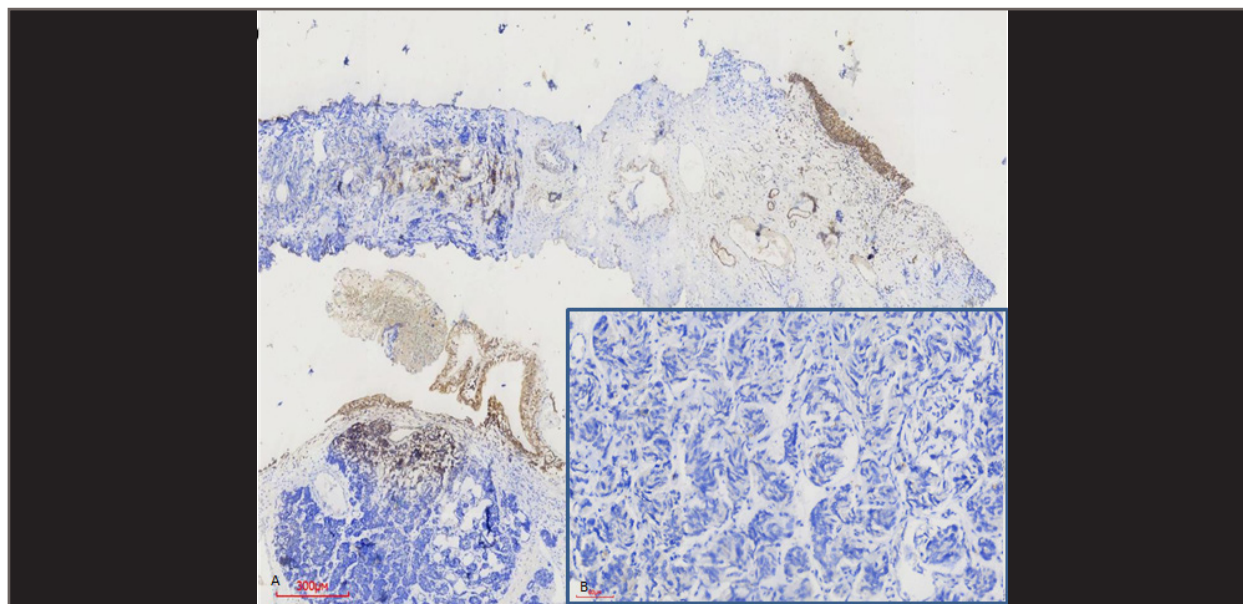


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Dear Colleagues,

We are pleased to have published the last issue of The New Journal of Urology for 2023. This issue includes eight (8) original articles, two (2) case reports and one (1) review. Published articles consist of uro-oncology, general urology, urolithiasis, neuro-urology and andrology. We believe that these studies will be read with interest, and these articles are expected to contribute to the current literature and they are going to be references for future studies.

The New Journal of Urology, which has been published in English for two years, has just converted completely into English Language with the changing of domain and website design. The New Urology Journal, which started to be published in 2004, has been indexed in the TÜBİTAK-ULAKBİM TR Index since the first issue of 2011. Our journal is indexed in Google Scholar, Turkish Medline, Turkish Citation Index, SOBIAD, OAJI, Ideal Online Database, EuroPub, J-GATE, and DOAJ databases, EBSCO and InfoBase Index. In addition, the New Journal of Urology is in collaboration with the Orcid and CrossRef DOI systems. The indexing process of our journal in ESCI, Pubmed, and EMBASE continues. Our goal is to increase the visibility of our journal both nationally and internationally with articles with high scientific levels and to become one of the most read urology journals. We receive the fact that more and more scientists prefer our journal in the course of the time, as proof of our international recognition and quality.

Our journal, which has been contributed by four valuable editors since its establishment, has reached very valuable levels. All our editors have increased the quality of our journal day after day and brought it to a certain position in the international arena. In addition, I am grateful to the valuable contributions of Assoc. Prof. Fatih Yanaral. I hope that we can take our journal to highest levels together with Assoc. Prof. Mithat Ekşi, with whom I share the duty.

We request that you submit your evidence-based articles to The New Journal of Urology, take timely and rigorous action as a referee, and read the articles published in the journal and cite them where appropriate.

Kind Regards,

Yavuz Onur Danacıoğlu

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Kasa İnvazive Olmayan Mesane Kanserinde Sistemik İmmün-İnflamasyon İndeksi ve Nötrofil-Lenfosit Oranının Hastalık Nüksü ve İlerleme Riski ile İlişkisi

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Özet

Amaç: Sistemik inflamatuvar yanıtı dayalı biyobelirteçler, kasa invazive olmayan mesane kanseri (KİOMK) hastalarının prognozunu tahmin etmede umut vericidir ve düşük maliyetle risk sınıflandırmasına katkıda bulunabilir. Bu çalışmada, KİOMK hastalarında hastalığın nüks ve progresyon riskinin öngörülmesi için nötrofil-lenfosit oranı (NLO) ve sistemik immün-inflamasyon indeksini (SII) değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışma, 2015-2019 yılları arasında üçüncü basamak bir üroloji merkezinde transüretral mesane tümörü rezeksiyonu (TUR-MT) uygulanan 211 hastanın verilerinin retrospektif bir analizini içeriyor. Eşik değeri belirlemek için receiver operating characteristic (ROC) eğrisi kullanıldı. Kaplan-Meier eğrileri ve log-rank testi, farklı inflamatuvar belirteç seviyelerine göre nüksüz ve progresyonsuz sağkalım oranlarını değerlendirmek için kullanıldı. Bağımsız prognostik faktörleri tahmin etmek için çok değişkenli regresyon analizi yapıldı.

Bulgular: ROC analizinde SII'nin optimal eşik değeri 568 olarak bulundu. Çok değişkenli analize göre, SII değeri, ilk TUR-MT sırasındaki tümör sayısı ve Avrupa Kanseri Araştırma ve Tedavi Örgütü (EORTC) nüks sınıflandırması, nüksü öngörmede istatistiksel olarak anlamlı parametrelerdi. Tek değişkenli analizde tümör boyutu, NLO ve SII istatistiksel olarak anlamlı

Abstract

Objective: Some systemic inflammatory response-based biomarkers are promising for predicting prognosis of non-muscle-invasive bladder cancer (NMIBC) patients and can contribute to the risk classification without any significant cost. We aimed to evaluate the neutrophil-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) for the prediction of recurrence and progression risk in patients with NMIBC.

Material and Methods: The study included a retrospective analysis of 211 patients who underwent transurethral resection of bladder (TURB) in a tertiary referral center between 2015 and 2019. The receiver operating characteristic (ROC) curve was used to determine the cut-off value. The Kaplan-Meier curves and the log-rank test were constructed to evaluate the recurrence-free and progression-free survival rates according to different levels of inflammatory markers. The multivariate regression analysis was undertaken to estimate the independent prognostic factors.

Results: The optimal cut-off value of SII was found to be 568 in the ROC analysis. According to the multivariate analysis, the SII value, number of tumors at the time of initial TURB, and European Organization for Research and Treatment of Cancer (EORTC) recurrence classification were statistically significant parameters in predicting recurrence. While

This study was reviewed and approved by the Haseki Training and Research Hospital Ethics Committee. Approval No: 04.06.2020/214. All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

seviyelere ulaşırken, çok değişkenli analizde anlamlı değildi.

Sonuç: SII, tümör sayısı ve EORTC nüks sınıflaması, nüks değerlendirilmesinde kullanılacak prognostik parametrelerdir. Ancak inflamatuvar parametreler, progresyon hızını tahmin etmede aynı öngörü yeteneğine sahip değildir.

Anahtar Kelimeler: Mesane kanseri; progresyon; nüks; sistemik immün-inflamasyon indeksi

tumor size, NLR, and SII achieved statistically significant levels in the univariate analysis, they didn't have significance in the multivariate analysis.

Conclusion: The SII, number of tumors, and EORTC recurrence classification are prognostic parameters that can be used in the assessment of recurrence. However, inflammatory parameters do not have the same predictive ability in the prediction of the progression rate.

Keywords: Bladder cancer; progression; recurrence; systemic immune-inflammation index

INTRODUCTION

Bladder cancer (BC) is the 11th most common cancer, with an incidence of 550 000 new cases being diagnosed every year [1]. At the time of initial diagnosis, 75% of patients present with non-muscle-invasive bladder cancer (NMIBC), and this rate is even higher in young (≤ 40 years old) adults [2]. Patients with NMIBC have a five-year probability of recurrence and progression, ranging from 31% to 78% and from less than 1% to 45%, respectively [3]. Since NMIBC includes very different clinical parameters, determining the risk of disease recurrence and progression in the postoperative follow-up is of quite critical importance in determining an appropriate treatment choice.

In current urology practice, the European Organization for Research and Treatment of Cancer (EORTC) and Club Urologico Espanol de Tratamiento Oncologico (CUETO) scoring systems are frequently used to evaluate the progression and recurrence rates of NMIBC [4-5]. However, the predictive accuracy of these models is suboptimal for the decision-making process [6]. In recent studies, it has been demonstrated that some inflammatory parameters determined in preoperative evaluations are methods that can be used for this purpose. In this context, the neutrophil-lymphocyte ratio (NLR) is the most frequently studied parameter, and meta-analyses have demonstrated it to be a beneficial tool to assess poor prognosis [7]. The systemic immune-inflammatory index (SII) is another inflammatory marker obtained by a formula using

neutrophil, lymphocyte, and platelet counts ($SII = P \times N/L$) and has been shown as a useful prognostic tool [8]. Two systematic meta-analyses revealed that SII might be a reliable prognostic factor for the poor outcomes of lung and hepatocellular cancers [9, 10]. In addition, studies investigating the relationship between SII and genitourinary system malignancies have recently shown that SII is a prognostic factor affecting survival analysis in MIBC and renal cell carcinomas. [11-14].

We hypothesized that these simple and easily applicable systemic inflammatory response-based biomarkers can predict the postoperative prognosis of patients with NMIBC without any significant cost and contribute to the risk classification of patients. In this context, we aimed to evaluate the prognostic significance of NLR and SII for the prediction of recurrence and progression risk in patients with NMIBC who underwent Transurethral resection of bladder (TURB) and followed up.

MATERIAL AND METHODS

Compliance with Ethical Standards

The current study was approved by the Ethic Committee of Haseki Training and Research Hospital (approval number: 04.06.2020/214) and was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices for Medical Research Involving Human Subjects. Additionally, written and verbal informed consent was obtained by all participants after an explanation of the study.

Study Design

The current study included a retrospective analysis of 211 patients under 80 years old who underwent TURB and follow-up in a tertiary referral center due to NMIBC between 2015 and 2019. The data consisted of records in the hospital's (Haseki Training and Research Hospital) digital data system. All patients had urothelial carcinoma, which was histologically verified, with only minimal (less than 10%) presence of variant components. The exclusion criteria were active infection or immune system diseases (8 patients) within the last one month, and the presence of any other neoplasm (6 patients). Fifteen patients with missing data (moving to different center in the follow-up or follow-up shorter than one year) were also excluded from the study. The remaining 182 patients were included in the final analyses (Figure 1).

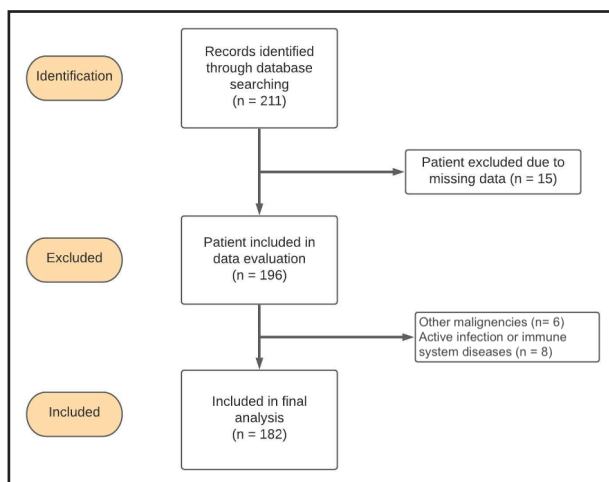


Figure 1. Flowchart of the included and excluded data

The demographic characteristics of the patients (age, sex, weight, height, and body mass index), laboratory results (hemoglobin, neutrophil, lymphocyte, monocyte and platelet counts), and pathological parameters (tumor size, number, grade, TNM stage, and concomitant carcinoma in situ) were noted. The NLR, platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and SII were also calculated. Recurrence and progression risk analyses of the patients were performed using the EORTC risk tables.

Transurethral Resection of Bladder Technique and follow-up

The patients were stratified into three risk groups (low-risk, intermediate-risk, and high-risk) according to the European Association of Urology (EAU) guidelines and followed up according to the recommended routine follow-up schedule [15]. After the first TURB, if the tumor was evaluated as low-risk, immediate single-dose intravesical chemotherapy installation (40 mg mitomycin-C) was added to the treatment algorithm. The patients with low-risk NMIBC were followed up by cystoscopy at the third and 12th months following TURB, and annually thereafter for up to five years. The patients with high-risk NMIBC underwent repeat TURB (re-TURB) at two to six weeks after the initial operation. Following the re-TURB, the patients were treated with six weeks of induction intravesical instillations of Bacillus Calmette-Guèrin (BCG), and then continued BCG maintenance therapy for at least one to three years according to patient compliance and the results of BCG therapy. In the high-risk group, routine cystoscopy with urine cytology was performed every three months in the first two years, followed by every six months for three years, and annually thereafter. The follow-up strategy for the intermediate-risk group was individualized according to the patient characteristics.

All patients were followed up by an experienced academician (Assoc. Prof. MFA) with a specific interest in bladder tumors. All pathological specimens were examined by a single pathologist team according to the recommendations of the TNM staging of the American Joint Committee on Cancer and the histological grading of the World Health Organization 1973 and 2004 classifications [16,17]. Disease recurrence was defined as any tumor relapse in the bladder during the follow-up after the initial TURB. Disease progression was defined as the upgrading of tumor stage to $\geq T2$ or an increase in the grade from low to high during the routine follow-up [18]. The patients with recurrences in the low-risk group were treated with TURB and adjuvant intravesical treatments. Among the patients

under intravesical BCG treatment, high-grade tumor recurrence or progression to muscle-invasive disease were considered as BCG failure, and radical cystectomy was recommended to these patients.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences version 22.0. The compliance of data to normal distribution was evaluated with the Shapiro-Wilk test. Categorical variables were summarized using actual counts and percentages, and continuous variables using the mean \pm standard deviation. The Pearson's chi-square or Fisher's exact test was used to compare categorical variables as appropriate. The Mann-Whitney U test or Independent t-test were used to assess the conformity of the data to a normal distribution. The receiver operating characteristic (ROC) curve was constructed to determine an appropriate cut-off value for SII. Multivariate logistic regression analysis was performed to evaluate the parameters that were predicted to be risk factors for the development of recurrence or progression. A two-tailed p value of <0.05 was considered as statistically significant.

RESULTS

Between January 2015 and December 2019, 211 patients were diagnosed with primary NMIBC. Twenty-nine patients were excluded from the study; six had concomitant malignancies, 15 were lost to follow-up, and eight had a history of active infection of any source for up to one month before the operation. Finally, a total of 182 patients were included in the sample, including 14 females (7.7%) and 168 males (92.3%), with mean age of 63.8 ± 10.9 years. At the time of the TURB, none of the patients had metastatic disease, concurrent upper tract urothelial carcinoma, or urethral cancer invasion. The mean follow-up time was 27.6 ± 12.3 months. The optimal cut-off value of SII was found to be 568 in the ROC analysis, with an area under the curve value of 0.675, p value of 0.014, sensitivity of 0.679, and specificity of 0.696 (Figure 2).

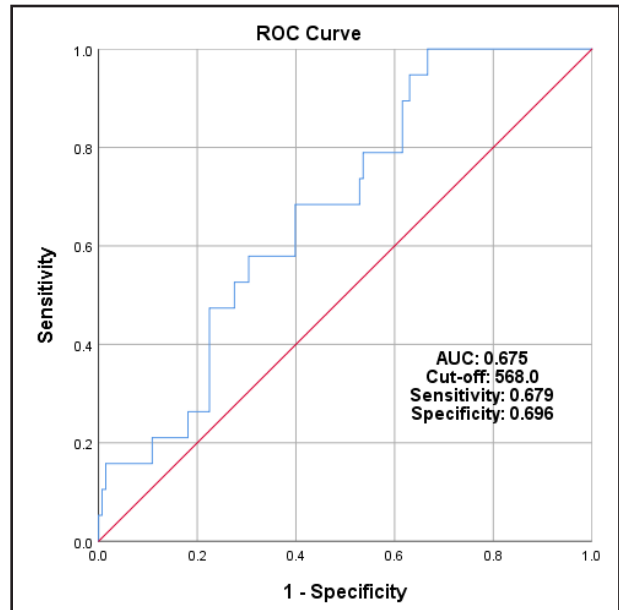


Figure 2. Receiver operating characteristic (ROC) curve of SII according to the patient outcomes. Area under the curve = 0.675, $p = 0.014$

Recurrence was observed in 20 patients (10.9%) and progression in 11 (6%). The recurrence and progression data are presented in separate tables (Table 1 and Table 2, respectively). According to the univariate analysis, the number of tumors at the time of initial TURB, EORTC recurrence classification, and SII value were statistically significant parameters in predicting the recurrence rate ($p = 0.010$, 0.018 , and 0.010 , respectively). However, well-known prognostic parameters, including pathological T stage, tumor grade, tumor size, and other inflammatory parameters (NLR, PLR, and LMR) were not statistically significant in the prediction of the recurrence rates (Table 1).

When prognostic parameters concerning progression were investigated, tumor size at the time of initial TURB, NLR, and SII were the parameters that achieved statistically significant levels ($p = 0.010$, 0.049 , and 0.047 , respectively). On the other hand, tumor grade, number of tumors, EORTC progression classification, and other inflammatory parameters (LMR and PLR) were not associated with the risk of progression (Table 2).

All the parameters found statistically significant in the univariate analysis (EORTC recurrence classification, SII, and number of tumors) for the recurrence rate also reached significant levels in the multivariate analysis ($p = 0.049$, 0.002 , and 0.008 ,

respectively) (Table 3a). However, although NLR, SII, and tumor size were found to be statistically significant in the univariate analysis regarding the progression rate, they did not demonstrate the same significance in the multivariate analysis (Table 3b).

Table 1. Comparison of the recurrence status according to the patients' demographic characteristics and pathological findings

	Overall (n = 182)	Recurrence Present (n = 20)	Recurrence Absent (n = 162)	P value
Age (years)*	63.8 ± 10.9	59.4 ± 10.9	64.4 ± 10.9	0.056 [†]
Gender, n (%)				0.371 [†]
Male	168 (92.3%)	20 (100.0%)	148 (91.3%)	
Female	14 (7.7%)	0 (0%)	14 (8.7%)	
BMI (kg/m ²)*	27.1 ± 5.7	27.5 ± 3.8	26.9 ± 5.6	0.657 [†]
TURB pathology, n (%)				0.488 [†]
Ta	105 (57.7%)	13 (65.0%)	92 (56.8%)	
T1	77 (42.3%)	7 (35.0%)	70 (43.2%)	
CIS, concomitant	13 (7.1%)	2 (10.0%)	11 (6.8%)	0.639 [†]
Tumor grade, n (%)				0.542 [†]
Low-grade	85 (46.7%)	8 (40.0%)	77 (47.5%)	
High-grade	97 (53.3%)	12 (60.0%)	85 (52.5%)	
Number of tumors, n (%)				0.010[†]
1	100 (54.9%)	6 (30.0%)	100 (61.7%)	
≥ 2	82 (45.1%)	14 (70.0%)	62 (38.3%)	
Tumor size (mm), n (%)				0.266 [†]
< 30	85 (46.7%)	7 (35.0%)	78 (48.1%)	
≥ 30	97 (53.3%)	13 (65.0%)	84 (51.9%)	
EORTC recurrence class, n (%)				0.018[†]
1-4	91 (50.0%)	5 (20.0%)	86 (53.1%)	
5-9	90 (49.5%)	15 (80.0%)	75 (46.3%)	
≥ 10	1 (0.5%)	0 (0%)	1 (0.6%)	
Neutrophil count (10 ³ /mm ³)*	5.3 ± 2.7	5.7 ± 3.0	5.2 ± 2.7	0.386 [†]
Lymphocyte count (10 ³ /mm ³)*	2.3 ± 1.2	2.6 ± 0.8	2.2 ± 1.3	0.246 [†]
Platelet count (10 ³ /mm ³)*	241.4 ± 64.1	258.8 ± 69.9	241.0 ± 65.3	0.229 [†]
NLR*	2.7 ± 1.9	2.4 ± 1.6	2.9 ± 2.7	0.431 [†]
PLR*	128.4 ± 85.3	109.9 ± 40.5	131.4 ± 93.3	0.313 [†]
LMR*	3.4 ± 1.2	3.5 ± 1.0	3.4 ± 1.4	0.713 [†]
SII*	511.8 ± 259.7	563.3 ± 192.5	466.7 ± 179.5	0.010[†]

BMI: Body mass index, TURB: Transurethral resection of bladder, CIS: carcinoma in situ, EORTC: European Organization for Research and Treatment of Cancer, LMR: lymphocyte-monocyte ratio, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, SII: systemic immune-inflammation index

* : mean ± standard deviation, †: Student's t test, ‡: Pearson's Chi-Square test

Table 2. Comparison of the progression status according to the patients’ demographic characteristics and pathological findings

	Overall (n = 182)	Progression Present (n = 11)	Progression Absent (n = 171)	P value
Age (years)*	63.8 ± 10.9	59.4 ± 10.9	64.4 ± 10.9	0.483 [†]
Gender, n (%)				0.569 [†]
Male	168 (92.3%)	10 (90.9%)	158 (92.4%)	
Female	14 (7.7%)	1 (9.1%)	13 (7.6%)	
BMI (kg/m ²)*	27.1 ± 5.7	28.2 ± 4.1	26.9 ± 5.5	0.440 [†]
TURB pathology, n (%)				0.360 [†]
Ta	104 (57.1%)	8 (72.7%)	96 (56.2%)	
T1	76 (42.9%)	3 (27.3%)	73 (42.7%)	
CIS, concomitant	2 (1.1%)	0 (0%)	2 (1.1%)	NA
Tumor grade, n (%)				0.189 [†]
Low-grade	84 (46.1%)	3 (27.3%)	81 (47.4%)	
High-grade	97 (53.9%)	8 (72.7%)	89 (52.6%)	
Number of tumors, n (%)				0.206 [†]
1	102 (56.0%)	4 (36.4%)	98 (57.3%)	
≥ 2	73 (44.0%)	7 (63.6%)	67 (42.7%)	
Tumor size (mm), n (%)				0.010[†]
< 30	85 (46.7%)	1 (9.1%)	84 (49.1%)	
≥ 30	97 (53.3%)	10 (90.9%)	87 (50.9%)	
EORTC recurrence class, n (%)				0.536 [†]
1-4	79 (43.4%)	3 (27.3%)	76 (44.4%)	
5-9	76 (41.8%)	6 (54.5%)	70 (40.9%)	
≥ 10	27 (14.8%)	2 (18.2%)	25 (14.6%)	
Neutrophil count (10 ³ /mm ³)*	5.3 ± 2.7	5.7 ± 3.0	5.2 ± 2.7	0.222 [†]
Lymphocyte count (10 ³ /mm ³)*	2.3 ± 1.2	2.2 ± 0.7	2.2 ± 1.2	0.917 [†]
Platelet count (10 ³ /mm ³)*	241.4 ± 64.1	241.0 ± 39.2	243.3 ± 67.6	0.914 [†]
NLR*	2.7 ± 1.9	2.3 ± 2.2	2.8 ± 2.4	0.464 [†]
PLR*	128.4 ± 85.3	114.5 ± 20.6	129.9 ± 89.9	0.573 [†]
LMR*	3.4 ± 1.2	4.2 ± 1.2	3.4 ± 1.3	0.049[†]
SII*	511.8 ± 259.7	683.6 ± 729.9	505.5 ± 204.9	0.047[†]

BMI: Body mass index, CIS: carcinoma in situ, EORTC: European Organization for Research and Treatment of Cancer, LMR: lymphocyte-monocyte ratio, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, SII: systemic immune-inflammation index, NA: Not Applicable

* : mean ± standard deviation, [†]: Student’s t test, †: Pearson’s Chi-Square test

Table 3a. Multivariate analysis of recurrence

	Odds Ratio	95% confidence interval		P value
		Lower	Upper	
EORTC	2.991	0.9	9.7	0.049
SII	1.005	1.0	1.1	0.002
Number of tumors	4.876	1.5	15.7	0.008

EORTC: European Organization for Research and Treatment of Cancer, SII: systemic immune-inflammation index

Table 3b. Multivariate analysis of progression

	Odds Ratio	95% confidence interval		P value
		Lower	Upper	
NLR	1.569	0.7	3.2	0.212
SII	1.002	1.0	1.3	0.075
Tumor size	8.256	0.9	21.7	0.052

NLR: neutrophil-lymphocyte ratio, SII: systemic immune-inflammation index

DISCUSSION

Today there are several prognostic tools to evaluate the recurrence and progression possibilities of NMIBC. In our study multivariate analysis revealed that SII, number of tumors, and EORTC recurrence classification were independent prognostic parameters to assess the recurrence rate. Although the univariate analysis showed statistically significant results for SII, NLR, and tumor size, the multivariate analysis did not produce the same results concerning the progression rate.

In our study group, we found the recurrence rate as 10.9%. According to the EORTC trials, the recurrence rate ranged between 15 and 61% [4]. Our results were lower than the lower limit given in the literature, which we think may be due to our small sample size. We combined the EORTC risk classification with patient characteristics, pathological results, and follow-up data. We showed that the EORTC classification was a prognostic factor. The number of tumors, which is a part of the EORTC risk assessment, was also determined to be a prognostic factor when evaluated alone. The above-mentioned parameters have been previously investigated and showed high power in the assessment of the recurrence rate in NMIBC. However, there is lack of information concerning the biochemical or inflammatory parameters of this model, which are also known as prognosticators.

Most oncological prognostic biomarkers are determined as a result of expensive and time-consuming analyses, such as polymerase chain reaction and immunohistochemistry methods [19]. Routine blood tests provide adequate clinical information about a patient's inflammatory status by formulating the values

of blood contents. Mediators and cytokines released during an inflammatory reaction are considered to cause cell damage and assist in the development of gene mutations, which are essential in cancer cell development and create a microenvironment that promotes cancer cell proliferation. Neutrophil, lymphocyte, and thrombocyte formulations are the most commonly used inflammatory parameters. SII is a parameter obtained as a result of the combination of all these blood elements, and it is one of the most actively studied parameters for predicting disease characteristics in a variety of cancer types [9,10]. Firstly, SII has been shown as a better predictor of prognosis than NLR and PLR MIBC patients by Zhang et al. [12]. Subsequently, a multicenter European cohort showed that SII also has predictive relevance in the patient population with NMIB, underlining the crucial role of SII in current medical care [20]. We also, determined SII as another prognostic factor to determine the recurrence rate, which is consistent with the literature currently available.

In our study, the progression rate was found to be 6.1%, and this result was in the range of one-year risk of progression in the EORTC trial [4]. In the univariate analysis, tumor size, which is part of the EORTC risk classification, reached a statistically significant level. However, the same results were not obtained from the multivariate analysis, and therefore we cannot state that tumor size is a prognostic parameter for evaluating the rate of progression. Furthermore, we were not able to demonstrate a relationship between NLR and the progression rate in our study. A recent study showed that a high NLR value and a high progression rate were associated in patients with NMIBC [21]. However,

similar to our study, some studies did not demonstrate the same relationship NLR and progression rate [22,23]. We consider that this situation lowers the reliability of NLR in relation to the prognosis rate. In another meta-analysis showing the significance of a high NLR value in predicting the recurrence, progression, and survival of bladder tumors, mainly muscle-invasive bladder tumor studies were included in the analysis (14 MIBC and four NMIBC studies) [24]; therefore, that meta-analysis can be considered limited in effectively assessing the ability of NLR to determine progression in the non-muscle invasive group.

We found that the best cut-off value of SII was 568 in the ROC analysis. In a large multicenter European cohort which investigates the prognostic value of SII in NMIBC, optimal cut-off value of SII was determined as 580 [20]. In an article investigating whether SII predicts BCG failure, the threshold value was found to be 672.75 [25]. In an additional study, the researchers reported that SII is an independent predictor of RFS in NMIBC patients and that individuals with high SII (525.26) have a significantly increased chance of tumor progression or recurrence [26]. In another study investigating inflammatory markers to predict postoperative recurrence among NMIBC patients treated with intravesical chemotherapy and intravesical chemo-hyperthermia, the SII threshold was 575.3 [27]. In light of our findings and current literature search, we think that SII values of above 500 should alert the clinician to suspect an NMIBC prognosis.

This study has several limitations. First, it had a retrospective nature with a single-center experience. Second, it had a short follow-up period. Third, we did not analyze the results using the CUETO classification. Despite these limitations, we consider that our results are promising and should be supported by further studies with large sample sizes and longer follow-up periods.

CONCLUSIONS

Our study suggests that SII, number of tumors,

and EORTC recurrence classification are prognostic parameters for the assessment of the recurrence rate. However, neither inflammatory parameters nor pathological findings had similar value in relation to the progression rate.

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Evaluation of the Quality of Life of Patients Who Use Intermittant Self-Catheterization by Themselves and by Their Caregivers

Temiz Aralıklı Kateterizasyon Uygulanan Hastaların Yaşam Kalitelerinin Kendileri Ve Bakım Verenleri Tarafından Değerlendirilmesi

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Özet

Amaç: Temiz aralıklı kateterizasyon (TAK) nörojenik mesanesi olan bireyler tarafından kullanılan bir cihazdır. TAK hasta veya bakıcı tarafından kullanılabilir. Bu çalışmanın amacı, TAK kullanan bireylerin TAK uygulama becerileri ile yaşam kaliteleri arasındaki ilişkiyi incelemektir.

Gereç ve Yöntemler: Haziran 2018 ve Mayıs 2019 tarihleri arasında, bir şehir hastanesi üroloji kliniğinde Temiz Aralıklı Kendi Kendine Kateterizasyon (TAK) kullanan 126 hasta çalışmaya dahil edildi. Tüm hastalar ISC-Q(T-ISC-Q) ve Qualiveen anketlerinin Türkçe versiyonunu doldurdu. TAK kullanıcıları iki gruba ayrıldı: Kendi kendine uygulayanlar ve bakım vericilerin ISC-Q ve Qualiveen arasındaki Spearman korelasyon katsayısı belirlendi.

Bulgular: Hastaların ortalama yaşı 51,53±16,47 yıl ve TAK kullanım süresi 42,15 ± 12,56 aydı. Toplam 72 hasta TAK uyguladığını bildirirken, bakıcı tarafından TAK uygulanan hasta sayısı 54 idi. ISC-Q puanları kullanım kolaylığı için 70,98±15,41, kolaylık için 42,85±18,40, mahremiyet için 75,71±14,97 ve psikolojik iyi oluş için 56,34±14,57 idi. Cronbach α sonuçları 0,782 idi. ISC-Q toplam puanı, Qualiveen toplam puanı ile pozitif korelasyon gösterdi ($r=0,567$, $p=0,04$). Kendi TAK kullanan hastalar, bakıcı tarafından TAK uygulanan hastalardan daha yüksek ISC-Q puanlarına sahipti.

Sonuç: Sonuç olarak, TAK kullanım

Abstract

Objective: The clean intermittent catheterization is a device used by individuals with neurogenic bladder. The ISC can be used by the patient or by a caregiver. The aim of this study is to examine the relationship between ISC practice skills and quality of life of individuals using ISC.

Material and Methods: Between June 2018 and May 2019, 126 patients using Clean Intermittent Self Catheterization (ISC) in a city hospital urology clinic was included in the study. All patients completed the Turkish version of the ISC-Q(T-ISC-Q) and Qualiveen questionnaires. ISC users were divided into two groups: Self-administered and caregiver practitioners. Spearman's correlation coefficients between ISC-Q and Qualiveen were used.

Results: The mean age of the patients was 51.53±16.47 years, and the duration of ISC was 42.15 ± 12.56 months. A total of 72 patients reported that they performed the ISC, while the number of patients who underwent ISC by the caregiver was 54. ISC-Q scores were 70.98±15.41 for ease of use, 42.85±18.40 for convenience, 75.71±14.97 for privacy, and 56.34±14.57 for psychological well-being, respectively. The results of the Cronbach α was 0.782. ISC-Q total score was positively correlated with Qualiveen total score ($r=0.567$, $p=0.04$). Patients who used their own ISC had higher ISC-Q scores than patients who had ISC administered by the caregiver.

The study was approved by University of Health Sciences Okmeydanı Training and Research Hospital Clinical Research Ethics Committee (Approval number: 2018/930). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

kolaylığı yüksek olmakla birlikte, TAK kullanan hastaların rahatlık ve psikolojik iyi oluşlarında azalma görülmektedir. Bu, bakıcı tarafından TAK uygulanan hastalarda daha düşüktü.

Anahtar Kelimeler: Aralıklı kendi kendine kateterizasyon, yaşam kalitesi, sonuç ölçüsü, bakım verici

Conclusion: As a result, while the ease of use of ISC is high, there is a decrease in the convenience and psychological well-being of the patients using ISC. This was lower in patients who had ISC administered by the caregiver.

Keywords: Intermittent self-catheterization, quality of life, outcome measure, caregiver

INTRODUCTION

A variety of diseases and events affecting the nervous system controlling the lower urinary tract (LUT) may cause neuro-urological symptoms (1). The resulting of these symptoms depends on mainly the location of the neurological lesion. For instance, the lesions, which locate above the pons or between the pons and the sacral cord, cause detrusor overactivity, resulting in urgency to void and urinary incontinence. Furthermore, lesions, which locate in the infra-sacral region cause noncontractile detrusor, resulting in increased residual urine. This increased residual urine may affect the upper urinary tract and cause to develop urinary tract infections (2). Therefore, it is crucial to empty the bladder in an effective way to prevent complications like infections. clean intermittent self-catheterization (ISC) is the most common minimally invasive procedure for the management of noncontractile bladder due to neuro-urological dysfunctions (3).

Although CISC provides great comfort to the patients to allow them to control when and where to empty their bladder without urinary leakage, it may impair the patients' quality of life (QoL) nonetheless (4). Bolinger et al. (5) suggested that the "out of home" situations may become stressful scenarios for some patients. The authors also reported that the steps of the ISC, which are hand sanitizing, cleaning the meatus, and lubricate the catheter, need some adequate countertops or shelves. However, the inadequately designed public bathrooms, make these steps difficult to do (6).

In 2012 Pinder et al. developed The Intermittent

Self-Catheterization Questionnaire (ISC-Q) to evaluate these patients' QoL. Although ISC-Q is a reliable and well-validated questionnaire, its feasibility for evaluating patients with reusable catheters is not clear so far (7). Nevertheless, since it is a very valuable questionnaire, it was validated in many languages (8, 9).

The aim of this study is to examine the relationship between ISC practice skills and quality of life of individuals using ISC.

MATERIALS AND METHODS

The Study Protocol

We designed a cross-sectional study. Between June 2018 and May 2019, 126 patients; who performed ISC at least three times a day, were enrolled in the study. The present study protocol was reviewed and approved by the Ethics Committee of Okmeydanı Training and Research Hospital (approval No. 2018/930). Informed consent was obtained by all subjects when they were enrolled.

The patients, who were under 18 years of age, unable to read or to have a psycho-neurological illness, were excluded from the study.

In the demographic characteristics form, the patient's age, gender, education status, smoking-alcohol use status, reason for using ISC, frequency of using ISC, and whether he/she drives to walk or not were questioned. All patients fulfilled the Turkish version of the ISC-Q (T-ISC-Q) and Qualiveen questionnaires at the beginning of the study and four weeks later. Demographic data, the experience of ISC usage, and the daily frequency were recorded.

Intermittent Self-Catheterization Questionnaire

The ISC-Q contains four domains (ease of use, convenience, discreetness, and psychological well-being) with 24 entries. It allows the clinician to evaluate both the physical and psychological problems of the patient. A 5-point scale system is used for each entry from 0 to 4, which means strongly disagree and strongly agree, respectively. The scores are calculated for each domain separately by multiplying the mean value of the entries by 25. This calculation gives a value from 0 to 100. The total score is the simple average of all four domains' values. High values mean high QoL. Turkish validation of this questionnaire made by Yesil et al. (10).

Statistical Analysis

SPSS 23.0 software was used for data analyses (SPSS, Version 23.0; IBM Corp, Armonk, NY). To determine the distribution, the Kolmogorov-Smirnov normality test was performed.

Intraclass correlations coefficient (ICC) and Bland-Altman method were performed to assess the test-retest reliability (11, 12). Furthermore, Cronbach's α was used to evaluate the internal consistency of the T-ISC-Q domains and the total scale. Spearman's correlation analysis was performed to evaluate coefficients between ISC-Q and Qualiveen for the distinctive and convergent validity of the translated scale. Independent sample t test was used for comparisons.

RESULTS

The mean age of the patients was 51.53 ± 16.47 years, the duration of ISC was 42.15 ± 12.56 months, and the frequency was 5.14 ± 0.94 times/day. Most of the patients were male (66.7%, 84/126). The percentage of people using devices for walking was 33.3%. The demographic data of the patients were demonstrated in Table-1.

A total of 72 patients reported that they performed the ISC, while the number of patients who underwent ISC by the caregiver was 54. T-ISC-Q scores were 70.98 ± 15.41 for ease of use, 42.85 ± 18.40 for

convenience, 75.71 ± 14.97 for privacy, and 56.34 ± 14.57 for psychological well-being, respectively (Table-2). Cronbach α was 0.782. ICC was found as 0.713. T-ISC-Q total score was positively correlated with Qualiveen total score ($r = 0.567$, $p = 0.04$). Furthermore, convenience domain of the T-ISC-Q had a strong correlation with the Qualiveen total scale ($p=0.001$) (Table-3).

Table 1. Demographic data of the patients (n=126)

	Mean±SD	Min-Max
Gender (male/female)	84/42	
Age (years)	51.53±16.47	21-86
Duration of ISC	42.15±12.56	2-84
Frequency of ISC times/day	5.14±0.94	3-7
Using the Walking Device (yes/no/%)	42/84 (33%)	
Smoking Status (yes/no)	40/86	
Alcohol Status (yes/no)	6/120	
Education Status (n-%)		
Primary	60	47.71%
High	36	28.57%
University	10	7.94%
Income Level (n-%)		
0-2000 TL	18	14.29%
2000-5000 TL	80	63.49%
>5000 TL	28	22.22%

Data are Mean ± SD or n (%).

ISC, clean intermittent self-catheterization.

Table 2. Intermittent Self-Catheterization Questionnaire scores

	Mean	SD	Min	Max
ISC(Easy To Use)	70.98	15.41	31.25	100.00
ISC(Convenience)	42.86	18.40	25.00	81.25
ISC(Discreetness)	75.71	14.97	50.00	100.00
ISC (Psychological Well-Being)	56.35	14.57	36.67	96.67
ISC(Total)	61.48	8.01	41.25	81.04

ISC, clean intermittent self-catheterization.

Table 3. Spearman correlations between Intermittent Self-Catheterization Questionnaire domains and total scores and Qualiveen® scores

		ISC (Easy to use)	ISC (Convenience)	ISC (Discreetness)	ISC (Psychological Well-Being)	ISC (Total)
Qualiveen Limitations	r	-0.101	0.212*	-0.111	-0.138	-0.033
	p	0.286	0.023	0.241	0.143	0.729
Qualiveen Constraints	r	-0.118	0.018	0.012	-0.013	-0.046
	p	0.187	0.840	0.891	0.889	0.606
Qualiveen Fears	r	-0.356**	0.666**	-0.496**	-0.244*	-0.041
	p	0.000	0.000	0.000	0.014	0.684
Qualiveen Feelings	r	0.286**	0.019	0.012	0.274**	0.302**
	p	0.002	0.838	0.897	0.002	0.001
Qualiveen Total	r	0.009	0.306**	-0.091	-0.012	0.163
	p	0.922	0.001	0.322	0.895	0.074

*p<0.05

**p<0.01

ISC; clean intermittent self-catheterization, Spearman correlation test

Table 4. Comparison between groups

ISC-Q Domains	Self-using	With caregiver	p
Ease of use	72.63 (18.01)	66.08 (17.44)	0.001
Discreetness	79.58 (20.07)	68.36 (24.50)	<0.001
Psychological well-being	59.76(18.88)	51.50 (25.31)	0.002
Convenience	44.55 (15.15)	39.03 (25.45)	0.001

Independent sample t test was used

ISC, clean intermittent self-catheterization

The ISC-Q all sub-dimension scores and the total score of the patients who used the ISC themselves were found to be higher than the patients who used the ISC with the help of their caregivers (Table-4).

DISCUSSION

According to our results, the quality of life was found to be higher in patients who used ISC themselves. In addition, the privacy of the patients is affected during ISC administered by the caregiver.

The use of ISC is a process that can be done in many steps and where effective hand hygiene plays a role. Although a lot of training is provided, its incorrect

application can lead to deterioration of the patient's quality of life and infections. Videos containing ISC training can be preferred by patients and caregivers in terms of ease of application(13).

Based on literature, the validity of a translated scale should be evaluated by using the gold standard tool (14); however, in the time being, there was no validated ISC related QoL questionnaire in Turkey. Nevertheless, according to our findings, the total T-SCI-Q correlated with Qualiveen. Furthermore, Pinder et al. proved the robust relationship between ISC-Q and Qualiveen in a previous study (7). Therefore, we assumed that our findings are consistent with the

literature. However, the discreetness domain of the T-ISC-Q did not correlate with the other domains but the fear domain of Qualiveen. In our opinion, this could indicate that the discreetness domain may reflect concerns about ISC in cultural background (10). As far as we know, the concept of discreetness can vary in different geographies (15). Therefore, it is reasonable to accept that the discreetness domain may be the most subjective in the scale. Furthermore, Yoshida et al. also reported similar results about the discreetness domain on Japanese users in a recent study (9). There was a negative correlation between Qualiveen -fear sub-dimension and all sub-dimensions of ISC-Q in patients. Patients' fears and concerns about the use of ISC reduce ease of use, reduce usefulness and psychological well-being. These results are similar to previous findings. In addition, it was observed that these scores were lower in patients who underwent ISC by their caregivers. This situation is thought to be related to the anxiety and fear that the patients experience because of the inability to hide their privacy.

However, we have some limitations that need to be addressed. First, the patients' data are from one hospital. Therefore, the generalizability of our findings is limited. Furthermore, all patients were disposable catheter users, and our validated scale was not tested on reusable catheter users. Therefore, it is not clear whether T-ISC-Q can be beneficial to assess the ISC-related QOL of different kind of catheter users.

CONCLUSION

To conclude, while the ease of use of ISC is high, there is a decrease in the convenience and psychological well-being of the patients using ISC. This was lower in patients who had ISC administered by the caregiver.

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Conflicts of Interest / Competing interests: None.

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Consent to Participant: Written consent was obtained from the patients.

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Assessment of Hematological Parameters in the Diagnosis Brucella Epididymorchitis: Comparison of Brucella Epididymorchitis and Non-Brucella Epididymorchitis

Brucella Epididimorşiti Tanısında Hematolojik Parametrelerin Değerlendirilmesi: Brucella Epididimorşiti İle Non-Brucella Epididimorşitlerin Karşılaştırılması

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Özet

Amaç: Brucella epididimorşiti (BEO) ile brusella dışı epididimorşitin (NBEO) ayırıcı tanısını kolaylaştırabilecek ve erken tanıyı kolaylaştırabilecek parametreleri araştırmak.

Gereç ve Yöntemler: Brusellozun yaygın olduğu Türkiye'nin doğusunda üçüncü basamak bir merkeze başvuran 23 BEO hastası ve 80 NBEO hastasının verileri retrospektif olarak incelendi. Yaş, hemogram parametreleri (beyaz kan hücresi (WBC), nötrofil, lenfosit, monosit, eozinofil, bazofil, trombosit, nötrofil-lenfosit oranı (NLR), monosit-lenfosit oranı (MLR), trombosit-lenfosit oranı (PLR), ortalama trombosit hacmi (MPV), kırmızı kan hücresi dağılım genişliği (RDW)), biyokimyasal parametreler (aspartat transaminaz ve alanin aminotransferaz), inflamatuvar belirteçler (C-reaktif protein, eritrosit sedimentasyon hızı ve prokalsitonin), idrar kültürü ve skrotal doppler ultrason bulguları retrospektif olarak incelendi. BEO ve NBEO gruplarının sonuçları karşılaştırıldı.

Bulgular: BEO ve NBEO gruplarının karşılaştırılmasında, iki grup arasında WBC sayısı, nötrofil sayısı, monosit sayısı, NLR, MLR, MPV ve prokalsitonin seviyeleri açısından anlamlı fark vardı (sırasıyla $p = 0,035$, $p = 0,007$, $p = 0,003$, $p = 0,005$, $p = 0,01$, $p < 0,001$, $p < 0,001$).

Sonuçlar: NLR, BEO'nun erken tanısında kullanım için umut verici olabilir. MPV de değerlendirilebilecek bir diğer parametre olarak

Abstract

Objective: To analyze the parameters that can facilitate the differential diagnosis of brucella epididymorchitis (BEO) and non-brucella epididymorchitis (NBEO) and to facilitate early diagnosis.

Material And Methods: The data of 23 BEO patients and 80 NBEO patients, who applied in a tertiary center in eastern Turkey, where brucellosis is common, were retrospectively analyzed. Age, hemogram parameters (white blood cell (WBC)), neutrophil, lymphocyte, monocyte, eosinophil, basophil, platelet, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), red blood cell distribution width (RDW), biochemical parameters (aspartate transaminase and alanine aminotransferase), inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, and procalcitonin), urine culture, and scrotal doppler ultrasound findings were analyzed retrospectively and were compared between BEO and NBEO groups.

Results: In the comparison of the BEO and NBEO groups, there was a significant difference between the two groups in WBC count, neutrophil count, monocytes count, NLR, MLR, MPV, and procalcitonin levels ($p = 0.035$, $p = 0.007$, $p = 0.003$, $p = 0.005$, $p = 0.01$, $p < 0.001$, $p < 0.001$, respectively).

Conclusions: The NLR may be promising

This study was reviewed and approved by the Van Training and Research Hospital medical ethics committee on March 21, 2019 (approval number: 2019/06). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

dikkat çekmektedir.

Anahtar Kelimeler: brucellozis, genitouriner, enfeksiyon, epididimorşit

for use in the early diagnosis of BEO. The MPV also drew attention as parameters that can be evaluated

Keywords: brucellosis, genitourinary, infections, epididymorchitis

INTRODUCTION

Brucellosis is an endemic zoonotic disease caused by gram-negative coccobacillus *Brucella* (1). It is one of the most common zoonoses, with over 500,000 cases each year (2). Although the incidence of brucellosis is low in developed countries, it occurs sporadically in occupationally exposed groups, such as farmers, veterinarians, laboratories, and abattoir workers (3). In Türkiye, the eastern and southeastern regions are especially affected (1).

Transmission of the agent to humans occurs through aerosols contaminated with the conjunctival sac by consuming unpasteurized dairy products, direct contact with animals, or animal secretions through cuts and abrasions on the skin. Clinical signs usually include a high fever, night sweats, joint pain, and splenomegaly (4). Epididymorchitis is the most common type of genitourinary complication. It causes granulomatous-type orchitis and can be seen in 2%–20% of infected men (1). Scrotal pain, swelling and fever are the most common findings in *Brucella* epididymorchitis (BEO) (5). These symptoms are not specific to BEO and are also seen in other epididymorchitis. Therefore, the differential diagnosis of BEO becomes even more important. At the same time, the treatments of BEO and non-*Brucella* epididymorchitis (NBEO) are different from each other. Combinations of doxycycline, rifampicin, and streptomycin are generally used for BEO, and the treatment takes longer (6, 7). In addition, it is very important to separate BEO from emergency urological conditions that cause acute scrotum to prevent unnecessary operations and organ loss (8).

In brucellosis, which is characterized by an increase in acute phase reactants, such as C-reactive protein (CRP) and erythrocyte sedimentation rate

(ESR), it has been predicted that it may change indirect inflammatory parameters, such as white blood cell (WBC) count, platelet count, mean platelet volume (MPV), red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and platelet lymphocyte ratio (PLR) (9).

This study aimed to reach parameters that can be beneficial in the diagnosis of BEO by evaluating hemogram parameters (WBC, neutrophil, lymphocyte, monocytes, eosinophil, basophil, platelet, MPV, RDW), NLR, MLR, PLR, aspartate transaminase (AST), alanine aminotransferase (ALT), inflammatory markers (CRP, ESR, and procalcitonin), pyuria and microorganism detection in the urine, and abscess formation on ultrasound (US).

MATERIALS AND METHODS

The data of 103 epididymorchitis patients, including 23 BEO patients and 80 NBEO patients, who applied to the infectious diseases and urology clinics of Van Training and Research Hospital, a tertiary center in eastern Turkey, between July 2017 and December 2021, were retrospectively analyzed. Patients diagnosed with BEO were determined as the case group, and patients diagnosed with NBEO were determined as the control group. The laboratory data of patients with BEO and NBEO were compared.

Since the region where the Van Training and Research Hospital is located is an area where brucellosis is endemic, hemogram parameters (WBC, neutrophil, lymphocyte, monocytes, eosinophil, basophil, platelet, MPV, and RDW), NLR, MLR, PLR, biochemical parameters (AST and ALT), inflammatory markers (CRP, ESR, and procalcitonin), Rose Bengal test, serum tube agglutination test, blood culture,

and scrotal Doppler US performed by a specialist radiologist are routinely performed in all patients with epididymorchitis clinic (scrotal swelling, pain, redness, fever, night sweats, and joint pains) who apply to urology or infectious diseases outpatient clinics.

A positive blood culture, positive Rose Bengal test result, or serum tube agglutination test above 1/160 as well as clinical and ultrasonographic findings of epididymorchitis were determined as the main diagnostic criteria for BEO.

Blood culture samples sent in BACTEC 9240 and BacT/Alert FA Plus culture bottles were analyzed using automated culture systems. Due to the late growth of Brucella bacteria, these bottles were kept for 30 days. Afterwards, samples were taken from the bottles with growth, inoculated on blood agar, eosin-methylene blue (EMB) agar, and chocolate agar media, and kept for up to 48 hours. The diagnosis was made by taking samples from growing media.

In the serum tube agglutination test, an equal amount of Brucella agglutination antigen was added to the patient's serum and diluted with physiological saline in the tubes. An evaluation was made after 48 hours of incubation at 37 °C. If agglutination was observed in a single sample at dilutions of 1/160 and above in the serum samples taken from the patients, the result of the test was considered positive.

The Rose Bengal test was carried out in an acidic environment using the Brucella antigen prepared from the Brucella bacteria and stained with Rose Bengal dye using special techniques. The test was considered positive as a result of the presence of Rose Bengal staining.

At the time of first admission of the patients diagnosed with BEO and the control group, the following sample parameters were recorded: white blood cells (ul), neutrophils (ul) lymphocytes (ul), monocytes (ul), eosinophils (ul), basophils (ul), platelets (ul), NLR, MLR, PLR, MPV (fL), red blood cell distribution width (%), AST, ALT, C-reactive protein (mg/dl), ESR (mm/h), Procalcitonin (ng/ml), pyuria (%), abscess formation, and microorganisms isolated in urine. These parameters were statistically

compared between the two groups.

This study was reviewed and approved by the medical ethics committee of Van Training and Research Hospital on 21 March 2019 (approval number: 2019/06).

Statistical Analysis

The normal distribution of continuous variables was evaluated using visual and analytical methods. In the descriptive findings, categorical variables are given as numbers (percent), and continuous variables are presented with median (minimum–maximum) or mean \pm standard deviation for normal non-scattering data. Categorical variables were analyzed using the appropriate chi-squared test, chosen between Pearson and exact tests. For the continuous variables, the statistical difference among groups was determined using Mann-Whitney U tests. The data that follows a normal distribution was analyzed using an independent t-test, while the data that does not follow a normal distribution was evaluated using the Mann-Whitney U test. Statistical significance was accepted as p and lt : 0.05. The statistical analysis of the research data was performed using R version 4.2.1.

RESULTS

Out of 103 patients, 23 (22.33%) were diagnosed with BEO, while 80 (77.67%) were in the NBEO group. The median age of the patients was 40 (20–80) in the BEO group and 42.5 (6–89) in the NBEO group. There was no statistically significant difference between the ages of the two groups.

The WBC count was 8100/ μ L in the BEO group and 10100/ μ L in the NBEO group. The WBC count was significantly higher in the NBEO group ($p = 0.035$).

While the number of neutrophils was 4400/ μ L in the BEO group, it was found to be 6500/ μ L in the NBEO group. The neutrophil count was significantly higher in the NBEO group ($p = 0.007$).

The monocyte count was 500/ μ L in the BEO group and 700/ μ L in the NBEO group. The number of monocytes was significantly higher in the NBEO group ($p = 0.003$).

The NLR was 1.68 in the BEO group and 3.21 in the NBEO group. The NLR was statistically significantly higher in the NBEO group ($p = 0.005$).

The MLR was 0.25 in the BEO group and 0.44 in the NBEO group. It was significantly higher in the NBEO group ($p = 0.01$).

The MPV was 9.2 fL in the BEO group and 10.1 fL in the NBEO group. It was statistically significantly higher than in the NBEO group ($p = <0.001$).

Procalcitonin was 0.02 ng/ml in the BEO group and 0.06 ng/ml in the NBEO group. It was significantly higher in the NBEO group ($p < 0.001$).

There was no statistically significant difference between the two groups in terms of lymphocyte count, eosinophil count, basophil count, platelet count, PLR, RDW, AST, ALT, CRP, ESR, pyuria rates, abscess formation, and microorganism isolation rate (Table 1).

Table 1. Demographic data and laboratory results of patients

	BEO (n=23, 22.33%) (median (IQR))	NBEO (n=80, 77.67%) (median (IQR))	p value
Age (year)	40 (22-52)	42.5 (23-66)	0.433
WBC (µl)	8100 (6100 – 11000)	10100 (7925 – 12900)	0.035
Neutrophil (µl)	4400 (3000 – 6900)	6500 (5200 – 8700)	0.007
Lymphocyte (µl)	2600 (1900-3500)	2200 (1420 – 3100)	0.175
Monocyte (µl)	500 (400 – 900)	700 (600 – 1200)	0.003
Eosinophil (µl)	80 (50 – 200)	90 (42.5 – 157.5)	0.911
Basophil (µl)	20 (20 – 40)	30 (10 – 40)	0.914
Platelet (µl)	238000 (207000 – 293000)	290500 (216500 – 333250)	0.114
NLR	1.68 (1.11 – 3.36)	3.21 (1.99 – 4.20)	0.005
MLR	0.25 (0.13 – 0.36)	0.44 (0.24 – 0.56)	0.01
PLR	108.75 (75.81 – 133.33)	128.41 (95.31 – 176.95)	0.051
MPV (fL)	9.2 (8.6 – 9.8)	10.1 (9.3 – 11.3)	<0.001
RDW (%)	13.5 (13.3 – 14.2)	13.25 (12.6 – 14.3)	0.163
AST (U/L)	27 (18 - 49)	28 (19.3 – 34.8)	0.981
ALT (U/L)	22 (18 – 59)	26.5 (19 – 35)	0.623
CRP (mg/dl)	14 (3 – 90)	13 (6.3 – 43.2)	0.877
ESR (mm/h)	10 (5 – 24)	8.5 (4 – 19.8)	0.297
Procalcitonin (ng/ml)	0.02 (0.01 – 0.03)	0.06 (0.03 – 0.1)	<0.001
Pyuria n (%)	3 (13.0 %)	24 (30.0 %)	0.103
Abscess formation n (%)	3 (13.0 %)	7 (8.8 %)	0.540
Microorganism isolated in urine sample n (%)	3 (13.0 %)	8 (10.0 %)	0.677

BEO: Brucella epididymorchitis, NBEO: Non-brucella epididymorchitis , WBC: White blood cell, NLR: Neutrophil/Lymphocyte Ratio, MLR: Monocyte/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, MPV: Mean Platelet Volume, RDW: Red blood cell distribution width, AST: Aspartate transaminase , ALT: Alanine aminotransferase, CRP: C – reactive protein, ESR: Erythrocyte sedimentation rate

DISCUSSION

Brucellosis can mimic many systemic diseases (10). This leads to a delay in diagnosis, misdiagnosis, and loss of time in treatment (11). BEO is a common complication of brucellosis. BEO does not come to mind as pre-diagnosis like systemic brucellosis. Therefore, there are delays in diagnosis and different complications develop. Since there are delays in the diagnosis, complications such as male infertility, necrotizing orchitis resulting in orchiectomy might develop. The diagnosis of BEO is made by laboratory tests (such as a serum tube agglutination test, Rose Bengal test, and blood culture), in addition to clinical findings. However, the increase in the number of additional tests brings into question the appropriate laboratory conditions and costs. Therefore, obtaining auxiliary parameters is very useful for easy diagnosis and cost reduction (12). Increases in CRP, ESR, WBC, AST, and ALT values can be seen in BEO cases (13). In some studies, an increase in acute-phase reactants was found to be an expected result in BEO cases (1). However, different results have been found regarding the levels of these parameters in different studies (1, 3, 5).

Due to the rarity of brucellosis in developed countries, as far as we know, there are not many studies in the literature, except for a few studies comparing BEO and NBEO in terms of inflammatory markers. (12-15).

In their study, Çift et al. found the mean age to be lower in the BEO group than in the NBEO group (12). The reason for this may be that agricultural workers, in whom brucellosis is common, comprise young people. In addition, considering that lower urinary system symptoms and recurrent urinary tract infections are facilitating factors in the formation of NBEO, it can be thought that this group may have an older population (16, 17). Contrary to this study, Papatsoris et al. and Aydın et al. found no difference in mean age in their studies, but they did not comment on this (15). The reason for this may be the consumption of raw milk and dairy products, which cause brucellosis, by people of all ages.

Non-Brucella epididymorchitis is an acute inflammation; therefore, a more pronounced WBC response can be expected. Our study supports this expectation as well as the studies by Papatsoris et al. and Çift et al. (16, 17). However, two studies by Aydın et al. and Korkmaz et al. did not report a difference in WBC count between the two groups (14).

In acute inflammation, leukocytosis is usually predominantly neutrophil. Since NBEO usually causes acute inflammation, a mostly neutrophil-dominated leukocytosis is expected (16, 17). Brucellosis is an inflammatory process that can often become chronic. In addition, since it is a facultative intracellular bacterium, the cellular immune response is dominant. Therefore, leukocytosis is expected with more lymphocyte dominance. Similar to other studies in the literature, our study also supports this finding (16, 17). With similar results obtained in different studies, the lymphocyte count may come to the fore as a preferable parameter in the differential diagnosis of BEO (16, 17).

Brucella is an intracellular microorganism; therefore, lymphocytosis is expected in brucellosis. With a decrease in neutrophils, the NLR becomes more meaningful than evaluating these two values separately. Therefore, we think that the NLR may be the most useful parameter in the early diagnosis of BEO and in the differential diagnosis from other causes of epididymorchitis. The statistical significance of this rate in our study suggests that it can be used in early diagnosis. We think that the deficiency in the studies of Papatsoris et al. and Aydın et al. is that neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts were not compared separately (14,15).

It has been shown in the literature that some chronic infections, such as brucellosis, are associated with monocytosis (12). However, contrary to expectations, in our study, the number of monocytes was higher in the NBEO group. This was not unexpected, given that the WBC count was also higher in the NBEO group. In fact, when the percentages of monocytes were examined, both groups were similar. Moreover, in the two studies by Çift et al. and Korkmaz et al.,

no significant difference was found between the two groups' monocyte counts (12).

In terms of MLR, different results have been obtained in the literature on Brucella orchitis. Aydın et al. and Çift et al. found the MLR to be lower in the BEO group (12). However, the MLR was found to be higher in brucellosis patients in a study by Balın et al. (18). The reason why the MLR was lower in the BEO group may largely be due to the lymphocyte dominance in the BEO group in our study, as previously explained.

Mean platelet volume is an indicator of platelet activation (19). The excessive release of proinflammatory cytokines seen in brucellosis may affect platelet maturation, thus causing a decrease in platelet size (20). Our findings also support this view. A study conducted by Çift et al. with 72 patients revealed that the MPV value was lower in patients with brucellosis (12). Another study showed no difference between the groups in this regard (21).

Brucella species are intracellularly located, cause less cytokine release, and their endotoxins are less toxic than other gram-negative bacteria. Therefore, procalcitonin, which is a very sensitive infective parameter, can be expected to increase less in BEO than in NBEO (19). Although our study supports this interpretation, we found only one study in the literature evaluating procalcitonin for Brucella orchitis, and the authors did not report a significant difference in this parameter (12).

There were some limitations to this study. The first is the retrospective nature of the study and the small number of samples. It would be better to support the results we found in our study with various prospective studies with larger samples. The lack of long-term follow-up of changes in inflammatory parameters after treatment is another limitation.

CONCLUSIONS

The NLR is particularly promising in terms of an additional parameter to be used to prevent both cost increases and delays in the diagnosis of BEO. Mean platelet volume and procalcitonin may be other parameters to be evaluated in this regard. However,

since Brucella is mostly seen in underdeveloped and developing countries, in this sense case reporting is insufficient. To conclude, multicenter and prospective studies can create stronger findings in this regard.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethics Statement: This study was reviewed and approved by the Van Training and Research Hospital medical ethics committee on March 21, 2019 (approval number: 2019/06).

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Effect of COVID-19 Pandemic on Male Sexual Behaviors and Erection Quality

COVID-19 Pandemisinin Erkek Cinsel Davranışlarına Ve Ereksiyon Kalitesine Etkisi

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Özet

Amaç: COVID-19 salgını tüm dünyada insanların yaşamlarını etkilemeye devam etmektedir. Yaşam tarzlarındaki değişikliklerden kaynaklanan kısıtlamaların insanların ruh sağlığı ve cinsel sağlığını etkilediği gösterilmiştir. Bu çalışma COVID-19 pandemi sürecinde evden çıkma yaşağı ve izolasyon uygulamasının erken ve geç dönemlerinde erkek cinsel davranışları ve ereksiyon durumlarındaki değişiklikleri ortaya koymayı amaçlamaktadır.

Gereç ve Yöntemler: Çalışmaya aktif cinsel hayatı olan 206 gönüllü erkek katılmıştır. Pandemi sırasında cinsel işlev ve ereksiyonu değerlendirmek için Uluslararası Eretil İşlev Formu (IIEF-15) ve ruh halini değerlendirmek için Beck Depresyon Envanteri (BDE) uygulandı.

Bulgular: Türkiye’de evde kısıtlamaların ve izolasyonun ilk ayı olan 2020 Nisan ayında ereksiyon, cinsel istek durumu, cinsel ilişki ve/veya masturbasyon sıklığı ve zevk alma durumunun anlamlı olarak arttığı ($p<0,001$), sürecin uzamasıyla mayıs ayında düştüğü ($p<0,001$) saptanmıştır. Pandemi sürecinde depresyon derecelerinin de anlamlı olarak arttığı saptanmıştır.

Sonuç: Katılımcıların nisan ayında bu durumu izne çıkma olarak değerlendirdiği ve evde olma rahatlığı ile cinsel davranış ve ereksiyona pozitif bir katkı sağladığı görülürken, sürecin uzaması ile kişilerin gelir durumlarında azalma, kaygı ve depresyon artışı ile mayıs ayında ereksiyon ve cinsel davranışlarda anlamlı bir düşme saptanmıştır.

Anahtar Kelimeler: Covid-19, Ereksiyon Kalitesi, Erkekler, Depresyon, Cinsel davranışlar

Abstract

Objective: COVID-19 pandemic continues to affect peoples’ lives throughout the world. It has been demonstrated that restrictions due to lifestyle changes affect peoples’ mental and sexual health. This study aimed to examine changes in male sexual behaviors and erectile status in early and late periods of lockdown and isolation during the COVID-19 pandemic.

Material and Methods: A total of 206 volunteer males with active sexual lives were enrolled in the study. International Index of Erectile Function (IIEF-15) was adopted to assess sexual function and erection and Beck Depression Inventory (BDI) was adopted to assess mental status during the pandemic.

Results: Erection, sexual desire, sexual intercourse and/or masturbation frequency and sexual pleasure increased significantly during the first month of the lockdown and isolation in Turkey, April 2020 ($p<0.001$), and it declined in May with the prolongation of the process ($p<0.001$). Levels of depression have increased significantly during the pandemic as well.

Conclusion: This is the first study to examine male sexual behaviors and erection status separately in April and May, in the early period when lockdowns and isolation started due to the pandemic and in the late period with the prolongation of the process, however further research is needed.

Keywords: Covid-19, Erection Quality, Men, Depression, Sexual behaviors

This study was reviewed and approved by the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee 29.06.2020/123-2263. All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Globally, as of the end of December 2020, within the ten month period since the onset of the corona virus disease (COVID-19) pandemic, the number of confirmed cases has approached 80 million and the number of deaths 1,800,000 (1). The number of confirmed cases in Turkey has exceeded 2,100,000 and the number of deaths has exceeded 19,000 as of the end of December 2020, since the first case on 11th March 2020 (2).

The COVID-19 pandemic has been continuing to affect the general well-being of society worldwide to a great extent. Individual health status and uncertainties about jobs, lockdown, social distancing and online education affect the mental state, anxiety and depression levels, as well as sleeping and eating habits (3).

The COVID-19 pandemic raises a wide range of concerns covering physical morbidity and mortality, mental health, economics, education and interpersonal relationships. Sexual health should also be questioned during the pandemic (4-8). The definition of sexual health is defined by the World Health Organization and defined as a state of physical, mental and social well-being related to sexuality.

The COVID-19 pandemic is very likely to affect sex life due to its personal, environmental and economic impacts. It can affect the individual sexual lives with its negative impact on mental and physical health. This concern can also lead to impairment of the sexual pleasure mental state. In contrast, it is also asserted that sexual intercourse frequency of individuals with their partners may increase during this process with prolongation of their home-stay periods (9).

The pandemic caused by COVID-19 has created serious negative effects on individual sexual behaviors as well (10, 11). People's lifestyles had to change due to the fears arising from the high risk of transmission of COVID-19, lockdowns imposed by governments and other restrictions. These new rules and changes have led to changes in our normal habits and behaviors by affecting us psychologically (8, 12, 13). Continuous diseases and disease-related death images led to increased anxiety, fear, depression, anger, guilt and stress.

In Turkey, forced lockdowns in April were well-tolerated by the society in the beginning as they created

a feeling of vacation, but prolongation of this process, changes in daily routines, restriction of freedoms, decrease or even reset of income levels have led to the development of feelings of helplessness. One of the most important fields of psychological consequences for males was in sexual behavior and erection (10).

There is very little published literature on male sexual behavior during lockdown in the pandemic. In this current study, we aimed to examine changes in male sexual behaviors and erectile status in lockdowns in April and May and isolation in Turkey during the COVID-19 pandemic.

MATERIAL AND METHODS

This study was executed with 206 heterosexual male patients, between ages 18-69, with active sexual lives who were admitted to the İstanbul Haydarpaşa Training and Research Hospital, Urology Clinic between 01.07.2020 and 31.07.2020 with different complaints. Ethical board approval was done. The study was in conformity with the Helsinki declaration. The patients were seen in the outpatient clinic. The patients receiving treatment due to erectile dysfunction, and those with comorbid diseases such as any malignancy, psychiatric, neurologic or cardiac disease, or renal impairment were excluded from the study. Moreover, individuals having problems in their marriages and whose COVID-19 test result was positive or who had close contact with COVID-19 patients during that period were also not included in the study.

Questions about age, education, working condition, income, presence of active sexual life, state of forced lockdown during the pandemic and elementary or extended family were posed to the participants to collect sociodemographic data for the study. Besides the demographic questions, the participants were questioned about their erectile status, sexual history and depression in April and May when strict quarantine measures were implemented. In addition to the survey we prepared, Turkish versions of the International Index of Erectile Function (IIEF) and Beck Depression Inventory (BDI) were administered to participants. The International Erectile Function Questionnaire-Erectile Function Domain (IIEF-15) Index containing 15 questions was used to define the erectile function of the participants. The IIEF-15 questionnaire is the most common scale to

evaluate sexual desire, orgasm, intercourse satisfaction and overall satisfaction in addition to erectile function. Its Turkish validated forms are used (14, 15). According to IIEF score, severity of erectile dysfunction (ED) is classified into four diagnostic categories: mild ED (EF score over 21); mild to moderate (EF score:16-21); moderate (EF score: 11-15); and severe (EF score: under 11). We used the BDI containing 21 questions to evaluate the participants' psychological state. The BDI is composed of items to evaluate psychological and physical symptoms (16). Scores between 0-13 indicate no depression, scores between 14-24 indicate moderate depression and scores over 25 indicate severe depression.

Statistical Analysis

Data analysis was done using the SPSS 25 package program. Frequency and percentage values of demographic variables are presented. The suitability of the data for normal distribution was tested with the Shapiro-Wilk test. Since the assumption of compliance with normal distribution could not be met, the analyzes were performed with non-parametric statistical methods. Wilcoxon signed-rank test was used for comparisons between two dependent non-parametric variables. P<0.05 was considered statistically significant.

RESULTS

Mean age of the participants was 45.5 years (18-69) and mean body mass index was 26.4kg/m² (20.1-32.9). Education level was 37.9% primary school, 35.4% high school and 26.7% university. About 83% of the participants with active sexual life indicated that they had sexual partners, whereas 17% of them stated that they had no regular partner. 21.8% of the participants worked in the public sector, 40.4% of them worked in the private sector, 8.7% of them were tradesmen, 9.7% of them were wage workers, 12.6% of them were retired and 6.8% were unemployed. 40.3% indicated that their monthly income did not change in the pandemic months, April-May 2020, whereas 58.7% indicated that their income decreased or reset, and 1% reported that their income increased. The participants expressed that they stayed at home at a rate of 88.8% during the same period. Demographic data of the participants is given in Table-1

and descriptive statistics about the participants' sexual states are given in Table-2.

Table 1. Demographic data of the participants (n=206)

		n	%
Education	Primary School	78	37.9
	High School	73	35.4
	University	55	26.7
Working Condition	Public Sector	45	21.8
	Private Sector	83	40.4
	Tradesman	18	8.7
	Wage worker	20	9.7
	Retired	26	12.6
	Unemployed	14	6.8
Income	Decreased	2	1
	Stable	83	40.3
	Cut by half	34	16.5
	Sharply decreased	60	29.1
	Zero	27	13.1
Were you at home?	Full time at home	183	88.8
	Half time at home	21	10.2
	Same as before	2	1
Family	Elementary Family	183	88.8
	Extended Family	23	11.2

According to IIEF scores, 67% of the participants did not have erectile dysfunction and 33% had moderate erectile dysfunction. It has been observed that with the change in their education level, working condition and income level, the participants' state of erection and sexual desire, and their frequency of sexual intercourse and/or masturbation increased significantly. Their sexual pleasure from sexual intercourse and/or masturbation increased (p<0.001) in April 2020, which was the first month of lockdown due to the pandemic. Full time home stay (p=0.31) and type of family (elementary or extended) did not affect these sexual states in the same period (p=0.74). In the second month of the pandemic, May 2020, in terms of working conditions, the state of erection, sexual desire, frequency of sexual intercourse and/or masturbation and sexual pleasure decreased significantly for employees of all sectors (p<0.001), moreover private sector employees, tradesmen and wage workers were much more affected

compared to public employees and retirees ($p < 0.001$). It has been observed that each of the three sexual states including erection decreased for all education levels and income groups ($p < 0.001$). In the same period, full time home stay

($p = 0.21$) and type of family (elementary or extended family) did not affect these sexual states ($p = 0.47$). Depression levels of the participants increased significantly in May according to the BDI ($p < 0.001$) (Table-3).

Table 2. Descriptive statistics about the sexual status of the participants

	APRIL Med (min-max)	MAY Med (min-max)	Z	p
State of Sexual Desire	5 (1-6)	4 (1-6)	-11,412	<0,001*
Sexual Intercourse Frequency	4 (2-6)	3 (2-6)	-11,598	<0,001*
Sexual Pleasure	4 (2-5)	4 (2-5)	-8,494	<0,001*

Wilcoxon

Table 3. Descriptive statistics about participants state of depression

May							
April	Depression of state	Minimum	Mild	Moderate	Severe	Total	p
	Minimum	55 (31,6)	44 (25,3)	51 (29,3)	24 (13,8)	174 (100)	<0,001*
	Mild	0 (0)	9 (30)	3 (10)	18 (60)	30 (100)	
	Moderate	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	
	Severe	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)	

Chi square

DISCUSSION

The COVID-19 pandemic has led to disruption in health systems, deterioration in social life, decrease in income levels, deterioration of people’s mood and a great number of deaths all over the world (17). A change in social life has been observed worldwide since the beginning of 2020 as a result of the COVID-19 pandemic (19). A substantial population has been isolated throughout the world since the beginning of April 2020 (17). Restrictions have been implemented in Turkey as of April. In this study, we evaluated the situations in April and May separately in order to investigate how the effects of the pandemic, social restriction and isolation changed male sexual behaviors and erection. This study is important since it is the first study to examine male

sexual behaviors and erection status in the early period of lockdown due to the pandemic and in a later period with the prolongation of the process.

There are a limited number of studies on sexual behaviors in the COVID-19 pandemic. Some of the research on this subject is on couples, whereas other research is on female sexual behaviors. In a study performed in Italy on couples, the majority of the couples did not report any difference in their sexuality despite the difficulties of the pandemic (18). In most of the studies conducted during the pandemic, the state of sexual activity and sexual intercourse frequency were evaluated. In a study performed in Spain, a decrease was detected in the state of sexual activity and sexual intercourse frequency in 31% of the participants,

an increase has been observed in 14% and masturbation rates increased 10%. It has been indicated that forced home working, stress of obeying social distancing, continuous presence of children at home and fear of infection decreased the frequency of sexual activity, intercourse and libido by affecting the individual's mental state, and also COVID-19 stress could cause erectile dysfunction. In contrast, other individuals experienced an increase in their sexual activity with their partners due to excess free time at home, and those without a partner could have an increase in masturbation with excess free time and lack of physical contact (10). In our study, similarly an increase in masturbation frequency was observed in April. Excess free time, lack of intimacy with others, stress caused by risk of infection in case of intimacy with people may be the basic reasons for the increase in masturbation. Even though masturbation helps some people achieve sexual satisfaction without risk of COVID-19 infection, a high rate of masturbation is associated with reduced quality of life and sexual satisfaction life, relationship, and mental health (19).

The majority of the participants in a study performed in Taiwan indicated that no difference occurred in their sexual lives, 13.4% of them reported that satisfaction in their sexual lives and sexual activities decreased, 1.9% stated that the satisfaction of their sexual lives increased and 2.9% indicated that their sexual activity frequency increased. Reasons for a decrease might be associated with an increase of general anxiety due to high infection risk and people might perceive having sex to be unsafe during the pandemic since the Taiwan government suspended the sex industry. In conclusion, decrease of sexual satisfaction has led to a decrease in sexual activity and sexual partner searching activities (4).

In a study performed in Turkey with only females, it was found that female sexual desire and sexual intercourse frequency significantly increased during the COVID-19 pandemic, however their quality of sexual life decreased significantly. The reason for the increase in sexual desire and sexual intercourse frequency has been demonstrated as more time passed at home and no loss of living space during pandemic, unlike disasters such as earthquakes and floods (9).

In another study performed in Italy, even though more than 40% of the participants reported an increased sexual desire in the quarantine period, they have not defined an increase in sexual intercourse frequency. In addition, while sexual satisfaction decreased substantially during the quarantine, more than half of the participants in the survey reported that their sexual satisfaction completely disappeared. These results were explained with an increase reported in autoerotism in 40% of the participants and a high prevalence of pornography use among the answers (18). It is known that there is a negative correlation between the use of pornography and sexual satisfaction (20).

In addition, it was observed that depression and anxiety increased in sexually active partners with the effect of the pandemic period. They reported that lack of sexual activity increased the risk of developing anxiety and depression (21).

In our study, it has been observed that depression levels of the participants increased significantly during the April-May 2020 pandemic period, according to the BDI ($p < 0.001$). It has been seen that erection and all three sexual status decreased for all education and income levels ($p < 0.001$). In the same period, full time home stay and type of family, elementary or extended, did not affect the sexual status ($p = 0.21$ and 0.47).

This study has some limitations. Number of participants in this study was relatively low. The study focused on the sexual behaviors only of males but changes in female sexual behaviors during a pandemic can affect the sexual behaviors of males.

CONCLUSION

It has been observed that, in April, the first month of the lockdown, the participants considered the situation as vacation with the comfort of being at home, and they were not affected negatively by the current pandemic. Even a statistically significant increase was detected in their erection quality, sexual intercourse and/or masturbation quantity, sexual desire and pleasure. With the prolongation of the home stay period and when income levels were affected, anxiety and depression levels increased, while erection, sexual desire, sexual intercourse and/or masturbation frequency and sexual pleasure decreased significantly.

Conflict of Interest: None.

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Ethics Committee: Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee 29.06.2020/123-2263.

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The Effects of *Viburnum Opulus L.* on Kidneys of Rats with Ethylene Glycol-induced Nephrolithiasis

Etilen Glikolla İndüklenmiş Nefrolitiazisli Sıçan Böbrekleri Üzerinde *Viburnum Opulus L.*'nin Etkileri

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Özet

Amaç: Son yıllarda yapılan çalışmalarda taş oluşumunda oksidatif stres ve serbest oksijen radikallerinin rolü olduğu üzerinde durulmaktadır. *Viburnum Opulus L.* (VO), antioksidan etkinliğiyle bilinen ve Türk geleneksel tıbbında taş düşürmek için suyu hazırlanarak kullanılan bir meyvedir. Bu çalışmanın amacı, etilen glikol (EG) ile indüklenmiş nefrolitiazisli sıçanlarda VO'nun kalsiyum oksalat (CaOx) kristalizasyonu ve oksidatif stres üzerindeki etkinliğini araştırmaktır.

Gereç ve Yöntemler: 50 adet yetişkin erkek Wistar Hannover türü sıçanlar 5 gruba ayrıldı: Kontrol (Grup 1), EG (Grup 2), EG + 50 mg/kg VO (Grup 3), EG + 100 mg/kg VO (Grup 4), EG + 200 mg/kg VO (Grup 5). 7., 14. ve 28. günlerde 24 saatlik idrar toplandı ve kan örnekleri alındı. 28. günde sıçanlar sakrifiye edildi ve böbrek dokusunda inflamasyon, oksidatif stres ve polarize ışık mikroskobu altında CaOx kristalizasyonu değerlendirildi.

Bulgular: 7., 14. ve 28. günde serumda inflamasyon, akut böbrek hasarı ve oksidatif stres, 28.günde dokuda inflamasyon ve oksidatif stres parametrelerinde Grup 2 (EG) ile Grup 1 (Kontrol) arasında istatistiksel olarak anlamlı farklılık saptandı. Bu parametrelerin Grup 3-5'te Grup 2 (EG)'ye göre iyileşme gösterdiği ve doz arttıkça istatistiksel olarak anlamlılığı arttığı

Abstract

Objective: Recent research has centered on the role of oxidative stress and free oxygen radicals in the formation of stones. *Viburnum opulus L.* (VO) is a fruit species known for its antioxidant activity, and its juice preparation is used in Turkish traditional medicine for stone removal. This study aimed to investigate the effects of VO on calcium oxalate (CaOx) crystallization and oxidative stress in rats with ethylene glycol (EG)-induced nephrolithiasis.

Material and Methods: Fifty adult male Wistar Hannover rats were divided into five groups: control (Group 1), EG (Group 2), EG + 50 mg/kg VO (Group 3), EG + 100 mg/kg VO (Group 4), and EG + 200 mg/kg VO (Group 5). On days 7, 14, and 28, 24-hour urine was collected, and blood samples were taken. On day 28, the rats were sacrificed, and inflammation, oxidative stress, and CaOx crystallization in kidney tissue were evaluated under polarized light microscopy.

Results: A statistically significant difference was found between Group 1 and Group 2 in terms of serum inflammation parameters, acute kidney injury, and oxidative stress evaluated on days 7, 14, and 28, and tissue inflammation and oxidative stress parameters evaluated on day 28. It was observed that these parameters improved in Groups 3-5 compared to Group 2, and the level of statistical significance increased

The study was approved by Bezmialem Vakıf University Animal Experiments Local Ethics Committee (Approval number: 2018/254, Date: 2018/10/30). All research was performed in accordance with relevant guidelines/regulations.

görüldü. 28. günde dokuların histopatolojik değerlendirilmesinde ortalama kristal sayısı Grup 2 (EG)'de Grup 1 (Kontrol)'e göre istatistiksel olarak anlamlı yüksek saptandı. Bu parametrelerin Grup 3-5'te Grup 2'ye göre iyileşme gösterdiği ve Grup 4-5'te istatistiksel olarak anlamlı farklılık olduğu görüldü.

Sonuç: VO'nun EG ile indüklenmiş nefrolitiyazisli sıçanlarda inflamasyon, oksidatif stres, akut böbrek hasarı ve CaOx kristalizasyonunu doz artışıyla doğru orantılı olarak iyileştirdiği saptanmıştır.

Anahtar Kelimeler: *Viburnum Opulus L.*, Böbrek taşı, Nefrolitiyazis, Kalsiyum okzalat, Etilen glikol, İnflamasyon, Oksidatif stres, Akut böbrek hasarı, Kristalizasyon

as the dose increased. In the histopathological evaluation of the tissues on day 28, the mean number of crystals was statistically significantly higher in Group 2 than in Group 1. These parameters improved in Groups 3-5 compared to Group 2, and there was a statistically significant difference when Groups 4 and 5 were compared to Group 2.

Conclusion: It was found that VO improved inflammation, oxidative stress, acute kidney injury, and CaOx crystallization in rats with EG-induced nephrolithiasis in direct proportion to the increase in dose.

Keywords: *Viburnum opulus L.*, Kidney stone, Nephrolithiasis, Calcium oxalate, Ethylene glycol, Inflammation, Oxidative stress, Acute kidney injury, Crystallization

INTRODUCTION

Urinary stone disease is seen common around the world, it is reported at a rate of 7-13% in North America, 5-9% in Europe, and 1-5% in Asia (1). In Türkiye, located in the endemic stone belt, two epidemiological studies on urinary stone disease have reported its prevalence to be 14.8% and 11.1%, respectively (2,3).

It is considered that the neutralization of oxidative stress through antioxidants may be beneficial for renal function and reduce the recurrence of kidney stones. In recent years, the efficacy of various antioxidants has been investigated in rats with experimentally induced calcium oxalate (CaOx) nephrolithiasis. Many antioxidants, such as green tea (4), pomegranate juice (5), and saffron (6), have been shown to have a protective effect on these rats. *Viburnum opulus L.* (VO), commonly known as the European cranberry bush, is a fruit species with known antioxidant activity (7). The juice prepared from VO fruit in Central Anatolia is used in Turkish traditional medicine for stone removal (8).

This study aimed to investigate the effects of VO on CaOx crystallization and oxidative stress in rats with ethylene glycol (EG)-induced CaOx nephrolithiasis.

MATERIALS AND METHODS

Extract Preparation

The fruit of VO was collected from Kayseri province. For extraction, dried VO fruit was ground

into powder, and 100 g of powder was mixed with 1,000 mL of cold distilled water for 24 hours. The resulting maceration extract was lyophilized by evaporation. The antioxidant profiles of the prepared extracts were photometrically measured based on total phenol, total flavonoid, total antioxidant levels and cupric-reducing antioxidant capacity (CUPRAC) (Figure 1).

Animals

Fifty adult, 12-week-old male Wistar Hannover rats, weighing approximately 350-400 g, were obtained from the Experimental Animals Laboratory of Bezmialem Vakif University. The rats were kept in rooms with a temperature of 22–23 °C under a 12-hour light and 12-hour dark cycle. The animals were fed a standard rat chow diet, and water was provided *ad libitum*.

Experimental Design

The rats were randomly divided into five groups and placed in metabolic cages three days prior to the experiments to acclimate them to the environment. Group 1 (control) was only given drinking water, Group 2 (EG) was given 0.75% EG in drinking water, Group 3 (EG + low-dose VO) was given 50 mg/kg of VO by oral gavage with 0.75% EG in drinking water, Group 4 (EG + medium-dose VO) was given 100 mg/kg of VO by oral gavage with 0.75% EG in drinking water, and Group 5 (EG + high-dose VO) was given 200 mg/kg of VO by oral gavage with 0.75% EG in

drinking water. These procedures were followed for 28 days. One rat in Group 2 was excluded from the study due to insufficient nutrition and significantly lower weight compared to the remaining rats.

On days 7, 14, and 28, the rats were placed in metabolic cages, and their 24-hour urine samples and blood samples were taken. The urine samples were stored at $-80\text{ }^{\circ}\text{C}$ until analysis. The blood samples were taken into gel biochemistry tubes. After waiting for 15 minutes for coagulation, the blood samples were centrifuged at $2,500\text{ }xg$ for 10 minutes to separate the serum. The separated sera were placed in Eppendorf

tubes and stored at $-80\text{ }^{\circ}\text{C}$ until analysis. After day 28, the rats were sacrificed under general anesthesia. One of the kidneys was fixed with a 10% neutral buffered formaldehyde solution for histopathological examinations. For biochemical examination, the other kidney was homogenized in 1 ml of phosphate-buffered saline (PBS) in a homogenizer, centrifuged at $10,000\text{ }xg$ at $+4\text{ }^{\circ}\text{C}$ for 30 minutes, and the supernatants were separated. After protein determination using the Bradford method, the samples were stored at $-80\text{ }^{\circ}\text{C}$ until analysis.

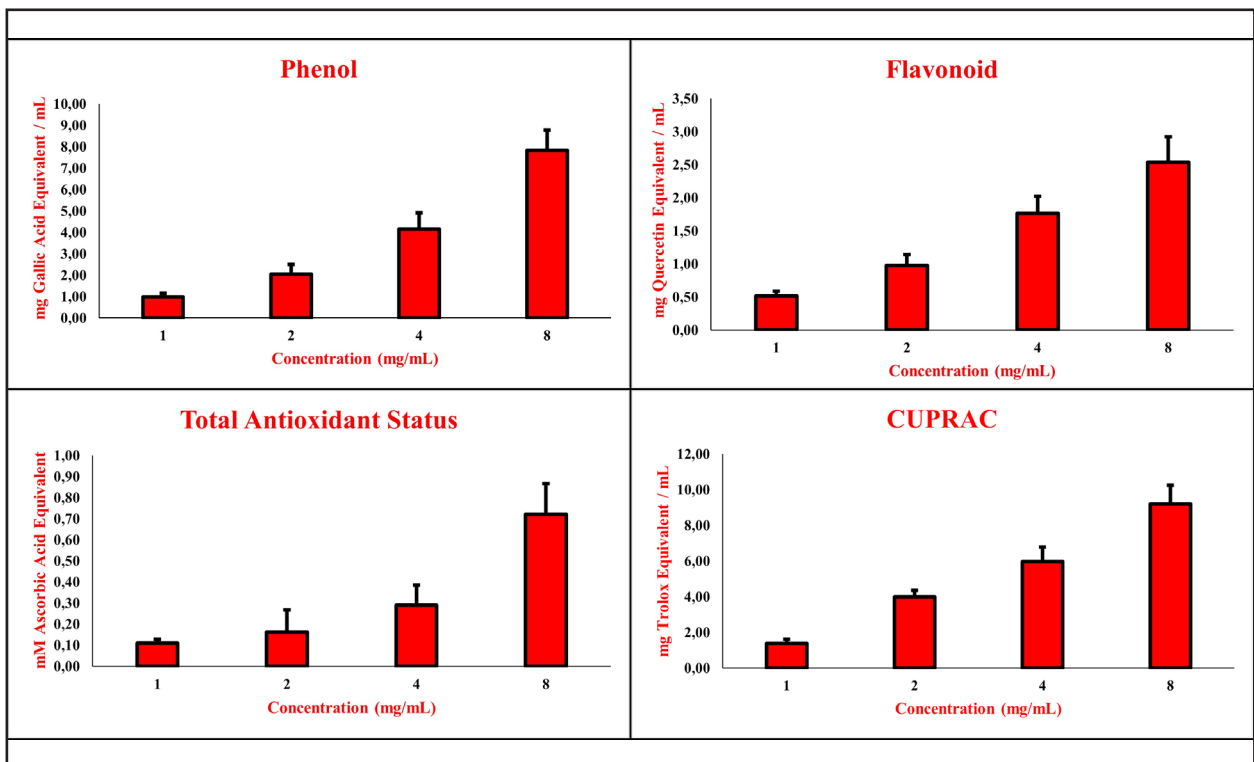


Figure 1. Antioxidant profiles of the prepared extracts

Serum Analyses

Serum urea, creatinine, sodium, and potassium values were measured in blood samples taken on days 7, 14, and 28 using an autoanalyzer (Abbott Architect ci16200). In addition, the blood samples taken on day 28 were used to photometrically determine serum cystatin C, neutrophil gelatinase-associated lipocalin

(NGAL), serum tumor necrosis factor-alpha (TNF- α), interleukin 1-beta (IL-1 β), IL-6, total oxidant status (TOS), total antioxidant status (TAS), total thiol, and native thiol values, using commercial enzyme-linked immunosorbent assay (ELISA) kits. The oxidative stress index (OSI) was obtained by mathematical calculation ($\text{OSI} = \text{TOS} / \text{TAS}$).

Urine Analyses

Urine volume, pH, creatinine, total protein, calcium, and leukocyte count, and the presence of CaOx crystals were evaluated from the 24-hour urine samples collected on days 7, 14, and 28 using an autoanalyzer (Dirui, H800).

Tissue Analyses

After making protein measurements of homogenized kidney tissues, commercial rat TNF α , IL-1 β , IL-6, TOS, and TAS ELISA kits were measured photometrically, and the results per mg protein were recorded. OSI was found by mathematical calculation ($OSI = TOS / TAS$).

Histopathological Examination

Kidney specimens were divided into two at the hilus plane through a transverse coronal complete

incision. After 24 hours of 10% buffered formaldehyde fixation, they were taken into routine pathology tissue processing. The tissues were dehydrated with increasing alcohol levels and finally cleared with xylene. After processing, the tissues of both kidney halves were embedded in paraffin blocks. For a routine hematoxylin examination, both anterior and posterior sections were taken using four micrometer-thick sections, as two sections per slide. CaOx crystals were determined as transparent crystals in the renal tubular and collecting system lumens and examined under polarized light. Each tissue pair was examined for the crystals' density, size, and localization (cortical or medullar). The number and density of CaOx crystals were counted, separately for the cortex and the medulla, based on observation birefringence under polarized light in five adjacent high-magnification fields where these crystals were most dense (Figure 2).

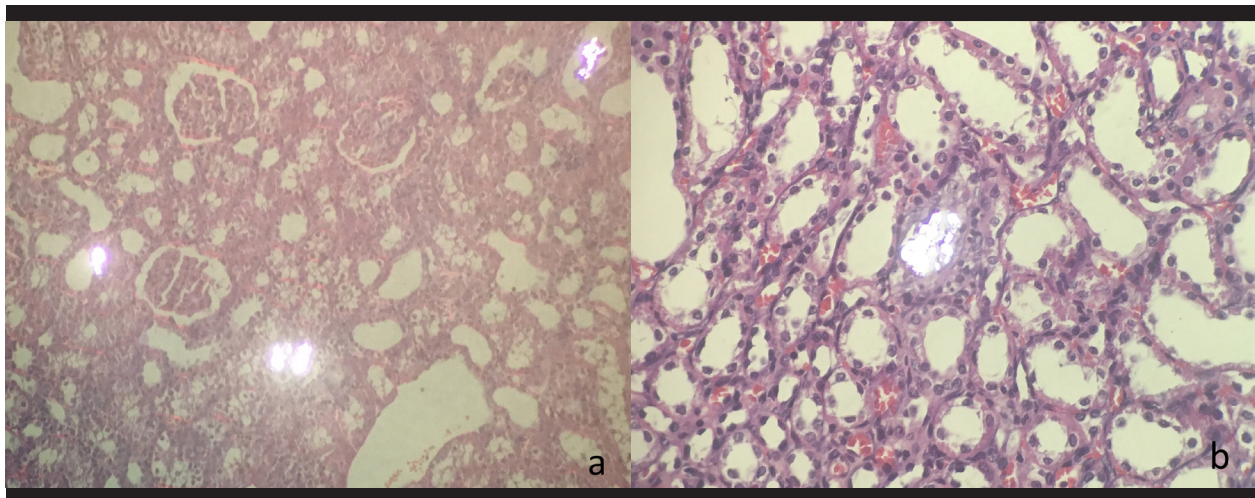


Figure 2. Histopathological examination of the kidney: the appearance of CaOx crystals a) in the cortex and b) in the medulla

Statistical Analysis

Categorical data were expressed as numbers and rates. Data for continuous variables were shown using mean and standard deviation values. The normality of the distributions for continuous variables was determined using the Shapiro-Wilk test. The

comparison of mean values between the two groups was undertaken with the independent-samples t-test for normally distributed data and the Mann-Whitney U test for the data without normal distribution. The frequencies of categorical variables were compared using the Pearson chi-square test.

RESULTS

Serum Biochemical Parameters

Serum urea, creatinine, sodium, and potassium values were found to be statistically significantly higher in Group 2 (EG) than in Group 1 (control) on days 7, 14, and 28. It was determined that these values improved in Groups 3-5 (EG + low-, medium-, and high-dose VO, respectively) compared to Group 2. This improvement was not statistically significant only for the potassium value measured in Group 3. The creatinine and sodium values in Group 5 approached the level of Group 1, with no statistically significant difference found between these two groups. The data on serum biochemical parameters are shown in Table 1.

Urine Parameters

There was no statistically significant difference between the groups in terms of pH and urine volume measured from 24-hour urine samples taken on days 7, 14, and 28. The creatinine, calcium, total protein, and leukocyte values were statistically significantly higher in Group 2 than in Group 1. These values were determined to improve in Groups 3-5 compared to Group 2. Urine CaOx crystals were observed in all rats in Group 2 on days 7, 14, and 28, while they were present in all rats in Groups 3-5 only on day 7, with the percentage of CaOx crystals being statistically significantly lower in Groups 3-5 than in Group 2 on days 14 and 28. The data on 24-hour urine parameters are given in Table 2.

Table 1. Comparison of serum biochemical parameters

	Urea (mg/dL)	Creatinine (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)
Group 1 (control)				
Day 7	26.9 ± 4.2	0.5 ± 0.06	139.7 ± 7	4.9 ± 0.5
Day 14	27.5 ± 2.8	0.6 ± 0.06	139.8 ± 5	5 ± 0.4
Day 28	26.2 ± 1.3	0.6 ± 0.04	141.2 ± 6.3	5.1 ± 0.4
Group 2 (EG)				
Day 7	57.6 ± 3.7**	0.7 ± 0.07**	178.4 ± 6.8**	7.3 ± 0.1**
Day 14	61.2 ± 3.6**	0.7 ± 0.06**	186.8 ± 7.5**	7.5 ± 0.2**
Day 28	65.8 ± 4.9**	0.7 ± 0.06**	191.8 ± 6.4**	7.8 ± 0.2**
Group 3 (EG + 50 mg/kg VO)				
Day 7	51.4 ± 5**,+	0.6 ± 0.05*,+	168.3 ± 9.8**,+	7 ± 0.4**
Day 14	55.1 ± 4**,+	0.7 ± 0.04**,+	176 ± 10.4**,+	7.4 ± 0.5**
Day 28	59.6 ± 3.6**,+	0.7 ± 0.05**,+	183.1 ± 8.9**,+	7.6 ± 0.4**
Group 4 (EG + 100 mg/kg VO)				
Day 7	46 ± 4.2**,+	0.6 ± 0.05**	158.8 ± 12.2**,+	6.4 ± 0.1**,+
Day 14	49.7 ± 3.1**,+	0.6 ± 0.05**	163.6 ± 12.2**,+	6.6 ± 0.2**,+
Day 28	52.6 ± 3**,+	0.6 ± 0.05*,+	168.4 ± 18.3**,+	6.8 ± 0.1**,+
Group 5 (EG + 200 mg/kg VO)				
Day 7	42.2 ± 2.7**,+	0.5 ± 0.02**	143.5 ± 15.2**	6.1 ± 0.1**,+
Day 14	45.2 ± 2.7**,+	0.6 ± 0.03**	148.3 ± 14.8**	6.6 ± 0.2**,+
Day 28	47.9 ± 2.3**,+	0.6 ± 0.04**	151.1 ± 14.3**	6.7 ± 0.2**,+

Significant difference compared to Group 1: *p < 0.05, **p < 0.01

Significant difference compared to Group 2: +p < 0.05, ++p < 0.01

EG: ethylene glycol, VO: *Viburnum opulus L.*

Table 2. Comparison of urine parameters

	Creatinine	Total protein	Calcium	Leukocyte	CaOx
	mg/day	mg/day	mg/day	cells/ μ L	%
Group 1 (control)					
Day 7	1241.6 \pm 131	140.5 \pm 17.2	161,9 \pm 36,5	0 \pm 0	0 (0)
Day 14	1259.7 \pm 121.4	150.2 \pm 11.5	171 \pm 35,5	0 \pm 0	0 (0)
Day 28	1231.1 \pm 93.5	152.2 \pm 10.3	169,3 \pm 34,4	0 \pm 0	0 (0)
Group 2 (EG)					
Day 7	2147.2 \pm 245.3**	241.4 \pm 13.7**	254,9 \pm 43,6**	106.6 \pm 27.5**	9 (100)**
Day 14	2444.3 \pm 273.3**	272.1 \pm 17.4**	286,8 \pm 39,6**	125 \pm 0**	9 (100)**
Day 28	2754.1 \pm 120.9**	312.1 \pm 14.6**	341,3 \pm 23,6**	125 \pm 0**	9 (100)**
Group 3 (EG + 50 mg/kg VO)					
Day 7	1899.2 \pm 137.8**,+	236.8 \pm 15.4**	244,5 \pm 17,7**	86.5 \pm 26.5**	10 (100)**
Day 14	2159.5 \pm 168.5**,+	242.32 \pm 19.8**,+	265,2 \pm 25,4**	92 \pm 28.4**,+	5 (50) ⁺
Day 28	2307.9 \pm 151**,+	247.9 \pm 20.4**,+	270,2 \pm 22,9**,+	97.5 \pm 28.9**,+	4 (40)*,+
Group 4 (EG + 100 mg/kg VO)					
Day 7	1684.5 \pm 175.8**,+	228 \pm 15.2**	241,3 \pm 34,3**	81 \pm 23.1**,+	10 (100)**
Day 14	1906.7 \pm 161.2**,+	235.9 \pm 7**,+	253,5 \pm 47,6**	86.5 \pm 26.5**,+	2 (20) ⁺
Day 28	2080.2 \pm 109.7**,+	241.1 \pm 8.5**,+	266,2 \pm 47,3**,+	92 \pm 28.4**,+	3 (30) ⁺
Group 5 (EG + 200 mg/kg VO)					
Day 7	1633.9 \pm 149.4**,+	215 \pm 9.9**,+	225,3 \pm 16**	70 \pm 0.0**,+	10 (100)**
Day 14	1724.8 \pm 168.3**,+	219 \pm 9.4**,+	243,8 \pm 16,4**,+	81 \pm 23.1**,+	5 (50)**,+
Day 28	1860 \pm 106.4**,+	222.1 \pm 13.3**,+	255,4 \pm 25,6**,+	81 \pm 23.1**,+	2 (20) ⁺

Significant difference compared to Group 1: *p < 0.05, **p < 0.01

Significant difference compared to Group 2: +p < 0.05, ++p < 0.01

EG: ethylene glycol, VO: *Viburnum opulus L.*, CaOx: calcium oxalate

Oxidative Stress Parameters

On days 7, 14, and 28, the serum TOS and OSI values were statistically significantly higher, and the TAS, total thiol and native thiol values were statistically significantly lower in Group 2 than in Group 1. It was determined that the TOS and OSI values of Groups 3-5 statistically significantly decreased compared to those of Group 2. Statistically significantly higher TAS values were detected in Groups 3 and 4 on days 14 and 28 and in Groups 5 on days 7, 14, and 28. Although the total thiol and native thiol values increased in Groups 3-5 compared to Group 2, statistically significantly higher levels were found only in Group 5 on days 7, 14,

and 28. Table 3 presents the serum values of oxidative stress parameters.

On day 28, the tissue TOS and OSI values were statistically significantly higher, and the TAS value was statistically significantly lower in Group 2 than in Group 1. Although an improvement in these values was observed in Group 3 compared to Group 2, there was no statistically significant difference. However, in Groups 4 and 5, the TOS and OSI values were statistically significantly lower, and the TAS value was statistically significantly higher when compared to Group 2. The values of oxidative stress parameters evaluated in kidney tissue are given in Table 4.

Table 3. Comparison of serum oxidative stress parameters

	TOS	TAS	OSI	Total thiol	Native thiol
	($\mu\text{mol H}_2\text{O}_2/\text{L}$)	(mM AAE)	(AU)	(μM)	(μM)
Group 1 (control)					
Day 7	8.8 ± 2.2	1.2 ± 0.1	7.3 ± 1.8	500.7 ± 0.8	469.5 ± 84.4
Day 14	8.1 ± 2	1.2 ± 0.1	6.7 ± 1.8	499.4 ± 79.2	461.4 ± 79.2
Day 28	8.5 ± 1.4	1.1 ± 0.1	7.3 ± 1.9	522.9 ± 59.8	482.9 ± 58.2
Group 2 (EG)					
Day 7	20.5 ± 2.9**	0.4 ± 0.1**	49.4 ± 15.3**	355.4 ± 29.4**	293.5 ± 19.1**
Day 14	23.1 ± 3.5**	0.3 ± 0.09**	71.8 ± 17.8**	260.4 ± 55**	159.8 ± 17.7**
Day 28	25.5 ± 1.5**	0.2 ± 0.05**	101 ± 24.4**	202.4 ± 40.9**	102.2 ± 8.3**
Group 3 (EG + 50 mg/kg VO)					
Day 7	16.3 ± 3.6**,+	0.4 ± 0.10**	34.4 ± 10.7**,+	367.5 ± 70.07**	308.8 ± 60.5**
Day 14	17.5 ± 1.6**,+	0.4 ± 0.06**,+	42.6 ± 7.5**,+	268.4 ± 32.5**	192.5 ± 48.5**
Day 28	18.1 ± 1.4**,+	0.3 ± 0.04**,+	49.9 ± 7.1**,+	234.9 ± 52.2**	183.4 ± 13.6**,+
Group 4 (EG + 100 mg/kg VO)					
Day 7	14.9 ± 2.3**,+	0.5 ± 0.04**	29.1 ± 5.7**,+	400.5 ± 65.8*	355.1 ± 42**,+
Day 14	15.9 ± 1.7**,+	0.4 ± 0.05**,+	35.8 ± 3.6**,+	301.5 ± 87.4**	204 ± 76.1**
Day 28	16.3 ± 2.5**,+	0.3 ± 0.06**,+	44.2 ± 11**,+	300.5 ± 50**,+	195.5 ± 45.9**,+
Group 5 (EG + 200 mg/kg VO)					
Day 7	13.1 ± 1.9**,+	0.5 ± 0.1**,+	23.2 ± 4.6**,+	435.9 ± 75.7**	395.1 ± 94.4**
Day 14	14 ± 1.3**,+	0.5 ± 0.05**,+	26.8 ± 3.7**,+	363.7 ± 96.9**,+	223.4 ± 90.4**,+
Day 28	15.1 ± 1**,+	0.4 ± 0.04**,+	35.8 ± 4.1**,+	340.8 ± 60.1**,+	207.7 ± 45.5**,+

Significant difference compared to Group 1: *p < 0.05, **p < 0.01

Significant difference compared to Group 2: +p < 0.05, ++p < 0.01

EG: ethylene glycol, VO: *Viburnum opulus L.*, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index, AAE: ascorbic acid equivalent

Table 4. Comparison of oxidative stress parameters measured in kidney tissue

	TOS	TAS	OSI
	($\mu\text{mol H}_2\text{O}_2/\text{L}$)	(mM AAE)	(AU)
Group 1 (control)	7.2 ± 1.2	0.4 ± 0.08	17.6 ± 3.9
Group 2 (EG)	15.3 ± 2.4**	0.1 ± 0.05**	84.8 ± 23.9**
Group 3 (EG + 50 mg/kg VO)	13.4 ± 2.8**	0.2 ± 0.04**	60.7 ± 9.8**
Group 4 (EG + 100 mg/kg VO)	11 ± 2.8**,+	0.2 ± 0.04**,+	47.8 ± 21.4**,+
Group 5 (EG + 200 mg/kg VO)	8.9 ± 3.3**	0.3 ± 0.06**,+	28.8 ± 11.8**,+

Significant difference compared to Group 1: *p < 0.05, **p < 0.01

Significant difference compared to Group 2: +p < 0.05, ++p < 0.01

EG: ethylene glycol, VO: *Viburnum opulus L.*, TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index, AAE: ascorbic acid equivalent

Inflammation Parameters

The serum and tissue inflammation parameters are given in Table 5. On days 7, 14, and 28, the serum IL-1 β , IL-6, and TNF α values were statistically significantly higher in Group 2 than in Group 1. These values were observed to improve in Groups 3-5 compared to Group 2. This improvement was not statistically significant only for the IL-1 β value of Group 3 measured on day 7. On day 28, the tissue IL-1 β , IL-6, and TNF α values were statistically significantly higher in Group 2 than in Group 1. It was observed that these values improved in Groups 3-5 compared to Group 2. This

improvement was not statistically significant only for the TNF α value of Group 3.

Acute Kidney Injury Parameters

On days 7, 14, and 28, the serum NGAL and cystatin C values were found to be statistically significantly higher in Group 2 than in Group 1. These values decreased in Groups 3-5, being statistically significantly lower than those in Group 2. Table 6 presents the serum values of acute kidney injury parameters.

Table 5. Comparison of serum and tissue inflammation parameters

	IL-1 β (pg/mL)	IL-6 (ng/L)	TNF α (ng/L)
Group 1 (control)			
Day 7	206.4 \pm 26.6	2.3 \pm 0.7	72.4 \pm 18.8
Day 14	219.7 \pm 36.8	2.2 \pm 0.3	71.2 \pm 13.4
Day 28	292.9 \pm 34.3	2.4 \pm 0.6	71.8 \pm 10.3
Group 2 (EG)			
Day 7	342.4 \pm 37.4**	9.1 \pm 1.8**	171.2 \pm 10.4**
Day 14	432.1 \pm 38.6**	11.6 \pm 2.8**	194.3 \pm 11**
Day 28	515.3 \pm 36.8**	13.7 \pm 2.7**	221.8 \pm 20.3**
Group 3 (EG + 50 mg/kg VO)			
Day 7	323.2 \pm 44.7**	7.4 \pm 1**,+	153 \pm 16**,+
Day 14	373.7 \pm 37.5**,+	9.3 \pm 1.3**,+	165.5 \pm 15.9**,+
Day 28	421.5 \pm 40.1**,+	10.6 \pm 1.2**,+	183.2 \pm 13.8**,+
Group 4 (EG + 100 mg/kg VO)			
Day 7	293.6 \pm 27.7**,+	6.3 \pm 0.9**,+	138.7 \pm 31**,+
Day 14	332.9 \pm 29.1**,+	7.8 \pm 0.7**,+	156.7 \pm 32.4**,+
Day 28	385.8 \pm 41.1**,+	9.1 \pm 0.9**,+	176.3 \pm 28.7**,+
Group 5 (EG + 200 mg/kg VO)			
Day 7	216.5 \pm 30.1**	4.8 \pm 0.6**,+	121.5 \pm 10.6**,+
Day 14	264.9 \pm 30.4**,+	5.6 \pm 0.6**,+	135.5 \pm 13.1**,+
Day 28	307.9 \pm 25.1**,+	6.3 \pm 1.5**,+	145.9 \pm 13.9**,+
Tissue			
Group 1 (control)	586.6 \pm 100	8.3 \pm 0.9	353 \pm 70.1
Group 2 (EG)	739.3 \pm 87.9**	28 \pm 3.7**	503.3 \pm 76.4**
Group 3 (EG + 50 mg/kg VO)	561.6 \pm 87.5**	23.7 \pm 2.4**,+	455.3 \pm 76.8**
Group 4 (EG + 100 mg/kg VO)	498.3 \pm 79.5**,+	20.6 \pm 2.1**,+	424.2 \pm 86.9**,+
Group 5 (EG + 200 mg/kg VO)	388.4 \pm 49.1**,+	16.6 \pm 5.2**,+	356 \pm 32.8**

Significant difference compared to Group 1: *p < 0.05, **p < 0.01

Significant difference compared to Group 2: +p < 0.05, ++p < 0.01

EG: ethylene glycol, VO: *Viburnum opulus* L., IL: interleukin, TNF: tumor necrosis factor

Table 6. Comparison of serum acute kidney injury parameters

	NGAL	Cystatin C
	(ng/mL)	(ng/mL)
Group 1 (control)		
Day 7	14.7 ± 2.2	5 ± 1.2
Day 14	15.6 ± 3.3	7.7 ± 1.1
Day 28	14.6 ± 3.9	8.9 ± 1.2
Group 2 (EG)		
Day 7	69.2 ± 8.7**	36 ± 5.8**
Day 14	75 ± 7.9**	46.2 ± 5.1**
Day 28	79.4 ± 6.9**	51.6 ± 4.3**
Group 3 (EG + 50 mg/kg VO)		
Day 7	62.2 ± 2.1**,+	30.3 ± 3.3**,+
Day 14	65.7 ± 2.4**,+	37.8 ± 3.5**,+
Day 28	68.2 ± 4.6**,+	41.4 ± 2.6**,+
Group 4 (EG + 100 mg/kg VO)		
Day 7	57.2 ± 4.2**,+	26.3 ± 3.3**,+
Day 14	60.3 ± 2.3**,+	32.7 ± 2.6**,+
Day 28	63.2 ± 1.6**,+	35.3 ± 2.3**,+
Group 5 (EG + 200 mg/kg VO)		
Day 7	53.2 ± 5.5**,+	22 ± 3.4**,+
Day 14	56.3 ± 2.6**,+	27 ± 2**,+
Day 28	58.6 ± 3.4**,+	29.2 ± 2.2**,+

Significant difference compared to Group 1: *p < 0.05, **p < 0.01

Significant difference compared to Group 2: +p < 0.05, ++p < 0.01

EG: ethylene glycol, VO: *Viburnum opulus* L., NGAL: neutrophil gelatinase-associated lipocalin

Histopathological Parameters

On day 28, the percentage of crystallization was 0% in Group 1, 66.7% in Group 2, 50% in Group 3, 30% in Group 4, and 20% in Group 5. A statistically significant increase was found in the mean number of crystals in Group 2 compared to Group 1. The mean number of crystals was found to decrease in Groups 3-5 compared to Group 2, and the total number of crystals in Groups 4 and 5 was statistically significantly lower than in Group 2.

DISCUSSION

In experimental studies, CaOx kidney stones are formed in rats using various agents, such as sodium

oxalate, ammonium oxalate, hydroxy-L-proline, EG, and glycolic acid, which are often combined with vitamin D, a magnesium-poor diet, or ammonium chloride. Applying approximately 0.75% EG to rats for approximately 12 days results in persistent crystalluria, and the application of approximately three weeks of this agent results in kidney crystallization (9). In the current study, CaOx crystals were present in the urine samples of all rats in Group 2 (EG) on days 7, 14, and 28, and this was statistically significantly higher than in Group 1. In addition, CaOx crystal formation was observed in 66.7% (6/9) of the rats in Group 2 on day 28. The mean number of crystals was statistically significantly higher in Group 2 than in Group 1.

The *Viburnum* genus, belonging to the Caprifoliaceae family, includes more than 230 species spread from South America to Southeast Asia, with most being endemic (10). VO, commonly known as the European cranberry bush, has red and oval fruit. It ripens in August-September and remains throughout the winter. The fruit is rarely used as food due to its bitter taste (11) but it is utilized in natural remedies for various diseases, such as circulatory, respiratory, digestive, and urinary system disorders (12). It has been shown that VO contains high amounts of total phenolics, ascorbic acid, flavonoids, and anthocyanins and has antioxidant activity (7,13). Prior to the experiment, we also evaluated the antioxidant profiles of VO extracts photometrically based on total phenol, total flavonoid, total antioxidant levels and CUPRAC. We found that these extracts had sufficient antioxidant activity.

The use of VO for stone removal in Turkish traditional medicine has paved the way for clinical studies. Tuglu et al. stated that VO could be substituted for potassium citrate in patients with mild or moderate hypocitraturic stones (14). Kızılay et al. found that VO facilitated the removal of stones smaller than 10 mm (15). In an animal study investigating the effects of different extracts of VO fruit on urolithiasis, İlhan et al. found that lyophilized VO juice had a preventive effect in rats with sodium oxalate-induced urolithiasis (16). In the current study, urinary CaOx crystals were found to be statistically significantly lower in Groups 3-5 (EG + low-, medium-, and high-dose VO, respectively) on days 14 and 28 compared to Group 2. Although the mean number of crystals in kidney tissue was lower in Group 3 than in Group 2, there was no statistically significant difference between the two groups. However, statistically significant differences were observed in comparing Groups 4 and 5 with Group 2. The main difference is our study from İlhan et al.'s study that (16) our evaluation of the effects of different doses of VO. We determined that the curative effect of VO on oxidative stress, inflammation, and acute kidney injury increased with increasing doses. Concerning crystallization, more improvement was

observed in Groups 4 and 5 than in Group 3.

Modern medical treatments to prevent the formation of kidney stones have centered on preventing supersaturation (17). However, although supersaturation is required to initiate this process, it does not always lead to the formation of CaOx stones (18,19). In many individuals, crystal aggregation and retention do not occur as a result of supersaturation, and crystals are excreted through urine before stone formation. In other words, renal cells respond to increased supersaturation. This response can be physiological or pathological. During this process, crystallization inhibitors play a crucial role in preventing the formation of stones, and damage to inhibitor-forming cells may lead to insufficient or ineffective inhibitor production. Free oxygen radicals seem to be responsible for damage to these cells; therefore, neutralization of free oxygen radicals and inhibition of oxidative stress can prevent urinary stone formation (18). In our study, we aimed to neutralize oxidative stress with VO. Consistent with similar studies, we detected oxidative stress most in Group 2, which was given EG, and observed that the VO used in Groups 3-5 improved oxidative stress in direct proportion to the application dose. Although oxidative stress parameters evaluated in kidney tissue showed an improvement in Group 3 compared to Group 2 on day 28, no statistically significant difference was found. However, there was a statistically significant difference between Groups 2 and Groups 4 and 5.

Human, animal, and cell culture studies have clearly revealed the relationship between CaOx accumulation and renal epithelial damage (20–23). Baggio et al. reported that renal enzymes, such as gamma-glutamyl-transpeptidase, angiotensin 1-converting enzyme, β -galactosidase, and N-acetyl- β -glucosaminidase, which indicate renal cell damage, were higher than normal in the urine samples of patients with idiopathic CaOx stones (21). Boonla et al. found that 8-hydroxydeoxyguanosine, which is used as a marker of oxidative DNA damage, was higher in patients with nephrolithiasis than in healthy individuals (22). Zuo et al. determined that the renal

and urinary excretion of kidney injury molecule-1, an essential marker of renal damage, was significantly increased in rats with hydroxy-1-proline-induced hyperoxaluria (23). Similarly, in our study, we found that the creatinine and total protein values measured from urine samples on days 7, 14, and 28 were higher in Group 2 than in Group 1, while these values indicated an improvement in Group 3-5. In addition, according to our evaluation of serum cystatin C and NGAL, which are important biomarkers of acute kidney injury (24), the values of these parameters on days 7, 14, and 28 indicated a statistically significant increase in Group 2 when compared to Group 1. There was a statistically significant improvement in Groups 3-5.

Human, animal, and cell culture studies also indicate that urinary stone formation elicits an inflammatory response (23,25–27). Boonla et al. found that low-grade inflammation occurred in patients with nephrolithiasis. In addition, the authors noted that the mRNA expressions of monocyte chemoattractant protein-1 and IL-6 were significantly higher in those with nephrolithiasis presenting with impaired renal function, which they attributed to renal damage (26). Mushtaq et al. detected increased excretion of anti-inflammatory proteins, such as anti-calgranulin, α -defensin, and myeloperoxidase, produced by neutrophils in response to inflammation in the urine samples of patients with stones (27). In the current study, the highest values of inflammation parameters were observed in Group 2, and VO improved inflammation in direct proportion to the dose applied. In contrast, Altun et al. investigated the anti-inflammatory activity of VO at doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg and found that VO did not show anti-inflammatory activity at these doses (28). In our study, VO may have shown an indirect anti-inflammatory effect by improving oxidative stress and renal epithelial damage.

This study has certain limitations. First, although most idiopathic stones are formed by binding to subepithelial calcium phosphate deposits on renal papillary surfaces, called Randall's plaques (29), none of the models developed to elicit kidney stone

pathogenesis are identical to the idiopathic stone formation process or provide the formation of stones that attach to Randall's plaques on the papillary surface. Instead, the crystals that form are intraluminal and resemble Randall's plugs (30). Second, our findings were not supported by immunohistochemical methods. The lower number of CaOx crystals than expected in light of similar previous studies constitutes one of the limitations of the study. Despite these limitations, our study is valuable since it is, to the best of our knowledge, the first to test the effects of different doses of VO on nephrolithiasis and evaluate oxidative stress, acute kidney injury, and inflammation, which are three essential factors in the pathogenesis of stone formation.

CONCLUSION

VO antioxidant activity can reduce CaOx crystallization and stone formation by improving oxidative stress, acute kidney injury, and inflammation in rat kidneys with EG-induced nephrolithiasis, and this effect is proportional to the dose of VO. These findings must be supported by human studies to produce more credible results.

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Ethical Approval: The study was approved by Bezmialem Vakıf University Animal Experiments Local Ethics Committee (Approval number: 2018/254, Date: 2018/10/30). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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Does Depth of Anesthesia Effect Clinical Results of Patients Who Underwent Radical Cystectomy in Accordance with Eras Protocols?

Eras Protokollerine Uygun Olarak Radikal Sistektomi Yapılan Hastalarda Anestezi Derinliği Klinik Sonuçları Etkiler Mi?

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Özet

Amaç: Radikal sistektomi ameliyatı geçiren hastalarda cerrahi sonrası hızlandırılmış iyileşme (ERAS [Enhanced Recovery After Surgery]) protokollerine uygun olarak uygulanan, düşük ve yüksek MAC (Minimum Alveolar Concentration) anestezi düzeyinin anestezi derinliği üzerine etkisinin olup olmadığını araştırmak.

Gereç ve Yöntemler: Hastanemizin yerel etik kurulunun onayı alındıktan sonra 2019-2022 yılları arasında radikal sistektomi uygulanan 41 hastanın retrospektif verileri toplandı, 35 hasta çalışmaya dahil edildi. Anestezisi 0,5 MAC ile sürdürülen hastalar düşük MAC (Grup L), 1 MAC ile sürdürülenler ise yüksek MAC (Grup H) olarak ayrıldı. Tüm hastalara ERAS protokolleri doğrultusunda hazırlanan standart anestezi protokolü uygulandı. Anestezi derinliği hasta durum indeksi (Pneumonia Severity Index [PSI]) ve baskılama oranı (Suppression Ratio [SR]), preoperatif ve postoperatif 24. saat Mini Mental Test sonuçları, postoperatif yoğun bakım (post-anesthesia care unit [PACU]) yatış sürelerini ve komplikasyonlarını içeren parametreler karşılaştırıldı.

Bulgular: Hastaların yaş ortalaması (Grup H ve L'de sırasıyla 61 ve 65 yaş) her iki grupta da benzerdi (p=0.234). PSI Grup H'de 60., 120. dakikalarda ve fasya kapanışında anlamlı olarak daha düşük bulundu (sırasıyla p=0.004, p=0.001 ve p=0.000). PSI <25 süresi grup H'de anlamlı

Abstract

Objective: To investigate whether low and high MAC (Minimum Alveolar Concentration) level of anesthesia have an effect on the depth of anesthesia, clinical results parameters in patients underwent radical cystectomy in accordance with ERAS (Enhanced Recovery After Surgery) protocols

Material and Methods: Retrospective data of 41 patients underwent radical cystectomy between 2019-2022 were collected, 35 of them were included. The patients were divided in two groups: Group H (1 MAC, n:18) and Group L (0.5 MAC, n:17). All patients were prepared and managed in line with ERAS protocols. Perioperative and early postoperative parameters including depth of anesthesia which was followed by PSI (Pneumonia Severity Index) and SR (Suppression Ratio), preoperative and postoperative 24th hours Mini Mental Test results, post-anesthesia care unit (PACU) unit admission and duration and complications were compared.

Results: The mean age of the patients (61 and 65 years, in the Group H and L, respectively) were similar (p=0.234) in both groups. PSI was found to be significantly lower in Group H at the 60th, 120th minutes and fascia closure (p=0.004, p=0.001, and p=0.000 respectively). PSI <25 duration was significantly higher in group H (139.0±186.7 and 17.6±54.8 in group H and L, respectively, p=0.001). The duration of SR>0

This study was reviewed and approved by the Bakirköy Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee 15.11.202/252. All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

olarak daha yüksekti (grup H ve L'de sırasıyla 139.0 ± 186.7 ve 17.6 ± 54.8 , $p=0.001$). SR>0 süresi Grup H'de anlamlı olarak daha yüksekti ($p=0.000$). Hem anestezi (474 dk) hem de ameliyat (432 dk) süreleri Grup H'de anlamlı olarak daha yüksekti (sırasıyla $p=0.013$ ve 0.029). Ameliyat sonrası 12. saatte bulantı ve kusma da Grup H'de yaygındı ($p=0.008$). Mini Mental Test de dahil olmak üzere karşılaştırılan diğer parametreler benzerdi.

Sonuç: MAC değerleri peroperatif ve erken postoperatif sonuçları anlamlı olarak etkilememiştir. Yüksek MAC seviyesi daha derin bir anestezi oluştururken, düşük MAC seviyesi daha düşük bir inhalasyon anestezi ajanı tüketimi sağlayarak etkili bir alternatif gibi görünmektedir.

Anahtar Kelimeler: ERAS, radikal sistektomi, MAC, anestezi

was significantly higher in Group H ($p=0.000$). Both anesthesia (474 min) and surgery (432 min) times were significantly higher in Group H ($p=0.013$ and 0.029 respectively). Nausea and vomiting at 12 hours postoperatively was also common in Group H ($p=0.008$). The rest of parameters that compared were similar, including the minimal test.

Conclusion: The MAC values did not significantly affect perioperative and early postoperative outcomes. While high MAC level MAC level generates a deeper anesthesia, low MAC level seems an effective alternative providing a lower inhalation anesthesia agent consumption.

Keywords: ERAS, radical cystectomy, MAC, anesthesia

INTRODUCTION

Enhancing Recovery After Surgery (ERAS) protocols are described to improve outcomes and reduce healthcare costs by standardizing medical care with evidence-based protocols. It was first introduced by Dr. Kehlet in 1997 and during early 2000s, and was brought to the agenda by Dr. Gustafsson and Dr. Ljunqvist with more comprehensive studies (1,2). ERAS protocols were developed for colorectal procedures and ERAS programs constitute the best comprehensive and evidence-based care in colorectal surgery. Modified ERAS protocols have also been used in many other specialties, including gynecology, thoracic surgery, vascular surgery, pediatric surgery and orthopedic surgery (3). ERAS protocol has not gained popularity in urologic procedures yet (4). Although radical cystectomy, a urological intervention, shares some similarities with colorectal procedures in terms of principles, it differs significantly due to unique aspects such as the surgical technique, involving small bowel anastomosis, presence of urine in the peritoneal cavity, and the need for both extra and intraperitoneal access (5). Therefore, advanced monitoring techniques can be used for fluid management. (Masimo Radical 7 Pulse CO-Oximeter with pleth variability index [PVI] software [Masimo SET, Masimo Corp., Irvine, CA, USA]) (6).

Although ERAS is recommended in many surgical branches today (7), more data are needed to prove it's

effectiveness in major urological procedures.

ERAS protocols recommend to standardize perioperative anesthesia management, to avoid deep anesthesia, and to use the lowest possible doses and possible short-acting anesthetic agents (4). Today, the minimum alveolar concentration (MAC) is widely used as an indicator of the potency of inhalation agents (8). The depth of anesthesia is patient state index (PSI) and suppression ratio (SR) monitored with the SEDLine Brain Function Monitor (Masimo Corp., Irvine, CA, USA) device used to estimate the depth of anesthesia. The PSI is designed to monitor patients' intraoperative sedation levels and drug effects (9). The PSI, a number ranging from 0 to 100, correlates with the clinical states that occur during the administration of an anesthetic agent. Decreasing values of the PSI indicate increasing levels of hypnosis. The range of 100-50 is associated with wakefulness and increasing depth of sedation as the number decreases, while the range of 50-25 indicates general anesthesia, and the range of 25-0 is related to deep anesthesia (10).

In this study, we retrospectively investigated whether low and high MAC concentrations of multimodal anesthesia has an effect on the depth of anesthesia, clinical parameter of the patient, reaching the postoperative discharge criteria and causes any complication in patients who underwent radical cystectomy in accordance with ERAS protocols.

MATERIAL AND METHODS

After obtaining the approval of the local ethics committee of our hospital with the decision number 2022-15-11, the data of the patients who underwent radical cystectomy between 2019-2022 were reviewed retrospectively. Data of the patients collected from hospital's electronic Database (Probel, Izmir, Turkey), anesthesia follow-up slips and pain follow-up charts. This study was retrospective, cross-sectional, and single-centered. The data of 41 patients in total were collected, and 6 patients were excluded (4 because different levels of depth of anesthesia was different the rest of the groups, 2 because epidural catheter could not be inserted). The patients were divided into two groups; Group H, whose anesthesia was maintained with 1 MAC and Group L, those with 0.5 MAC. All patients were prepared and managed in line with ERAS protocols with standard anesthesia protocol. All patients were seen the day before, informed about anesthesia, and Mini Mental Tests were performed. In the operating room, in addition to ASA standard monitoring, patient state index (PSI) for depth of anesthesia, suppression ratio (SR), SEDLine Brain Function Monitor (Masimo Corp., Irvine, CA, USA) (Masimo Root, California, USA), pleth variability index (PVI) Masimo Radical 7 Pulse CO-Oximeter with PVI software (Masimo SET, Masimo Corp., Irvine, CA, USA) monitoring for invasive arterial pressure and fluid management were performed.

Preventive pain treatment was started with preoperative non-opioid paracetamol (Paracerol, Polifarma). Prophylactic anti-emetic therapy was given. An epidural catheter was inserted. Radial artery cannulation and intra-arterial pressure monitoring (IABM) were done. MAC values that were calculated automatically by the device were followed and recorded.

Crystalloid infusion was started at a rate of 3-5 ml/kg/h. PVI was aimed to be less than 15 by using PVI monitoring in fluid management. If it exceeded 15, 250 cc bolus crystalloid was given. In the follow-up of the depth of anesthesia, the dose of remifentanyl was titrated to a PSI of 25-50 and an SR of 0. The vaporizer

was turned off as the fascia began to close. At the end of the case, the duration of surgery and anesthesia, and whether the patient was transferred were recorded. Patient-controlled analgesia was used through an epidural catheter for postoperative pain control. Their 24-hour follow-up was done by the pain team and recorded. The Mini Mental Test was repeated at the postoperative 24th hour in all patients.

All the data were recorded at the specified times (1-start of ventilation, 2-30. min, 3-60. min, 4-120. min, 5-fascia closing, 6-after extubation).

Statistical Analysis

Statistical comparison of hemodynamic data (mean arterial pressure [MAP] and peak heart rate [HR]) at the same time will be made. Demographic data of the patients, BMI's (Body Mass Index), ASA scores (American Society of Anesthesiology), whether the surgery is robotic or open, anesthesia and surgery times, the amount of fluid given as perioperative bolus and infusion, the amount of blood and blood products used, the number of patients admitted to the post-anesthesia care unit (PACU) unit, and duration of stay in PACU, any surgical complications, need for analgesics within 12 hours, nausea and vomiting, and discharge times were also recorded.

Statistical Analysis: The Statistical Package for Social Sciences (version 28.0) program was used for statistical analysis. Mean, standard deviation, median, minimum, maximum, frequency and ratio values were used in descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. Independent sample t test and Mann-Whitney U test were used to analyze quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fisher test was used when chi-square test conditions were not met.

RESULTS

A total of 35 patient data, 18 high MAC (Group H) and 17 low MAC (Group L) were analyzed. The mean age of the patients in the Group H was 61

years, 65 years in the Group L. Male gender was dominant between the groups. There was no statistical differences between groups regarding patients ages and BMI (p=0.234) (Table 1).

The percentage of robotic surgery was 50% in Group H, and 24% in Group L. Anesthesia times were 474.6±112.8 / 389.1±103.5 minutes and surgery times were 432.5±115.6 / 356.8±102.2 minutes in Group H and Group L respectively and these differences were found statistically significant (p=0.013 and p=0.029). The total amount of fluid was 3389 ml in Group H and 2917 ml in Group L and there was no significant difference between groups (p>0.05, Table 2). ES (Erythrocyte Suspension) and FFP (Fresh Frozen Plasma) usage rates did not differ significantly between the groups (p>0.05). Of the group H patients, 1 ES was given to one of the 3 open surgery cases, and 2 ES to the other two. Of the group L patients, 3 ES were given to 4 open surgery cases and 2 ES to 1 robotic case. FFP was given to 6 patients in Group H and 5 patients in Group L. There was no statistical difference between the minimal test results of the patients in both groups at the preoperative and postoperative 24th hour (p>0.05, Table 2). Table 2 shows the surgical

methods, anesthesia and surgery durations, as well as the perioperative data of the patients.

PSI, at the 60th, 120th minutes and fascia closure were 25.9±5.3, 25.9±6.3, 25.4±2.5 (respectively) in Group H and 30.6±7.4, 32.5±6.6, 34.2±7.8 (respectively) in Group L and these differences were significantly lower in Group H (p=0.004, p=0.001, and p=0.000, respectively). The duration of SR>0 was 86.8±123.5 (mean 24.5) in Group H and 1.0±2.0 (mean 0.0) in group L, and was significantly higher in Group H (p=0.000). PSI <25 times were 139.0±186.7 and 17.6±54.8 in group H and L respectively, and was significant higher in group H (p=0.001, Table 3). Hemodynamic data was measured at time periods simultaneous with evaluation of depth of anesthesia did not differ between the two groups (p>0.05, Table 4). The hemodynamic data of both groups are shown in Table 4. Presence of nausea and vomiting at postoperative 12th hour was positive in 16 of group H patients (88.9%) and in 8 of group L patients (47.1%) and this difference was significantly higher in group H. No significant difference was found between the two groups in the evaluation of the post-operative processes of the patients (Table 5).

Table 1. Demographic Values

		Group H			Group L				P		
		Mean.±ss/n-%		Median	Mean.±ss/n-%		Median				
Age		61.6	±	7.3	63.0	65.2	±	7.7	66.0	0.234	^m
Gender	Female	2		11%		1		6%		1.000	^{x²}
	Male	16		89%		16		94%			
BMI		24.8	±	3.7	25.0	26.1	±	3.3	25.1	0.509	^m
ASA	II	9		50%		8		47%		0.862	^{x²}
	III	9		50%		9		53%			

^{x²} Ki-Kare test / ^m Mann-Whitney u test

MAC: minimum alveolar concentration, BMI: Body mass index, ASA: American Society of Anesthesiology

Table 2. Perioperative Datas

	Group H				Group L				P	
	Mean±ss/n-%		Median		Mean±ss/n-%		Median			
Surgical technique										
Open	9		50%		13		76%		0.105	x ²
Robotic	9		50%		4		24%			
Minimental Test										
Preop	23.1	±	4.4	23.0	24.1	±	4.3	26.0	0.497	^m
Postop	23.3	±	3.3	22.0	24.0	±	3.5	25.0	0.583	^m
Cristalloid fluid										
Infusion	1536	±	432	1650	1303	±	456	1250	0.091	^m
Bolus	1631	±	708	1600	1497	±	1208	1100	0.457	^m
Colloid fluid	222.2	±	255.7	0.0	117.6	±	218.6	0.0	0.199	^m
ES	(-)	15	83.3%		12		71%		0.657	x ²
	(+)	3	16.7%		5		29.4%			
I	1		5.6%		3		18%			
II	2		11.1%		2		12%			
FFP	(-)	12	66.7%		12		70.6%		0.657	x ²
	(+)	6	33.3%		5		29.4%			
I	2		11.1%		3		17.6%			
II	4		22.2%		2		11.8%			
Anesthesia time	474.6	±	112.8	490.0	389.1	±	103.5	390.0	0.013	^m
Surgery time	432.5	±	115.6	440.0	356.8	±	102.2	370.0	0.029	^m

x² Chi-Square test / ^t Independent Sample t test / ^m Mann-Whitney u test

Table 3. Perioperative Anesthesia Depth Status

	Group H				Group L				P	
	Mean.±ss/n-%		Median		Mean±ss/n-%		Median			
PSI										
Beginnig of ventilation	30.9	±	4.9	30.5	29.6	±	6.0	28.0	0.518	^m
30. minute	25.9	±	5.1	25.0	29.1	±	7.0	26.0	0.154	^m
60.minute	25.9	±	5.3	24.5	30.6	±	7.4	28.0	0.004	^m
120. minute	25.9	±	6.3	24.0	32.5	±	6.6	33.0	0.001	^m
Fascia closure	25.4	±	2.5	25.0	34.2	±	7.8	32.0	0.000	^m
Extubation	87.9	±	3.9	88.0	87.6	±	3.7	88.0	0.932	^m
SR > 0 time	86.8	±	123.5	24.5	1.0	±	2.0	0.0	0.000	^m
PSI < 25 time	139.0	±	186.7	45.0	17.6	±	54.8	5.0	0.001	^m
PSI> 50 time	0.0	±	0.0	0.0	0.0	±	0.0	0.0	1.000	^m

^m Mann-Whitney U test, PSI: Patient State Index

Table 4. Perioperative Hemodynamic values

	Group H				Group L				P	
	Ort.±ss/n-%		Median	Ort.±ss/n-%		Median				
Mean BP (mm/Hg)										
Initiation of ventilation	76.3	±	12.6	76.0	77.9	±	12.1	73.0	0.843	^m
30. minute	65.9	±	9.3	66.5	66.8	±	12.0	63.0	0.987	^m
60. minute	69.1	±	13.0	63.5	73.4	±	13.2	69.0	0.306	^m
120. minute	79.4	±	11.7	77.5	80.3	±	13.3	80.0	0.792	^m
Fascial closure	73.1	±	15.2	72.0	82.4	±	16.2	82.0	0.083	^m
Extubation	88.4	±	17.8	83.0	87.6	±	12.0	87.0	0.766	^m
HB										
Initiation of ventilation	79.3	±	15.3	77.5	71.1	±	9.7	73.0	0.099	^m
30. minute	69.6	±	11.4	66.0	63.8	±	10.6	63.0	0.160	^m
60. minute	69.7	±	14.6	64.0	64.6	±	11.5	67.0	0.391	^m
120. minute	70.7	±	15.2	66.5	65.0	±	9.9	64.0	0.409	^m
Fascial closure	74.6	±	17.0	73.5	72.1	±	14.4	73.0	0.856	^m
Extubation	92.0	±	15.0	90.5	84.5	±	11.5	85.0	0.228	^m

^m Mann-Whitney U test

Table 5. Postoperative parameters

	Group H				Group L				P		
	Mean.±ss/n-%		Median	Mean±ss/n-%		Median					
PACU admission	(-)	13		72%		8		47%	0.105	^{x²}	
	(+)	5		28%		9		53%			
PACU period (day)		0.33	±	0.59	0.00	0.76	±	1.03	1.00	0.133	^m
Surgical complications	(-)	16		89%		15		88%	0.129	^{x²}	
	(+)	2		11%		2		12%			
Postop 12h analgesic requirement	(-)	12		66.7%		15		88.2%	0.129	^{x²}	
	(+)	6		33.3%		2		11.8%			
PONV 12h	(-)	2		11.1%		9		52.9%	0.008	^{x²}	
	(+)	16		88.9%		8		47.1%			
Anesthesia time		474.6	±	112.8	490.0	389.1	±	103.5	390.0	0.013	^m
Surgical time		432.5	±	115.6	440.0	356.8	±	102.2	370.0	0.029	^m
Hospital stay		13.6	±	8.7	10.5	15.9	±	11.0	13.0	0.497	^m

^{x²} Chi-Square test / ^t Independent Sample t test / ^m Mann-Whitney u test

PACU: post-anesthesia care unit, PONV: Postoperative nausea and vomiting

DISCUSSION

In this retrospective clinical study, we investigated whether low and high MAC concentrations of multimodal anesthesia has an effect on the depth of anesthesia and if MAC level effect clinical parameters in patients who underwent radical cystectomy surgery in accordance with ERAS protocols.

PSI, showing the depth of general anesthesia at the 60th, 120th minutes and fascia closure were recorded significantly lower in Group H. The duration of SR>0 (suppression ratio) and PSI <25 times were statistically significantly higher in Group H. Nausea and vomiting at 12 hours postoperatively was also common in Group H. We did not found any statistical significant difference between the groups that compared, including perioperative and postoperative clinical parameters and minimal test results.

Although ERAS protocols offer preoperative, perioperative and post-operative recommendations, the main purpose is to improve the post-operative process. To reach that goal a well-coordinated multidisciplinary study group which consist of patients, surgeons, anesthesiologists, pain specialists, and nurses is essential (10)(11).

This retrospective study was carried on the radical cystectomy cases who had been managed according to the ERAS protocols. Because ERAS protocols favor less inhalation anesthesia agent consumption, we have focused on perioperative MAC levels of our patient. At this point we constituted group H, composes of the patients with MAC level 1. Among all patients' data we also collected lower MAC level patients' data and constituted group L composed of the patients with MAC level 0,5 so that we were able to compare the results, to achieve our goal.

While conducting an interdisciplinary consensus study, a group of researchers reviewed meta-analyses, randomized controlled trials, and large prospective cohort studies and published a consensus statement for each item of the perioperative treatment pathway and stated that anesthetists control several preoperative, intraoperative, and postoperative ERAS elements (12). In the early 2000s, there were

no prospective single-intervention studies evaluating the value of a standardized anesthesia protocol for cystectomy (13). By 2022, when the groups with and without ERAS protocols were compared, It was found that the hospitalization period was 13 days and 15 days in the ERAS group and in without ERAS group, respectively. It was also emphasized that the two groups differed significantly in terms of intraoperative data, and the significant difference that changed the results over time was increased minimally invasive surgical intervention ratio and differences with anesthesia protocols (14). In radical cystectomies, less intraoperative blood loss and less intraoperative fluid infusion were seen in patients treated according to the ERAS protocol and also average length of stay decreased from 12 days to 9 days in (15).

In our study groups all patients were followed and managed according ERAS protocol. In this main group we selected and compared the patients who received deep (Group H) and superficial (Group L) standard anesthesia. Therefore, we were able to see if the depth of the anesthesia effects the results. The average hospital stay was 13 days in Group L and 15 days in Group H in our patients. Although this difference was no statistically significant, we believe that a mean 2-days hospitalization difference is clinically significant. At this point robotic surgery ratio which is higher in group H may be an important parameter that effects length of hospitalisation. In a meta-analysis, covering the years 2005-2021, the evidence for the effectiveness of ERAS protocols on postoperative complication rates, length of hospital stay, investigated and it was found that length of hospital stay was shorter when ERAS protocol applied but postoperative complication rate did not show any significant difference (16). Galich et al. investigated the use of robotic radical cystectomy with extracorporeal urinary diversion in 13 consecutive patients and compared the results with a homogeneous group of 24 patients who underwent standard open radical cystectomy. They found a lower length of hospital stay and less blood loss in the robotic group, while the operative time was significantly longer (17). We

attribute the significantly higher duration of surgery and therefore anesthesia time in our study Group H to the higher percentage of robotic surgery in these group of patients.

There are studies suggesting that not all ERAS elements are equally weighted in terms of the effect on postoperative complications and healing (18). Each of the intraoperative strategies deserves to be investigated separately. We think the depth level of anesthesia is one of them. End-tidal inhalation anesthetic concentration (ETAC), raw or processed electroencephalography (EEG), or other specialized monitors are often used to estimate anesthetic depth. None of the available inhalation or IV anesthetic agents are ideal for all patients, and they all have potential adverse side effects. In a meta-analysis including 40,317 patients, an association between increased depth of anesthesia (measured by processed EEG, such as a Bispectral Index [BIS] monitor) and decreased postoperative survival has been noted in some observational studies (19). We avoid excessive depth of anesthesia and significant hypotension, especially in elderly patients, patients at risk of developing perioperative neurocognitive impairment. However, there is insufficient evidence to recommend the use of EEG monitoring to prevent postoperative delirium or other neurocognitive disorders (20).

We use PSI monitoring to reach the lowest possible anesthesia depth level without creating awareness. In our study, the PSI values of our patients in both groups were between 25-50, which corresponds to general anesthesia. In Group H, suppression rates ranging from 0-100%, which measure how much the electrical activity of the brain's frontal and prefrontal cortex are suppressed as a percentage of time, were found to be significantly lower at the 60th, 120th minutes and fascia closure. In our study groups we also found a statistically significant higher duration of SR>0 and PSI <25 duration in group H. All these data support that higher MAC level causes deeper anesthesia as expected. However, the depth level of anesthesia did not seem to have a significant negative effect on any of the results of the patients, including the postoperative

minimal test results.

We also analyzed our hemodynamic data at the same measurement times. There was no significant difference between the groups. Mean arterial pressure was in the range of 65-88 mm/Hg, indicates that the patients were not hypotensive. In the first 12 hours postoperatively, nausea and vomiting were significantly less in group L (p:0,008) where open technique surgery was more common. We attributed this to the fact that the need for analgesia (IV analgesics) was less even though the surgery was open technique.

Different ERAS protocols for radical cystectomy have been published. A meta-analysis of 860 studies was performed through databases; hospitalization times were in favor of the protocols in terms of complications. Early mobilization focused on the implementation of optimized fluid management. The meta-analysis concluded that these protocols are useful to be applied in clinical practice (21). This meta-analysis emphasizes the importance of per operative fluid management. Compared to colorectal surgery, fluid monitoring is more challenging in cystectomy patients as urine output can be unreliable. We used plet variability index (PVI) monitoring to plan our intraoperative fluid management in our patients as it is an important component of ERAS protocols. Both groups of patients received restrictive fluid therapy and PVI was kept below 15 to avoid hypervolemia (6).

In ERAS protocols, inhalation anesthesia or total intravenous anesthesia (TIVA) technique can be used for intraoperative anesthesia maintenance. For both techniques, it is wise to use short-acting agents at the lowest possible doses, as they may delay healing or cause other adverse effects. In a 2022 meta-analysis (23 studies; 1611 participants) in which the intravenous maintenance technique and inhalation technique in anesthesia maintenance were compared, it was found that mean inflammatory biomarker levels measured after various types of surgery were not effected (22).

Our study showed that MAC values did not significantly affect perioperative and early postoperative outcomes in patients who underwent radical cystectomy, but the higher MAC level

generates a deeper anesthesia. In accordance with ERAS protocols, perioperative low MAC level seems an effective alternative providing a lower inhalation anesthesia agent consumption, but this should be supported by larger, prospective studies.

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How Is High Power (200w) Thulium Laser Vapoenucleation of the Prostate Impacting Functional Parameters? Short-Term Follow-Up Results

Prostatın Yüksek Güçlü (200w) Thulium Lazer Vapoenukleasyonu Fonksiyonel Parametreleri Nasıl Etkiliyor? Kısa Dönem Sonuçlarımız

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Özet

Amaç: Literatürde yüksek güçlü Thulium:YAG lazer vapoenukleasyon tekniğinin sonuçlarını irdeleyen çalışmalar kısıtlıdır. Sunulan çalışmada, benign prostat hiperplazisi tedavisinde kullanılan 200 W Thulium:YAG lazer vapoenukleasyonun, etkinlik ve güvenilirliğinin, bu prosedürün alt üriner sistem semptomları, erektil, ejakülatuar fonksiyonlar üzerindeki etkisinin analiz edilmesi amaçlanmıştır.

Gereç ve Yöntemler: Aralık 2021 ile Haziran 2022 arasında, benign prostat hiperplazisinin belirti ve semptomlarını tedavi etmek için kliniğimizde Thulium vapoenukleasyon (ThuVEP) uygulanan hastaların verileri prospektif olarak toplandı. Hariç tutma kriterleri uygulandıktan sonra 50 vakalık bir örneklem büyüklüğü elde edildi ve veriler retrospektif olarak analiz edildi. Ameliyatı takip eden 1. ve 6. aylarda tüm hastalar alt üriner sistem semptomları, erektil fonksiyon ve ejakülasyon semptomları açısından ameliyat öncesi durumları ile karşılaştırıldı. Oluşan komplikasyonları sınıflandırmak için Modifiye Clavien-Dindo Sınıflandırması da kullanıldı.

Bulgular: Hastaların IPSS skorlarında 6 aylık takip sonunda belirgin ve anlamlı bir iyileşme görüldü (27'ye karşı 5; $p<0.001$). Ameliyat öncesi durumla karşılaştırıldığında, IIEF-5 skoru ile ölçülen erektil fonksiyonlar ameliyatla önemli ölçüde değişmedi (17'ye karşı 18; $p=0.067$). Takip süresinin sonunda, MSHQ-EjD skoru ile ölçülen ejakülasyon fonksiyonlarında önemli bir bozulma

Abstract

Objective: There are limited studies in the literature analyzing the results of the high-power Thulium:YAG laser vapoenucleation technique. In this current study, it was aimed to examine the effectiveness and reliability of 200 W Thulium:YAG laser vapoenucleation used in the treatment of benign prostatic hyperplasia and the effect of this procedure on lower urinary tract symptoms, erectile and ejaculatory functions.

Material and Methods: Data were collected prospectively from patients who underwent Thulium vapoenucleation (ThuVEP) in our clinic between December 2021 and June 2022 to treat signs and symptoms of benign prostatic hyperplasia. Following the application of the exclusion criteria, a sample size of 50 cases was obtained, and the data were analyzed retrospectively. In the first and sixth months following surgery, all patients were compared to their preoperative status in terms of lower urinary tract symptoms, erectile function, and ejaculatory symptoms. The Modified Clavien-Dindo Classification was also used to classify the complications that occurred.

Results: The patients' IPSS scores showed a notable and significant improvement at the end of the 6-month follow-up (27 vs. 5; $p<0.001$). When compared to the preoperative state, erectile functions as measured by the IIEF-5 score did not significantly change with the surgery (17 vs. 18; $p=0.067$). At the end of the follow-up period, there

This study was reviewed and approved by the Kafkas University Faculty of Medicine Ethics Committee 30.11.2012/09.

All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

oldu (10'a karşı 6.5; $p < 0.001$). İşlem sırasında ve sonrasında hastaların 2'sinde (%4) Clavien 3a seviyesinde komplikasyon görüldü, ancak bu seviyenin üzerinde komplikasyon görülmedi.

Sonuç: Semptomatik benign prostat hiperplazisinin cerrahi tedavisinde kullanılan yüksek güçlü (200 W) ThuVEP yöntemi kısa dönem sonuçlarına göre fonksiyonel sonuçlar açısından güvenilir ve etkilidir.

Anahtar kelimeler: thulium, lazer vaporizasyon, impotans, alt üriner sistem semptomları

was a substantial deterioration of ejaculatory functions as measured by the MSHQ-EjD score (10 vs. 6.5; $p < 0.001$). During and after the procedure, complications at the Clavien 3a level were seen in 2 (4%) of the patients, but no complications above this level were seen.

Conclusion: The high-power (200 W) ThuVEP method used in the surgical treatment of symptomatic benign prostatic hyperplasia is reliable and effective in terms of functional results according to short-term results.

Keywords: thulium, laser vaporization, impotence, lower urinary tract symptoms

INTRODUCTION

A century after its anatomical description in 1550, Herr hypothesized that an enlarged prostate could cause retention by interfering with urine flow (1). Since then, there has been a huge improvement in the knowledge about the pathophysiology of benign prostatic hyperplasia (BPH) and methods for treating it. More than 210 million men around the world currently have been diagnosed with BPH (2). Many new options for the interventional treatment of symptomatic BPH have arisen thanks to remarkable developments in technology and surgical instruments, but transurethral resection of the prostate (TUR-P) is still the gold standard³. However, laser-assisted prostate enucleation in prostates larger than 80 ml has been incorporated into recommendations (3).

Two methods, thulium laser vapoenucleation of the prostate (ThuVEP) and thulium laser enucleation of the prostate (ThuLEP), were primarily described for the surgical management of BPH using thulium: yttrium-aluminum-garnet (Tm: YAG) lasers (4,5). Both approaches attempt to enucleate the adenoma over the capsule, with the primary distinction being the relative intensity of the laser energy and the mechanical force utilized. Anatomical dissection using lower power and more mechanical force is often preferred in ThuLEP, even though enucleation with a higher amount of vaporization using a higher laser intensity is acceptable in ThuVEP (6). According to the latest guidelines, ThuLEP seems to offer similar efficacy and safety when compared to TURP, bipolar

enucleation, and holmium laser enucleation of the prostate (HoLEP); whereas, ThuVEP is not supported by randomized controlled trials (RCT). Based on the limited number of RCTs there is a need for ongoing investigation of these techniques³. Therefore, it is of great priority to investigate the effects of the ThuVEP technique, which incorporates enucleation and vaporization simultaneously.

A 200-watt Tm: YAG laser was acquired by our urology clinic at the end of 2021 to begin the ThuVEP procedure because we were unable to ignore the advice made in the guidelines and the rapidly growing laser prostatectomy trend. We conducted the current observational study using a high-power (200 W) Tm: YAG laser system in order to evaluate the safety and effectiveness of ThuVEP and determine how it affects patients' lower urinary tract symptoms, erectile, and ejaculatory functions. We aimed to investigate this since we realized there wasn't enough information in the literature.

MATERIAL AND METHODS

Between December 2021 and June 2022, we prospectively gathered information about patients who had ThuVEP to treat symptoms of benign prostatic hyperplasia in our clinic. The research project that we conducted was sanctioned by the university's board of ethics (30.11.2022; 80576354-050-99/178). The Helsinki Declaration's ethical guidelines were strictly followed. All patients gave their written consent after being fully informed of all potential risks and benefits.

The patients were informed about the ThuVEP technique and it was emphasized that this technique is one of the newest methods applied in the surgical treatment of BPH and is not yet among the first treatments recommended in the guidelines. The study did not include patients with a history of bladder outlet obstruction surgery (one patient), neurogenic bladder (one patient), or prostate cancer (three patients). In addition, the study did not include patients who were not sexually interested (two patients). Moreover, patients who had indwelling bladder catheters for longer than 1 month were not included in the study due to concerns that this factor could bias the results of surveys (two patients). In addition, the results of three patients who did not come for follow-up examinations were not included in the study. Based on these assessments, we obtained a sample size of 50 patients. A flowchart of the study is given in Figure 1.

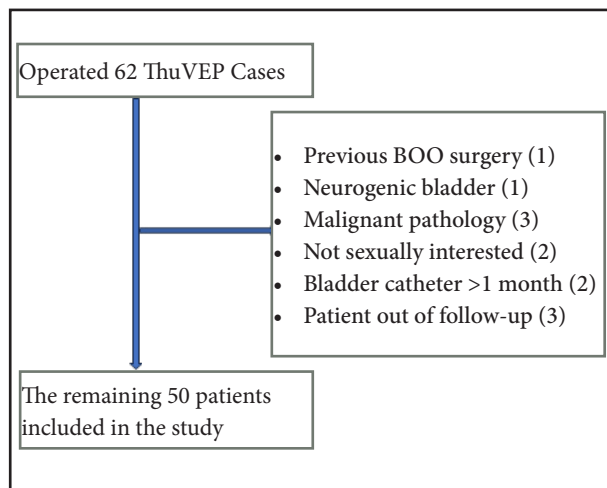


Figure 1. Flowchart of the study
BOO: Bladder outlet obstruction.

Demographic data, including the patients who had a detailed physical examination and a set of tests in the laboratory, including prostate-specific antigen (PSA), were recorded. If the patient had a high PSA level or suspicious digital rectal examination, a 12-core transrectal ultrasonography-guided prostate biopsy was performed. In addition, preoperative uroflowmetry and postvoid residual volume (PVR)

evaluations were carried out as part of the standard preoperative procedures (if the patient did not have a catheter). PVR was measured with a transabdominal probe using the prolate ellipsoid formula (Volume = length x width x height x 0.52). Also, all patients had to go through a detailed ultrasonic evaluation (Aplio 400, ©Toshiba Medical Systems Corporation), and prostate volumes were calculated using a transrectal probe with the prolate ellipsoid formula (7). Additionally, patients were asked to complete 3 validated questionnaires preoperatively and at postoperative follow-up. These were the International Index of Erectile Function (IIEF)-5, International Prostate Symptom Score (IPSS), and Male Sexual Health Questionnaire-Ejaculatory Disease (MSHQ-EjD) (8,9,10). All data were collected prospectively and analyzed retrospectively.

Technique

All operations were performed under general anesthesia. All operations were performed by 3 different experienced surgeons with more than 10 years of endourology background. A Cyber TM 200 W device (Quanta System, Solbiate Olona, Varese, Italy) was used for every surgery, and a 26 French resectoscope (Karl Storz™) was used to send a 550 m laser fiber through it. Enucleation was done using the earlier-described en-bloc technique (11). The bladder neck was approached after an early apical release and a circumferential advance. For the purpose of apical liberation, settings of 60 W resection and 40 W coagulation were chosen. Since we are surgeons at the beginning of the learning curve for this technique, entering the right plan in circumferential en-bloc enucleation was frequently not achievable. The tissue leaves created were swiftly vaporized with 200 W power in all of our 50 cases. A Hawk morcellator (Hawk Medical Instrument Co. Ltd.) was used for all morcellation processes. Each patient had a 22 Fr three-way urethral catheter inserted, and their bladder was irrigated continuously until the urine turned a clear color. Enucleation time, morcellation time, and specimen weight were recorded for every instance. Vaporization of the remaining adenomatous tissue after enucleation is shown in Figure 2.

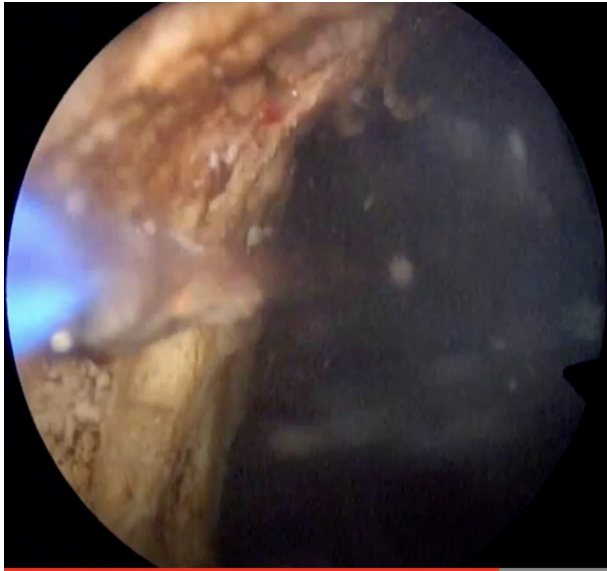


Figure 2. Vaporization of the remaining adenomatous tissue after enucleation

Follow-up

Patients were assessed with PSA levels, uroflowmetry, and PVR as a part of the periodic examination. Additionally, the three valid questionnaires (IIEF, IPSS, and MSHQ-EjD) that patients completed before the procedure were asked to be repeated, taking into account their altered condition, at both the postoperative first and sixth month.

We used Modified Clavien-Dindo Scoring System to evaluate and classify the complications (12). All demographic data, laboratory findings, and valid questionnaire scores were given in a comprehensive manner.

Statistical Analysis

The SPSS v25.0 statistical package was used for the analyses (SPSS Inc, Chicago, IL, USA). The Shapiro-Wilk test was utilized to examine the distribution for normalcy between the groups. Numbers and percentages were provided for the categorical variables, while the median and interquartile range were provided for the continuous variables. When comparing across repeated measurements, the Wilcoxon test was utilized. The significance level for the p-value was set at 0,05.

RESULTS

A total of 50 men underwent surgery. Prior to surgery, PVR was estimated to be at a median of 150 mL (IQR=100–200), and Qmax was 1.75 ml/s (IQR= 0-8.4). The median prostate size was 60 mL (IQR= 76-100). The median enucleation weight was 26 g (IQR= 26-39), and the median enucleation time was 49.5 min. (IQR= 35-70). The estimated median enucleation efficiency was 0.5 g/min (IQR= 0.4-0.8). The median total operation time was found to be 64.5 min (IQR= 45-80), while the median morcellation time was 13.5 min. (IQR= 10-20). Our measured Hgb decrease value was found to be a median of 0.35 g/dL, while the median postoperative catheter stay time was 1 day (IQR= 1-2). The hospital stay was 1 day (IQR= 1-2). Demographic and operative data of patients are given in Table 1.

The median IPSS [27, (IQR=23-30)] statistically significantly reduced at the first [5, (IQR=2-8), $p < 0.001$] and six-month follow-up first [5, (IQR=2-8), $p < 0.001$]. PVR [150, (IQR= 100-200)] was statistically significantly decreased at both first [0, (IQR= 0-25)] and sixth-month [0, (IQR= 0-50)] examinations. Additionally, Qmax (ml/s) was statistically increased at the first-month follow-up [19.00 (16.00-23.00), $p < 0.001$]. However, Qmax changes decreased at the six-month follow-up, but it was still significantly higher than the baseline value [18.25 (IQR=15-21), $p < 0.001$]. Additionally, the postoperative IIEF score was pretty similar at first [17.00 (IQR=11.7-20), $p=0.357$] and sixth months [18.00 (IQR=14.00-21.00), $p=0.067$] when compared to the preoperative status [17, (IQR= 11.7-20)]. Patient's postoperative MSHQ-EjD scores were significantly lower than their preoperative ratings [10, (IQR= 6-15.2)] at both the first [6.5, (IQR= 4.75-9)] and sixth-month [6.5, (IQR= 4.75-9)] evaluations. Postoperative outcomes are given in Table 2.

Perioperative complications were seen in only 4 (8.0%) patients, and capsular perforation was seen in only two (4.0%) patients. Partial right ureteral orifice resection was observed in 1 patient, which did not require any additional intervention, while bleeding requiring cauterization with a resectoscope due to

intraoperative bleeding was observed in another patient. The postoperative complications were generally minor complications, and Clavien 3a complication was seen in only two (4.0%). These patients experienced urethral stricture following surgery and needed cystoscopic

dilatation. Stress incontinence was a complication for one of our patients, which resolved on its own without further medical attention. Perioperative and postoperative complications are given in Table 3.

Table 1. Demographic and operative data

		Value
Age (years) ^a		66.5 (60-72)
PSA (ng/mL) ^a		2 (1.2-5.19)
Preoperative PVR (mL) ^a		150 (100-200)
Preoperative Qmax ^a		1.75 (0-8.4)
ASA ^b	ASA 1	18 (36.0%)
	ASA 2	26 (52.0%)
	ASA 3	6 (12.0%)
Charlson Comorbidity Index ^a		2 (0-3)
Preoperative Catheter ^b	None	26 (52.0%)
	Urethral	24 (48.0%)
Preoperative Biopsy History		18 (36.0%)
Prostate Volume (mL) ^a		60 (76-100)
Enucleation Weight (g) ^a		26 (20-39)
Enucleation Time (min.) ^a		49.5 (35-70)
Morcellation Time (min.) ^a		13.5 (10-20)
Total Operation Time (min.) ^a		64.5 (45-80)
Enucleation Efficacy(g/min) ^a		0.5 (0.4-0.8)
Hgb Drop (g/dL) ^a		0.35 (0.1-0.8)
Postoperative Catheter (day) ^a		1 (1-2)
Hospitalization Time (day) ^a		1 (1-2)

^aData was expressed as median and interquartile range

^bData was expressed as count and frequency

Table 2. Postoperative outcomes

	Preoperative	Postoperative 1st month	Postoperative 6th month	p value
IPSS	27 (23-30)	5 (2-8)	5 (2-8)	<0.001, <0.001
IIEF-5	17 (12-20)	17 (11.7-20)	18 (14-21)	0.357, 0.067
MSHQ-EjD	10 (6-15.2)	6.5 (4.75-9)	6.5 (4.75-9)	<0.001, <0.001
Qmax (mL/s)	1.75 (0-8.4)	19 (16-23)	18.25 (15-21)	<0.001, <0.001
PVR (mL)	150 (100-200)	0 (0-25)	0 (0-50)	<0.001, <0.001
PSA (ng/mL)	2 (1.2-519)	Null	0.5 (0.3-2.4)	<0.001

Data was expressed as median and interquartile range

Wilcoxon test was used

Table 3. Perioperative and postoperative complications

		Value
Perioperative Complication	Absent	46 (92.0%)
	Present	4 (8.0%)
Postoperative Complication (Clavien-Dindo)	None	35 (70.0%)
	Clavien I	7 (14.0%)
	Clavien II	6 (12.0%)
	Clavien IIIa	2 (4.0%)

Data was expressed as count and frequency

DISCUSSION

Our study’s vital finding was that high-power ThuVEP surgery considerably reduced lower urinary system symptoms while having no discernible positive or negative effects on erectile performance. Even though there was no discernible change in erectile function, ejaculatory functions were unquestionably negatively impacted.

The use of lasers to perform prostate enucleation is growing in popularity and is quickly becoming the gold standard for the surgical treatment of enlarged prostates. These developments have piqued the interest of endourologists in that region (13). Laser prostatectomy has advanced in recent years, and questions about its efficacy and safety have come with it. However, several studies have shown that this procedure is safe and effective (14). There was concern that the heat action of the laser on the prostate tissue would cause damage to the surrounding tissues when the use of high-power and continuous-wave (CW) thulium laser in the treatment of BPH was initially announced in 2005 (15,16). Theoretically, thulium CW lasers might generate beams between 2010 and 2013 nanometers in wavelength, depending on the manufacturer. At these wavelengths, electromagnetic energy is transformed into heat, which induces the evaporation of prostate tissue with a penetrating depth of around 0.2 mm (17,18).

Various functional aspects of the TURP procedure, which still maintains its status as the gold standard, have been repeatedly investigated. Studies have shown that although TURP provides significant improvement

in lower urinary tract symptoms of patients, it does not have a significant effect on erectile functions. In addition, severe impairments in ejaculatory functions were observed after TURP. In the present study, the effect of ThuVEP on functional parameters was found to be similar to the aforementioned TURP studies (19,20). According to the results of a meta-analysis investigating the results of thulium vaporessection and bipolar-monopolar TURP, it was stated that thulium vaporessection was superior to other methods in terms of bleeding, catheterization time, and hospital stay, as well as causing severe regression in the symptoms of patients as in TURP (21).

Our study’s functional findings corroborated those of other research that looked at ThuLEP’s effect on erectile functions, which is a positive factor. The average IIEF-5 score at the conclusion of the 6-month follow-up did not significantly differ from the preoperative state, even though we used higher power (200W) than in prior investigations (22,23). Similar findings were seen after 12 months of follow-up in another prospective research of 72 individuals examining the influence of ThuVEP on erectile functions (24). Results from a 2016 study by Saredi et al., including the impact of ThuLEP on ejaculatory functions, were presented (25). The patients’ mean MSHQ-EjD scores decreased dramatically, as seen in the study’s follow-up data. This result is to be expected, given that our surgical approach does not involve conserving the bladder neck fibers.

In their ThuVEP series of 65 patients, Netsch et al. observed a significant decline in IPSS scores [21.5

(IQR 15.5-23.75) vs. 5 (IQR 3-8)] and a rise in Qmax median values [7.7 (IQR 6.3-10) vs. 28.3 (IQR 21.25-39.2) ml/s]. We found fairly comparable results in our study; however, there was a modest but not statistically significant drop in Q-max values between the first and sixth postoperative months. Using high power (150-200 W) with a thulium laser, Chang et al. also significantly reduced the IPSS in their series (26).

Median PSA levels at the 6-month follow-up in our research dropped by 75% compared to baseline levels (0.5 ng/mL against 2.0 ng/mL). This is significant since it provides evidence of the efficacy of enucleation, and comparable reductions have been documented in other research (25). However, in our series, there was a disparity between the median prostate volume (60 mL) and the enucleation weight (26 g), and we believe that this is because of the considerable quantity of tissue vaporized during ThuVEP. Due to the fact that we are at the beginning of our learning curve and the vaporization impact of the 200 Watt laser, we might assume that our enucleation efficiency appears to be lower than the studies in the literature (27).

In the operation and follow-up duration, 8 individuals experienced complications that were Clavien 2 or 3a, which translates to a rate of 16%. During the 6-month follow-up, 2 of our patients developed urethral stenosis that required endoscopic intervention. Additionally, we must emphasize that one of our patients had significant stress incontinence that spontaneously resolved five months after we discovered it. The absence of complications more than Grade 3a, or what we would consider severe complications, was consistent with the literature despite there are ThuLEP studies showing reduced overall complication rates (28–30). In terms of hemoglobin decline, ThuVEP surgery offered us a great deal of confidence, and like in other research, hemoglobin decrease was limited (31). In the study by Praiser et al., in which the outcomes of high-power thulium vaporization were reported, no complications above Clavien grade 3 were seen (32).

Limitations

There are limitations in our research, obviously.

What stands out most is that our study did not include a control group. Additionally, our research was not randomized. One further drawback is that there is a limited number of cases. Additionally, more than the 6-month follow-up time may be required for monitoring some complications, such as bladder neck stricture. However, because we are a reference center, relatively few of our patients comply with long-term follow-up, as we have seen from our previous works. In addition, the fact that not all operations were performed by the same surgeon stands out as another handicap of the study. In spite of the fact that, the experience level of the surgeons is similar, different results may have been obtained specific to this procedure. Despite these drawbacks, we believe that providing the impact on functional outcomes with the data gathered prospectively in an area of interest, such as the employment of high-power thulium lasers in the treatment of BPH, will contribute to the literature.

CONCLUSION

The high-power (200 W) ThuVEP method used in the surgical treatment of symptomatic benign prostatic hyperplasia is reliable and effective in terms of functional results according to short-term results. In this area, more thorough follow-up randomized controlled trials are required.

Conflict of Interest Statement

The authors declare no conflict of interest.

Ethics Committee

Kafkas University Faculty of Medicine Ethics Committee 30.11.2012/09.

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Could Renal Tumour Scoring Systems Predict Tumour Aggressivity?

Böbrek Tümör Skorlama Sistemleri Tümör Agresivitesini Tahmin Edebilir Mi?

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Özet

Amaç: Bu çalışmanın amacı, T1 böbrek tümörlerinde R.E.N.A.L. nefrometri skoru (RNS), Padua skoru (PS), C-indeks ile tümör agresivitesi arasındaki ilişkiyi incelemek ve bu skorlama sistemlerinin, tümörün anatomisine ek olarak patolojisi hakkında klinik değerlendirmeyi yönlendirmek için bilgi sağlayıp sağlamadığını sorgulamaktır.

Gereç ve Yöntemler: Preoperatif klinik evrelendirmeye göre evre 1 (T1N0M0) 83 berrak hücreli renal hücreli karsinom (cRCC) hastası değerlendirildi. Patolojik sonuçlarına göre hastalar iki gruba ayrıldı: Fuhrman derecesi 1 veya 2 (FG1-2) olan hastalar (Non-agresif grup (NAG)) ve FG3-4 ve/veya TNM Evre 3 olan hastalar (Agresif grup (AG)). Her hastanın RNS, PS ve C-indeks puanları hesaplandı. Son olarak, nefrometri skorları ile patolojik agresivite arasındaki ilişki karşılaştırıldı.

Bulgular: Ortalama RNS, 7.3 ± 2.4 olarak hesaplandı. Toplam RNS, AG'de (9.2 ± 1.2) NAG'den (6 ± 2.2) anlamlı derecede yüksekti ($p < 0.001$). RNS, patolojik agresif hastalığın bağımsız bir öngörücüsüydü ($p < 0.001$). En yüksek eğri altı alan için RNS' nin eşik değeri 8 olarak bulundu ($p < 0.001$). Ortalama PS, 8.1 ± 1.6 olarak hesaplandı. PS ayrıca patolojik agresif hastalığın bağımsız bir öngörücüsüydü ($p < 0.001$). En yüksek eğri altı alan için PS'nin eşik değeri 8 olarak bulundu ($p < 0.001$). AG'nin ortalama C-indeks puanı (1.4 ± 0.4), NAG'den (2.7 ± 2.0)

Abstract

Objective: The aim of this study is to investigate the relationship between R.E.N.A.L. nephrometry score (RNS), Padua score (PS), Centrality (C)-index and tumour aggressivity in T1 renal tumours and to question whether these scoring systems would provide information about the pathology of renal tumours to manage clinical judgement rather than the anatomy of tumour.

Material and Methods: We evaluated 83 patients with stage 1 (T1N0M0) clear cell renal cell carcinoma (cRCC) according to preoperative radiological and pathological staging. Patients were divided according to pathological results of cRCC into two groups: Patients with Fuhrman grade 1 or 2 (FG1-2) (Non-aggressive group (NAG)) and patients with FG3-4 and/or TNM Stage 3 (Aggressive group (AG)). RNS, PS and C-index scores were calculated for each patient. Finally, the relationship between nephrometry scores and pathological aggressivity were compared.

Results: The mean RNS was calculated as 7.3 ± 2.4 . Total RNS was significantly higher in AG (9.2 ± 1.2) than in NAG (6 ± 2.2) ($p < 0.001$). RNS was an independent predictor of pathological aggressive disease ($p < 0.001$). The cut off value of RNS at the highest area under curve was 8 ($p < 0.001$). The mean PS was calculated as 8.1 ± 1.6 . PS was also an independent predictor of pathological aggressive disease ($p < 0.001$). The cut off value of PS at the highest area under

This study was reviewed and approved by the Taksim Education Hospital Ethical Committee (No:23/23.03.2016).

All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

anlamli derecede düřüktü ($p < 0.001$). C-indeks, patolojik agresiviteyi tahmin etmede anlamlıdır ($p < 0.001$).

Sonuçlar: Daha yüksek RNS ve PS puanları ile düşük C-indeks puanlarının böbrek tümörlerinin tümör agresivitesi ile ilişkilendirildiğini sonucuna varılmıştır.

Anahtar Kelimeler: Böbrek hücreli karsinom, Padua, C-indeks, R.E.N.A.L. nefrometri, tümör agresivitesi, Fuhrman Derecesi

curve was 8 ($p < 0.001$). The mean C-index score of AG (1.4 ± 0.4) was significantly lower ($p < 0.001$) than NAG (2.7 ± 2.0). C-index is significant in predicting pathological aggressiveness ($p < 0.001$).

Conclusions: Our results suggested that higher RNS and PS scores, lower C-index scores were associated with tumour aggressivity of renal tumours.

Keywords: Renal cell carcinoma, Padua, C-index, R.E.N.A.L. nephrometry, tumour aggressivity, Fuhrman Grade

INTRODUCTION

The number of patients diagnosed with renal masses is increasing with the widespread use of cross-sectional imaging methods (1). Pathological uncertainty exists when an incidental renal mass is identified. Preoperative counselling and treatment planning are often made in the context of this uncertainty, even though 20-30% of these lesions ultimately prove benign, and only 10-30% are found to be potentially aggressive (2-5). Preoperative variables, including percutaneous biopsy and pathologic predictive models, have been developed to address this uncertainty, while kidney biopsies, involving the extraction of a small tissue sample from the renal mass, have emerged as valuable tools in this diagnostic puzzle, providing critical insights into the histological nature of the renal mass to aid clinicians in making more informed treatment decisions, albeit with associated complications such as the risk of bleeding, infection, and injury to adjacent structures (6-8).

Evidence of the relationship between the pathology and anatomy of the renal mass began to emerge in various publications in the literature (9-11). Objective anatomical scoring systems, including R.E.N.A.L. Nephrometry Score (RNS), Padua Score (PS), and C-index, have been developed to identify renal mass anatomy (12-14). Radiographic anatomical attributes are used in these systems. Preoperative determination of tumour aggressivity is essential for treatment planning. In our study, we aimed to explore the relationship between RNS, PS, and C-index with tumour aggressivity in T1 renal tumours. We aim to demonstrate that these scoring systems can provide not only anatomical but also pathological information, aiding in treatment management.

MATERIAL AND METHODS

The records of patients who underwent renal surgery due to T1 renal masses from February 2008 to February 2016 were collected from the electronic medical database after obtaining ethical approval (Ethical Approval Number:23, Date:23.03.2016). Radical nephrectomy (RN) (62.6%) or partial nephrectomy (PN) (37.4%) was performed in 102 patients. Among them, 83 (81.4%) patients had clear cell pathology. Fuhrman Grade (FG) is of prognostic value only in clear cell pathology; therefore, 19 (18.6%) patients with other pathological diagnoses were excluded, including 4 with papillary RCC (3.9%), 5 (4.9%) with chromophobe RCC, 5 (4.9%) with angiomyolipoma, and 5 (4.9%) with oncocytoma. Clinical characteristics, pathological slides, and computed tomography (CT) images were retrieved for all patients. All specimens were reviewed by a pathologist. Only patients with clear cell carcinoma (cRCC) were included, and those with other renal cell carcinoma subtypes (19 patients) were excluded. Preoperative CT images were reviewed by a urologic surgeon (AÖ); RNS, PS, and C-index were calculated as previously described (12-14).

Patients were divided according to postoperative pathological results of cRCC into two groups: Patients with FG1-2 were considered as the non-aggressive group (NAG), and those with FG3-4 and/or TNM Stage 3 were considered as the aggressive group (AG). RNS, PS, and C-index scores and components were compared between patients with AG vs. NAG.

Descriptive statistics for the data encompassed mean, standard deviation, median, interquartile range, frequency, and ratio values. To assess the distribution of variables, the Kolmogorov-Smirnov

test was employed. If the variables were not normally distributed, quantitative data were analysed using the Mann-Whitney U test. In contrast, if the variables were normally distributed, an independent sample t-test was used. Qualitative data were subjected to analysis using the Chi-square test, with the Fischer exact test being applied when the conditions for the Chi-square test were not met. The determination of effect level and cut-off values was carried out through the utilization of the ROC curve. Statistical analyses were conducted using SPSS 22.0 software.

RESULTS

Among the included 83 patients, the median patient age was 58.7 years (IQR: 50-64.9) with a male predominance (54.2%). The ages were divided into AG (n = 48, 58%) and NAG (n=35, 42%) according to the pathology results as described. Age and gender distribution of patients were similar (p > 0.05). The RCCs were removed by radical nephrectomy in 52 (62.7%) and partial nephrectomy in 31 (37.3%) patients. Table 1 presents a comprehensive overview of the detailed pathological examinations. Collecting system and/or renal sinus invasion were observed in 2 (2.4%) cases; In 3 (3.7%) cases, lymph node positivity was observed; 11 cases (13.3%) were pathological stage 3; 9 patients were pathologically diagnosed as T3A (10.8%). Two of stage 3 tumours were pathologic stage 3 due to lymph node positivity, and the other 9 cases were stage 3 due to extracapsular spread and/or collecting system and/or renal sinus invasion.

The mean RNS for all patients was 7.3 ± 2.4 . According to the components of the RNS: Tumours with increased diameter (R) (p < 0.05), endophytic nature (EII-III) (p < 0.05), distance to the collecting system or sinus < 4 mm (N III), posterior location of the tumor (P) (p < 0.05), and a central location within the polar lines of the kidney (LII-III) (p < 0.05) were significantly higher in AG than in NAG. The total RNS was significantly higher in AG (9.2 ± 1.2) than in NAG (6 ± 2.2) (p < 0.05) (Table 2). RNS was an independent predictor of pathological aggressive disease [0.863 (0.785-0.940)] (p < 0.001). The cutoff value of RNS at

the highest area under the curve was 8 [0.807 (0.710-0.905)] (p < 0.001). Sensitivity was 88.6%, the positive predictive value was 70.5%, specificity was 72.9%, negative predictive value was 89.7% (Figure).

The mean PS for all patients was 8.1 ± 1.6 . According to the components of the PS: Tumour with medial localization (M), polar localization, and tumour size between 4-7 cm were significantly higher in AG than in NAG (p < 0.05); Collector system and renal sinus involvement were although higher in AG than in NAG but not statistically significant (p > 0.05); The rate of exophyticity (Exophyticity II-III) was significantly higher than that of NAG (p < 0.05). PS AG (9.2 ± 1.1) was significantly higher than NAG (7.3 ± 1.4) (p < 0.05). PS is significant in predicting pathological aggressiveness [0.846 (0.762-0.929)] (p < 0.001) (Table 2). The cutoff value of PS at the highest area under the curve was 8 [0.761 (0.653-0.868)] (p < 0.001). Sensitivity was 77.1%, the positive predictive value was 69.2%, specificity was 75.0%, negative predictive value was 81.8% (Figure).

The C-index value was calculated for each patient. All patients had a mean age of 39.8 ± 10.7 mm, a mean r (mm) of 22.9 ± 9.1 mm, and a mean C-index of 2.2 ± 1.7 . When parameters are considered separately, c (mm) in AG was not significantly different from NAG (p > 0.05), r (mm) in AG was significantly higher than NAG (p < 0.05). The C-index in AG (1.4 ± 0.4) was significantly lower (p < 0.05) than in NAG (2.7 ± 2.0) (Table 2). C-index is significant in predicting pathological aggressiveness [0.787 (0.690-0.883)] (p < 0.001). The highest cutoff value for the sub-curve area was 1.55. Sensitivity was 77.1%, the positive predictive value was 77.1%, specificity was 68.6%, and the negative predictive value was 68.6% (Figure).

DISCUSSION

The diverse nature of enhancing renal masses presents a multifaceted clinical challenge, with varying biological characteristics. Achieving the alignment of renal mass biology with an optimal treatment approach continues to be a challenging objective in contemporary urologic oncology (15).

For patients in good health with T1 tumours suitable for nephron-sparing surgery, partial nephrectomy is presently considered the established standard of care. Nevertheless, the American Urological Association includes thermal ablation and active surveillance as potential choices for patients with tumours measuring 7 cm or smaller (16). The prevalence of small tumours, particularly in elderly or comorbid patients, is on the rise. The utilization of observation/surveillance approaches and ablative treatments that could be deemed safer for less aggressive cancers has gained prominence, primarily due to the limited availability of short- to medium-term oncological outcomes (17).

The widespread hesitance surrounding the adoption of percutaneous biopsy, driven by concerns over potential complications or its inherent limitations in accurately determining grading, further underscores the potential applicability of a system capable of precisely predicting malignancy or aggressiveness (18). Because of these purposes, various systems were designed using nomograms (7,8). RNS, PS, and C-index have been used to predict warm ischemia time, urine leak, blood loss, urine leakage hospital length stay, and patient recovery time for PN previously. Recently, there have been some studies to correlate nephrometry scores, especially RNS, with tumour biology and pathology.

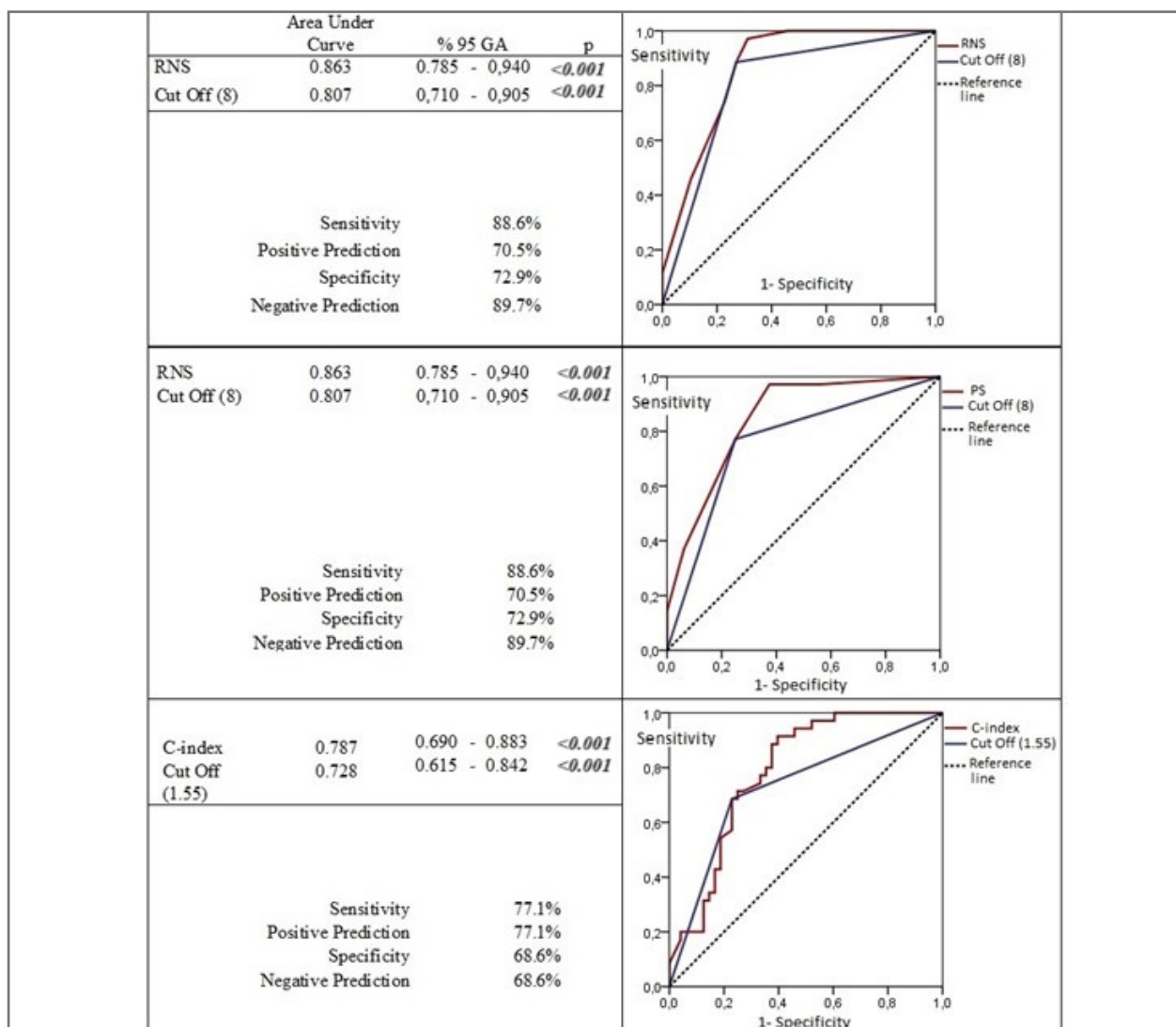


Figure: ROC curve, area under curve and Cut off value of RNS, PS, and C-index

Table 1. Demographic and pathological features of the cases.

	Non-aggressive group (NAG) (n=48)		Aggressive group (AG) (n=35)		Total	P
	Mean ± sd / n %	Median (IQR)	Mean ± sd / n %	Median (IQR)		
Age, year	57.5 ± 10.3		57.2 ± 14.0		57.4±11.9	0.896
Gender, n (%)	Male	22 (45.8%)	23 (65.7%)		45 (54.2%)	0.073
	Female	26 (54.2%)	12 (34.3%)		38 (45.8%)	
Tumour size (mm)	35.4 ± 16.9	32.0 (24-50)	55.9 ± 11.7	55.0 (48-70)		<0.001
Surgical modality, n (%)	RN	20 (41.6%)	32 (91.4%)		52 (62.6%)	
	PN	28 (58.4%)	3 (8.6%)		31 (37.4%)	
Fuhrman Grade, n (%)	I	15 (31.2%)	-		15(18.1%)	
	II	33 (68.8%)	8 (22.8%)		41 (49.4%)	
	III	-	25 (71.4%)		25 (30.1%)	
	IV	-	2 (5.8%)		2 (2.4%)	
Collector system /renal sinus involvement, n (%)	-		2 (5.7%)		2 (2.4%)	
Pathological (T) Stage	T1A	34 (70.8%)	8 (21%)		42 (50.6%)	
	T1B	14 (29.2%)	18 (51.4%)		32(38.5%)	
	T3A	-	9 (27.6%)		9(10.8%)	
Pathological (N) Stage	N0	48 (100%)	32 (91.4%)		80 (96.3%)	
	N1	-	3 (8.6%)		3 (3.7%)	

Abbreviations: RN: Radical Nephrectomy; PN: Partial Nephrectomy.

Table 2. Nephrometries and features

		Non-aggressive group (NAG)			Aggressive group (AG)			P
		Mean ± sd / n%	Median (IQR)	Mean ± sd / n%	Median (IQR)			
(R)adius	I	32	66.7%	6	17.1%	<0.001		
	II	16	33.3%	29	82.9%			
(E)xophytic/ endophytic	I	32	66.7%	4	11.4%	<0.001		
	II	15	31.3%	19	54.3%			
	III	1	2.1%	12	34.3%			
(N)earness	I	28	58.3%	2	5.7%	<0.001		
	II	7	14.6%	4	11.4%			
	III	13	27.1%	29	82.9%			
(A)nt/Post	A	17	35.4%	4	11.4%	<0.001		
	P	31	64.6%	31	88.6%			
(L)ocalisation	I	27	56.3%	4	11.4%	<0.001		
	II	12	25.0%	15	42.9%			
	III	9	18.8%	16	45.7%			
R.E.N.A.L Score		6.0 ± 2.2		5.0 (4-8)	9.2 ± 1.2		9.0 (8-10)	<0.001
<u>Renal Rim</u>								
Lateral	1	41	85.4%	23	65.7%	0.035		
Medial	2	7	14.6%	12	34.3%			
<u>Tumour size (cm)</u>								
≤4	1	32	66.7%	6	17.1%	<0.001		
4.1-7	2	16	33.3%	29	82.9%			
>7	3	-	-	-	-			
<u>Renal sinus</u>								
Not involved	1	48	100.0%	32	91.4%	0.071		
Involved	2	0	0.0%	3	8.6%			
<u>Polar Location</u>								
Superior/Inferior	1	30	62.5%	8	22.9%	<0.001		
Middle	2	18	37.5%	27	77.1%			
<u>Collecting system</u>								
Not involved	1	46	95.8%	33	94.3%	1.000		
Dislocated/infiltrated	2	2	4.2%	2	5.7%			
<u>Exophytic rate</u>								
≥50%	1	32	66.7%	5	14.3%	<0.001		
<50%	2	15	31.3%	20	57.1%			
Endophytic	3	1	2.1%	10	28.6%			
Padua Score		7.3 ± 1.4		7.0 (6.0-8.75)	9.2 ± 1.1		9.0 (9-10)	<0.001
C (mm)		40.2 ± 10.3		40.0 (30.5-50.0)	39.2 ± 11.3		40.0 (30.0-47.0)	0.691
r (mm)		19.0 ± 8.7		17.5 (12.0-25.0)	28.4 ± 6.5		30.0 (24.0-35.0)	<0.001
C-index		2.7 ± 2.0		2.2 (1.6-3.1)	1.4 ± 0.4		1.3 (1.1-16)	<0.001

Kutikov et al (19), based on some results that correlated the anatomical features of the tumour with pathological findings, have created a nomogram that integrates age and sex with some elements of RS with high predictive ability. However, the patients taken into this study had a high proportion of advanced and/or large tumours (>25 cm), and the malignancy or aggressiveness of such tumours were not required to be predicted, because of the high grade in nearly all the cases, and that was the flaw of the study. Whereas in our case, all patients had T1 and clear-cell pathology tumours. Wang et al. (20) affirmed a robust predictive capability for high-grade tumours when analysing an exclusively malignant tumour cohort that exhibited similarities to the Kutikov cohort. Conversely, Bagrodia et al. (21) reported a weak predictive performance for malignancy but an exceptionally high predictive accuracy for tumor grading in a small patient cohort with tumours up to 8 cm who underwent partial nephrectomy. In contrast, Koo et al. (22) examined an extensive cohort of clinically T1 renal tumours and found an acceptable predictive performance for malignancy but a notably poor performance in predicting high-grade tumours. On the other hand, Antonelli et al. (23) and Mullin et al. (24) failed to identify any correlations between malignancy or high-grade pathology in large cohorts of cT1a patients (506 patients and 754 patients), possibly due to the lower nephrometry scores of the tumours. A limitation of these studies lies in the heterogeneity of the patient groups included in their analyses.

Pathological aggressiveness is not only due to nuclear grading; there are also some prognostic parameters according to pathological results. We should use not only nuclear grading but also add upstaging (from stage 1 to stage 3) to make pathological aggressiveness; from this point of view, our study is different from the others (25–27).

Kutikov et al. (19) and Chen et al. (28) compared individual components of the RNS with nuclear grade, and their results showed that R score, E score, and L score were strongly associated with high-grade pathology. It has also been reported that a high

percentage of endophytic tumours were associated with clear-cell histology and higher-grade tumours (29,30). That is consistent with our study. We demonstrated that in RNS, tumours with increased diameter (R) ($p < 0.05$), endophytic nature (EII-III) ($p < 0.05$), distance to the collecting system or sinus $< 4\text{mm}$ (N III), posterior location of the tumour (P) ($p < 0.05$), and with a central location within the polar lines of the kidney (LII-III) are associated with aggressive pathology. The components of the PS demonstrated that larger tumours (4-7 cm) ($p < 0.05$), location relative to the polar lines, and endophytic tumours (Exophyticity II-III) ($p < 0.05$) were more likely to be classified as aggressive pathology diagnosed with cRCC. In previous studies, there is not any cut-off point about RNS, PS, and C-index for predicting aggressivity of RCC. We demonstrated that when RNS and PS are higher than 8, and the C-index is lower than 1.55, aggressivity risk is rising.

CONCLUSION

Overall, this study uncovered that there is a relationship between nephrometry scores (RNS, PS, and C-index) and final aggressive tumoral pathology. The prediction of malignant and metastatic potential of the tumour alters the management of T1 renal tumors. This is of great practical importance for preoperatively predicting renal mass aggressivity. Using these data, which will help urologists choose appropriate therapies for patients. RNS, PS, and C-index represent a novel tool that can help preoperatively predict the aggressivity of renal masses and make therapeutic decisions. However, well-designed randomized controlled trials are needed to produce comparable results.

Ethics Committee

Our study was approved by Taksim Education Hospital Ethical Committee (No:23/23.03.2016).

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Paraganglioma of Urinary Bladder: A Case Report

Mesane Paragangliomu: Olgu sunumu

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Özet

Mesane lezyonlarının büyük çoğunluğu, papiller ve/veya düz görünümlü ürotelyal neoplazilerdir. Ürotelyal tümör dışındaki neoplaziler oldukça nadirdir. Paragangliomalar, sempatik gangliyon veya kromafin hücre kaynaklı katekolamin salınımı yapan nadir görülen tümörlerdir. Paragangliomaların yaklaşık %10'u adrenal dışı bölgede görülür, bunun %10'u mesanede izlenir ve tüm mesane tümörlerinin %0.05'ini oluşturur.

42 yaşında kadın olguda, mesane sol anterolateralinde, lümene protrüde 50x43 mm boyutlarında santrali nekrotik, periferinde vaskülarite artışı olan solid kitle görüldü. Dış merkez ve hastanemizde yapılan mesane tümörünün transüretral rezeksiyon materyeline ait örnekler patolojide incelendi ve paraganglioma tanısı aldı. Nadir görülmesi ve ürotelyal karsinom ile karışabilmesi nedeniyle mesanede tümörlerinde paraganglioma her zaman akılda tutulmalıdır.

Anahtar Kelimeler: mesane, paraganglioma, ekstra adrenal

Abstract

Objective: The majority of bladder lesions are papillary and/or flat-appearing urothelial neoplasms. Neoplasms other than urothelial tumors are extremely rare. Paragangliomas are rare catecholamine-releasing tumors of sympathetic ganglion or chromaffin cell origin. Approximately 10% of paragangliomas occur in the non-adrenal region, of which 10% are seen in the bladder and constitute 0.05% of all bladder tumors. About 10% of paraganglioma occur in extra-adrenal sites, of which, 10% are located in bladder wall accounting for 0.05% of all bladder tumors.

In a 42-year-old female patient, a mass on the anterolateral wall of the bladder, measuring 50x43 mm solid mass protruding into the lumen with necrotic center and increased vascularity on the periphery was reported. The specimens of the, transurethral resection bladder material obtained from an external center and our hospital were examined by pathology and diagnosed as paraganglioma. Because of its rarity and confusion with urothelial carcinoma, paraganglioma should always be recognized when dealing with bladder tumors.

Keywords: bladder -paraganglioma -extra adrenal

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INTRODUCTION

The majority of bladder lesions are papillary and/or flat-appearing urothelial neoplasms. Neoplasms other than urothelial tumors are extremely rare (1). Rare tumors may be misdiagnosed because they morphologically resemble urothelial neoplasia. Bladder paraganglioma is an example. Paragangliomas are catecholamine-releasing tumors originating from sympathetic ganglia or chromaffin cells. They are more common in women and in the 3rd-4th decade (2). About 10% of paraganglioma occur in extra-adrenal sites, of which, 10% are located in bladder wall accounting for 0.05% of all bladder tumors (3,4). Approximately 200 bladder paragangliomas are reported in the English literature by 2017 (5).

Nearly half of paraganglioma cases are associated with hereditary conditions. Among bladder tumors, hereditary tumors have a very high incidence. Hypoxia (SDH, VHL, EGLN1, EGLN2), WNT pathway (SCSDE1, MAML3), kinase signaling pathways (RET, TNEM127, HRAS, NF1) and MAX mutation-related genes are involved in hereditary cases (4, 6). Histopathologic examination is essential for clinical diagnosis. Although prognosis for bladder paragangliomas is excellent, about 15% of these cases are capacity to metastasize. The World Health Organization recommends the use of the term “potential to metastasize” instead of “malignant” in paraganglioma in the initial diagnosis as in other neuroendocrine tumors. Indicators for potential metastatic disease includes young age, bulky tumor, and a micturition-induced sympathomimetic attacks, vascular invasion or SDHB mutation (4). Paraganglioma may show muscle infiltration in the bladder and is not a criterion for malignancy.

The diagnosis of malignancy in paraganglioma is finalised when it metastasizes to the lymph node and other organs (3).

Paragangliomas of the urinary bladder can mimic urothelial carcinomas and misdiagnose. In this article, we will discuss the important morphological, clinical, and immunohistochemical studies in differential diagnosis.

CASE REPORT

A 42-year-old woman's bladder biopsy with two paraffin blocks and H&E stained slides were sent to our laboratory for consultation. Since the diagnosis of invasive urothelial carcinoma in the first center was not compatible with her clinical presentation, a second opinion was requested. It was diagnosed paraganglioma by histopathologic and immunohistochemical examination. The patient presented to the urology outpatient clinic with paraganglioma report. It was learned that she had painless coagulated hematuria which started 2 months ago, thyroidectomy 2 years ago and 30 pack years of smoking. Physical examination and system examination were unremarkable. Ultrasound scan demonstrated a mass on the anterolateral wall of the bladder, measuring 50x43 mm solid mass protruding into the lumen with necrotic center and increased vascularity on the periphery was reported. Intravenous pyelography showed bilateral orifices with natural appearance. A solid tumoral formation was seen adjacent to the left orifice extending to the left side wall and bladder neck. Enhanced computed tomography with contrast (CT) (Figure 1) revealed a solitary, low-density lesion located on the left wall of bladder, with a size of 50x43 mm. In laboratory tests, plasma normetanephrine was also significantly elevated (520.9 pg/mL, reference < 200 pg/mL). Other laboratory findings were unremarkable. Since the tumor was observed, transurethral resection bladder (TUR-B) was planned. During trans-urethral resection, the patient became severely hypertensive. Therefore, TUR-B could not be completed effectively. After 2 months, the control TUR-B was planned. The second TUR-B could not be full completed either because of the tumor size.

Microscopic Findings

15 cc curetted tissues were followed up on 8 cassettes. In the sections examined, a tumor was observed separated into islets with thin fibrous septae, containing thin-walled vascular structures, consisting of large polygonal, central nucleus, salt-pepper pattern,

thin chromatin, amphibolic cytoplasm, and cells with marked pleomorphism. Mitosis and atypical mitosis were not observed. The tumor was seen to be nested in the muscle tissue and invaded in a nodular pattern.

The tumour cells stained strongly positive for chromogranin a (Ventana,mouse antibody, Clone: LK2H10), synaptophysin (Ventana,rabbit antibody, Clone: MRQ-40), gata3 (Ventana, mouse antibody, Clone: L50-823), S100 (Ventana, mouse antibody, Clone: 4C4.9) protein high lights sustentacular cells and negative for, cd10(Ventana,rabbit antibody, Clone: SP67), inhibin (Ventana, mouse antibody, Clone: R1), panck (Ventana, mouse antibody, Clone: AE1/AE3/PCK26), p63 (Ventana, mouse antibody, Clone: 4A4).

Ki67 (Ventana,rabbit antibody, Clone: 30-9) stained approximately 1% positive. Further there was loss in succinate dehydrogenase A (SDHA) (Dako,mouse antibody, Clone: F2) immunohistochemically.

Control TUR-B material sent two months after these biopsies showed nodular tumor infiltration in the muscularis propria and dysplasia was not observed in the surface epithelium. In immunohistochemistry, tumor cells stained diffusely positive with chromogranin a, synaptophysin, gata3. The patient was contacted later. It was learned that she underwent partial cystectomy in an external center and the diagnosis was confirmed in the material of that operation. The patient is alive and healthy for 5 years.



Figure 1. CT. This images showed 50 mm × 43 mm low-density mass on the left side of the bladder with clear edges, and Calcium density shadow was seen inside

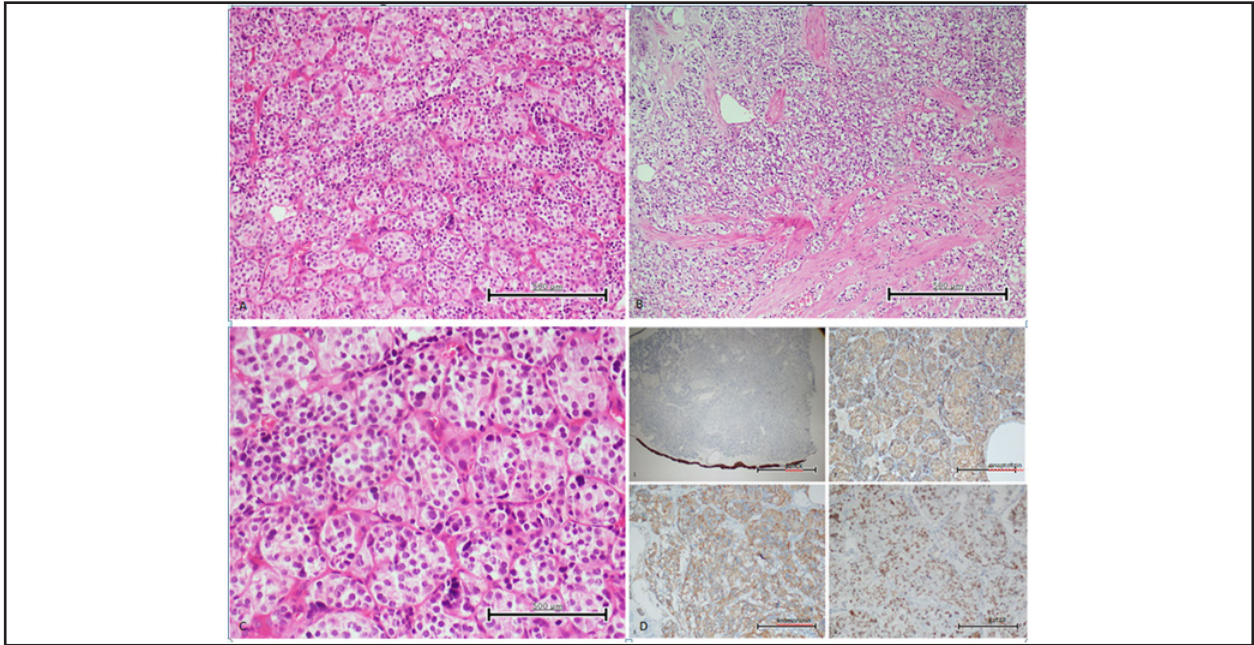


Figure 2. A-H&E 40x, “zelballen” islets. B-H&E, 40x, Tumor cells between detrusor muscle bundles. C-H&E, 400x, Tumor cells with thin chromatin and amphibolic cytoplasm D -1-4: 40x, panck, synaptophysin, chromogranin a, gata 3

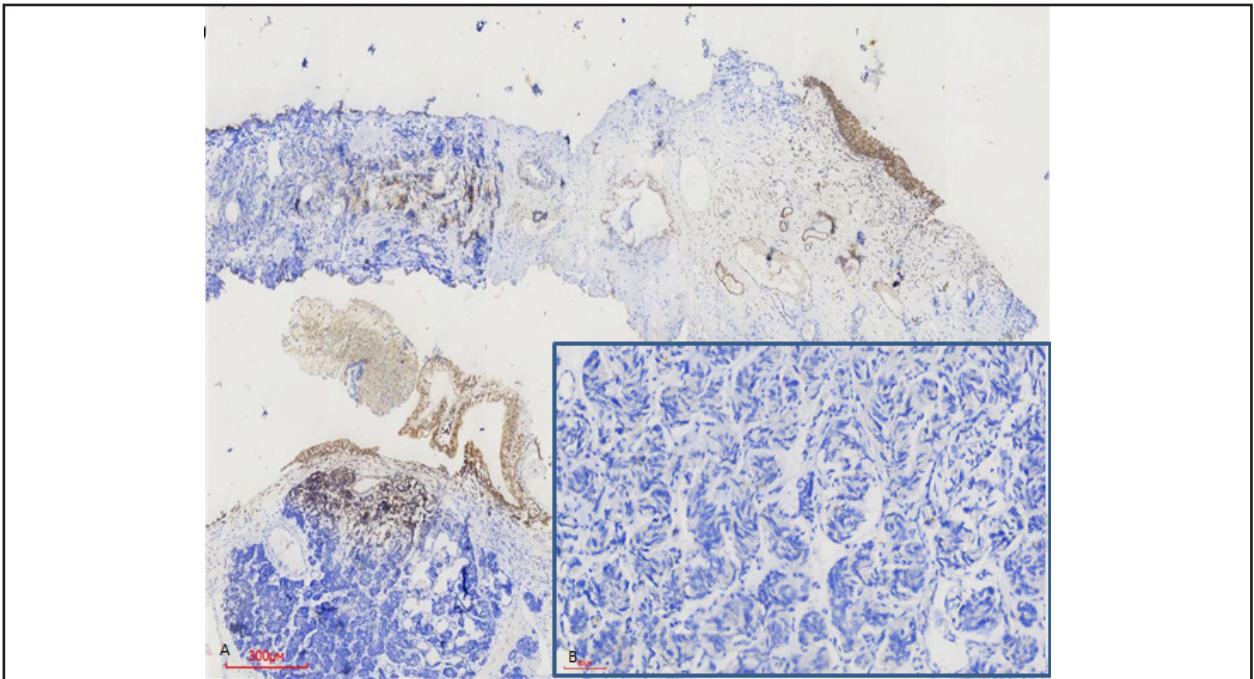


Figure 3. SDHA immunohistochemistry. A- x40 immunostaining for SDHA showing absent cytoplasmic labelling but retained granular cytoplasmic labelling in normal urothelial epithelium and endothelial cells (internal positive control) B- x400 The tumor negative for SDHA

DISCUSSION

The histopathologic differential diagnosis of bladder paraganglioma is quite broad; first of all, it is critical to exclude urothelial carcinoma.

In addition, cautery artifact, which is frequently encountered in cases of transurethral resection, may obscure the structural and cytologic features of paraganglioma.

Cases misdiagnosed as urothelial carcinoma have been reported in the literature because paraganglioma also shows features such as diffuse growth, necrosis, and infiltration of muscle bundles (7).

It may be confused with nested variant urothelial carcinoma because of their nest structures; therefore, zellballen structures are very helpful in diagnosis.

Tumor cells with large cytoplasm in paraganglioma may also be confused with urothelial carcinoma, clear cell variant (8, 9). Paraganglioma have muscularis propria invasion without a desmoplastic reaction. In urothelial carcinomas, a stromal reaction is expected to accompany muscle invasion. Sometimes pleomorphic or bizarre cells that are considered neuroendocrine atypia can be observed in paraganglioma. These cells can be confusing for urothelial carcinoma, but the absence of mitosis supports the diagnosis of paraganglioma.

The distinction between paraganglioma and urothelial carcinoma is extremely important because of the different treatments. Nowadays, for non-muscle invasive urothelial carcinomas, intravesical chemotherapy using with epirubicin, mitomycin C, adriamycin, and gemcitabine, intravesical bacillus Calmette-Guerin (BCG) immunotherapy, re-TUR-B, and cystoscopic follow-up are commonly performed, whereas for localized muscle-invasive urothelial carcinoma requires more aggressive treatment in form of radical cystectomy or chemotherapy and radiotherapy. TUR-B/partial cystectomy with complete removal of tumor is treatment of choice in paraganglioma, even if the muscles are infiltrated. Chemotherapy and radiotherapy may be required in rare metastatic paraganglioma on the other hand treatment modalities for urothelial carcinoma are

dependent on the stage of the disease (2, 5).

The differential diagnosis includes metastatic renal cell carcinoma (RCC), prostate cancer, malignant melanoma, carcinoid or other neuroendocrine tumors and granular cell tumor (2, 7).

RCCs are usually morphologically distinct from paraganglioma, although they show an intertwined growth pattern, thin vascular septa and sometimes granular cytoplasm.

In men, prostate adenocarcinoma may exhibit a nested, island tumor appearance, especially in pattern 4. It may contain nuclei with a uniform, monotonous appearance. However, nuclei with prominent nucleoli are typical. Melanoma can mimic many tumors, including paragangliomas. Paragangliomas may be confused with S100 positivity and melanin pigment. Carcinoid and other neuroendocrine tumors typically have a zellballen-like insular pattern. It is differentiated from paraganglioma by nuclear morphologic features and Panck negativity.

Granular cell tumor may morphologically resemble paraganglioma. However, it is positive for S-100 and negative for neuroendocrine markers.

Our patient also had a history of thyroidectomy, whose diagnosis we could not reach. Metastatic disease of the bladder accounts for less than 1% of all bladder neoplasms. Follicular thyroid carcinoma metastases to the lung and rarely to the liver and kidneys. Lymph node metastasis is common in papillary carcinomas of the thyroid. Differentiation from thyroid carcinoma metastasis is not difficult with the help of morphologic features and immunohistochemistry (10).

The age and gender of the present case are consistent with the mean age and female predominant gender reported in the literature (2, 9). Extra-adrenal paragangliomas are most commonly found in the head and neck region and are nonfunctional. When located in the bladder, it is observed on the lateral wall and frequently in the trigone region with a mean diameter of 2 cm. In our case, the tumor was localized on the lateral wall, but the largest tumor diameter was 5 cm (5). Frequently reported symptoms are painless hematuria and flank pain, which were also observed

in our case (3). Histomorphologically, the zelballen pattern, which is most commonly observed, and the absence of atypical mitosis are compatible with the histomorphologic findings in our case (7).

In cases with paraganglioma, genetic examination is recommended for patients under the age of 50 years, with a family history, bilateral, multifocal and extra-adrenal localization, since the hereditary incidence in tumors is quite high (4). There was no family history in our patient. Because of his age and the location of the tumor in the bladder, he was referred to an external center for genetic examination.

CONCLUSION

Urinary bladder paraganglioma is a rare entity. Although it has characteristic histologic and immunohistochemical features, it is often mistakenly diagnosed as urothelial cancer because of its morphology overlapping with urothelial cancer and pathologists' failure to include paraganglioma in the differential diagnosis of bladder tumors.

In summary, treatment approaches for paraganglioma and urothelial carcinoma are very different from each other; therefore differential diagnoses should be made carefully.

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An Unusual Presentation of Penile Kaposi's Sarcoma in an HIV-Negative Patient with a Circumcised Penis

HIV Negatif ve Sünnetli Bir Hastada Penil Kaposi Sarkomunun Olağandışı Prezantasyonu

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Özet

Kaposi sarkomu (KS), esas olarak ekstremiteelerde ortaya çıkan multifokal hemorajik bir sarkomdur. Penisle sınırlı KS nadirdir ve genellikle edinilmiş immün yetmezlik sendromu (AIDS) ile ilişkilidir. KS'nin penisteki klinik prezantasyonu ve seyri değişkenlik göstermektedir. Burada glans peniste primer maküler lezyon saptanan KS'nin klasik formu olan 27 yaşında bir erkek hastayı sunuyoruz. Daha ayrıntılı değerlendirmelerde immün baskılama veya hastalığın sistemik tutulumuna dair hiçbir kanıt bulamadık. Cerrahi eksizyon uygulanan hastada nüks olmadı ve takibe alındı.

Anahtar Kelimeler: HHV-8, Kaposi sarkomu, Penil nodül

Abstract

Kaposi sarcoma (KS) is a multifocal hemorrhagic sarcoma that occurs mainly in the extremities. KS limited to the penis is rare and usually associated with acquired immunodeficiency syndrome (AIDS). The clinical presentations and courses of KS in the penis demonstrate variability, with limited reports of non-HIV-related primary KS. Herein, we present the case of a 27-year-old male patient with a classic form of KS who had a primary glans penile macular lesion. In more detailed evaluations, we found no evidence of immunosuppression or systemic involvement of the disease. There was no recurrence in the patient who underwent surgical excision, and he was followed up.

Keywords: HHV-8, Kaposi sarcoma, Penile nodule

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INTRODUCTION

Kaposi sarcoma (KS) is a rare angioproliferative disease of the vascular endothelium. KS is a malignant tumor originating from lymphatic endothelial cells. Its close relationship with Human Herpesvirus 8 (HHV-8) infection was demonstrated in 1994 (1). Classical (sporadic), endemic (usually in seronegative individuals for Human Immunodeficiency Virus (HIV) in Africa), epidemic (associated with AIDS), iatrogenic (iatrogenic immunodeficiency as in organ transplant recipients), and non-epidemic (homosexual, HIV seronegative, non-immunocompromised men) are the five types of KS (2). The lesions are asymptomatic, with brown-red, purple, or blue patches, plaques, and nodules located on the lower extremities, especially the ankle and soles (2). Penile KS usually occurs in HIV-positive patients (3). Herein, we present a rare HIV-negative primary penile KS.

CASE REPORT

A 27-year-old male patient, identified as heterosexual, visited the clinic with a painless, purplish nodular lesion in the vicinity of the urethral meatus on his penis, which he had noticed approximately three months earlier. The patient was sexually active and did not have any suspicious sexual intercourse. He had no known illnesses and was circumcised.

On physical examination, a 5 × 4 mm lesion adjacent to the glans penis area was palpated (Figure 1a). No lymph nodes were observed in the inguinal region. The complete blood count, blood biochemistry, and urinalysis results were normal. Enzyme-linked immunosorbent test (ELISA) serology results were negative for *Treponema pallidum* and HIV.

The abdominal ultrasonography and chest radiography findings were normal. A complete surgical excisional biopsy of the lesion was performed using boundary control (Figure 1b). Histopathological examination of the biopsy specimen revealed spindle cell proliferation and sieve-like vascular enlargement in the dermis.

Histopathological examination revealed a dermal tumor consisting of extravasated red blood cells and intersecting spindle cell fascicles arranged around slit-like vascular cavities, mixed with scattered inflammatory cells. ETS-related gene (ERG) and HHV 8 expression was observed, and PanCK expression was negative (Figure 2). The surgical margins were negative. The distance of the tumor to the surgical margin was 3 mm at its closest point. The patient was not prescribed a systemic treatment. Following a 3-month follow-up, no recurrence of the disease was observed (Figure 1c).

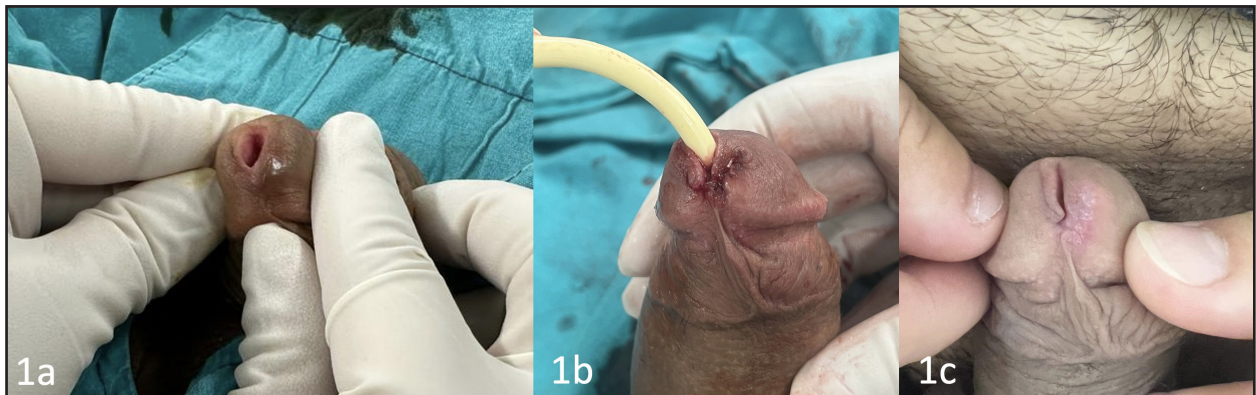


Figure 1a. A purplish macular lesion on the ventral side of the glans penis. **1b.** View immediately after excision of penile lesion. **1c.** Third-month postoperative view.

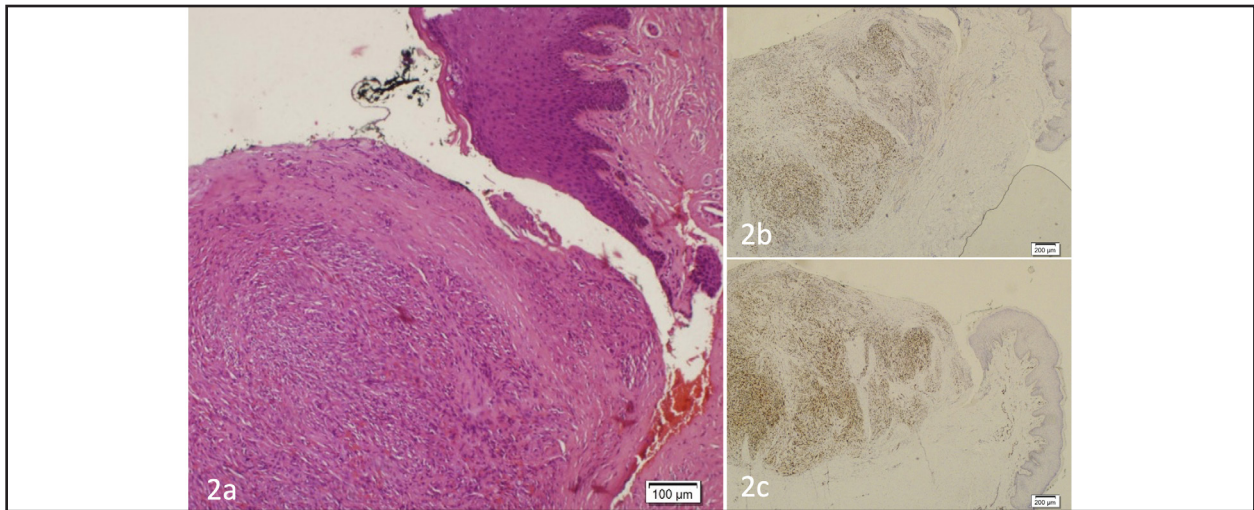


Figure 2a. Spindle cell proliferation with intracytoplasmic lumen containing red cells. **2b.** Neoplastic cells are strongly positive for human herpes virus type 8 latent nuclear antigen 1. **2c.** Positive staining for ERG

DISCUSSION

Kaposi sarcoma was first described by Moritz Kaposi in 1872 and is called 'multiple benign pigmented idiopathic hemorrhagic sarcoma' (4). KS is a multifocal angioproliferative disease originating from endothelial cells (5). The primary symptom is plaque or nodular structures, which appear especially on the skin of the extremities and, to a lesser extent, on other organs. A pathological diagnosis can usually be made using conventional hematoxylin and eosin (H&E) staining. Vascular proliferation in the dermis shows some characteristic features, such as an increase in the number of vessels without endothelial cell coating, the presence of extravasated blood, and the expression of endothelial markers by spindle cells (5). This multicentric angioproliferative disease, which mainly involves the skin, rarely causes mucosal or internal involvement (6). Although genital lesions are seen in 20% of KS cases, only 3% have a primary localized lesion in the glans penis, as in our case (3,6).

Kaposi sarcoma is most commonly associated with Acquired Immunodeficiency Syndrome (AIDS). In the literature review, involvement was the first sign of HIV and AIDS in very few of the patients presenting with KS involving the penile region (7). In the case

published by Tammam et al. in 2022, a 35-year-old male patient was admitted to the hospital with an ulcerated penile lesion and systemic findings. After receiving antiviral and antibacterial treatment for a while, the patient who remained without follow-up and had low treatment compliance died in a metastatic state shortly after diagnosis despite surgery (7).

Primary KS of the penis may also occur even more rarely in HIV seronegative patients, as in our case. The first case of solitary penile KS with HHV8 positivity in an HIV seronegative patient was published by Morelli et al. in 2003 (8). Another publication in which cases with primary penile involvement are evaluated belongs to Cito et al. evaluated 33 cases of KS where the penis was the first site of origin. According to epidemiological evidence, there is a strong association between disease pathogenesis and HHV-8 infection. Most patients with penile KS had positive results in serology HHV-8 research. (9). Our case supports the literature in this respect.

Kaposi sarcoma is more common in men, with a reported male/female ratio of 3:1. Few cases have been reported in individuals under 50 (10). Our patient is unusual because of his young age. Primary penile KS clinical course is variable, but local recurrence

is rare. There is no standard treatment method for primary penile KS. In the literature, some cases underwent local surgical excision, radiotherapy, laser treatment, and chemotherapy (3,9). To date, there has been no standardized follow-up. In general, local recurrences are rare if the primary tumor is completely removed (9).

CONCLUSION

Although penile Kaposi sarcoma is a rare condition in HIV-negative men, it should be considered in the differential diagnosis and treatment of nonspecific lesions in the penis. A rare presentation of KS may present as a single lesion on the penis without any known risk factors. Therefore, histological evaluation is recommended for patients with penile lesions. The treatment should be customized according to the clinical and immunological status of the patient.

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Informed Consent: Written informed consent was obtained patient who participated in this case.

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Hemodialysis Vascular Access and Care

Hemodiyaliz Damar Erişim Yolları ve Bakımı

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Özet

Hemodiyaliz böbrek yetmezliğinin tedavisinde en yaygın kullanılan tek yöntem olmaya devam etmektedir. Hemodiyalizdeki yaşam süresi ve kalitesi, diyalizin kalitesiyle doğru orantılıdır ve bu kalite de hastanın damar erişim yolunun güvenilirliğine ve bütünlüğüne bağlıdır. En ideal damar erişim yolu, diyalizi uygulamak için güvenilir, komplikasyonsuz erişim sağlayan ve aynı zamanda hastanın ihtiyaçlarına uygun olmalıdır. Son altmış yıldır hemodiyaliz vasküler erişim seçenekleri büyük ölçüde değişmemiştir ve arteriovenöz fistül (AVF) tercih edilen erişim olmaya devam etmektedir.

AVF, hemodiyaliz için klinik uygulama kılavuzlarında önerilen ve tercih edilen vasküler bir girişim olmasına rağmen tromboz, hematoma, ödem, periferik iskemi, kanama ve enfeksiyon gibi ciddi komplikasyonlarda gelişebilmektedir. Bu komplikasyonların önüne geçilmesinde hastalara AVF bakımına ilişkin eğitim verilmesi son derece önemlidir. Bu derleme hemodiyaliz hastalarına bakım veren sağlık çalışanlarına rehber olması için hazırlanmıştır.

Anahtar Kelimeler: Damar yolu, hemodiyaliz, arteriovenöz greft, santral venöz kateter, arteriovenöz fistül, bakım, eğitim

Abstract

Hemodialysis remains the most widely used method for treating renal failure. Life expectancy and quality in hemodialysis are directly proportional to the quality of dialysis, and this quality depends on the reliability and integrity of the patient's vascular access route. The ideal vascular access route provides reliable, uncomplicated access to dialysis and is also suitable for the patient's needs. Hemodialysis vascular access options have not changed substantially over the past six decades, and arteriovenous fistula (AVF) remains the access of choice.

Although AVF is a vascular intervention recommended and preferred in clinical practice guidelines for hemodialysis, it can develop into serious complications such as thrombosis, hematoma, edema, peripheral ischemia, bleeding, and infection. To prevent these complications, it is extremely important to educate patients about AVF care. This review has been prepared as a guide for healthcare professionals who care for hemodialysis patients.

Keywords: Vascular access, hemodialysis, arteriovenous graft, central venous catheter, arteriovenous fistula, care, education

INTRODUCTION

Chronic renal failure (CRF) is a progressive and irreversible kidney damage characterized by a decrease in glomerular filtration rate (GFR), the inability to adjust the fluid-electrolyte balance of the kidneys, the inability to fulfill their endocrine functions, and deterioration in metabolic activities. The prevalence of CRF continues to increase in our country and all over the world (1-3).

Renal replacement therapy (RRT) methods are used in the treatment of CRF; hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KT)(1-3). According to the 2021 data from the Turkish Society of Nephrology (TNS), 70% of CRF patients were treated with central HD, 1.3% with home hemodialysis (HHD), 4% with PD, 24% with KT treatment. As can be seen from the usage rates, HD treatment is the most frequently used one among RRT (4).

An intravenous line, dialyzer containing dialysis membrane, dialysate fluid, and dialyzer are, required for HD treatment. The systems that allow the blood to be drawn into the machine for HD treatment are called vascular access. For HD application, a vascular intervention is required for temporary or permanent use. To emphasize the importance of vascular access for hemodialysis patients, analogies are made as “life path”, “the indispensable part of hemodialysis” and “Achilles tendon” (1-3).

1. Temporary vascular access

Temporary catheters are preferred in patients who need urgent HD and short-term dialysis treatment. It is usually inserted under local anesthesia and accompanied by ultrasound, and the patient can be dialyzed immediately after the procedure. Catheters used for temporary use for hemodialysis can be single or double-lumen.

Frequently preferred sites for inserting a venous catheter percutaneously are the subclavian, femoral, and internal jugular veins. Catheter placement in the internal jugular vein is gaining popularity and is preferred especially in children. The femoral vein

is a good choice for very short-term hemodialysis, hemoperfusion, and plasmapheresis treatment (3,5,6).

1.1. Single lumen catheters

Blood taken from the patient is returned to the patient through a second catheter after passing through the dialyzer, or the blood drawn in the first phase is returned to the patient in the same way in the second phase with the Y adapter connected to this single lumen catheter (3,5,6).

1.2. Double-lumen catheters

Double lumen hemodialysis catheter contains two separate cannulas in a single body, the arterial end is at the more proximal and side wall of the catheter. After the blood taken from this end and passed through the dialyzer with the pump of the hemodialysis machine is cleaned, it is returned to the body with the venous part at the distal end of the catheter (3,5,6).

Use and care of the catheter

The absence of catheter infections in hemodialysis units is one of the important indicators of quality patient care. Catheter dressing is one of the main factors in the prevention of catheter infections. An ideal catheter dressing; should be sterile, protected against contamination, keep the catheter site dry, not allow colonization, be non-irritating, be aesthetic and comfortable, be easy to insert and remove, allow the access area to be evaluated, be secure, easy to fix and be economical. Catheter care should pay attention to the following points (3,5,6).

- Ultrasonography support should be used as much as possible to reduce the complications that may develop while inserting the catheter and to increase the chance of success.
- The catheter exit site should be checked for infection at the end of each dialysis, the dressing should be done, and if the suture is dislodged, stitches should be placed again. If possible, fixation should be made with transparent and airtight dressings.
- The skin entry dressing should be changed by

- wiping every 2-5 days.
- After each use, both lumens of the catheter should be flushed with heparinized SF (100U/ml).
- When not in use, they should be washed every other day or at least every other day.
- Excessive use of heparin may lead to the risk of bleeding. Before each dialysis, both lumens should be aspirated to remove any soft clots that may form and remove residual heparin.
- The patient should take a bath without wetting the catheter. If the skin entry dressing gets wet during bathing, it should be changed immediately.

2. Permanent vascular access

Permanent vascular access is preferred in longer-term HD procedures. The most preferred vascular access route in patients undergoing chronic hemodialysis treatment is the AVF (1,2,3). According to the report of the TNR, the preferred vascular access routes in 2021 are; 72.44% were arteriovenous fistula (AVFs), 0.96% were arteriovenous graft (AVGs), 23.63% were indwelling (tunneled) catheters, and 2.97% were temporary (un tunneled) catheters (4).

2.1. Arteriovenous Graft

It is a method used in patients who do not have the appropriate vascular anatomy for AVF opening. Mostly synthetic grafts made of polytetrafluoroethylene are used. It is placed subcutaneously between an artery and a vein (1-3).

2.2. Arteriovenous Fistula (AVF)

AVF is the creation of an anastomosis with a surgical operation between a suitable artery and a most suitable vein. The most commonly used and most preferred site for AVF is between the radial artery and the cephalic vein at the wrist level. Alternative arteriovenous fistula sites are the ulnar artery and the basilic vein, the brachial artery and the cephalic or brachial vein, and the femoral artery and the saphenous vein. When opening the AVF, the patient is started from the most distal, if the attempt is unsuccessful, it is climbed higher. AVF is usually

created in the non-dominant arm. Thus, there is no restriction on the functional arm (1,2,3,5).

2.2.1. Creation of AVF

It is possible to provide approximately 200-300 ml/min blood flow through the fistula by using peripheral veins. Following local anesthesia, a skin incision is made. The artery is carefully released under the fascia and suspended with thick 2nd silk. The vein is located under the skin, it is released and suspended. 1 mg/kg of heparin is given systemically through the liberated vein or from another vein. After the artery and vein are closed with atraumatic vessel clamps, the artery, and vein are opened vertically so that the vein rests on the artery. In the created anastomosis, a fistula is formed by coming to the side of the artery and vein or by coming over the artery to the end of the vein. The passage of current through the fistula is visually noticeable and a thrill (vibration) is felt over it with the finger. The turbulence of the high flow on the vessel wall creates a thrill. The absence of a thrill indicates that the vein is not filling and that there may be a technical error that needs to be sought (1,2,3,5).

2.2.2. Postoperative care of AVF

The hand is held up so that it remains above the level of the heart. The fistula is thrilled and a murmur is looked for using a stethoscope. If there is no murmur, the fistula is closed. If there is a murmur and no thrill can be heard, it is expected that the blood flow through the fistula will increase over time and the fistula will mature (1,2,3,5).

2.2.3. Using the AVF

After the fistula is created, a period of approximately 1-2 months is waited for the fistula to mature. It is generally unsuitable for use before this time, but it is often used earlier in practical practice. If the patient requires urgent dialysis during this waiting period, a temporary vascular access route may be provided.

Two needles are used in the AVF entrance. The blood that will go to the machine is taken from the inlet close to the anastomosis area, and the blood

returning from the machine is given to the venous circulation from the far line. The arterial line is placed 3 cm away from the fistula and the vein line is placed 5 cm away from the arterial line. Thus, recirculation is minimized. For patients with pain sensitivity, it is recommended to apply local anesthetic creams locally before HD.

During HD, patients should be evaluated and monitored for AVF complications (bleeding, thrombosis, venous stenosis, venous hypertension, infection, insufficient flow, high-flow fistula, hand ischemia, etc.). Patient education is extremely important in the management of AVF complications. Training on AVF care should be given to patients regularly and systematically (1,2,3,5).

2.2.4. Complications of AVF

Although AVF is a vascular intervention recommended and preferred in clinical practice guidelines for hemodialysis, it can develop into serious complications such as thrombosis, hematoma, edema, peripheral ischemia, bleeding, and infection. AVF complications constitute a rate of 16-23% among causes of death and hospitalization in HD patients. To prevent these complications, educating patients about AVF care is extremely important. In addition, the AVF opening should not be left until the last months. The fistula must be opened early to allow time for the fistula to mature and to learn to live with the AVF a few months before undergoing HD. In the follow-up of AVFs, a multidisciplinary team consisting of a nephrologist, surgeon, education and hemodialysis nurse should work together (5-11).

Insufficient flow: Insufficient blood flow for dialysis results in increased recirculation percentage and ineffective dialysis. The most common cause of insufficient flow is a partial obstruction in the venous tract due to fibrosis caused by frequent needles inserted. Lesions that can be corrected are repaired surgically or by balloon angioplasty. In addition, patients should be routinely examined every month, AVF blood flow should be checked during the

examination, and training should be repeated for AVF care and protection (5,6).

Thrombosis: The cause of thrombosis seen in the early period is often technical error and requires surgery. During HD, thinning of the wall as a result of using the same site at the entrance of the AVF causes aneurysm formation and can lead to embolism and thrombosis if not treated. Clot formation seen in the late period is often the result of weak flow. Removal of the clot can be done surgically or medically with thrombolytic drugs (9-11).

Venous Hypertension: Exposure of the venous system to high pressure and high flow after fistula operation causes mild venous stasis findings. The flow load from the artery side to the vein side in the distal fistula causes an increase in venous pressure in the distal fistula. If venous hypertension does not resolve spontaneously, the vein distal to the anastomosis should be ligated or rotated to the end position on the anastomosis vein side (1,4,6).

Neuropathy and Ischemia in the hand: In patients who develop arterial insufficiency or steal syndrome, pain, coldness, numbness, and sometimes motor dysfunction in the hands and fingers occurs in the distal extremity. In patients with diabetes or atherosclerosis, whose circulation was not good before, pain, coldness, the feeling of coldness, and non-healing ulcers in the hand should suggest ischemia. If ischemia develops due to the steal phenomenon, it is transformed from the edge position to the end anastomosis in the arterial par and palmar circulation is provided with the ulnar artery. Carpal tunnel syndrome due to peripheral nerve lesion develops in a small number of patients with fistulas at the wrist level. The treatment is the surgical release of the nerve (2,5,12,14).

Infection: Infection can be transmitted by not paying attention to sterility while performing fistula surgery, keeping non-sterile materials in the operating environment, and also from areas where needles are

inserted. Local and systemic blood culture samples should be taken and antibiotics effective against staphylococci should be used in the treatment. For HD, the body's barriers to infection are crossed during each cannulation. Therefore, it is extremely important to comply with aseptic techniques (1,4,5).

Congestive heart failure: HD is a procedure performed directly on the circulatory system, and with it, the cardiac output is loaded approximately 200-500 ml/min during dialysis. Although there is no serious deterioration in heart functions with long-term follow-ups, the increase in cardiac output may cause congestive heart failure in elderly people and people with heart disease. Treatment is surgical narrowing or taping to reduce fistula flow. In HD patients, heart failure may develop due to reasons such as anemia, HT, and fluid overload. Sometimes it is difficult to determine whether the heart failure is due to the fistula or other causes (10-12).

2.2.5. Patient Education for AVF Care

The adequacy of an AVF is directly proportional to its openness to allow long-term hemodialysis, the low number of complications, and its easy applicability. It is extremely important that the patients are constantly supported by the HD team and that their training needs are met so that they can adapt to the opening of the AVF, its readiness for use, and the adaptation to the continuous use process (15-19).

In studies examining the fistula care knowledge level of HD patients in the literature, it has been determined that the knowledge level of patients about fistula care is not at the desired level in general and that training should be given to provide patients with self-care knowledge and behaviors (23-25).

Alizade et al. (20) and Sousa et al. (21) provided education to patients to improve the fistula care behaviors of hemodialysis patients, and it was found that education improved the fistula health behaviors of hemodialysis patients. Köse et al. (22) determined that fistula self-care behavior is effective in the development of complications and recommended

that patients be supported with education programs about fistula complications. These results reveal the importance of patient education. The following topics should be included in the education to be given to the patients.

- The new fistula should be kept in elevation (arm above the heart level).
- The arm exercises that should be done for a newly opened fistula are exercises such as plastic ball squeezing exercises.
- Fistula exercises recommended by health personnel should be performed regularly for the fistula to continue to function healthily.
- The thrill, that is, the vibration should be felt at the site of the fistula surgery, and the murmur, the sound from the fistula, should be heard. The fistula should be checked for vibration at least twice a day. In cases where vibration is not felt or heard, the doctor should be informed.
- To prevent infection before coming to the dialysis session, it is necessary to wash the fistula arm with soap and warm water and dry it with a clean towel (if possible, use disposable paper towels). The fistula should be monitored for signs of infection (redness, itching, swelling, increase or decrease in temperature, etc.). If there is a sign of infection, you should go to the health institution immediately.
- Behaviors that will pressurize the fistula should be avoided. Some of these behaviors are; These are behaviors such as lying on the fistula arm while sleeping, wearing clothes that will tighten the arm, and wearing bracelets, wristwatches, or jewelry. These behaviors damage the fistula by obstructing blood flow.
- Check if your hand changes in temperature and color on the arm on the side of the fistula every day.
- It is necessary not to perform an invasive procedure from the fistula arm, not to take blood, and not to measure blood pressure, even for therapeutic purposes.
- Heavy work should not be done with the fistula arm, and weight should not be lifted above 1 kg.
- Care should be taken in the work done with cutting

and piercing tools, if possible, such work should not be done and the fistula arm should be protected against all kinds of impacts it may be exposed to.

- Apply pressure on the bleeding area against serious bleeding that may occur as a result of the impact, and go to the nearest health institution.
- All kinds of situations that may cause low blood pressure should be avoided to prevent the deterioration of blood flow to the fistula.
- Excessive fluid intake between two dialysis can cause cramps, headache, and chest pain. Therefore, a fluid restriction must be observed.

CONCLUSION

Vascular access routes are an important parameter that affects the quality of life and duration of patients receiving hemodialysis treatment. For this reason, the hemodialysis team should meticulously implement and develop new strategies for the follow-up, care, and patient education processes of vascular access routes.

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The journal's financial expenses are covered by the Eurasian Uro-oncological Association. The journal is published quarterly – three times a year- in February, June and October, respectively and the language of the journal are English and Turkish.

The purpose of the New Journal of Urology is to contribute to the literature by publishing urological manuscripts such as scientific articles, reviews, letters to the editor, case reports, reports of surgical techniques, surgical history, ethics, surgical education and articles of forensic medicine.

The target group of the journal consists of academicians working in the field of urology, urologists, residents of urology and all other fields of expertise and practitioners interested in urology.

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The New Journal of Urology (New J Urol) is a journal published by Eurasian Uro-oncological Association and is published three times a year- in February, June and October.

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