory disease involving the skeletal system, chronic renal disease (GFR < 15 mL/min or haemodialysis treatment), right heart failure and advanced pulmonary hypertension, history of cancer and cases given more than 4 mL/kg of contrast agent. Patients were hydrated with 0.9% saline at 1 mL/kg/hr for 24 hours after admission to the intensive care unit and coronary catheterization. In patients with acute coronary syndrome and decompensated heart failure, the hydration rate was reduced to 0.5 mL/kg/h. A non-ionic, low osmolality, iodinated contrast agent (Iohexol-Omnipaque®) was used for catheterization. Maximal contrast agent usage was limited to 4 mL/kg. Although the amount of opaque administered to each patient varied, less opaque material was tried to be used in patients with chronic renal failure. Informed consent was obtained from all patients. This study was approved by the ethics committee of our hospital.

Study protocols and definitions

Patients conforming to the standards stated above were included and then divided into two groups (CIN developing group [group 2] and non-CIN developing group [group 1]). Clinical characteristics and in-hospital outcomes were extracted from patients' medical records. Serum ALT, AST, GGT, ALP levels and other biochemical parameters were measured before cardiac catheterization by the enzymatic colorimetric test at 37°C. This analysis was done

with the Roche/Hitachi analyzer (Mannheim, Germany). CRP, levels of total cholesterol, triglyceride, Ldl, Hdl and glucose levels were measured using standard enzymatic methods within 24 hours. Serum creatinine concentrations were measured before and within 48–72 hours of contrast agent administration in every patient. Patient demographics, clinical and baseline laboratory data were assessed. Renal function was assessed by the eGFR using the Modification of Diet in Renal Disease Study (MDRD). The MDRD formula is $(186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}) [\times 0.742 \text{ if female}]$. CIN is defined as a ≥ 0.5 mg/dL rise in serum creatinine or a 25% increase, assessed within 48–72 hours after administration of contrast medium (CM)⁽¹⁾.

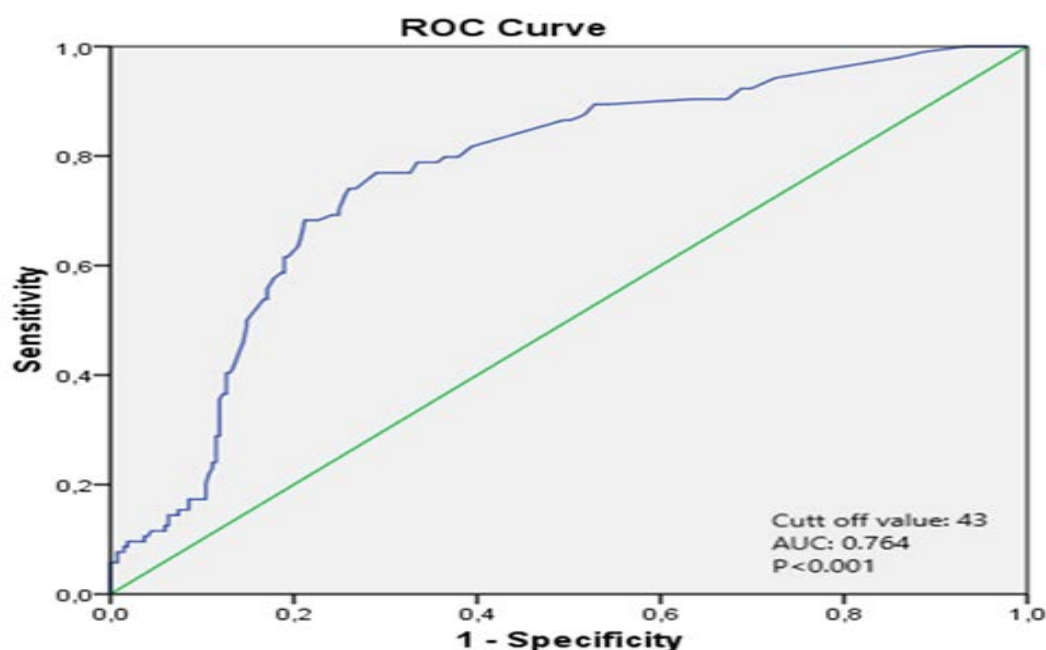
Statistical analysis

Statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). Mean \pm standard deviation, median and [maximum–minimum] were used for continuous variables, while percentages were used for categorical variables. The Kolmogorov-Smirnov test was used to test the normal distribution of the data. Continuous variables were expressed as mean \pm SD or median (interquartile range) and compared with Student's t or Mann-Whitney U tests according to distribution. Categorical variables were expressed as percentages and numbers and compared with the Chi-square test. Spearman correlation analysis was performed to determine the correlation of creatinine increase rate with other continuous variables. In addition, Univariate and multivariate regression analyses were performed to determine the independent predictors of CIN. The baseline variables for which evident significance ($p < 0.10$) was found by univariate analysis were included in the multivariate logistic regression analysis. Receiver operating characteristic (ROC) analysis was performed to determine the optimum cut-off value of the AST level for predicting CIN. The results of the model were reported as a 95% confidence interval (CI) and p-values. All p-values were two-sided in the tests and p-values less than 0.05 were considered to be statistically significant.

Results

373 patients who were diagnosed as acute coronary syndrome were included in our study. The baseline demographics and clinical characteristics of the patients are set out according to the development of contrast-induced nephropathy in Table 1. 227 (60%) of the patients were male and 146 (40%) were female. There was no statistically significant difference between the groups in terms of gender, diabetes mellitus (DM), hypertension, hyperlipidemia and smoking. CIN was observed in 27% of patients. Advanced age, low initial creatinine, low albumin and low Hdl as well as high ALT, AST levels were correlated with the development of CIN (Table 1).

Figure 1. Receiver operating characteristic curve analysis of aspartate aminotransferase and contrast-induced nephropathy



Positive correlation was detected between CIN and advanced age, ALT, AST levels in the correlation analysis and negative correlation was detected between eGFR, initial creatinine and albumin levels (Table 2). Advanced age and high ALT, AST levels were found to be predictors of CIN development in univariate regression analysis and advanced age and a high AST level was found to be predictors of CIN development in multivariate binary logistic regression analysis [OR 1.006, 95% CI 1.003–1.009, $p < 0.001$] (Table 3). The best cut-off value of AST in predicting the development of CIN was determined by ROC analysis (Figure 1). Accordingly, the sensitivity of an AST level ≥ 43 in predicting the development of CIN was 77%, and the specificity was 71% (area under the curve [AUC]: 0.764, 95% confidence interval [CI]: 0.712-0.817, $p < 0.001$)

Table 1. Distribution of clinical and dem characteristics of the patients according to the development of contrast-induced nephropathy

Variables	Group 1 (CIN-) n=269	Group 2 (CIN+) n=104	P
Age*	59.5 ± 11.3	62.6 ± 13.2	0.025
Gender ,male (%)	169 (%62)	58 (%55)	0.388
Diabetes mellitus, (%)	81 (%30)	37 (%35)	0.309
Hypertension ,(%)	163 (%60)	66 (%63)	0.610
Hyperlipidemia ,(%)	214 (%79)	87 (%83)	0.368
Smoking, (%)	148 (%55)	54 (%51)	0.591
Initial glucose,(mg/dL)**	122 (99-75)	125 (99-169)	0.653
Initial creatinine ,(mg/dL)**	0.8 (0.70-1.00)	0.7 (0.66-0.90)	0.001
Postprocedural creatinine, (mg/dL)**	0.9 (0.73-1.0)	1.0 (0.90-1.29)	<0.001
Uric acid ,(mg/dL)**	5.2 (4.3-6.1)	5.0 (3.9-6.1)	0.579
Albumin, (mg/dL)**	4.2 (4.0-4.5)	4.0 (3.7-4.4)	0.001
Triglycerides ,(mg/dL)**	150 (100-209)	135 (102-197)	0.664
Total cholesterol, (mg/dL)*	177±41	182±48	0.457
High-density lipoprotein ,(mg/dL)**	35 (30-41)	34 (26-39)	0.033
Low-density lipoprotein, (mg/dL)*	108 ± 35	109 ± 39	0.699
C-Reactive protein, (mg/dL)**	0.54 (0.16-1.32)	0.66 (0.20-1.52)	0.335
e-GFR, (mL/min)**	92 (74-101)	90 (75-102)	0.956
White blood cell, (x1000/mm3)**	9.0 (7.4-11.3)	9.6 (7.1-12.6)	0.477
Hemoglobin, (mg/dL)*	14 (13-15)	13 (12-15)	0.110
Hematocrit, (%) **	143 (39-47)	41 (38-46)	0.380
Platelet count (x1000/mm3)**	256 (214-302)	265 (223-315)	0.308
Alanine aminotransferase 0-34 U/L) **	26 (18-40)	40 (21-75)	<0.001
Aspartate aminotransferase(0-35 U/L)**	29 (20-51)	76 (45-97)	<0.001
Gama glutamil transferase (U/L) **	25 (18-40)	27 (18-45)	0.302
Alkaline phosphatase (mg/dL)**	83 (68-103)	86 (70-110)	0.141

Abbreviations: CIN: contrast-induced nephropathy;e-GFR: estimated glomerular filtration rate; * sign ; shows the Student's t test applied for the normal distribution. ** sign ; points to the Mann-Whitney U test applied for variables that do not fit the normal distribution.

Table 2. Correlation analysis between creatinine increase rate and laboratory parameters

Variables	r	P
Age	0.127	0.014
Alanine aminotransferase (0-34 U/L)	0.161	0.002
Aspartate aminotransferase (0-35 U/L)	0.318	<0.001
Estimated glomerular filtration rate, (mL/min)	0.218	0.014
High-density lipoprotein, (mg/dL)	-0.034	0.507
Albumin,(mg/dL)	0.164	0.002
Initial creatinine,(mg/dL)	-0.298	<0.001
C-Reactive protein, (mg/dL)	0.004	0.936

Table 3. Univariate and multivariate logistic regression analysis of CIN

Variables	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.022 (1.003-1.043)	0.026	1.022 (1.002-1.043)	0.034
Aspartate aminotransferase	1.006 (1.003-1.009)	<0.001	1.006 (1.003-1.009)	<0.001
Alanine aminotransferase	1.015 (1.008-1.040)	<0.001	1.004 (1.001-1.008)	0.10
Diabetes mellitus	1.282 (0.794-2.068)	0.309		
Hypertension	1.129 (0.707-1.804)	0.610		
Albumin	1.034 (0.933-1.146)	0.519		
C-Reactive protein	1.015 (1.008-1.023)	0.460		
White blood cell	1.007 (0.976-1.040)	0.651		

DISCUSSION

In this study, we aimed to investigate the relationship between basal liver function test levels and contrast-induced nephropathy. The main finding of our study was: Basal AST levels was significantly higher in patients who developed CIN and was an independent predictor for the development of CIN.

The liver is the body's largest single discrete organ. It has four major functions: metabolism and synthesis; excretion; storage; and the detoxification of potential poisons. These diverse functions mean that a single test does not give enough information to assess fully how the liver is functioning (12). These tests consist of markers of hepatocellular injury (ALT,AST and ALPs); tests of liver metabolism (total bilirubin); and tests of liver synthetic function (serum albumin and prothrombin time) (13). The routine use of such tests has led to the increased detection of liver diseases in otherwise asymptomatic patients, often providing the first clue of the presence of liver pathology. Aminotransferases are markers of hepatocyte injury and do not reflect liver synthetic function (13). Therefore, in this study, we aimed to reveal the relationship between routine liver function tests and CIN, which are only associated with hepatocellular damage.

The liver contains a large number of enzymes in high concentration, some of which are found in very low concentrations in serum. Processes leading to necrosis of hepatocytes or damage to the hepatocyte cell membrane with increased permeability result in release of AST and ALT into the blood within a few hours of liver injury. Serum enzyme tests can be divided into two groups: Elevated serum aminotransferases suggest injury of hepatocytes; and elevations in ALP, GGT suggest injury to any part of the biliary tree (14). The distinction between these 2 main models of liver injury provides clues for further testing. However, in practice, patients present with a mixed pattern of liver damage (15).

ALT and AST are normally intracellular enzymes with mitochondrial and cytoplasmic forms (16). Their names reflect specifically their role in catalyzing chemical reactions during gluconeogenesis, in which the amino groups of alanine and aspartic acid are transferred to the alpha-keto group of ketoglutaric acid. ALT and AST are commonly found in cells throughout the body and are found in the liver, skeletal muscle, brain, kidney, heart, and pancreas. ALT is cytoplasmic only and is mainly found in the liver and kidney, with very minor amounts in the heart and skeletal muscle(16). Therefore, ALT is more specific to the liver.

In addition to liver damage, aminotransferase may be affected by many factors such as hyperthyroidism, alcohol consumption, exercise, high BMI, celiac sprue, anorexia nervosa, Addison disease, muscle injury (17-19). Evaluating the pattern and extent of elevation in liver enzymes can help elucidate the cause of liver injury and guide subsequent diagnostic testing and management. Any liver cell injury can cause moderate elevations in serum aminotransferase levels. Levels up to 300 IU/L are non-specific and can be seen in any liver disorder (20). Aminotransferase levels greater than 1000 IU/L suggest ischemic hepatitis, viral hepatitis, and toxic hepatitis.

Serum ALP is a membrane-anchored ectoenzyme that catalyses the hydrolysis of organic pyrophosphate, which has been shown to be a protective factor for vascular integrity (21).Elevation in serum ALP occurs when the hepatocyte canalicular membrane is disrupted, causing translocation from the canalicular membrane to the basolateral (ie, sinusoidal) surface of the hepatocyte and leakage into serum (13). Hepatic GGT is a microsomal enzyme found on the surface of hepatocytes and biliary epithelia. Clinically, its main utility is suggesting a hepatic source for an elevated AP (22). Both ALP and GGT are markers of cholestasis and their levels increase in hepatobiliary diseases (14,20).

Contrast-induced nephropathy is a common cause of renal failure and is associated with significant morbidity and mortality (23,24). Multiple studies in the medical literature have estimated a risk of 2% in low-risk patients, rising to 50% in those with risk factors such as DM, pre-existing renal disease, congestive heart failure, advanced age, anemia, and dehydration (6,25,27). There are some markers, including creatinine, GFR, cystatin C, and neutrophil-gelatinase-associated lipocalin (NGAL), that are administered by clinicians to assess the individual risk for the development of CIN following coronary angiography. However, there is still debate about predisposing factors for CIN (28,29). The exact mechanism of CIN is still unclear. In addition to the direct toxic effects of the contrast medium, renal blood flow disturbances, vasoconstriction of renal vessels, oxidative stress, free radical damage and endothelial dysfunction are thought to be major mechanisms in the development of CIN (30,32).

We found a statistically significant relationship between the development of CIN and high ALT,AST levels in our study. We did not find a significant relationship between development of CIN and GGT , ALP levels. We postulated that excessive sympathetic activity and cardiac depression during acute coronary syndrome creates hepatic ischemia by increasing hepatic and splanchnic oxygen requirements. The higher incidence of CIN in patients with anterior myocardial infarction and left anterior descending artery stent implantation patients may support this view (31).

Hypoxic liver injury is defined as a massive, but transient, increase in serum transaminase levels due to an imbalance between hepatic oxygen supply and demand in the absence of other acute causes of liver damage. It typically occurs in elderly individuals with right-sided congestive heart failure and low cardiac output (34). An imbalance between oxygen demand and supply as liver also plays a role in radiocontrast-induced outer medullary hypoxic damage (35). Cardiorenal and hepatorenal syndrome, which has been well defined before, is important in terms of showing the interrelationship of all 3 vital organs (heart, kidney, liver) (36,37). Renal and hepatic hypoperfusion due to hypotension and/or decreased flow rate developing during acute coronary syndrome causes increased sympathetic activity, increased secretion of renin angiotensin aldosterone and arginine vasopressin, and ultimately water-salt retention, peripheral vasoconstriction, organ congestion, which predisposes both the liver and kidney to ischemic injury (37,38). Since the common mechanisms in hepatorenal syndrome and cardiorenal syndrome and the development mechanisms in contrast mediated acute renal failure are similar, it can be said that all three organs are closely related to each other in terms of acute damage. Although cardiorenal syndrome and hepatorenal syndrome

develop on the basis of more advanced and chronic diseases, the same developmental mechanisms are also present in case of acute damage to 3 vital organs (37,38). Therefore, the increase in hepatic damage enzymes (ALT, AST), which may indicate that acute cardiac damage is more advanced, may predict that the kidney may be more vulnerable for the development of CIN. The lack of a significant increase in cholestasis enzymes (ALP, GGT) compared to damage enzymes (ALT, AST) supports this hypothesis. The fact that AST increase is statistically more significant than ALT can be attributed to the presence of AST in all 3 vital organs (heart, kidney and liver) (13). Thus, in cardiac and hepatic damage, the increase in AST will be greater than that of ALT, which is more specific to the liver.

In our study, the risk of contrast nephropathy was higher in those with low albumin levels. Although iodinated contrast agents have a plasma protein binding rate of less than 2% (39), less CIN observed in patients with higher albumin levels may be attributed to the attenuation of the nephrotoxic effects of the contrast agent by binding to plasma proteins. Less CIN seen in those with higher Hdl values can be attributed to the vasculoprotective and antioxidant properties of Hdl (40).

Interestingly, contrast nephropathy development was higher in patients with low baseline creatinine, unlike the literature. This may be due to the fact that very small increases in low basal creatinine values immediately reach the 25% increase limit proportionally, even though they remain within the normal range. For example: a patient with a baseline creatinine of 0.4 mg/dl will have a 0.1 mg/dl increase in postprocedural creatinine values, which meets the 25% increase limit, but a patient with a baseline creatinine of 0.5 mg/dl, 0.1 mg/dl increase in creatinine values after the procedure does not meet the 25% increase limit. Therefore, in our opinion, the definition of classical contrast nephropathy cannot adequately cover the patient group with very low baseline creatinine.

Limitation of the study

This study has the following limitations. First, this was a single center study with a relatively small sample size. Second, the duration of the procedure, and whether there was percutaneous intervention which played roles in the development of CIN, were not evaluated. Therefore, multicenter studies with larger sample sizes are needed to further clarify the correlation between CIN and liver function test levels.

CONCLUSIONS

Our results suggest a possible relationship between the role of ALT and AST levels in the development of CIN. A high ALT and especially AST level may predict the development of CIN.

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Morphometric Analysis of Tibial Plateau for Knee Arthroplasty and Prosthesis Design*Diz Artroplastisi ve Protez Tasarımı için Tibial Platonun Morfometrik Analizi***Serdar BABACAN¹**, **İlker Mustafa KAFA²**¹Department of Anatomy, Faculty of Medicine, Harran University, Şanlıurfa/TURKİYE²Department of Anatomy, Faculty of Medicine, Bursa Uludağ University, Bursa/TURKİYE**Abstract**

Background: The knee is the largest joint in the human body and provides weight-bearing of the body besides locomotion. The knee joints can be deformed by fractures, osteoarthritis, or other sorts of traumas. One of the treatments is total or unicompartmental knee replacement. To have an accomplished outcome the prosthesis and the resected bone should match irreproachably. The aim of this study was to demonstrate the tibial plateau anatomy, the differences between medial and lateral condyles particularly, and provide that the Anatolian population has differences as other ethnicities have.

Materials and Methods: The current study was conducted on 159 tibia bones. The bones were stored at Anatomy Department in Bursa Uludağ University. The tibial plateau bones were photographed in a standardized contrivance and transferred to a digital platform. 16 different parameters on the tibial plateau were measured. The measurements were obtained using Image J software and for the statistical analyses, SPSS (ver 20.0) software was performed.

Results: As the result of the statistical analyses between Byzantine and contemporary bones; statistical significance was revealed between the medial and lateral condyle. In a comparison of lateral and medial condyles area, breadth and length were greater in medial condyle in contemporary; when area, circumference, and length were greater in the medial condyle, breadth was greater in lateral condyle in Byzantine.

Conclusions: To accomplish designing the optimum knee prosthesis, the prosthesis should be designed by considering the basis of differences between not only medial and lateral condyles but also populations.

Key Words: Tibial plateau, Knee arthroplasty, Anatolian population, Morphometric analyses

Öz

Amaç: Diz, insan vücudundaki en büyük eklemdir ve hareketin yanı sıra vücut ağırlığının taşınmasını sağlar. Diz eklemi kırıklar, osteoartrit veya diğer travmalar nedeniyle deforme olabilir. Tedavilerden biri total veya tek kompartmanlı diz protezidir. Başarılı bir sonuç elde etmek için protez ve rezeke edilen kemiğin kusursuz bir şekilde eşleşmesi gerekir. Bu çalışmanın amacı, tibial plato anatomisini, özellikle medial ve lateral kondiller arasındaki farklılıkları ortaya koymak ve diğer etnik gruplarda olduğu gibi Anadolu popülasyonunun da farklılıklara sahip olduğunu belirtmektir.

Gereç ve Yöntem: Mevcut çalışma 159 tibia kemiği üzerinde yapıldı. Kemikler Bursa Uludağ Üniversitesi Anatomi Anabilim Dalından temin edildi. Tibia plato standart bir düzenekte fotoğraflandı ve dijital platforma aktarıldı. Tibia platoda 16 farklı parametre ölçüldü. Ölçümler Image J yazılımı kullanılarak elde edildi ve istatistiksel analizler için SPSS (ver 20.0) yazılımı kullanıldı.

Bulgular: Bizans ve çağdaş kemikler arasında yapılan istatistiksel analizler sonucunda; medial ve lateral kondil arasında istatistiksel olarak anlamlılık ortaya çıktı. Lateral ve medial kondil alanı karşılaştırıldığında, çağdaşta medial kondilde genişlik ve uzunluk daha fazlaydı; Bizans'ta medial kondilde alan, çevre ve uzunluk daha fazla iken, lateral kondilde genişlik daha fazlaydı.

Sonuç: Optimum diz protezi tasarlamayı başarmak için protez, sadece medial ve lateral kondiller arasındaki farklılıklar değil, aynı zamanda popülasyonlar arasındaki farklılıklar da dikkate alınarak tasarlanmalıdır.

Anahtar Kelimeler: Tibia plato, Diz artroplastisi, Anadolu popülasyonu, Morfometrik analiz

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Introduction

The knee is the largest joint in the body, consisting of two joints: one between the femur and tibia, and the other between the femur and patella. The knee joint supports the majority of the body's weight, and as a consequence. The knee joint can often have affected by an acute injury or iterative micro-traumas, with the development of osteoarthritis in later life (1). The articular surfaces of the tibiofemoral joint in combination with the primary ligaments play an important role in controlling the biomechanical behavior of the joint (2). Osteoarthritic changes of the knee cause change to the structural geometry. Significant differences were found with regards to a few parameters between the person with arthritis and the non-arthritic knee (3).

The total knee arthroplasty is a precision surgery. It requires accurate bone cutting, adequate balancing of soft tissues and proper coverage of the resected bony surface by the components for achieving a successful outcome (4). Total knee arthroplasty is applied because of a variety of reasons, especially degenerative and inflammatory arthritis. The rise of the daily activities and lifetime, understanding of mechanics of total knee arthroplasty, development of surgical techniques and finding new solutions on emerging problems and having wide knowledge on this way has lead the total knee arthroplasty indications enlargement by covering young and wide range deformity group (5). Encouraging results have been published about unicompartmental knee arthroplasty, mostly in the medial compartment. Unicompartmental knee arthroplasty is a suitable procedure for elderly patients with unilateral knee osteoarthritis. However, indications are still not well designed, especially in the lateral compartment (6).

Ideally, Total knee arthroplasty should allow a reasonable range of motion should not change the joint kinematics and should provide anatomical integrity. Because of these reasons, the components of total knee arthroplasty should be designed according to the geometry and kinematics (7). Obtaining specific local anthropometric data for the development of implant for total knee replacement is crucial for positive long-term outcomes (8). Morphometric parameters of the upper end of the tibia can be used for used to guide treatment and monitor outcome of total knee replacement surgeries. An accurate and repeatable tibial measurement system aids in the definition of tibial deformity and improvement of tibial prosthesis design (9). Recent anthropometric studies have suggested that current designs of unicompartmental knee arthroplasty do not address the racial anthropometric differences. This leads to the problem of an implant size or shapes mismatch with the resected bony surface in different populations (10).

The purpose of this study was to draw attention to anatomical differences between medial condyle and lateral condyle, and morphometric differences between ethnicity by the measurements of tibia plateau and comparing between sides and races for the process of designing total knee prosthesis and unicompartmental knee prosthesis in order to have an accomplished outcome after total or unicompartmental knee arthroplasty.

Materials and Methods

This study was based on 159 human tibia bones of 129 from Byzantine, 30 from contemporary. The bones were stored in Bursa Uludag University, Department of Anatomy. The human tibia bones of Byzantine belong to adult males who were burned in the Roman outdoor theatre in the 13th century and excavated in Nicea/Bursa by Ozbek et al. in 1980-83 (11). The tibia bones had deformity or fracture on the plateau were excluded from the study. The plateau of tibia bones was photographed in a standardized contrivance using five mp and 2592x1944 maximum photo resolution pixels Apple camera. All the measurements of the parameters (Figure1, Table 1) were recorded using Image J software.

The data obtained was performed using SPSS (ver.20.0) software and expressed as means \pm standard deviation (SD) followed by application of Student's t-test on both right and left-sided bones of Byzantine and contemporary and p-value < 0.05 , 0.01 and 0.001 were considered significant for analysis. All of the statistical tests were scrutinized and were discussed by comparing some other literature.

Table 1. The parameters measured on tibial plateau

ALC	Area of the lateral condyle
CLC	Circumference of the lateral condyle
BLC	Breadth of the lateral condyle
LLC	Length of the lateral condyle
AMC	Area of the medial condyle
CMC	Circumference of the medial condyle
BMC	Breadth of the medial condyle
LMC	Length of the medial condyle
ALEI	Anteroposterior length of the eminentia intercondylaris
LAIA	Length of the area intercondylaris anterior
LAIP	Length of the area intercondylaris posterior
MLEI	Mediolateral length of the eminentia intercondylaris
WAIA	Width of the area intercondylaris anterior
WAIP	Width of the area intercondylaris posterior
DAFN	Distance of anterior foramen nutricium
DPFN	Distance of posterior foramen nutricium

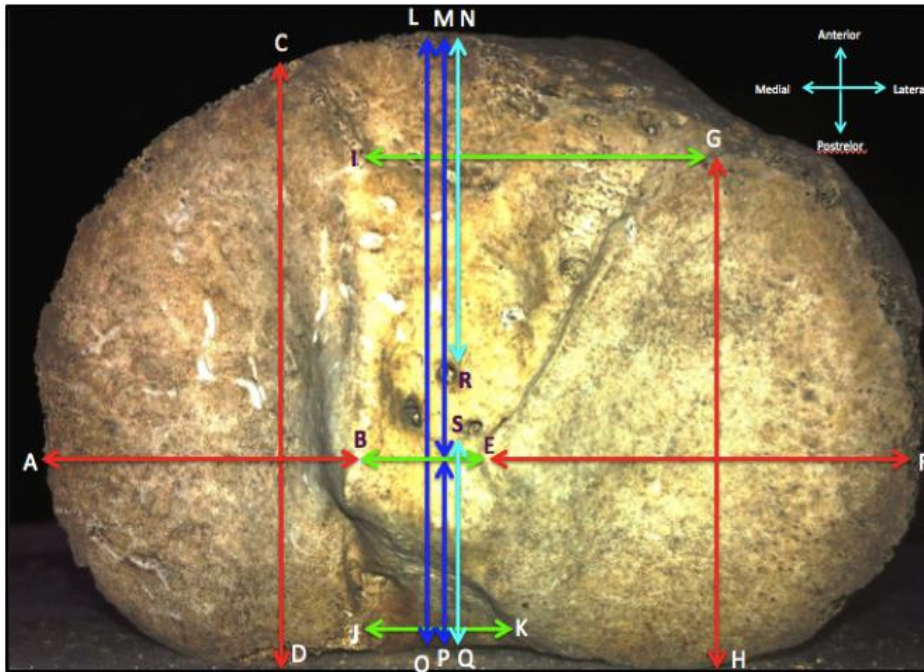


Figure 1. Parameters measured on tibial plateau

AB- Maximum transverse distance of medial condyle, *CD-* Maximum anteroposterior distance of medial condyle, *EF-* Maximum transverse distance of lateral condyle, *GH-* Maximum anteroposterior distance of lateral condyle, *LQ-* Maximum anteroposterior distance of tibial plateau, *MS-* Maximum anteroposterior distance of area intercondylaris anterior, *SP-* Maximum anteroposterior distance of area intercondylaris posterior, *BE-* Maximum transverse distance of intercondylar eminence, *GI-* Maximum transverse distance of area intercondylaris anterior, *JK-* Maximum transverse distance of area intercondylaris posterior, *NR-* Maximum anteroposterior distance between anterior foramen nutricum and anterior border of tibia plateau, *SQ-* Maximum anteroposterior distance between posterior foramen nutricum and posterior border of tibia plateau

Results

Morphometric study of 16 parameters conducted on the tibial plateau of Anatolian population revealed the under-mentioned essential observations. Abbreviations related to parameters were given in Table 1.

The descriptive statistical analysis of measurements of the study was given in Table 2. and Table 3. When we compared the results of measurements of tibia plateau belong to Byzantine and contemporary; the differences between area of lateral condyle, length of lateral condyle, length of medial condyle, length of area intercondylaris posterior, mediolateral length of intercondylar eminence and distance of posterior foramen nutricum were statically significant (p-value <0.001); the difference between circumference of the lateral condyle was statistically significant (p-value <0.01) and the difference between anteroposterior length of intercondylar eminence was statistically significant (p-value < 0.05). At the same time, measurements of ALC, LLC, LMC, LAIP, DPFN, CLC and ALEI were greater on tibial plateau of Byzantine but measurement of MLEI was greater in tibial plateau of contemporary.

Table 2. Descriptive statistics of contemporary

Parameters (mm)	Range	Minimum	Maximum	Mean ± SD
Maximum anteroposterior distance of tibial plateau	16.44	20.04	36.48	45.98 ± 5.61
Area of the lateral condyle ***	682.67	620.46	1303.13	944.07 ± 166.54
Circumference of the lateral condyle **	35.79	101.89	137.68	119.48 ± 9.35
Breadth of the lateral condyle	20.26	22.50	42.76	31.69 ± 4.77
Length of the lateral condyle ****	17.28	29.00	46.28	37.14 ± 4.46
Area of the medial condyle	760.32	807.00	1567.32	1099.97 ± 211.13
Circumference of the medial condyle	43.85	110.22	154.08	131.93 ± 12.29
Breadth of the medial condyle	24.29	22.83	47.12	32.07 ± 5.45

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Length of the medial condyle**	24.60	30.78	55.38	42.61 ± 6.65
Anteroposterior length of the eminentia intercondylaris*	16.32	38.28	54.59	46.18 ± 4.22
Length of the area intercondylaris anterior	12.04	24.01	36.05	29.53 ± 3.15
Length of the area intercondylaris posterior***	8.12	12.47	20.60	16.45 ± 2.49
Mediolateral length of the eminentia intercondylaris***	13.49	5.22	18.71	9.96 ± 3.10
Width of the area intercondylaris anterior	20.63	11.28	31.90	24.37 ± 4.46
Width of the area intercondylaris posterior	6.00	11.41	17.41	14.06 ± 2.03
Distance of anterior foramen nutricium	11.06	18.86	29.92	23.93 ± 3.08
Distance of posterior foramen nutricium ***	12.00	11.30	23.30	17.40 ± 3.18

*** *p-value < 0.001 between contemporary and Byzantine*

** *p-value < 0.01 between contemporary and Byzantine*

* *p-value < 0.05 between contemporary and Byzantine*

The comparison right and left tibia were given in Table 4. On comparing right and left; the difference between the area of the medial condyle is significant statistically (*p-value < 0.05*) and the AMC on the left tibial plateau was greater. On the other hand: the parameters between area of the lateral condyle, breadth of the lateral condyle, area of the medial condyle and breadth of the medial condyle were statistically significant (*p-value < 0.001*), the parameters between circumference of the lateral condyle and circumference of the medial condyle were statistically significant (*p-value 0.01*), and the parameters between anteroposterior length of intercondylar eminence was statistically significant (*p-value < 0.05*). In addition, when the measurements of ALC, CLC, BLC, and MLEI were higher on the right tibial plateau of Byzantine, the sizes of AMC, CMC and BMC were higher on the left.

Table 3. Descriptive statistics of Byzantine

Parameters (mm)	Range	Minimum	Maximum	Mean ± SD
Maximum anteroposterior distance of tibial plateau	33.29	32.12	65.41	47.46 ± 6.29
Area of the lateral condyle***	844.44	591.64	1436.08	1069.69 ± 148.72
Circumference of the lateral condyle **	57.69	96.93	154.62	125.51 ± 8.94
Breadth of the lateral condyle	18.70	21.19	39.88	32.69 ± 3.66
Length of the lateral condyle ****	23.01	30.96	53.98	41.12 ± 3.89
Area of the medial condyle	909.07	762.89	1671.97	1175.74 ± 178.04
Circumference of the medial condyle	59.10	108.20	167.30	136.65 ± 11.55
Breadth of the medial condyle	18.22	21.66	39.87	31.05 ± 3.81
Length of the medial condyle **	18.92	36.73	55.66	46.55 ± 3.88
Anteroposterior length of the eminentia intercondylaris*	25.31	30.71	56.02	47.76 ± 3.44
Length of the area intercondylaris anterior	16.71	20.82	37.53	29.06 ± 3.07
Length of the area intercondylaris posterior***	16.58	11.30	27.88	18.80 ± 3.22
Mediolateral length of the eminentia intercondylaris***	9.77	3.88	13.66	8.32 ± 1.91
Width of the area intercondylaris anterior	21.76	11.65	33.41	24.41 ± 4.43
Width of the area intercondylaris posterior	11.77	9.29	21.06	14.15 ± 2.06
Distance of anterior foramen nutricium	15.41	14.84	30.25	25.00 ± 2.62
Distance of posterior foramen nutricium ***	12.23	13.66	25.88	19.28 ± 2.47

*** *p-value < 0.001 between contemporary and Byzantine* ** *p-value < 0.01 between contemporary and Byzantine*

* *p-value < 0.05 between contemporary and Byzantine*

The comparison of the lateral and medial condyles was stated in Table 5. When it was compared; the parameters between the breath of lateral and medial condyles were statistically significant (p -value < 0.001), the parameters between the area of the medial and lateral condyles and length of lateral and medial condyles were statistically significant (p -value < 0.01). Furthermore, AMC, BMC, and LMC of the contemporary tibial plateau were greater. The parameters between area, circumference, breadth, and length of the medial and lateral condyles were statistically significant (p -value < 0.001). However, AMC, CMC, and LMC were greater, BLC was higher on the tibial plateau of the Byzantine.

Table 4. Comparison of right and left tibia

Parameters (mm)	Right	Left	P	Right	Left	P
	Mean \pm SD	Mean \pm SD		Mean \pm SD	Mean \pm SD	
ALC	992.013 \pm 172.02	892.71 \pm 149.60		1132.31 \pm 130.74	1004.76 \pm 138.95	$p < 0.001$
CLC	122.07 \pm 9.73	116.70 \pm 8.39		127.83 \pm 7.64	123.10 \pm 9.60	$p < 0.01$
BLC	33.24 \pm 4.14	30.04 \pm 4.98		34.68 \pm 2.94	30.64 \pm 3.18	$p < 0.001$
LCL	37.85 \pm 4.76	36.38 \pm 4.16		41.75 \pm 3.25	40.47 \pm 4.39	
AMC	1022.71 \pm 211.01	1182.75 \pm 183.83	$p < 0.05$	1095.18 \pm 143.76	1259.27 \pm 172.57	$p < 0.001$
CMC	128.41 \pm 11.97	135.70 \pm 11.88		133.71 \pm 11.95	139.70 \pm 10.37	$p < 0.01$
BMC	30.36 \pm 6.24	33.90 \pm 3.88		28.70 \pm 3.10	33.48 \pm 2.83	$p < 0.001$
LMC	41.07 \pm 6.53	44.26 \pm 6.62		46.02 \pm 3.60	47.10 \pm 4.10	
ALEI	45.78 \pm 4.20	46.61 \pm 4.36		47.85 \pm 3.82	47.67 \pm 3.04	
LAIA	28.96 \pm 2.76	30.14 \pm 3.52		29.32 \pm 3.03	28.80 \pm 3.11	
LAIP	16.75 \pm 2.29	16.13 \pm 2.74		18.48 \pm 2.87	19.12 \pm 3.55	
MLEI	9.66 \pm 2.76	10.27 \pm 3.51		8.72 \pm 1.78	7.91 \pm 1.97	$p < 0.05$
WAIA	24.52 \pm 5.20	24.21 \pm 3.70		25.06 \pm 4.10	23.73 \pm 4.69	
WAIP	13.63 \pm 1.89	14.53 \pm 2.14		13.97 \pm 2.05	14.34 \pm 2.08	
DAFN	23.50 \pm 2.94	24.40 \pm 3.26		25.12 \pm 2.48	24.87 \pm 2.78	
DPFN	16.92 \pm 3.38	17.91 \pm 2.99		19.44 \pm 2.32	19.11 \pm 2.62	

Table 5. Comparison of the right and left condyles

Parameters (mm)	Contemporary			Byzantine		
	Lateral	Medial	P	Lateral	Medial	P
	Mean \pm SD	Mean \pm SD		Mean \pm SD	Mean \pm SD	
Area of the condyles	944.07 \pm 166.54	1099.97 \pm 211.13	$p < 0.01$	1069.69 \pm 148.72	1175.74 \pm 148.72	$p < 0.001$
Circumference of the condyles	119.48 \pm 9.35	131.93 \pm 12.29		125.51 \pm 8.94	136.65 \pm 11.55	$p < 0.001$
Breadth of condyles	31.69 \pm 4.77	32.07 \pm 5.45	$p < 0.001$	32.69 \pm 3.66	31.05 \pm 3.81	$p < 0.001$
Length of the condyles	37.14 \pm 4.46	42.61 \pm 6.65	$p < 0.01$	41.12 \pm 3.89	46.55 \pm 3.88	$p < 0.001$

Discussion

The anatomy of the knee, the largest joint in the body, is very complicated. Its role as one of the main weight-bearing joints exposes it to the risk of injury and osteoarthritic degeneration (1). One of the processes used by orthopedists is total knee arthroplasty or unicompartmental knee arthroplasty. To be successful on knee arthroplasty prosthesis must match the resected surface of tibia plateau; otherwise, it may cause problems. Because of this reason, to improve a design for prosthesis, the shape of the knee was studied widely (9,12,13).

In some other populations, one of the reasons of mismatching between the prosthesis and resected tibial plateau is the anthropometric differences between people. Because currently the prostheses that can be found in the markets are produced according to the anatomical features of European and North American populations (10). Hence, the rate of surgical treatment for osteoarthritis of the knee varies dramatically according to sex, race or ethnic group, and region (14). It must be taken into account that the Turkish population also have different anthropometric differences with respect to Asian, European, and North American populations, as demonstrated in anthropometric studies (15).

Sun et al. (2014) measured the anteroposterior diameter of the medial plateau and anteroposterior diameter of the lateral plateau for the Chinese population (51.04±4.21, 44.46±3.30 respectively) (16). They found that the anteroposterior diameter of the medial plateau was greater than the lateral plateau. Kwak et al. (2007) measured the medial anteroposterior, and lateral anteroposterior length for Korean population (48.05±4.2, 42.02±3.7 respectively). As a result, they also found that measurement of medial anteroposterior was greater than lateral (4). Servien et al., (2008) measured anteroposterior measurements of medial and lateral condyles in the French population and they found that the medial condyle was greater than lateral (50.08±3.3; 47.2±3.3 respectively) (6). In current study we found the length of the medial condyle as 42.61 ± 6,65 mm in contemporary times and 46.455±3.88 mm in the Byzantine period. We found the length of the lateral condyle as 37.14±4.46 mm in contemporary times and 41.12±3.89 mm in the Byzantine period.

Hussain and Abdulkadir (2010) measured the tibial mediolateral length and anteroposterior tibial length for Malay populations (72.06±6.8, 48.1±4.7 respectively) (8). We found the maximum anteroposterior distance of tibial plateau for contemporary times as 45.98±5.61 mm and 47.46±6.29 mm for the Byzantine period.

Yue et al. (2011) compared differences of knee anthropometry between Chinese and White men & women based on not only tibia but also femur and as a result they found that the dimensions of Chinese knees were generally smaller than white knees (17). Gandhi et al. (2014) also measured tibial plateau respectively sex and side for North Indian population and the results were BLC (28.62±3.1 mm in male's right and 28.32±3.12 mm in male's left; 26.14±.5 mm in female's right and 26.00±3.06 mm in female's left) , LLC (40.86±3.79 mm in male's right and 40.69±4.13 mm in male's left; 36.78±3.03 mm in female's right and 37.30±3.81 mm in female's left); BMC (30.18±2.83 mm in males right and 29.38±3.14 mm in male's left; 27.25±3.05 mm in female's right and 26.96±2.18 mm in female's left) , LMC (48.45±4.14 mm in male's right and 47.73±4.37 mm in male's left; 42.39±4.19 mm in female's right and 42.36±4.65 mm in female's left) , ALEI (47.19±2.93 mm in male's right and 49.11±3.97 mm in male's left; 43.09±3.62 mm in female's right and 44.64 mm in female's left) , LAIA (23.84±2.90 mm in male's right and 21.96±6.76 mm in male's left; 25.48±2.38 mm in female's right and 25.04±3.48 mm in female's left), LAIP (17.86±2.98 mm in male's right and 23.22±1.55 mm in male's left; 21.84±2.64 mm in female's right and 22.38±2.84 mm in female's left), MLEI (7.18±1.4 mm in male's right and 7.41±0.95 mm in male's left; 6.72±1.006 mm in female's right and 6.38 0.79 mm in females left) , WAIA (24.82± .22 mm in male's right and 25.40±4.20 mm in male's left; 22.33±3.48 mm in female's right and 22.61±2.41 mm in female's left) and WAIP (7.18±1.14 mm in male's right and 7.41±0.95 mm in male's left; 6.72±1.06 mm in female's right and 6.38±0.79 mm in female's left). Gandhi et al. (2014) also compared the results with Danish, French, and Korean population (9).

Eboh (2022) studied on 133 dry tibias belonging to the Nigerian population. He found the anteroposterior length of medial tibia plateau 44.36 (4.96) mm, the anteroposterior length of medial tibia plateau 30.93 (3.40) mm, the anteroposterior length of medial tibia plateau 39.45 (4.87) mm, the anteroposterior length of medial tibia plateau 3.36 (3.89) mm (18).

The anthropometric studies in literature demonstrate that not only medial and lateral condyles but also populations have varieties. To have an accomplished total or unicompartmental knee replacement outcome, the surgeons should pay attention the matching of the prosthesis and resected tibia, and in addition, the manufacturers should consider the differences between medial and lateral condyles and also the differences (9,10,12,13).

Conclusion

Our study provides anthropometric data for the tibial plateau of Anatolian populations and demonstrates that as other communities have differences, Anatolian society also has variations on the tibial plateau. We have the prospect that our study will give a lead for designing prosthesis considering not only the differences between condyles but also populations.

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Author Contributions: Concept: SB, İMK; Literature Review: SB; Design: SB, İMK; Data acquisition: SB; Analysis and interpretation: SB, İMK; Writing manuscript: SB; Critical revision of manuscript: SB, İMK.

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The Effect of Positions on Sleep-Wake Status of Preterm Babies: A Systematic Review *Pozisyonların Preterm Bebeklerin Uyku-Uyanıklık Durumu Üzerine Etkisi: Sistematik Derleme***Fatma BOZDAĞ¹**, **Serap BALCI²**¹İstanbul Üniversitesi-Cerrahpaşa, Lisansüstü Eğitim Enstitüsü, Çocuk Sağlığı ve Hastalıkları Hemşireliği Doktora Programı, İstanbul, Türkiye²İstanbul Üniversitesi-Cerrahpaşa Florence Nightingale Hemşirelik Fakültesi, Çocuk Sağlığı ve Hastalıkları Hemşireliği AD, İstanbul, Türkiye**Abstract**

Background: This review, was carried out to examine the effects of different positions on sleep-wake states in preterm infants in a randomized controlled and quasi-experimental design nursing study results.

Materials and Methods: This study is a systematic review. For this purpose, 5 databases including PubMed, MEDLINE, Google Scholar, Science Direct and Cochrane were scanned by matching with the keywords “preterm, sleep, position, infant, sleep-wakefulness”. All related English studies published in the literature between 1999-2022 were included in the evaluation.

Results: In this study, a total of 1033 records were reached as a result of scanning the databases. A total of 11 publications that met the inclusion criteria were included in the study and evaluated in terms of results. It has been determined that positions are generally given during invasive procedures, after care and feedings, in order to improve the sleep of preterm infants. Positions given include hammock, nesting, facilitated fetal tucking, right or left lateral, supine and prone positions. **Conclusions:** It has been determined that the sleep-wake status of preterm infants is affected by positions. It has been determined that prone, hammock and facilitated fetal tucking positions can be given to improve the sleep-wake status of preterm infants receiving care in neonatal intensive care units.

Key Words: Infant, Position, Preterm, Sleep, Sleep-Wakefulness.

Öz

Amaç: Bu derleme, farklı pozisyonların preterm bebeklerde uyku-uyanıklık durumu üzerine etkisinin randomize kontrollü ve yarı deneysel tasarımda olan hemşirelik çalışma sonuçlarını incelemek amacıyla gerçekleştirilmiştir.

Gereç ve Yöntem: Bu çalışma sistematik derleme niteliğindedir. Bu amaçla “preterm, sleep, position, infant, sleep-wakefulness” anahtar kelimeleri ile eşleştirilerek PubMed, MEDLINE, Google Scholar, Science Direct ve Cochrane olmak üzere 5 veri tabanı taranmıştır. Literatürde yayınlanmış 1999-2022 tarihleri arasında ilgili tüm İngilizce çalışmalar değerlendirme kapsamına alınmıştır.

Bulgular: Bu çalışmada veri tabanlarının taraması sonucunda toplam 1033 kayda ulaşılmıştır. Dahil edilme kriterlerine uygun toplam 11 yayın çalışma kapsamına alınmış ve sonuçlar açısından değerlendirilmiştir. Preterm bebeklerin uykusunun iyileştirilmesi için pozisyonların genellikle invaziv işlemler sırasında, bakım ve beslenmelerden sonra verildiği saptanmıştır. Verilen pozisyonlar arasında hamak, yuvalama, cenin, sağ veya sol lateral, supine ve prone pozisyonu bulunmaktadır.

Sonuç: Preterm bebeklerin uyku-uyanıklık durumunun pozisyonlardan etkilendiği saptanmıştır. Yenidoğan yoğun bakım ünitelerinde bakım almakta olan preterm bebeklerin uyku-uyanıklık durumunu iyileştirmek için prone, hamak ve cenin pozisyonunun verilebileceği belirlenmiştir.

Anahtar Kelimeler: Bebek, Pozisyon, Preterm, Uyku, Uyku-Uyanıklık.

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Status of Preterm Babies: A Systematic

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Introduction

Preterm infants constitute the majority of Neonatal Intensive Care Units (NICU), and preterm infants in this environment are exposed to excessive noise, long-term bright lights, and frequent invasive and painful procedures (1). This environment interrupts and shortens the sleep time of preterm babies, whose sleep cycles have not yet developed, and causes an uncomfortable and stressful environment (2-4). However, adequate sleep is required for the growth of preterm babies and the development of neural pathways in the brain (5,6). The clinical consequences of sleep interruption have an adverse effect on growth and development, delaying hospital discharge (7).

It is tried to support the sleep of preterm infants with pharmacological and non-pharmacological interventions. However, pharmacological interventions have potential side effects. Pharmacologically, sedation is generally applied. It is known that these drug groups have serious side effects on the gastrointestinal system and respiratory system (8). Non-pharmacological modalities include positions, music therapy, non-nutritive sucking, touching, bedspreads, massage, cycled light, kangaroo care practices etc. (9-12). The positions included in these applications are very important for the development of preterm babies in the NICU (13). Inappropriate positions, cause motor and behavioral disorders, impaired cardiorespiratory response, sleep-wake disorders, chronic pain, sudden infant death syndrome (SIDS), increase in gastric residue and permanent posture disorders in the infant (14-19).

Thanks to the correct position, babies are allowed to heal themselves, and there are many studies proving that positions have a positive effect on the sleep of preterm babies (11,20-23).

Aim: This review, was carried out to examine the effects of different positions on sleep-wake states in preterm infants in a randomized controlled and quasi-experimental design nursing study results.

Research Question: In the systematic review, an answer was sought for the research question created in line with the following criteria determined according to PICOS.

P: Preterm newborns

I: Positioning

C: Comparison of sleep-wake level with different positioning methods

O: Sleep-wake level

S: Studies with randomized controlled and quasi-experimental design

What is the effect of different positions given to preterm newborns on the sleep-wake state of babies?

Material and Method

Scanning Strategy

This study is a systematic review. It was carried out as a retrospective review of research articles on the subject. For this purpose, 5 databases including PubMed, MEDLINE, Google Scholar, Science Direct and Cochrane were scanned by matching with the keywords “preterm, sleep, position, infant, sleep-wakefulness”. All related English studies published in the literature between 1999-2022 were included in the evaluation. In this systematic review, literature review, article selection, data extraction and evaluation of article quality were performed independently by one and the second researchers to reduce the risk of possible bias.

Selection of Studies

Inclusion Criteria: Inclusion criteria are that the study was published in an international journal between 1999-2022, the research article is in English, the sample group consists of preterm newborns, the full text of the article is available, and the studies are in a randomized controlled or quasi-experimental design.

Exclusion Criteria: Meta-analysis studies on the subject, review articles, articles whose abstracts can only be accessed, articles published in non-scientific journals, thesis studies, oral/poster presentations presented in congresses and case presentations were determined as exclusion criteria.

Getting Data

A data extraction tool developed by the researchers was prepared to obtain data in the study, and they were collected under a single title (characteristics and results of studies included in the systematic review). The names of the authors of the

included studies, the country in which they were conducted, the year the study was conducted, the sample, age group, duration of the intervention, etc. were prepared and coded. The reliability of the coded data was provided by comparing the coding of two researchers who are experts in their fields.

Evaluation of Methodological Quality of Studies

The methodological quality of the studies included in this systematic review was evaluated by checklists published by the Joanna Briggs Institute (24). Accordingly, the quality assessment of randomized controlled and non-randomized studies was done with 13 and 9-item checklists (25,26). Each item in this list is evaluated as “yes, no, unclear and not applicable”. The situation determined for each study is given in Table 2-7.

Analysis of Data

The analysis of the outputs obtained from the studies within the scope of the review was carried out in line with the writing guide of “Preferred Reporting Items for Systematic Reviews and Metaanalysis (PRISMA)” (27).

Results

In this study, a total of 1033 records were reached as a result of scanning the databases. After selecting the title and summary using the planned screening strategy, 26 studies were examined. After removing the duplicates, 20 articles remained. When selection was made according to the inclusion criteria, a total of 9 articles were excluded because the sample of two articles did not consist of preterm infants, the risk of SIDS was evaluated in three articles, parameters other than sleep were evaluated in two articles, one article was a systematic review, and one article was a study protocol. The remaining 11 articles were included in the analysis. The flow chart of the study is given below (Figure 1).

Figure 1. PRISMA 2009 Flow Diagram

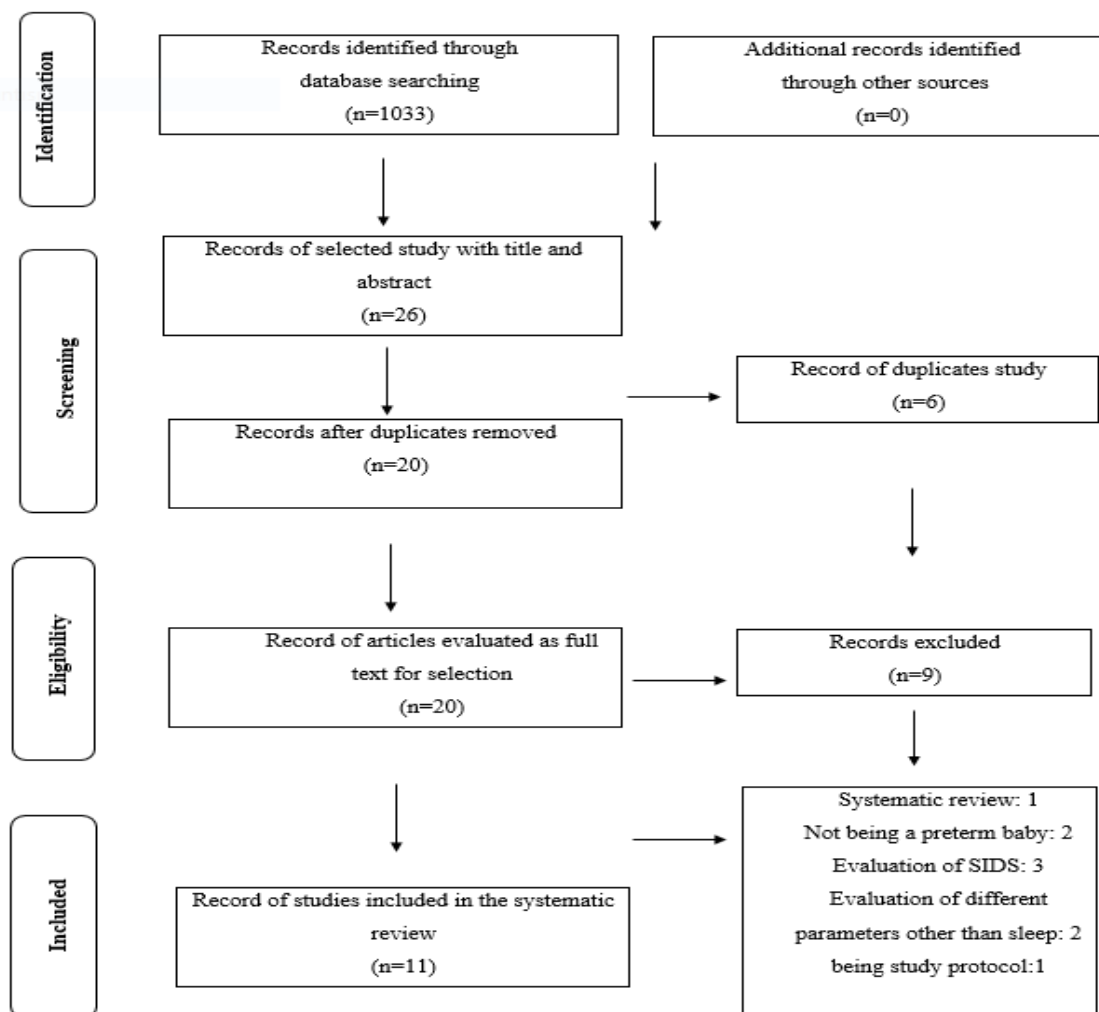


Table 2. Characteristics and Results of Studies Included in the Systematic Review

AUTHOR, YEAR, COUNTRY	Costa et al. 2019 Brazil	Ribas et al.2019 Brazil	Modesto et al. 2016 Brazil
AIM	It was aimed to compare the physiological parameters and sleep-wake states of preterm babies between the hammock and nesting position after diaper change.	It was aimed to compare the effects of hammock and nesting position on sleep-wake and pain states of preterm infants.	It was aimed to evaluate the frequency of positions of preterm infants during sleep and the effect of their positions on sleep and arousal.
SAMPLE	20 Preterm Newborns (32-37 GW) Study Group: Hammock Position (N=6) Control Group: Routine Nesting Position (N=14)	26 Preterm Newborns (30-37 GW) Study Group: Hammock Position (N=13) Control Group: Traditional (nesting) position (N=13)	Preterm babies born at 32 weeks of gestation (N=10) It was stated that preterm babies were followed in the supine, right lateral, left lateral and prone positions.
METHOD	Preterm babies were evaluated 6 times by the researchers in the hammock and nesting positions. 5 minutes before diaper change, 1 minute before, during diaper change, 1 minute after diaper change, 5 minutes after and 10 minutes later. It was stated that the sleep and wakefulness phases were analyzed according to the states defined by Pretchel.	Preterm infants were followed by the researchers in a hammock or traditional positioning for 2 hours a day for 5 days. It was stated that the results were evaluated with the Brazelton Neonatal Behavioral Rating Scale 10 minutes before and immediately after the intervention.	Preterm infants were followed by researchers in 4 different positions within 24 hours (supine, right lateral, left lateral and prone). It was stated that data were collected by polysomnographic recordings and Electroencephalography defined by Alice 5.
CONCLUSION	It has been reported that there is no significant difference between preterm babies followed in nesting and hammock positions, but it is easier for babies in the hammock group to fall asleep.	It has been reported that statistically significantly better sleep-wake status, higher SpO2, lower heart rate and respiratory rate were detected in preterm infants followed in the hammock position	It has been reported that preterm babies are mostly followed in the supine position. Statistically the longest time spent sleeping and the most frequent awakenings occurred in the supine position, while the number of arousals per hour was reported to occur in the supine position and the least in the prone position.
QUALITY SCORE	Yes:12 No:1	Yes:12 No:1	Yes:7 No:2

Table 3. Characteristics and Results of Studies Included in the Systematic Review

AUTHOR, YEAR, COUNTRY	Valizadeh et al. 2016 Iranian	Cândia et al. 2014 Brazil	Liaw et al. 2012 Taiwan
AIM	It was aimed to compare the sleep times of preterm infants between the facilitated fetal tucking and free positions.	It was aimed to evaluate the effect of prone position on physiological and behavioral responses of stress and position changes in preterm infants	It was aimed to evaluate the effects of caregiving, positioning and non-nutritive sucking on sleep-wake status of preterm infants receiving care in the NICU.
SAMPLE	32 Preterm Newborn (33-36 GW) Preterm infants were followed in 4 different positions in supine position (free posture), right or left lateral position (free posture), supine facilitated fetal tucking position and right or left lateral facilitated fetal tucking position.	16 Preterm Newborn (26-36 GW) It was stated that preterm babies were followed in the supine or lateral position for 40 minutes and then in the prone position for 30 minutes.	30 Preterm Newborn (27-37 GW) Preterm babies were followed by the researchers by giving them four different positions as right lateral, left lateral, prone and supine.
METHOD	Preterm babies were followed for 12 hours in each position between 08:00 and 20:00 for 4 days by the researchers. It was stated that the faces of preterm babies were recorded with 900 TVL closed circuit video cameras.	It has been reported that saliva samples are collected twice, 40 minutes after the lateral or supine position is placed, and 30 minutes after the prone position is placed in preterm babies. It was noted that heart rate, respiratory rate, peripheral oxygen saturation, and Brazelton sleep score were recorded before the first sampling, while the infants were placed in the prone position, and at the end of the procedure. Data were generally collected by the researchers by taking saliva samples between 06:00 and 07:30, when preterm infants are stable, and using the Brazelton Sleep Score.	It is stated that preterm babies are observed by nurses with an interval of 1 minute for 3 days. Data were collected by 6 trained nurses with a 1-minute interval. It is reported that nurses received training for 4 weeks.
CONCLUSION	It has been reported that statistically significantly more sleep and less wakefulness occur in preterm infants followed in lateral and facilitated fetal tucking position compared to preterm infants followed in supine and free positions.	It has been reported that salivary cortisol level, respiratory rate and Brazelton Sleep Score were found to be statistically significantly lower in preterm infants followed in the prone position.	It has been reported that the silent sleep times of preterm babies in the lateral and prone positions were found to be statistically significantly higher.
QUALITY SCORE	Yes:7 No:2	Yes:7 No:2	Yes:7 No:2

Table 4. Characteristics and Results of Studies Included in the Systematic Review

AUTHOR, YEAR, COUNTRY	Jarus et al. 2011 Israel	Bhat et al. 2006 England	Grunau et al. 2004 America
AIM	It was aimed to evaluate the effect of prone and supine position on sleep and behavioral status in preterm infants.	It was conducted to test the hypothesis that preterm infants with or without bronchopulmonary dysplasia, who are preparing for discharge in the NICU, will sleep longer and have less arousal and more central apnea in the prone position.	It is aimed to evaluate pain in prone and supine positions during blood collection in preterm infants.
SAMPLE	32 Preterm Yenidoğan (25-35 GW) It was stated that they were followed for 48 hours in the prone and supine positions.	Preterm babies with a mean gestational age of 27.9 weeks (N=24) It has been stated that preterm babies are followed for 3 hours in 2 different positions, prone and supine.	Preterm babies born before 32. weeks of gestation (N=38) Prone Position: 21 Supine Position: 17
METHOD	The position of preterm babies was changed to prone or supine every 3-4 hours after each feeding and they were followed by the researchers for a total of 24 hours in each position for 48 hours. It was stated that the data were collected with the actigraphy device and the Natural Observations of Newborn Behavior (NONB) Form.	Preterm infants were followed by the researchers for 3 hours in each position (prone and supine) after feeding for 2 days. It was stated that video-polysomnographic recordings were taken using the Alice 4 Sleep Study System.	It is reported that the data were collected by the researchers during and before routine heel blood collection. It was stated that the data were collected using the Natural Observations of Newborn Behavior (NONB) Form and video recording.
CONCLUSION	It has been reported that statistically significantly more sleep was detected in preterm infants in the prone position and more awakening in the supine position.	It has been reported that preterm babies sleep longer in the prone position. It was reported that awakening and waking per hour were statistically significantly higher in preterm infants followed in the supine position.	The duration of deep sleep was reported to be statistically significantly higher in preterm infants who were placed in the prone position, except during the heel draw blood.
QUALITY SCORE	Yes:7 No:2	Yes:7 No:2	Yes:7 No:2

Table 5. Characteristics and Results of Studies Included in the Systematic Review

AUTHOR, YEAR, COUNTRY	Chang et al. 2002 Taiwan	Goto et al. 1999 USA
AIM	It was aimed to evaluate the effects of prone and supine positions on behavioral status and stress responses in preterm infants followed up on mechanical ventilation.	It was aimed to evaluate the effect of positions on sleep and cardiorespiratory response in preterm infants when they are ready to be discharged.
SAMPLE	28 Preterm Newborn (25-36 GH) It has been stated that preterm infants were randomly assigned to the prone/supine or supine/prone position.	16 Preterm Newborn (27-36 GW) It has been reported that preterm infants are followed randomly in the prone and supine positions after each feeding. The preterm baby was randomly placed in the prone/supine or supine/prone position.
METHOD	It was stated that preterm babies were given the opportunity to stabilize 10 minutes before positioning, and then the data were collected by following each position for 2 hours. It was stated that the data were collected using the Anderson Behavioral Status Scoring System.	It has been reported that 6-hour recordings were taken by the researchers between 11:00 and 17:00, usually between two feedings. The preterm baby was randomly placed in the prone/supine or supine/prone position. It was stated that the data were collected by taking video-polysomnographic records.
CONCLUSION	The prone position is reported to improve sleep in preterm infants.	It has been reported that there is a significantly higher rate of awakening in preterm infants followed in the supine position than those followed in the prone position, but overall sleep status is not affected by the position.
QUALITY SCORE	Yes:7 No:2	Yes:7 No:2

Discussion

According to the results obtained from the analysis of 11 studies evaluated, it is seen that positions are generally given during invasive procedures, after care and feedings to improve sleep in preterm infants. Positions given include hammock, nesting, facilitated fetal tucking, right or left lateral, supine and prone positions.

Costa et al. (2019) found that although no difference was found between the hammock and the nesting position in terms of total sleep and waking, preterm babies in the hammock group fell asleep faster (20). In contrast, Ribas et al. (2019) reported better sleep-wake status, higher SPO₂, lower heart rate and respiratory rate in preterm infants followed in the hammock position compared to preterm infants in the nesting position (11,20) (Table 2). Costa et al. (2019), while the sleep status of preterm infants was evaluated before, during and after diaper change, Ribas et al. (2019), on the other hand, it is noteworthy that preterm babies were evaluated for sleep during the hours when they were not disturbed (11,20) (Table 2). The difference in results may be due to the fact that care interrupts the sleep cycle. At the same time, the small sample size in both studies is another factor that causes uncertainty in the evaluation of the effect of hammock position on the sleep-wake state of preterm infants. It is thought that studies with more samples and in similar time periods are needed in order to reach more precise results and make comparisons.

Valizadeh et al. (2016) reported in their study that the facilitated fetal tucking and lateral position increases the sleep duration of preterm infants and decreases the frequency of awakenings (22) (Table 3). Giving preterm babies a facilitated fetal tucking position as in the mother's uterus may have improved their sleep quality by making them feel more secure (23).

In the studies, preterm babies were followed in four different positions as supine, prone, right and left lateral and more sleep, less waking and stress, higher SPO₂, lower heart rate and respiratory rate are reported in the prone position (21,28,29)

(Table 2, Table 3). In all of these studies, there are differences in the measurement tools used to determine the sleep-wake status of preterm infants and in the total follow-up period (21,28,29) (Table 2, Table 3). Despite these differences, the fact that the prone position was determined to be more effective in the results of the study supports that the prone position has a higher effect on improving sleep in preterm babies compared to other positions. Likewise, in studies comparing the sleep-wake status of preterm infants only in prone and supine positions, it has been reported that sleep time is longer in the prone position, and alertness time is longer in the supine position (30-34) (Table 4, Table 5). In most of the studies, it is seen that the sleep-wake status of infants is evaluated after feeding when no intervention is made (30,31,34) (Table 4, Table 5). Grunau et al. (2004) evaluated preterm infants before and during heel blood collection and reported that the prone position supports deep sleep except during heel blood collection (32) (Table 4). It is thought that more studies evaluating the effects of positions on sleep-wake status during and after different invasive procedures in preterm infants will contribute to the literature. Along with all these, it is known that the prone position increases the risk of SIDS, and recent studies have reported that the prone position may lead to low blood pressure, cerebral oxygenation and impaired autonomic cardiovascular control in preterm infants (35-37). In another recent study, Shepherd et al. (2020) reported that the prone position reduces bradycardia, the frequency of desaturation and the duration of desaturation in very preterm preterm infants (38). The conflicting results of the studies in the literature show that preterm infants followed in the prone position in the NICU should be followed closely by nurses in terms of both SIDS risk and other undesirable negative results. In the NICU, the sleep of preterms is mostly interrupted during invasive procedures, care and feeding. When studies are examined, it is seen that prone position can be given to preterm babies before invasive procedures or after baby care. It is thought that the increase in sleep duration of preterm babies will contribute to their growth and development by protecting their energy.

Conclusion

It has been determined that the positions of preterm infants affect sleep-wake status. In NICUs, prone, facilitated fetal tucking and hammock positions can be given to preterm infants to improve sleep-wake status, especially after care, after feeding and during invasive procedures

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A Case of Pediatric Foreign Body Aspiration: Case Report and Literature Review

Bir Pediatrik Yabancı Cisim Aspirasyonu Vakası: Vaka bildirimi ve Literatürün Gözden Geçirilmesi.

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Abstract:

Foreign body aspiration is one of the leading causes of preventable mortality and morbidity in children. Foreign body aspiration cases are most common in the first 3 years of life. Not leaving children out of adult supervision is the most important precaution for foreign body aspiration. Educating parents about first aid and the heimlich maneuver will prevent potential negative consequences. In this article, it is aimed to present a case who was brought to the emergency department in cardiac arrest after foreign body aspiration and to examine the subject of foreign body aspiration in the light of current literature.

Key Words: emergency medicine, foreign body aspiration, airway obstruction

Öz

Yabancı cisim aspirasyonu çocuklardaki önlenebilir mortalite ve morbidite nedenlerinin başında gelir. Yabancı cisim aspirasyonu vakaları en sık hayatın ilk 3 yılı içerisinde görülür. Çocukları yetişkin gözetimi dışında bırakılmaması, yabancı cisim aspirasyonları açısından en önemli önlemdir. Anne babaların ilkyardım ve heimlich manevrası konusunda eğitilmeleri olası kötü sonuçları önleyecektir. Bu makalede yabancı cisim aspirasyonu sonrası kardiyak arrest halde acil servise getirilen bir olgunun sunumu ve yabancı cisim aspirasyonu konusunun güncel literatür ışığında incelenmesi amaçlanmıştır.

Anahtar Kelimeler: acil tıp, yabancı cisim aspirasyonu, havayolu obstruksiyonu

Introduction

Foreign body aspiration (FBA) is one of the leading causes of preventable mortality and morbidity in children. While FBA is the 4th most common cause of accidental death in children under 4 years of age, it ranks 3rd under 1 year old. 7% of deaths under 3 years of age are associated with foreign body aspirations(1). FBA constitutes 5% of accidental deaths under 3 years of age in the United States of America (USA)(2).

FBA cases are most common in the first 3 years of life. The reason for this is that the molar teeth are not developed, the neuromuscular reflexes that provide swallowing are insufficient, and the children in this age group put everything they hold into their mouths. In addition, crying, talking and walking around while eating at the same time can be shown as a reason(3). FBA is seen more frequently in boys than in girls, which is explained by the fact that boys are more active than girls(1). Lack of attention to children, leaving them without adult supervision, leaving objects around that can be aspirated are other risk factors(1).

The mortality rate in foreign body aspirations occurring outside the hospital is around 36%. This rate is around 0.26% - 13.6% in-hospital aspiration cases(2). The most frequently aspirated foreign bodies are foods(4). Frequent aspirated foods vary by country and region. Nuts, peanuts and seeds of various plants are generally the most frequently aspirated foreign bodies(4).

Although food is the most common cause of FBA, the clinical situation may differ depending on the type of food aspirated. More serious clinical conditions have been shown to occur after aspiration of meat products. In a study conducted in the USA and Canada, it was shown that aspiration of delicatessen products is more associated with fatal clinical pictures(5,6).

Clinical severity is related to the shape, size and origin of the aspirated body. When inorganic bodies are aspirated, if they don't close the airway completely, they can remain asymptomatic for a long time. On the other hand, organic bodies cause more obstructive symptoms when they are aspirated, since they cause inflammatory processes(6). Large foreign bodies will be more occlusive than small ones. Round or egg-shaped foreign bodies will also close the airway completely and cause more asphyxiation, as they will better fit the airway shapes of the children (7).

In this article, it is aimed to present a case who was brought to the emergency department in cardiac arrest after FBA and to examine the subject of FBA in the light of current literature.

Case

A 2-year-old male patient was brought to the emergency room after being told that he had fallen out of the chair. When the emergency health technician reached the scene, he said that the patient was not breathing and his heart was at cardiac arrest. He said that they brought the patient with cardiopulmonary resuscitation (CPR) and tried endotracheal intubation, but they were unsuccessful, they continued by ambulating. In the emergency room examination; cardiac arrest is present. Pupillary bilateral mydriatic, no light reflex. The skin is pale and cold. There are 2 cm bruises under both eyes. There is no examination finding to suggest skull fracture. Abdominal distention presents. No signs of trauma on the thorax, abdomen or extremities.

The patient was immediately intubated and CPR was started. When the lungs were auscultated after intubation, low respiratory sounds were heard in the left lung. This finding was thought to be due to pneumothorax, since CPR was applied to the patient while he was being brought to the emergency department. Cardiac rhythm was restored at the 55th minute of CPR, which was performed in accordance with the European Resuscitation Council Guidelines 2021: Paediatric Life Support(8). Fingertip oxygen saturation was 98 and arterial blood pressure (TA) was 90/60. Brain, thorax and abdominal tomography (CT) was planned for the patient with suspected trauma. We talked to the relatives of the patients in order to deepen the anamnesis. It was learned that the boy was playing with his cousins at his grandmother's house, and his parents were in the neighbor's house at that time. It was learned that when they came because of other children's calls, they found the child on the floor, fallen from the sofa and there was a hazelnut in a bowl next to him. The patient's brain CT imaging showed diffuse cerebral edema, which was associated with prolonged hypoxia. **(Figure 1)** No pathological finding or foreign body was found in thorax CT. **(Figure 2)** Abdominal CT showed hypodense areas in both kidney and liver parenchyma, these findings were interpreted as ischemic infarct areas.

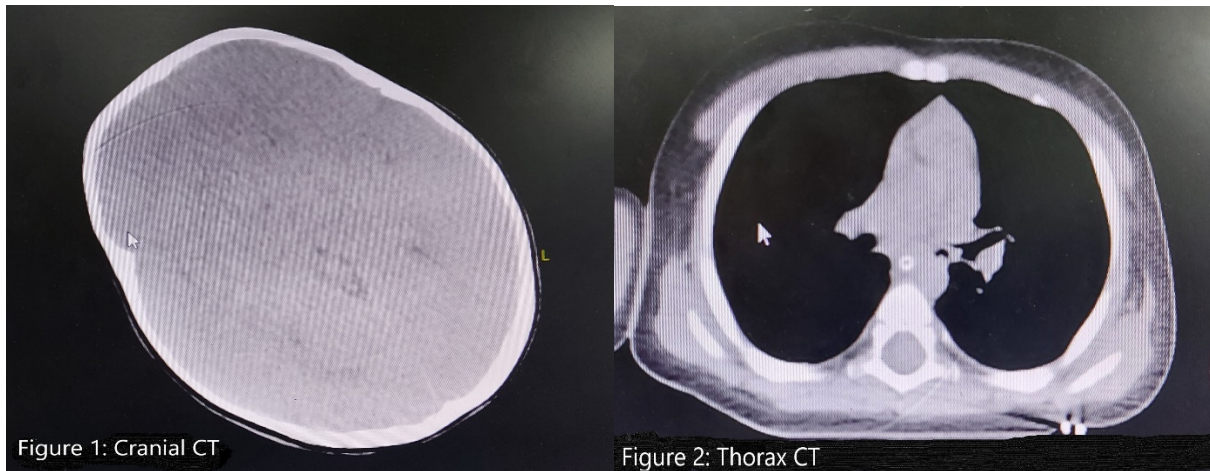


Figure 1: Cranial CT

Figure 2: Thorax CT

Blood gas results showed Ph: 6.61, PCO₂: 38 mmHg, HCO₃: 3.6 mmol/L, SO₂: %97. NaHCO₃ push and infusion was applied to the patient. In the blood gas taken 30 minutes later, it was seen as Ph: 6.88, HCO₃: 8.2 mmol/L, SO₂: %97. It was thought that the patient with no low saturation and treatment-resistant metabolic acidosis might be intoxicated with drugs. It was learned that there was no medicine around the child. Deep metabolic acidosis was attributed to kidney damage resulting from prolonged cardiac arrest and hypoxia. During the follow-up of the patient in the emergency room, there was no urine output from the catheter.

The patient was referred to Ondokuz Mayıs University Medicine Faculty Hospital for bronchoscopy and intensive care follow-up. In bronchoscopy performed there, it was learned that 2 hazelnuts were seen in the left main bronchus. It was learned that the patient died due to cardiac arrest that developed shortly afterwards.

Discussion:

Not leaving children out of adult supervision is the most important precaution for FBA. However, it should be noted that many cases of FBA develop under adult supervision. Hard foods such as hazelnuts and peanuts with a high risk of aspiration should not be given to children without adult supervision(9). In our case, it is seen that the 2-year-old child was left with his cousins a few years older than him, without adult supervision, and was next to the hazelnut, which could potentially aspirate.

Studies have shown that FBA is more common in boys. This is explained by the fact that boys are more active than girls(1). Our patient was also a boy.

The typical physical examination finding in FBAs is decreased breath sounds on the affected side. Wheezing is also a common finding (4). In our patient, respiratory sounds were found to be low in the left lung after intubation. This situation suggested that there may be foreign body aspiration.

The first medical intervention to a child who is thought to have aspirated a foreign body is cleaning the inside of the mouth with a finger and then the heimlich maneuver. The Heimlich maneuver is a fast and effective method for removing foreign bodies in the respiratory tract. It is easy to learn and apply. Complications are rare (10). For infants under one year old, alternating sequences of five back blows and five chest thrusts are performed until the object clears or the infant becomes unresponsive. If child becomes unresponsive, basic life support must be performed(10). abdominal compression should not be applied in children because their livers are more vulnerable to injury (11). In our case, it is not known how many minutes passed after the child aspirated foreign body until adults came. It was stated that the ambulance arrived about 15 minutes after the call, but no intervention had been made until then. The medical team who came to the scene tried to intubate the patient, but when

they were unsuccessful, they ambulated him with CPR and brought him to the emergency room. It has been learned that this journey took about 20 minutes.

Direct chest X-ray is the first-stage imaging method in FBAs. Lateral radiographs may also be helpful. However, a normal chest X-ray does not exclude the diagnosis of FBA. Computed tomography (CT) can also be performed, but FBs that are not radio-opaque will not be seen. Atelectasis or increased aeration on the obstructed side may be seen as secondary signs of obstruction. Non-opaque objects can also be seen as filling defects on barium radiographs (12). No foreign body was observed in the thorax CT taken in our patient.

In the studies, it was found that the right bronchus is the area where FBs are most frequently inserted in the respiratory tract. This is explained by the fact that the right main bronchus is shorter, wider and in a more upright position. Rigid bronchoscopy is the gold standard in the detection and removal of FBs in the respiratory tract (13). In our case, the patient was referred to an advanced center for bronchoscopy and intensive care follow-up after successful resuscitation. In our patient, 2 hazelnuts were found in the left main bronchus in the bronchoscopy performed in Ondokuz Mayıs University Medical Faculty Hospital. It should not be forgotten that the patient was intubated before bronchoscopy, CPR was performed for a long time, and the nuts may be at a higher position before intubation.

The expected blood gas results in a patient with airway obstruction are respiratory acidosis, hypoxia, and hypercarbia. However, deep metabolic acidosis was present in the blood gas of our patient and it was resistant despite bicarbonate treatment. therefore, intoxications were among our preliminary diagnoses (14). It should be kept in mind that deep metabolic acidosis, which is seen in patients who remain hypoxic for a long time due to airway obstruction and whose cardiac arrest and resuscitation time is prolonged, may develop due to kidney damage.

Conclusion

FBA is an important cause of childhood mortality and morbidity. Educating families, teachers, and babysitters about FBA is important to prevent fatal complications. Educational programs to be organized throughout the country and educational programs to be included in the media can be beneficial in this regard. It would be beneficial for newly born parents to be warned about frequently aspirated foreign bodies before discharge. Educating parents about first aid and the heimlich maneuver will prevent potential negative consequences. Above all, it should be ensured that children are not left alone without parental supervision.

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*Case Report***RETINITIS PIGMENTOSA AND ACUPUNCTURE. WHY NOT!***RETINITIS PIGMENTOSA VE AKUPUNKTUR. NEDEN OLMASIN!*Ayşegül Elbir Şahin^{1,2} , Çetin Göktaş^{1,3} , Rümeysa Karaçuha Sürücü² , İsmail Şen¹ , Onur Öztürk^{1,4} ¹ UHS Samsun Education and Research Hospital, Traditional and Complementary Medicine Center, Samsun, Turkey² UHS Samsun Education and Research Hospital, Clinic of Anesthesiology and Reanimation³ UHS Samsun Education and Research Hospital, Clinic of Ophthalmology⁴ UHS Samsun Education and Research Hospital, Department of Family Medicine**Corresponding author:**

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PIGMENTOSA AND ACUPUNCTURE.

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Abstract:

Retinitis pigmentosa (RP) is the most common hereditary retinal degeneration. Complaints of night blindness and peripheral visual field loss are felt in the foreground. Examination findings, radiological evaluations and satisfaction in our case suggest that acupuncture can also be used in the treatment of RP disease.

Keywords: Retinitis pigmentosa, Acupuncture**Öz**

Retinitis pigmentosa (RP) en sık görülen kalıtsal retina dejenerasyonudur. Gece körlüğü ve periferik görme alanı kaybı şikayetleri ön planda hissedilmektedir. Vakamızdaki muayene bulguları, radyolojik değerlendirmeler ve memnuniyet RP hastalığı tedavisinde akupunkturdan da yararlanılabileceğini düşündürmektedir.

Anahtar Kelimeler: Retinitis pigmentosa, Akupunktur**Introduction**

Retinitis pigmentosa (RP) is the most common hereditary retinal degeneration. It seriously reduces the quality of life. Its prevalence is around 1/4000 on average (1). The factors affecting the development of RP have not been fully defined, but it is generally believed that genetics is the most important factor (2). Rod and then cone photoreceptors are affected first. RP is manifested by night blindness and peripheral visual field loss reflecting rod photoreceptor dysfunction. Loss of central visual acuity is seen in the last period of cone function loss. The classic triad of RP disease is thinning of the retinal vessels, bony spicule-like pigmentations in the retina, and pallor of the optic disc in the form of wax. Photoreceptor responses evaluated by electroretinography are decreased or unrecorded (3,4).

In this case report, the path that a patient with retinitis pigmentosa, who is a difficult-to-treat pathology, traveled from integrative medicine applications with acupuncture was mentioned.

Presentation of the case

A forty-eight-year-old male patient was admitted to our integrative medicine clinic with complaints of decreased vision when he moved from a sunny, open area to a closed area, and dark vision as if he were wearing sunglasses. It has been learned that his complaints have been present since childhood, and his vision has gradually decreased in the last 20 years. There is no history of any other chronic disease. He worked as a taxi driver for twenty years. He had cataract surgery on both eyes when he was forty-two years old, and after the operation he started to use close glasses. It was learned that her mother had a diagnosis of RP.

The patient could not make eye contact at the first interview and could not see the place shown to sit. In the eye examination, visual acuity was evaluated as 1/10 in both eyes, both eye pressure was determined as 15 mm Hg, and both eyes have intraocular lenses. On fundus examination, pigment changes in the form of diffuse bone corpuscle were observed in the retina. Pre-treatment optical coherence tomography image is shown in **Figure 1**. The findings were evaluated in favor of RP. Other systemic examinations are normal. Complete blood count, liver and kidney function tests, fasting blood sugar and HbA1C level, cholesterol panel, vitamin B12 level, iron panel, electrolyte values and electrocardiography are normal.

In the first session, the patient for whom we recommended acupuncture was applied to the local body points of GB-14, BL-1-2, ST-1, Ex-HN-3-4-5 with disposable 0.20x13 mm sterile steel needles for 20 minutes. The remote point is not selected. According to the French auricular acupuncture, it was scanned with a detector and placed on the Shen-men and eye point with a 0.22x1.5 mm permanent steel needle with double plasters to be changed weekly (**Figure 2**), the ears were needled bilaterally. The patient received 10 sessions of body acupuncture and 5 sessions of ear acupuncture, each lasting approximately 20 minutes, over 40 days. The patient's complaints decreased, he could see his surroundings more clearly and could make eye contact. In the examination performed by an ophthalmologist for control purposes, his visual acuity was evaluated as 2/10 in both eyes, the pressure in both eyes was 15 mm Hg, fundus findings were as detected in the first examination. Post-treatment optical coherence tomography image is shown in **Figure 3**.

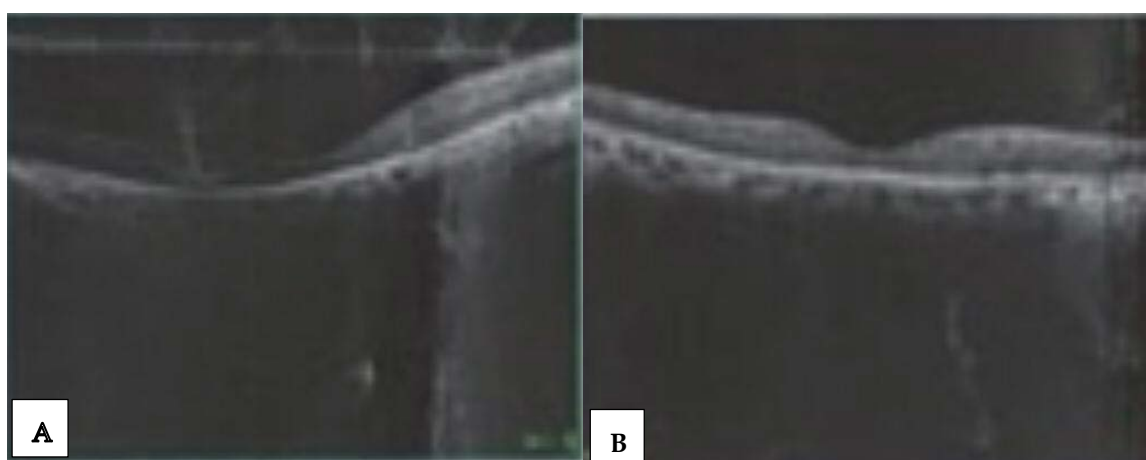


Figure 1. Optical coherence tomography image before treatment **A:**Right eye **B:** Left eye



Figure 2. Acupuncture points used on the patient

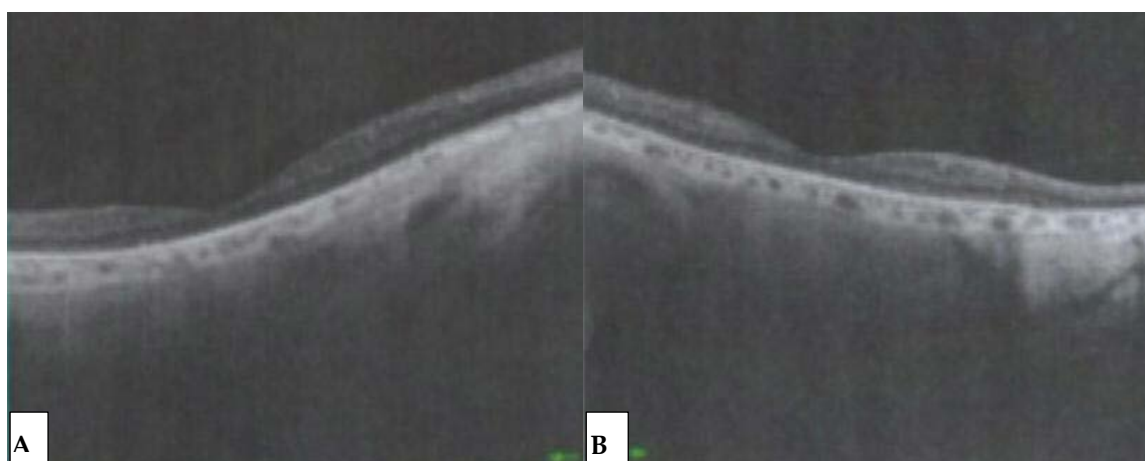


Figure 3. Optical coherence tomography image after treatment. **A:** Right eye **B:** Left eye

Discussion

When the relevant diagnosis and treatment method are searched together, few works are encountered. It is known that acupuncture is used in the treatment of RP in Chinese medicine. One of the conditions in which acupuncture can be applied, which is included in the traditional and complementary medicine practice regulation in force in Turkey since 2014, is chronic eye diseases. Acupuncture was applied to our patient in the light of these informations.

In RP patients, the complaint of not being able to see at night, “nictalopia” is typical. In addition, concentric narrowing of the visual field is typical and peripheral visual field loss is insidious, slow and progresses over years. It usually progresses symmetrically in both eyes. Photopsia, dyschromatopsia, photophobia, visual hallucinations, nystagmus and refractive errors may accompany (5,6). Our case is compatible with the literature in terms of its symptoms.

RP may only be an eye-catching picture, or it may be in the form of syndromic RP with systemic findings. Usher syndrome, accompanied by deafness and balance disorder, is the most common syndromic form of RP. In areas with retinal atrophy, choroidal vessels are clearly visible, there may be cell infiltration in the vitreous, cataracts, and subretinal exudations that become evident in some forms. In addition, keratoconus, epiretinal membrane formation, optic disc drusen, optic disc astrocytic hamartoma and myopia can be seen more frequently in RP patients (3,4). In our case, there is a coexistence of cataracts.

In all RP patients, the rate of cases in which genetic transmission cannot be determined, called simplex, is more than half, but it is known that autosomal dominant, autosomal recessive or X-linked transmission may occur. Digenic inheritance and maternal (mitochondrial) inheritance are rarely seen. Genetic examination was not performed in our case, but the presence of the same diagnosis in her mother suggests a hereditary transmission.

It is known that there is no valid treatment yet, research focuses on retinal transplantation and gene therapy (7). It has been shown that acupuncture has a positive effect on the repair of the function of optic nerve cells and the regenerative capacity of the central nervous system is greater than is generally believed. Acupuncture can improve the microcirculation of local ocular tissues and limit the pathological reaction involved in RP (8). Xu et al. tried to treat 26 RP patients with acupuncture and reevaluated the patients after 3 months of treatment, during a 20-year study. At the end of the sessions, two-thirds of the participants found improvement in visual acuity and quality of life (9). Huang et al. created a randomized controlled trial protocol on this subject in 2021 (2). Fereydouni et al. conducted a study with 23 RP patients and found significant improvement in visual acuity after acupuncture sessions (10). The regression of the complaints of our case with acupuncture may pave the way for future studies.

Conclusion

Examination findings, radiological results and satisfaction in our case suggest that acupuncture can also be used in the treatment of RP disease.

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