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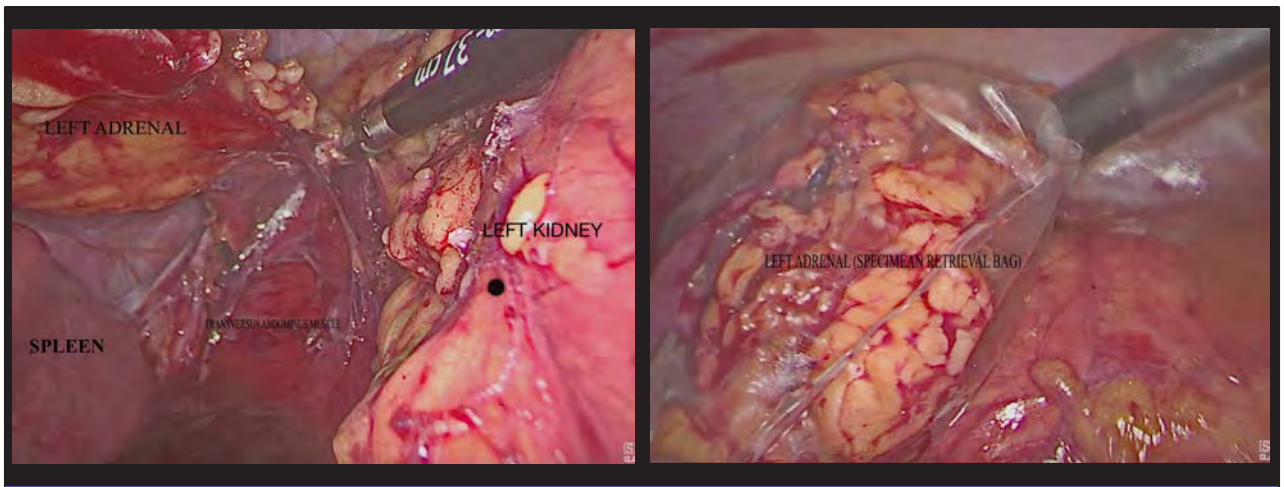

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Dear Colleagues,

We are pleased to have published the first issue of The New Journal of Urology for 2023. This issue includes 14 original articles. Published articles consist of general urology, urooncology and endourology. We believe that all the current articles will be read with interest and these articles are expected to contribute to the literature and serve as a reference for future studies.

The New Urology Journal has been indexed in the TUBİTAK-ULAKBİM TR Index since the first issue of 2011. 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 of high scientific quality and to become one of the most read urology journals. We would like to inform you that only articles in English will be considered for publication.

The editorial team is very grateful to all the authors and reviewers who have contributed to this issue. We are aware that this is a painstaking effort, and we cannot thank you enough for it.

We request that you submit your 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.

Respectfully yours.

Ali İhsan TAŞÇI
Editor-in-Chief

Fatih YANARAL
Editor

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Original Research

EDITORIAL BOARD

Efficacy of tamsulosin versus silodosin as medical expulsive therapy on stone expulsion in patients with distal ureteral stone: A retrospective single center study

Distal üreter taşı olan hastalarda taş düşürmede medikal ekspulsif tedavi olarak tamsulosinin silodosine karşı etkinliği: Geriye dönük tek merkezli bir çalışma

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Özet

Amaç: Bu çalışma ile, semptomatik komplike olmayan distal üreter taşı olan hastalarda medikal ekspulsif tedavi olarak tamsulosin ve silodosinin etkinliği karşılaştırılması amaçlandı.

Gereç ve Yöntemler: Haziran 2019 ile Ocak 2022 tarihleri arasında 4-10 mm boyutlarında distal üreter taşı olan ve medikal ekspulsif tedavi uygulanan erişkin hastaların verileri geriye dönük olarak belgelendi. Hastalar iki gruba ayrıldı. Grup 1'deki hastaları 4 mg silodosin tedavisi verilen ve Grup 2'deki hastaları 0,4 mg tamsulosin verilen hastalar oluşturdu. Tedaviye maksimum 3 hafta devam edildi. Taş düşürme oranı, taş düşürme süresi, taş yükü ve taş boyutu kaydedildi. Yardımcı tıbbi tedavi olarak tamsulosin ve silodosinin etkinliği belirlendi.

Bulgular: Çalışmaya toplam 152 hasta dahil edildi. Demografik veriler iki grup arasında benzerdi. 116 (%76,3) hasta takip sonunda taşsızdı. Grup 1' de 47 hastada (%73,4), Grup 2' de 69 hastada (%78,4) taşın düştüğü hesaplandı (P = 0,477). Çok değişkenli analizde taşın üreterovezikal bileşkeye olan mesafesi, başarılı taş düşürme ile anlamlı şekilde ilişkiliydi (P=0,032).

Sonuç: Distal üreter taşları için medikal ekspulsif tedavi olarak tamsulosin ve silodosin arasında anlamlı bir üstünlük yoktu. Taşın üreterovezikal bileşkeye olan mesafesi, çok değişkenli analizde taş düşürülmesinin tek bağımsız belirleyicisiydi.

Anahtar Kelimeler: Medikal ekspulsif tedavi, üreter taşı, silodosin, tamsulosin

Abstract

Objective: This study aimed to compare the efficacy of tamsulosin and silodosin as medical expulsive therapy in patients with symptomatic uncomplicated distal ureteric stones.

Material and Methods: The data of adult patients who had distal ureteric stones in size between 4 and 10 mm and were treated with medical expulsive therapy between June 2019 and January 2022 were retrospectively documented. Patients were divided into two groups. Patients in Group 1 received silodosin 4 mg, and Group 2 received tamsulosin 0.4 mg. Therapy was given for a maximum of 3 weeks. Stone expulsion rate, time to stone expulsion, stone burden, and stone size were recorded. The efficacy of tamsulosin and silodosin as adjunctive medical therapy was determined.

Results: A total of 152 patients were included in the study. Demographic profiles were comparable between the 2 groups. 116 (76.3%) patients were stone-free at the end of the follow-up. The stone expulsion rate was calculated in 47 patients (73.4%) in Group 1, and 69 patients (78.4%) in Group 2 (P = 0.477). The distance of the stone to the ureterovesical junction was significantly associated with successful stone expulsion in multivariate analysis (P=0.032).

Conclusion: There was no significant superiority between tamsulosin and silodosin as medical expulsive therapy for distal ureteral stones. The distance of the stone to the ureterovesical junction was the only independent predictor of stone expulsion in multivariate analysis.

Keywords: Medical expulsive therapy, ureteral stone, silodosin, tamsulosin

The study was approved by Antalya Training and Research Hospital Ethics Committee (Approval number: 2022-017). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Urolithiasis is one of the most prevalent urological conditions worldwide with increasing incidence (1). Twenty-two percent of all urinary tract stones are located at the ureter and 68% of ureteral stones are found in the distal part (2). Treatment modalities for patients with ureteral stones comprise extracorporeal shock wave lithotripsy (ESWL), endoscopic lithotripsy, and surgical stone removal (open, laparoscopic, and robotic approaches). Conservative management rather than an intervention may reduce the complications of the therapy. Medical expulsive therapy (MET) has proven to be a non-invasive treatment choice and has comparatively inexpensive features for distal ureteral stones in recent years (3). MET is a broad term and consists of plenty of fluid intake and medications such as alpha blockers, calcium channel blockers, corticosteroids, or phosphodiesterase type 5 inhibitors (PDE5i). The objective of MET is to increase the spontaneous stone passage possibility and improve the quality of life by reducing pain. Alpha-1-adrenergic receptors (AR) are highly concentrated in the smooth muscle of the ureter. Blockade alpha-1-AR in the distal part of the ureter decreases basal smooth muscle tonus and produces propulsive antegrade peristalsis that facilitates spontaneous passage and reduces associated renal colic (4). The European Association of Urology (EAU) and the American Urologic Association (AUA) recommend that patients with distal ureteral stones should be offered MET (5,6). However, the results of MET in the treatment of ureteral stones were conflicting with the high-quality trials and meta-analyses (7-9). Additionally, there is a paucity of studies comparing the efficacy of alpha-blockers. MET prescription has been under controversy for distal ureteric stones. Thus, this study aimed to evaluate tamsulosin and silodosin as MET in patients with symptomatic uncomplicated distal ureteral stones.

MATERIAL AND METHODS

Adult patients who presented with renal colic and were diagnosed as uncomplicated distal ureteral stones in size between 4 and 10 mm, and subsequently treated with MET from June 2019 to January 2022 were retrospectively assessed. Ethics Committee approval was obtained at Antalya Training and Research Hospital (Approval number: 2022-017). Exclusion criteria were as follows patients with urinary tract infection, fever, pregnancy, multiple or bilateral ureteral stones, impaired renal function, solitary kidney, history of intake of an alpha-adrenergic blocker due to benign prostatic hyperplasia, and requiring emergency intervention. Patients lost to follow-up and who wished immediate surgical removal of stone were also excluded from the study.

After physical examination, urinalysis, complete blood count, serum creatinine, urinary ultrasonography (USG), and X-ray kidney, ureter, and bladder (KUB) were generally used as the primary diagnostic tools. Non-contrast computed tomography (CT) was performed for all patients to confirm the diagnosis. We prescribed tamsulosin 0.4 mg or silodosin 4 mg once daily for 3 weeks as MET. Additionally, 50 mg/day of diclofenac sodium was prescribed to all patients for pain relief. Patients were instructed to strain their urine to detect stone expulsion and take plenty of fluids. Patients were warned to note the period of stone expulsion. The patients were followed up weekly for 3 weeks and reassessed by physical examination, serum creatinine levels, urinalysis, and USG or X-ray KUB. Medications were continued until the stone passed or up to 3 weeks. The expulsion of the stone was determined based on physically seeing the stone in the urine. Suspicious expulsions or unsuccessful stone passes were verified with a control CT at the end of the 3rd week. Persistent stone at 3 weeks was accepted as an unsuccess of MET. For those patients, endoscopic lithotripsy was performed.

The patients' characteristics (age, gender, and body mass index [BMI]) and the stone features (stone size, stone burden, and the distance of stone to the ureterovesical junction[UVJ]) were noted. The stone size was identified as the maximum diameter of the stone. The stone burden was calculated by multiplying the largest length of the stone by the shortest perpendic-

ular length and was recorded in square millimeters. A clinician (HA), blinded to medications and the clinical outcomes, evaluated all CTs separately.

Two main groups were created according to the medication. Group 1 included patients who were given silodosin 4 mg. Group 2 was prescribed tamsulosin 0,4 mg. Firstly, the stone factors, the stone expulsion rate, and the stone expulsion interval were evaluated for comparison between the two groups. Furthermore, the factors affecting the expulsion rate were evaluated by univariate and multivariate analyses.

Statistical Analysis

The data of the study are presented as mean ± standard deviation, or median and interquartile range (25th - 75th, IQR) according to the type of data. The assumption of normality distribution was evaluated with the Shapiro-wilk test. Student's t-test was used for normally distributed continuous variables. Mann-Whitney U test was used for non-normally distributed continuous variables. Categorical variables are presented as frequency (n) and percentage (%). Chi-squared or Fisher exact test was used for categorical data. Univariable and multivariable binary logistic regression analyses were used to identify the predictive factors of spontaneous passage. A P value of < 0.05 was accepted as statistical significance. All statistical analyses were done using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY).

RESULTS

A total of 152 adult patients who completed the treatment and follow-up period, were included in the study. Group 1 (64 patients) consisted of 51 men and 13 women, and Group 2 (88 patients) consisted of 78 men and 10 women. Table 1 demonstrates the comparison of parameters between Group 1 and Group 2. There were no significant differences between the groups in terms of age, BMI, male to female ratio, stone size, stone burden, and distance to UVJ. (all, p>0.05). Overall 116 (76.3%) patients successfully passed the stone. The stone expulsion interval and spontaneous expulsion rate were also similar between groups. The distance of the stone to the UVJ was significantly associated with a successful stone pass in univariate and multivariate analyses (Table 2).

Table 1. Comparison of baseline characteristics according to groups

Variables	Group 1 (n:64)	Group 2 (n:88)	P value
Median (IQR) age, years	43.5 (36.2-52)	43 (31.7-59)	0.94†
Mean ±SD, BMI, kg/m^2	25.3±2.6	25.1±2.9	0.676ᵀ
Gender (male/female)	51/13	78/10	0.128¥
Median (IQR), maximum diameter of stone, mm	5 (4-7)	5 (4-6.5)	0.399†
Median (IQR), stone burden, mm^2	15 (10-30)	15 (11-26.5)	0.195†
Median (IQR), distance to UVJ, mm	10 (6-14)	8 (5-12)	0.611†
Median (IQR), expulsion time, day	9 (6-13)	9 (6-13)	0.638†
Expulsion rate, n, (%)	47 (73.4)	69 (78.4)	0.477¥

***Group 1**: silodosin, **Group 2:** tamsulosin. **BMI:** Body Mass Index, **SD:** standard deviation, ᵀ: Student's t test*

***IQR:** interquartile range, †: Mann Whitney-u test, **¥:** Chi-Sqaure test*

Table 2. Multivariate analysis of factors affecting the spontaneous passage

					95% C.I. for EXP (B)	
	B	**S.E.**	**P value**	**Exp (B)**	**Lower**	**Upper**
Treatment						
Silodosin	Reference					
Tamsulosin	-.010	.445	.982	.990	.414	2.366
Age, year	.006	.020	.777	1.006	.967	1.046
Gender						
Male	Reference					
Female	.066	.593	.912	1.068	.334	3.410
Stone size, mm	.235	.388	.544	1.265	.591	2.706
Stone burden, mm^2	-.073	.039	.059	.929	.861	1.003
Distance of stone to the UVJ, mm	-.105	.049	**.032**	.900	.817	.991
BMI, kg/m^2	-.127	.098	.196	.881	.727	1.067

DISCUSSION

ESWL, surgical stone removal, and endoscopic lithotripsy are the treatment options for distal ureteral stones. But, these approaches are associated with complications and high costs. Most ureteral stones can pass spontaneously and intervention is usually not required. The spontaneous stone passage rate was reported as 76% for stones 2-4 mm and %75 for distal ureteral stones (10). Therefore, conservative management is a more suitable and cost-effective strategy than active stone removal (11). MET has recently emerged as a conservative treatment for patients with uncomplicated distal ureteral stones. The main aims of MET are to increase the rate of stone expulsion, reduce renal colic pain, and avoid the need for invasive interventions. The EAU and AUA stone disease guidelines recommend the utilization of MET for distal ureteral stones (5,6).

Many medical agents have been used as MET which includes alpha-blockers, calcium channel blockers, corticosteroids, antispasmodics, and PDE5i. Additionally, combination therapies and herbal medicines have been also investigated to improve stone passage (8,12). Alpha-blockers are the most investigated and widely used treatment option. Park et al. demonstrated that alpha-1-ARs were present in all ureters and the distal ureter had a higher density of alpha-1-ARs than the proximal and mid ureter (13). In the distal ureter, the distribution of alpha-1-ARs was α1D > α1A > α1B (14). Blockade of alpha-1-ARs reduces the tone of ureteral smooth muscle, the frequency of peristalsis, intraluminal pressure, and amplitude of the ureter. These effects have been used for promoting stone expulsion (3,7,9).

High-quality randomized controlled prospective studies have reported conflicting results. Several studies reported no significant benefit to alpha-blockers (7,15,16). The others demonstrated that alpha-blockers had a significantly higher stone expulsion rate when compared to placebo (17,18). Despite contradictory results, a recent meta-analysis showed that there was a significantly better expulsion rate and lower mean expulsion time in tamsulosin, alfuzosin, and silodosin groups compared to placebo (19). The success rate for tamsulosin in distal ureteral stones smaller than 10 mm ranges between 50% and 87% (7,9,16,17). The rate of the stone pass in patients who were given silodosin was between 78.6% and 91.4% (18,20,21). In our cohort of patients with unilateral uncomplicated distal ureteral stones managed by silodosin and tamsulosin, we had a successful spontaneous expulsion rate of 73.4% and 78.4%, respectively, the difference being statistically insignificant. Success rates for silodosin and tamsulosin were comparable with the earlier studies.

Hsu et al. conducted a meta-analysis to evaluate the effectiveness of silodosin and tamsulosin as MET for ureteral stones and concluded that silodosin had a significantly better stone passage rate for patients with ureteral stones compared to tamsulosin (22). Furthermore, the findings of another meta-analysis demonstrated that silodosin was the most efficacious alpha-blocker as MET for distal ureteric stones (19). The results of two meta-analyses suggest that silodosin is more effective than tamsulosin for the spontaneous stone pass (19,22). However, in our study, we did not identify a better expulsion rate as MET with silodosin than with tamsulosin. The reason for a similar expulsion rate between silodosin and tamsulosin in our study may be due to the use low dose of silodosin. On the other hand, two recent meta-analyses found that the combination of different drugs was shown to be superior to the use of individual agents such as MET (8,23). The possible explanation for a higher success rate in combination therapy may be due to the different and more mechanisms of action. More studies are needed to confirm the advantage of combination therapy.

Previous studies also evaluated the secondary outcomes of MET. The patients treated with tamsulosin had a shorter expulsion time compared to the placebo (17). The results of Hsu et al. demonstrated that the expulsion time in the silodosin group was significantly shorter than in the tamsulosin group (22). However, Arda et al. reported that the stone expulsion interval was similar between the tamsulosin and silodosin groups, in line with our results (20). For pain management, the patients in the tamsulosin group experienced fewer pain episodes and consumed fewer analgesics compared with the placebo (17). We could not conduct a quantitative analysis of the pain episodes and the amount of analgesic require due to the retrospective nature of the study. Furthermore, previous studies also found METs were well tolerated by most patients, and no severe adverse effects required discontinuation of the study medication (17, 19,20,22). Thus, it seems safe and well-tolerated to receive MET for reducing the need for surgical intervention.

Accurately selecting those patients with an uncomplicated ureteral stone who might benefit from MET is crucial. Factors affecting the spontaneous expulsion of stones, such as stone location, stone size, stone structure, and stone volume have been investigated. Stone size and location have been proven as predictive factors in patients with ureteral stones (24). We evaluated the factors influencing the passage of ureteral stone, the distance of the stone to the UVJ was the only independent predictor of stone expulsion in multivariate analysis. Pain control and diuresis by drinking water are important for facilitating the passage of ureteral stones. Smoking habits, BMI, and the frequency of sexual intercourse could also affect the successful stone passage.

The present study had some limitations. First of all, it was a retrospective study with relatively few patients. Secondly, the frequency of pain attacks, side effects of medications, and additional analgesic usage could not be evaluated. Lastly, there was no control group to show the efficacy of silodosin and tamsulosin. Larger sample-sized prospective studies can help to negate these issues.

CONCLUSION

There was no significant superiority between tamsulosin and silodosin as medical expulsive therapy for distal ureteral stones. The distance of the stone to the ureterovesical junction was the only independent predictor of stone expulsion in multivariate analysis.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Antalya Training and Research Hospital Ethics Committee (Approval number: 2022-017). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design: Karamık K, Kısaarslan M, Ateş N, Data acquisition: Karamık K, Kısaarslan M, Ateş N, Data analysis and interpretation: Karamık K, Kısaarslan M, Anıl H, Drafting the manuscript: Karamık K, Anıl H, Critical revision of the manuscript for scientific and factual content: Karamık K, Anıl H, Statistical analysis: Anıl H, Supervision: Kısaarslan M, Ateş N.

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At what stage are we in active surveillance for localized prostate cancer? Our clinical experience

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Özet

Amaç: Prostat kanseri (PCa) erkeklerde en sık görülen bir malignitedir ve taramayla erken tanı konulabilir. Aktif izlem (Aİ), düşük riskli prostat kanserli (DRPK) hastalarda tedavi yönetimi seçeneklerinden biridir. Bu çalışmada prostat kanserinde Aİ ile ilgili klinik deneyimimizi değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Ocak 2014 ile Aralık 2019 tarihleri arasında PCa tanısı konan 1650 hastanın verileri retrospektif olarak incelendi. Dahil edilme kriterleri; 75 yaş altı olma ve 10 yıllık yaşam beklentisi mevcudiyeti, klinik T1-T2a evre, PSA düzeyi <10 ng/dl, biyopsi kor ≤2 pozitif olmak ve biyopsi örneğinin patolojik incelemesinin sonucu olarak Gleason skoru ≤6 olunması olarak tanımlandı. Dahil edilme kriterlerinden herhangi birini karşılamayan hastalar çalışma dışı bırakıldı.

Bulgular: Dahil etme ve hariç tutma kriterlerinden sonra 176 hasta Aİ'i kabul etti ve çalışmaya dahil edildi. Ortalama takip süresi 25,2 ± 13 aydı. Toplam 57 hasta (32,3%) kesin tedavi için Aİ programından ayrıldı. Kesin tedavi 38 (65,5%) hastada radikal prostatektomi, 18 (31%) hastada radyoterapi ve bir (1,7%) hastada hormonoterapi idi.

Sonuç: Aİ, DRPK hastalarında kesin tedavinin komplikasyonlarını önlemeye yardımcı olan bir yöntemdir. Bu hastalarının yönetiminde kesin tedaviye alternatif bir seçenek olarak kullanılabilir. Ancak Aİ hastalarının 30%'unda definitif tedavi ihtiyacı doğuran patolojik upgrade'ler olabileceği unutulmamalıdır.

Anahtar Kelimeler: prostat kanseri, aktif izlem, düşük riskli prostat kanseri

Abstract

Objective: Prostate cancer (PCa) is the most common malignancy in men and early diagnosis can be made by screening. Active surveillance (AS) is one of the options for disease management in patients with low-risk prostate cancer (LRPC). In this study, we aimed to evaluate our clinical experience in AS for prostate cancer.

Material and Methods: Data from 1650 patients who were diagnosed with PCa in the period between January 2014 and December 2019, were retrospectively reviewed. Inclusion criteria were defined as being under 75 years of age and having a 10-year life expectancy, being at clinical stages of T1-T2a, having a PSA level of <10 ng/dl, having positive biopsy cores of ≤2, and having a Gleason score of ≤6 as the result of the pathological examination of the biopsy specimen. Patients not meeting any of the inclusion criteria were excluded from the study.

Results: After the inclusion and exclusion criteria, 176 patients agreed to undergo AS and were included in the study. The mean follow-up duration was 25.2 ± 13 months. A total of 57 patients (32.3%) left the AS program to undergo definitive treatment. Definitive treatment was radical prostatectomy in 38 (65.5%) patients, radiotherapy in 18 (31%) patients, and hormonotherapy in one (1.7%) patient.

Conclusion: AS is a method that helps avoid the complications of definitive treatment in LRPC patients. It can be used as an alternative option to definitive treatment in the management of these patients. However, it should not be forgotten that pathological upgrades may occur in 30% of AS patients, indicating the need for definitive treatment.

Keywords: prostate cancer, active surveillance, low-risk prostate cancer

The study was approved by Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinic Investigations Ethic Committee (Approval No: 2020-19-11, Date: 21/09/2020). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Prostate cancer (PCa) ranks first among non-cutaneous cancers in men and is the second leading cause of cancer death in American men (1). The introduction of prostate-specific antigen (PSA) testing and the improvements in diagnostic procedures such as imaging studies and ultrasound-guided biopsy techniques have led to an increase in the diagnosis of PCa. It is seen that the majority of patients present with localized and low-risk prostate cancer (LRPC) (2). Along with increasing rates of early diagnosis, a decline has occurred in PCa mortality (3-5). It receives the attention that individuals with low-risk disease (Gleason scores of ≤ 6, PSA levels of <10 ng/mL, and a clinical stage T2a tumor; LRPC) have a better prognosis among all PCa patients. The options in the management of localized PCa include active surveillance (AS), radical prostatectomy (RP), and radiotherapy (RT). Conservative treatment strategies including AS are critical to decreasing complication rates associated with RT and RP. Such complications may include erectile dysfunction, urinary incontinence, cosmetic problems, surgically-induced hernia, ileus, and infections. The use of conservative treatment in the management of LRPC is gradually increasing in our country and the world (6).

In this study, we aimed to evaluate our clinic's experience in AS for prostate cancer.

MATERIAL AND METHODS

Data from 1650 patients who were diagnosed with PCa at Bakırköy Dr. Sadi Konuk Health Training and Research Hospital in the period between January 2014 and December 2019, were retrospectively reviewed. Inclusion criteria were defined as being under 75 years of age and having a 10-year life expectancy, being at clinical stages of T1-T2a, having a PSA level of <10 ng/dl, having positive biopsy cores of ≤2, and having a Gleason score of ≤6 as the result of the pathological examination of the biopsy specimen. Patients not meeting any of the inclusion criteria were excluded from the study.

AS and other options for definitive treatment were explained to the patients. Patients; who accepted the AS protocol, were included in the study. The demographic and clinical characteristics of the patients at the time of diagnosis, the follow-up times, multiparametric magnetic resonance imaging (mpMRI) lesion scores, pathological examination results of biopsy specimens, numbers and percentages of cores, and reasons for dropping out from the AS protocol were recorded retrospectively. All these processes were carried out in compliance with the principles of the Declaration of Helsinki. Permission was obtained from the local ethics committee to retrospectively screen the clinical data for the objectives of our study.

Follow-up Protocol

The recommended AS protocol required PSA testing and digital rectal examinations (DRE) at 3-month intervals and obtaining follow-up mpMRI images within 12 months. In addition to the standard confirmation biopsy, MRI fusion-guided biopsies were performed in the same session in patients with PIRADS 3 lesions or above. A standard confirmation biopsy was performed on patients, who did not have any lesions detected in mpMRI. Patients meeting the follow-up criteria were instructed to undergo biopsy or mpMRI annually. After the confirmation of the diagnosis via standard procedures, periodic transrectal ultrasound-guided surveillance biopsy or MRI fusion biopsy procedures were performed every 12 to 24 months based on clinical risks and observed disease processes. Diagnostic biopsy specimens obtained from referring institutions were reviewed by experienced genitourinary pathologists. Surveillance biopsies were performed by extended octant sampling to obtain a minimum of 10 cores. Indications for recommending definitive treatment to the patient included patient preferences, clinical progression, advancing Gleason grade, an advanced clinical stage, an increased tumor volume, elevated PSA levels, and an increased level of patient anxiety. The date of obtaining the first positive biopsy specimen at any institution was recorded as the date of diagnosis; which was recorded at the time of enrollment. The duration of follow-up was calculated as the time from the date of diagnosis to the date of the last contact with the patient.

Statistical Analysis

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for

the statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency, percent, minimum, and maximum) were used to evaluate the study data. The conformity of the quantitative data to a normal distribution was tested by the Shapiro-Wilk test and graphical methods.

RESULTS

Of 243 patients meeting the inclusion and none of the exclusion criteria, 176 agreed to undergo AS and were included in the study. Of the patients undergoing AS the mean age was 63±7 years and the mean follow-up duration was 25.2 ± 13 months. The demographic data of the patients and the characteristics for inclusion in the AS program are shown in Table 1. Of the patients included in the study, 100 patients underwent a confirmation biopsy. Seventy-six patients (43.2%) did not undergo a confirmation biopsy and were followed up with mpMRI. mpMRI was used in the follow-up of 175 (99.4%) patients included in the AS protocol. One patient could not undergo follow-up mpMRI due to contrast allergy. A total of 57 patients (32.3%) left the AS program to undergo definitive treatment. The reasons for switching the patients to definitive treatment are presented in Table 2. Pathological examination results of the confirmation biopsy specimens or RP specimens led to upgrading in 34.1% of the patients. Definitive treatment was RP in 38 (65.5%) patients, RT in 18 (31%) patients, and hormonotherapy in one (1.7%) patient. Findings obtained during the AS program and the results of curative treatment are listed in Table 2.

DISCUSSION

The majority of the patients are found to have LRPC at the time of diagnosis, in which overtreatment is associated with the high cost and increased need for post-intervention care. For these reasons, it is important to distinguish the fatal disease from others to prevent overtreatment (2). AS is a suitable option for patients; who are candidates for undergoing curative treatment but do not require immediate intervention at the time of diagnosis. Most LRPCs are slow-growing and eligible for surveillance through the examination of biopsy samples as they remain within the definitive curability limits (7). AS protocols include PSA testing, DRE, the use of imaging methods, and TRUS-guided biopsies. Such protocols may vary according to the institutions, where they are applied. The majority of the protocols only include patients with Gleason 3+3 disease; however, some institutions accept moderate-risk patients with Gleason 3+4 disease eligible for AS (8, 9). In different studies using the data from the "Cancer of the Prostate Strategic Urologic Research Endeavor" study; AS was preferred in the United States of America (USA) at a rate of 6.2% at the beginning of the 2000s, 10% at the year 2006, and 40% for low-risk tumors in the period between the years 2010 and 2013. That rate was reported to be 76.2% in patients over 75 years of age (10,11).

One of the most important steps in selecting AS as an option for the management of localized PCa is patient eligibility. Patient eligibility depends on the grade of the tumor, clinical characteristics of the patient, and finally patient preferences. Tumor-related features; including primarily the Gleason scoring and PSA testing, provide information about the clinical stage, progression, and extent of the disease (6). PCa is a slow-growing disease; in which the patient's age, comorbidities, expected life span, and patient preferences about living with cancer and treatment side effects are the other important parameters involved in the decision-making process (6, 12, 13). However, it has attracted the attention of the researchers that the primary diagnosis based on the needle biopsy results may not always be correct and that patients may be in the high-risk group despite the diagnosis of low-risk disease. Epstein et al. evaluated the total prostatectomy specimens of 7643 patients, who underwent RP and who were previously diagnosed with Gleason 5-6 disease based on needle biopsy findings. They found that only 36% of the patients had high-grade tumors (14).

The criteria used in the studies in the literature may vary across centers. Such criteria are summarized in Table 3. Those series usually include patients with T1c and T2a stage diseases, Gleason scores of <7, PSA levels of <10 ng/mL, and less than 50% involvement in positive cores (15-23). Recommendations about AS are similar to the American and European urology guidelines. Such guidelines recommend AS for patients with a

Table 1. The demographic data of the patients and the characteristics for inclusion in the AS programme.

Variables	Mean ± SD
Age at diagnosis (years)	63.07 ± 7.04
Follow-up period (months)	25.29 ± 13.94
Charlson Comorbidity Index	2.26 ± 0.96
Prostate volume (cc)	53.27 ± 22.5
PSA at the time of diagnosis (ng/dl)	5.93 ± 1.97
Lesion size on MRI (mm)	6.97 ± 2.7
Number of total biopsy cores (n)	10.78 ± 2.42
Number of positive biopsy cores (n)	1.29 ± 0.52

PSA: *prostate-specific antigen,* ***MRI:*** *magnetic resonance imaging*

Table 2. Findings obtained during the AS programme and the outcomes of curative treatment

Variables	N (%)
Confirmation biopsy	100 (56.8)
Confirmation biopsy Gleason Score	
Benign	30 (30)
3+3	51 (51)
3+4	10 (10)
4+3	8 (8)
4+4	1 (1)
Higher	0 (0)
Curative Treatment	57 (32.4)
Reason for leaving active surveillance	
Patient request	10 (17.5)
PSA increase	7 (12.2)
Positive core increase	20 (35)
Gleason score increase	19 (33.3)
Metastasis	1 (1.7)
Curative treatment option	
Radiotherapy	18 (31.5)
Radical prostatectomy	38 (66.6)
Hormonotherapy	1 (1.7)
Radical Prostatectomy Spesmen Gleason Score	
3+3	13 (34.2)
3+4	15 (39.5)
4+3	6 (15.8)
4+4	3 (7.9)
4+5	1 (2.6)
Extraprostatic extension	4 (10.5)
Seminal vesicle invasion	1 (2.6)
Surgical margin	5 (13.2)

Table 3. Inclusion criteria that are applied in various treatment centers

Center	Gleason score	Number of positive core	Tumor percentage	PSA	T stage
Royal Marsden NHS Trust	≤ 3+4	_	≤%50	≤15 ng/mL	≤2a
Miami University	≤ 3+3	≤ 2	≤%20	≤10 ng/mL	≤2
Johns Hopkins University	≤ 3+3	≤ 2	≤%50	PSAD≤0,15 ng/mL/ mL	1
University of California	≤ 3+3	≤ %33	≤%50	≤10 ng/mL	≤2
University of Toronto	≤ 3+3	≤ 2	≤%50	≤10 ng/mL	≤2
ERSPC*	≤ 3+3	≤ 2	_	PSA≤10ng/mL PSAD≤0,2ng/mL/m	1c-2
Bakirkoy Dr. Sadi Konuk	≤ 3+3	≤ 2	≤%50	≤10 ng/mL	≤2a

ERSPC: *The European Randomized Study of Screening for Prostate Cancer* ***PSA:*** *Prostate spesific antigen*
PSAD: *Prostate spesific antigen density*

low risk of tumor progression (24, 25). The AS criteria that have been applied in our clinic include PSA levels of <10 ng/mL, ≤2 positive cores in the rectal ultrasound-guided prostate biopsy, 50% rate of tumor presence in positive cores, a ≤ PIRADS 3 lesion, and T ≤ 2a lesion in mpMRI.

The rationale for the AS option may seem reasonable to physicians dealing with PCa but the reasons for not treating a potentially fatal disease at a treatable stage may not always be adequately understood by patients and their families. It has been reported that men frequently prefer to undergo AS to avoid unfavorable treatment effects on urinary and sexual functions (26-29). Long-term outcomes of AS, as a treatment option, are still unavailable. In a limited number of studies; the psychological conditions of patients, who preferred to participate in an AS program, were examined both at the time of the diagnosis and during the follow-up period. The number of patients switching from AS to definitive treatment for psychological reasons is substantial. Therefore, it should be kept in mind that the provision of information and psychological support to AS patients are critical (26-29). It has been reported that patients were switched to definitive therapy because they no longer met the AS criteria such as having increased Gleason scores in the confirmation biopsy results, increased numbers or percentages of cores, or elevated PSA levels. It has also been reported that patients were switched to definitive therapy solely based on the patient's request (26-29). In our study, 10 patients voluntarily withdrew their consent from participating in the AS program and decided to undergo definitive treatment despite continuing to meet the inclusion criteria.

The main reason for patients' selection of AS at the time of diagnosis is to avoid the potential complications of radical treatment such as urinary incontinence and erectile dysfunction (30, 31). On the other hand, patients have reported that they did not prefer to undergo AS at the time of diagnosis mainly because of the concern that cancer might progress to an incurable stage (30, 32). In the study conducted by Duffield et al; it was found that the disease was limited in the organ in 65% of the patients, who underwent radical surgery due to the detection of progression in the follow-up biopsy after a mean of 29.5 months in the AS program. However, 71% of the patients were found to have at least one of the following untoward histopathological characteristics; including extracapsular extension (EPE), a Gleason score of 4, or a tumor volume of > 1 cm^3 (33). It was reported in a study from Johns Hopkins that; among patients with stage progression in a control biopsy, 23% of RP patients had unfavorable histopathological pathological findings resulting in less than 75% chance of being disease-free in the 10 years after surgery (34). However; this rate was not different from that of patients, who had the same clinical features and who underwent radical surgery within 3 months after the diagnosis of PCa (34). The international multicenter prospective Prostate Cancer

Research International: Active Surveillance (PRIAS) study reported RP outcomes in LRPC patients, who were followed up in an AS program. The study reported that; of the patients, who underwent radical surgery after a median period of 1.3 years, the organ-limited disease was found in 80.8% but 29% of the patients had unfavorable histopathological findings including pT3-4 disease and/or a Gleason score of ≥4 + 3 (35). In our study, the rate of having upgraded disease in AS patients was found to be 34.1% after a confirmation biopsy or RP. Of our study patients, who preferred to undergo RP as a definitive treatment, the histopathological examination results were Gleason scores of 4+4 in three patients and 4+5 in one patient. Again, in this patient group, four patients had EPE and one patient had seminal vesicle invasion (SVI). When the results of the studies in the literature are evaluated together, it is seen that information about the outcomes of radical surgery after AS is still limited in LRPC patients and it is too early to reach a certain conclusion. However, it is observed that the pathological features of the disease meet the criteria indicating the need for treatment in at least a quarter of the patients. It remains to be a matter of curiosity about how this ratio will change in longer periods of surveillance and what the prognosis of such patients will be after treatment. In this context; considering the increasing experience in mpMRI, the inclusion of mpMRI in AS criteria will help the clinician to identify a second index lesion, anteriorly located or small-sized tumors, and difficult to detect tumors.

The number of patients included in this study could be considered small as a limitation of this study. Another limitation could be that our long-term results are not available.

CONCLUSION

AS is a method that helps avoid the complications of definitive treatment in LRPC patients. AS can be used as an alternative option to definitive treatment in the management of LRPC patients. However, it should not be forgotten that pathological upgrades may occur in 30% of AS patients, indicating the need for definitive treatment. Therefore; detailed information about all possibilities and options should be provided to patients, who are recommended to be followed up in an AS program.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinic Investigations Ethic Committee (Approval No: 2020-11-19, Date: 2020/09/21) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Evren İ, Danacıoğlu YO, Hacıislamoğlu A, Polat H, Data acquisition; Danacıoğlu YO, Ayten A, Polat H, Data analysis and interpretation; Özlü DN, Ayten A, Drafting the manuscript; Danacıoğlu YO, Ekşi M, Özlü DN, Arıkan Y, Critical revision of the manuscript for scientific and factual content; Evren İ, Ekşi M, Özlü DN, Arıkan Y, Statistical analysis; Evren İ, Hacıislamoğlu A, Ayten A, Supervision; Evren İ, Hacıislamoğlu A, Polat H.

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Original Research / Özgün Araştırma

What is the best anesthesia method for circumcision? Comparison of local and general anesthesia: Prospective clinical study

Sünnet cerrahisi için en uygun anestezi yöntemi nedir? Lokal ve genel anestezinin karşılaştırılması: Prospektif klinik çalışma

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Özet

Amaç: Sünnet öncesi ve sonrasını kapsayan sünnet çalışması anketi ile lokal anestezi ve genel anestezi yöntemlerinin karşılaştırılması amaçlandı.

Gereç ve Yöntemler: Haziran ve Aralık 2021 tarihleri arasında sünnet için başvuran ve çalışmaya katılmayı kabul eden 0-12 yaş arası çocukların evebeynlerinin sünnet çalışması anketini doldurmaları sağlandı. Tüm hastalar aynı cerrah ve aynı cerrahi yöntem ile opere edildi. Uygulanan anestezi şekline göre hastalar lokal ve genel anestezi olarak iki gruba ayrıldı ve veriler karşılaştırıldı.

Bulgular: Çalışmamıza anket verileri tamamlanan 282 hasta dahil edildi. 132 hastaya (%48,9) genel anestezi, 144 hastaya (%51,1) lokal anestezi uygulandı. Lokal anestezi uygulanan hastaların yaş ve kilo ortalamaları, sünnet için uygun yaş tercihleri genel anestezi uygulanan gruptan anlamlı olarak düşük bulundu (p:0,001). Her iki gruptaki evebeynlerin sosyoekonomik düzeyleri, eğitim durumları ve sünnet yaptırma sebepleri arasında anlamlı fark görülmedi (p≥0,05). Hastaların işlem sonrası bakım ihtiyacı ve iyileşme süresi, lokal anestezi uygulanan grupta anlamlı olarak daha düşük bulundu (p:0,001).

Sonuç: Sünnet lokal veya genel anestezi ile güvenle yapılabilen bir cerrahi işlemdir. Erken aylarda sünnet yaptırmak isteyen evebeynler daha çok lokal anesteziyi tercih etmektedir. Bu grupta iyileşme süresi daha kısadır. Cinsel gelişim dönemini de kapsayan ileri yaşlarda, anestezi tercihin genel anestezi lehine değiştiği görülmüştür. Toplumumuzun sünnet ile ilgili hassasiyeti ve bilinç düzeyi geçmiş yıllara göre artmıştır.

Anahtar Kelimeler: sünnet, genel anestezi, lokal anestezi, üriner sistem enfeksiyonu

Abstract

Objective: It was aimed to compare the methods of local anesthesia and general anesthesia with circumcision study questionnaire applied before and after circumcision.

Material and Methods: Parents of children aged 0-12 years who applied for circumcision between June and December 2021 who agreed to participate in the study were asked to fill out the circumcision study questionnaire. All patients were operated with same surgeon and surgical method. Patients were divided into local and general anesthesia groups, and data were compared.

Results: Our study included 282 patients; general anesthesia was applied to 132 patients (48.9%), and local anesthesia was applied to 144 patients (51.1%). Age and weight averages of patients who were administered local anesthesia and age preferences suitable for circumcision were significantly lower than those in general anesthesia group (p:0.001). There was no significant difference between socioeconomic levels, educational status and reasons for circumcision in both groups (p≥0.05). Patients' need for postoperative care and recovery time was significantly lower in the local anesthesia group (p:0.001).

Conclusion: Circumcision is a surgical operation that can be performed safely with local or general anesthesia. Parents who want circumcision in the early months of life mostly prefer local anesthesia. Postoperative recovery time is shorter in this group. Preference for anesthesia has changed in favor of general anesthesia in advanced ages, including the sexual development period. The knowledge and awareness level of our society about circumcision has increased compared to previous years.

Keywords: circumcision, local anesthesia, general anesthesia, urinary tract infection

The study was approved by Ethics Committee of Karamanoğlu Mehmetbey University (Approval No: 04-2021/05, Date: 25/05/2021). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Circumcision is a surgical operation that has been widely practiced since the first periods of written records in human history. The earliest evidence of human circumcision dates back to 4000 BC in Egypt (1). Basically, it is the removal of the prepuce covering the glans penis by cutting. According to the World Health Organization (WHO) research, approximately 30% of men worldwide are circumcised, and two-thirds are Muslims (2). Circumcision is practiced in every society for different reasons. Religious and cultural habits, medical necessity, and hygienic reasons can be shown among these reasons. Nearly 100% of men in our country have had circumcision surgery. It is still one of the most frequently performed surgical operations in our country and the world (3).

Although it has been applied millions of times over the years, the debates continue until today. A comprehensive report on circumcision published by the American Academy of Pediatrics (AAP) in 2012 has sparked controversy (4). A multidisciplinary working group consisting of the AAP board of directors and special region representatives, members of the disease control and prevention center, gynecology and obstetrics specialists, and related branch physicians performing circumcision surgery prepared the report. The report emphasized that the medical benefits of circumcision outweigh the potential risks and harms. Circumcision is protective against diseases such as urinary tract infections, sexually transmitted diseases, HIV, penile cancer, phimosis, paraphimosis, balanitis, and lichen sclerosis. It has been stated that the complication rates after circumcision performed in health institutions and by experienced surgeons are very low. It has been shown that most complications can be resolved with minor interventions. In addition, there was no adverse effect on glans penis sensitivity, sexual pleasure, and satisfaction. It is recommended that clinicians inform parents about circumcision impartially during pregnancy and in the early postpartum period. (4). There are also medical opinions advocating that argue the opposite of these results. Some opinions argue that the medical benefits of circumcision are not certain, the possibility of complications is higher, and the operation should be postponed until the child can give informed consent (5, 6).

All these ongoing discussions about circumcision blur the process for parents who plan circumcision for their children. It does not seem possible to expect the parents to make a clear decision on whether to perform the operation, the appropriate time, the type of anesthesia, and the method to be used in a matter for which a decision has not been reached even by the medical authorities. Mainly, the choice of general or local anesthesia to be applied before the operation, the method to be used, the surgical branch that will perform the operation, the operation's recovery time, its complications, and possible psychological effects on the child are wondered by the parents. In addition, the impact of all these details on the recovery period after surgery is essential for physicians.

In our study, parents were provided with detailed information about circumcision before the operation with the circumcision study questionnaire covering the periods before and after circumcision. Based on the preferred anesthesia method for the operation, all parents' preferences about circumcision were recorded. By comparing the anesthesia methods, it was studied whether there was a significant difference in the parameters of the pre-and post-operation.

MATERIAL AND METHODS

The study was planned prospectively and ethics committee approval was obtained. All study steps were carried out in accordance with the Declaration of Helsinki (Ethics Committee of Karamanoğlu Mehmetbey Faculty of Medicine, Date: 25.05.2021. Approval No: 04-2021/05).

The study included healthy boys between the ages of 0-12, who applied to the outpatient clinic with a request for circumcision between June and December 2021, had no medical contraindications for the operation, and whose parents agreed to participate in the survey. Before the examination and informed about the operation, the parents were asked to answer the first ten questionnaire questions concerning the preoperative period. General information about the operation, possible complications, applied anesthesia, and circumcision methods were explained. The type

of anesthesia used was decided by the parents' preference, except for absolute contraindications. Complete blood count and coagulation parameters of all patients were seen. The anesthesiologist evaluated the patients who will undergo General Anesthesia/Sedation before the operation. Informed consent was obtained from all patients before the operation. Local anesthesia was applied as dorsal penile block and circumferential infiltration to the penile radix using lidocaine and bupivacaine. All operations were performed by the same surgeon using the dorsal slit and excision technique. The patients who were followed up after the operation were discharged on the same day. It was ensured that the parents answered the last four questionnaire questions about the postoperative period 15 days after the operation.

All data were recorded and statistical analysis was done with SPSS (IBM Version 20, New York, USA). Compliance of numerical data with normal distribution was tested with the Shapiro–Wilk test. Continuous variables are expressed as mean (SD) or, if variables were not normally distributed, as median (minimum-maximum)and categorical variables as the number of cases and percentage. The sample was divided into general and local anesthesia groups according to the type of anesthesia applied and compared with each other. While the t-test and Mann-Whitney U test were used to compare independent variables, the Chi-square test was used to compare categorical variables.

RESULTS

Our study included 282 patients who fulfilled the stated conditions and completed questionnaire data. General anesthesia was applied to 48.9% (n=132) of the patients, and local anesthesia was applied to 51.1% (n=144) of them. The mean age and weight of the patients administered local anesthesia were significantly lower than those in the general anesthesia group (p:0.001). The frequency of urinary tract infection was also higher in the patients administered general anesthesia (p:0.001). There was no significant difference between the two groups in terms of the socioeconomic income level of the parents, the education level, the reasons for having the operation, the reasons for fear-anxiety about the operation, and who can perform the operation ($p \geq 0.05$). While 47.2% of parents who preferred local anesthesia for circumcision were between 0-1 years old, 26% of parents preferred general anesthesia were between 2-5 years old (p:0.001). Demographic data are shown in Table 1 in detail.

When the postoperative data were analyzed, postoperation recovery time, need for care, and suture absorption time were significantly lower in the local anesthesia group (p:0.001). There was no significant difference between the two groups in the postoperation behavioral changes ($p \geq 0.05$). Postoperative data are shown in Table 2 in detail.

DISCUSSION

Circumcision is a surgical operation performed for religious, cultural or medical reasons throughout history. Management of pain perception that may occur during and after the operation is necessary. Societies have also accepted this operation as a sacred ceremony in which the individual proves his resilience to pain. Today, many anesthesias and analgesia methods are used for the operation. These are local anesthesia, regional anesthesia, sedoanalgesia, and general anesthesia (7,8). Among these techniques, local anesthesia and sedoanalgesia/general anesthesia are commonly used in our country. Patients and physicians must analyze the frequency of use of these techniques and their superiority against each other.

The anesthesia method to be applied for circumcision and the age and weight of the patients are essential in terms of patient and physician preference. In our study, the mean age and weight of the local anesthesia group were significantly lower than the general anesthesia group (p=0.001). In our country, the age of circumcision is mostly between 0-12 years old. Although the local anesthesia method was explained in detail in patients over a certain age and weight, it was observed that the concern that the patient might try to act with a feeling of discomfort and complicate the operation was the common thought among the parents. It was observed that the parents' preferences were commonly general anesthesia for patients of relatively higher age and weight. Therefore, in our study, it was impossible to provide a homogeneous distribution in age and weight in patients in both anesthesia groups. 144 pa-

Table 1. Pre-operative evaluation data

	General anesthesia(n=138)	Local anesthesia(n=144)	p value
Age (median (min-max)) (months)	56 (6-110)	14 (1-90)	0.001*
Weight (mean± S.D.) (kg)	16.1 ± 5.4	10.3 ± 2.5	0.001
Number of UTIs (in last one year) (median (min-max))	2 (1-3)	1 (1-3)	0.001*
Socioeconomic status			0.249+
0-2800 ₺	29 (%21)	26 (%18)	
2801-5600 ₺	47 (%34)	49 (%34)	
5601-10000 ₺	41 (%29.7)	43 (%29.9)	
>10000 ₺	21 (%15.3)	26 (%18.1)	
Mother Educational status			0.254+
Illiterate	5 (%3.6)	7 (%4.8)	
Elementary-Middle School	48 (%34.7)	33 (%23)	
High school	53 (%38.5)	58 (%40.2)	
University	32 (%23.2)	46 (%32)	
Father Educational status			0.478+
Elementary-Middle School	44 (%31.9)	35 (%24.3)	
High school	52 (%37.7)	59 (%41)	
University	42 (%30.4)	50 (%34.7)	
Reason for procedure			0.466+
Religious reasons	75 (%54.3)	60 (%41.6)	
Tradition	46 (%33.4)	35 (%24.4)	
Environmental oppression	4 (%2.8)	9 (%6.2)	
Medical reasons	13 (%9.5)	40 (%27.8)	
Fear-Restraint			0.224+
Infection	52 (%37.7)	31 (%21.5)	
Penile damage	20 (%14.5)	16 (%11.2)	
Late recovery	12 (%8.7)	30 (%20.8)	
Pain	24 (%17.3)	44 (%30.6)	
Inability to urinate	9 (%6.5)	7 (%4.8)	
All	13 (%9.5)	12 (%8.3)	
None	8 (%5.8)	4 (%2.8)	
When is the appropriate age for circumcision?			0.001+
0-1 (age)	10 (%7.2)	68 (%47.2)	
1-2 (age)	27 (%19.6)	39 (%27)	
2-5 (age)	36 (%26)	18 (%12.6)	
5-7 (age)	35 (%25.4)	6 (%4.2)	
7 (age)	30 (%21.8)	13 (%9)	
Who can perform the circumcision?			0.748+
Pediatric surgeon / Urologist	116 (%84)	115 (%79.9)	
Pediatric surgeon / Urologist and other healthcare providers	22 (%16)	29 (%20.1)	

** : Mann-Whitney U Test,t-test, + : Chi-square test*

***UTI:** Urinary tract infection*

***S.D. :** standard deviation, **Min:** Minimum, **Max:** Maximum*

Table 2. Post-operative evaluation data

	General anesthesia(n=138)	Local anesthesia(n=144)	p value
Healing time (days)(mean± S.D.)	7.4 ± 2.6	5.4 ± 2.1	0.001*
Time for care (days)(mean± S.D.)	4.4 ± 2.1	3.6 ± 1.4	0.001*
Suture absorption time (days)(mean± S.D.)	10.3 ± 2.3	8.91 ± 1.2	0.001*
Was there any beahvioral changes?			0.124+
Yes	59 (%42.7)	81 (%56.2)	
No	79 (%57.3)	63 (%43.8)	

** T test + Ki-square testi*
***S.D**. : standard deviation*

tients (51.1%) were operated on under local anesthesia, and 138 patients (48.9%) were operated on under general anesthesia. It was observed that the number of urinary tract infections in the last year was significantly higher in the general anesthesia group. It was thought that this result was caused by the significant age difference between the groups, not the type of anesthesia or the surgical operation. In our study, the median age and mean weight were 14 months and 10.3 kg in the local anesthesia group and 56 months and 16.1 kg in the general anesthesia group. In a study conducted in 2004 on the subject, 411 circumcised children aged between 2 and 11 were evaluated and the average age of circumcision was calculated as 7 years (9).

It was observed that the question "What is the most appropriate age for circumcision surgery?" asked the parents participating in our study. While the local anesthesia group mostly preferred the 0-1 age group, the general anesthesia group preferred the 2-5 age group. (p=0,001). When all patients were evaluated, it was seen that 0-1 age (27.6%) response was given in the first place. Compared to previous studies, it can be said that parents have preferred circumcision at a younger age in recent years. In another study involving 98 people related to age preference, it was seen that parents answered 3-6 years old (36.7%) in the first place (10). This study stated that circumcision performed in the newborn period is the most appropriate because it prevents many physical and psychological problems. In addition, it has been stated that circumcision performed in 2-6 years, called the sexual development period, may cause castration anxiety and should not be done (10-12). This view has not been scientifically substantiated by a high-evidence meta-analysis or a placebo-controlled, double-blind, prospective, randomized study. Therefore, circumcision between 2-6 years of age cannot be accepted as an absolute contraindication. With the increasing use of the internet and social media in recent years, it has been observed in our study that most of the parents in our country have concerns that circumcision surgery is absolutely contraindicated in the 2-6 years old period. There are also scientific studies that argue the opposite of this view. In a study by Schlossberger et al., the effects of circumcision on child mental health were examined and stated that the operation did not have a significant negative impact on body images in terms of anxiety (13). In addition, although circumcision has been practiced frequently for years between the ages of 2 and 6 in our country, castration anxiety is not a common health problem (14,15). Circumcision may be sanctified by society, seen as the first step towards masculinity, and encouraging the person to do so may contribute to this. As a result, it can be said that parents' knowledge in our country is increasing for this age group due to their research. When the data in our study were examined in detail, it was seen that parents did not give up circumcision between the ages of 2-6, but general anesthesia was more preferred for this age group.

When the reasons for circumcision were analyzed, it was seen that religious reasons came first in both groups that were administered general or local anesthesia. Although circumcision surgery is not defined as a pillar of Islam, it has become an obligatory ritual

in practice (16). Medical reasons are in second place in the local anesthesia group. In the surveys conducted in our study, it was seen that the parents, who primarily considered the medical benefits of circumcision, mostly preferred the 0-2 age group to obtain the possible benefits at an earlier age, and therefore local anesthesia was more preferred. In another study, it was stated that the rate of circumcision for medical reasons was 15.3%. It has been reported that families prefer circumcision to prevent smegma accumulation, urinary system infection, balanitis, and phimosis (17). The desire to undergo circumcision for traditional reasons was in second place in the group performed under general anesthesia. Considering circumcision as the "first step towards masculinity" in our country is a traditional and cultural reason for circumcision. It was seen that social pressure was the last reason for circumcision in both groups. In a study conducted by Kavaklı et al., it was observed that due to social pressure, some children stated that they did not feel male unless they were circumcised (18).

In our study, it was observed that the education and socioeconomic levels of the parents did not significantly change the anesthesia preference. In today's information age and communication, the ease of access to information at all levels may have led to similar tendencies in patient preferences. In another study on the subject, 74 mothers who applied for the circumcision operation were evaluated, and it was seen that the educational status of the mothers did not significantly affect the circumcision decision, the appropriate age selection, and the person to be circumcised, but only the reason for circumcision (10).

When we analyzed the fears and reservations of parents about circumcision based on all patients, it was seen that the first concern was the possibility of infection. It was observed that the fact that the penis was in a closed area and contact with urine and stool increased the concerns of the families on this issue. After completing the questionnaire, detailed information was given to the parents. It was explained that the contact of urine with the wound does not increase the possibility of infection. Information was provided about antibiotic pomade treatments and wound care. Giving this information to the families before the operation may help reduce the pre-circumcision anxiety of the parents. When both groups were evaluated separately, it was seen that the families in the local anesthesia group had the most pain concerns before the operation. It was observed that the reasons such as the possibility of not providing adequate analgesia in local anesthesia and the inability of children to be inactive during the operation increased these concerns. It was thought that providing more effective analgesia during the operation in general anesthesia reduced pain anxiety in this group. For this reason, circumcision with general anesthesia can be offered to parents who experience significant anxiety due to pain. In a small number, the families were worried about penile damage, delayed recovery and inability to urinate. In the literature, it is seen that there are serious complications such as urethral injury and glans amputation during circumcision (19, 20). It was stated that the likelihood of complications decreased in operations performed in health centers by urologists or pediatric surgeons.

When the postoperative data of the questionnaire were analyzed, it was seen that the recovery time, the need for care and the suture absorption time were significantly lower in the local anesthesia group. This situation may be related to the younger patient population in this group rather than the type of anesthesia. Accordingly, faster wound healing may cause this result. Some of the parents stated that they thought that having the penis in the diaper provides faster wound healing. For this reason, they said that they wanted to have circumcision before toilet training was given. When the studies on this subject are analyzed, it has been reported that rapid wound healing is not related to the use of diapers, and circumcision performed at younger ages heals faster (21). As a result of our study, the shorter healing time and time of care in the local anesthesia group may be due to the younger age of the patients in this group, not because of the type of anesthesia. But also, local anesthesia provides the opportunity or obligation to perform circumcision in younger age groups; it provides an advantage indirectly, if not directly.

When the families were asked to evaluate the behavioral changes in children after the operation, there was no significant difference between the two groups. However, it was observed that there was a higher rate

of behavioral changes in the local anesthesia group. This may be related to the more substantial analgesic effect of general anesthesia in the early postoperative period and the more anxiety experienced during the operation in local anesthesia.

It was observed that the answer to the question of who can perform the circumcision was mostly urologists or pediatric surgeons in both groups. In a study conducted by Ceylan et al. in 2007, it was reported that the rate of circumcision performed by specialist doctors in the hospital was meager (22). In another study conducted by Çelik et al. in 2021 on this subject, 85.3% of parents stated that a specialist doctor circumcised their child1. This situation shows that the knowledge level of Turkish society about circumcision has increased over the years.

When the results of our survey study are analyzed, there are some limitations. In comparison to the anesthesia method, it was impossible to obtain similar groups in terms of age and weight due to parental preferences. Data such as the recovery and care periods of the patients and behavioral changes were obtained with the information obtained from the parents. Multicenter prospective studies with a more significant number of patients and longer patient follow-ups are needed.

CONCLUSION

In conclusion, circumcision is a surgical operation that can be performed safely with the help of local or general anesthesia. General information about circumcision and the knowledge about the person who should do the operation has increased in our society. In circumcision surgery performed in the early months, local anesthesia is preferred and a shorter recovery time is observed. However, it is seen that the preference for general anesthesia increases between the ages of 2-6, which is called the sexual development period. Multicenter prospective studies with a larger number of patients and longer patient follow-ups are needed.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Ethics Committee of Karamanoğlu Mehmetbey Faculty of Medicine (Date: 25.05.2021. Approval No: 04-2021/05) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Kandemir E,, Data acquisition; Kandemir E, Data analysis and interpretation; Kandemir E, Efiloğlu Ö, Drafting the manuscript; Kandemir E, Efiloğlu Ö, Critical revision of the manuscript for scientific and factual content; Kandemir E, Toprak K, Tahra A, Efiloğlu Ö, Atış G, Yıldırım A, Statistical analysis; Toprak K, Tahra A, Supervision; Yıldırım A.

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Original Research / Özgün Araştırma

Preventive effects of montelukast against acetaminophen-induced nephrotoxicity: An experimental study

Asetaminofenin indüklediği nefrotoksisiteye karşı montelukastın önleyici etkisi: Deneysel bir çalışma

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Özet

Amaç: Bir astım ilacı olan Montelukast, dokular üzerinde anti-inflamatuar etkiye sahiptir. Sıçan modellerinde montelukastın (MK) asetaminofen (APAP) ile indüklenen böbrek hasarı üzerindeki tedavi edici etkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Yirmi dört sıçan rastgele her biri altı hayvandan oluşan dört gruba ayrıldı. APAP intraperitoneal olarak 1000 mg/kg/gün tek doz olarak uygulandı. Tedavi grubundaki MK dozu 10 mg/kg olup APAP sonrası oral gavaj ile uygulandı. Diğer gruplar APAP + Salin grubu ve kontrol grubuydu. Nefrotoksisiteyi belirlemek için doku malondialdehit (MDA), indirgenmiş glutatyon (GSH) ve Nitrik oksit (NO) seviyelerini ölçtük**.**

Bulgular: APAP grubundaki serum üre ve kreatinin seviyeleri kontrol ve APAP + MK gruplarındaki sıçanlara göre anlamlı derecede yüksek ölçüldü. APAP ile tedavi edilen sıçanlarda GSH seviyesi önemli ölçüde azaldı. Bununla birlikte, MK verilmesi tedavi grubunda GSH seviyesini önemli ölçüde arttırdı. Tek başına APAP ile tedavi edilen sıçanlardaki doku MDA seviyeleri kontrol grubu ve APAP + MK grubuna kıyasla önemli ölçüde yüksekti. NO seviyesi, APAP ile tedavi edilen grupta yükselmiş olarak ölçüldü. Bununla birlikte, MK tedavi grubundaki NO seviyeleri, APAP ile tedavi edilen gruptan önemli ölçüde düşüktü. Ayrıca, tek başına APAP grubuna kıyasla MK tedavi grubunda bazı morfolojik geri kazanımlar gözlendi.

Sonuç: MK'nin APAP kaynaklı renal toksisite ve disfonksiyonu üzerinde faydalı etkileri vardır. Ancak uygun kullanımı ve etkileri göstermek için klinik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: asetaminofen, böbrek, montelukast, nefrotoksisite, oksidatif stres

Abstract

Objective: Montelukast, an asthma drug, has an anti-inflammatory effect on tissues. We aimed to investigate therapeutic effect of montelukast (MK) on acetaminophen (APAP) - induced renal damage in rat models.

Material and Methods: Twenty-four rats were randomly divided into four groups of six animals each. APAP was administered intraperitoneally as a single dose of 1000 mg/kg/day. In the treatment group, MK dose was 10 mg/kg and administered by oral gavage after APAP. The other groups were APAP + Saline group and the control group. We measured tissue malondialdehyde (MDA), reduced glutathione (GSH), and Nitric oxide (NO) levels to determine the nephrotoxicity.

Results: Serum Blood Urea Nitrogen (BUN) and creatinine levels were measured significantly higher in APAP group than rats in the control and APAP + MK groups. The level of GSH was significantly diminished in APAP-treated rats. However, the administration of MK significantly increased the level of GSH in the MK treatment group. Tissue MDA levels in rats treated with APAP alone were significantly higher compared to the control group and APAP + MK group. The level of NO was measured as elevated in APAP treated group. However, NO levels in the MK treatment group were significantly lower than APAP treated group. Furthermore, some morphological recoveries were observed in the MK treatment group compared to APAP alone group.

Conclusion: MK has beneficial effects on APAP-induced renal toxicity and dysfunction. However, clinical studies are needed to demonstrate appropriate use and effects.

Keywords: acetaminophen, kidney, montelukast, nephrotoxicity, oxidative stress

The study was approved by Istanbul University Animal Experiments Local Ethics Committee in 16/01/2015. Approval no is 20.
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

The kidney is a crucial organ and it has important roles in controlling the volume of body fluids, blood osmolality, acid-base balance, various electrolyte concentrations and removing toxins. In addition to environmental variables, some drugs also may affect these functions (1)no single animal model would be completely satisfactory because the etiology and development of renal failure are diverse. During recent years injection of uranyl nitrate has been found to be the most effective and easiest method to produce renal dysfunction in laboratory animals. Changes over the last 10 years in government regulations on the production and use of radioactive substances make the compound less available. There is, therefore, a need for a more accessible compound comparable to uranyl nitrate as an inducer of renal failure. The present study compares the effects of another known nephrotoxin, cisplatin, with uranyl nitrate in the rat. Cisplatin was chosen because of its ability to produce kidney damage and its identical site and mechanism of action on the kidneys as uranyl nitrate. In the present study, rats were given different i. v. doses of uranyl nitrate or cisplatin dissolved in 0.9% of saline solution. The effects of nephrotoxins were evaluated on the basis of changes in body weight, creatinine and blood urea nitrogen (BUN. N-acetyl-p-aminophenol (APAP) molecule is also called paracetamol or acetaminophen. Paracetamol has analgesic and antipyretic properties at therapeutic dosage (2). APAP is primarily metabolized with sulfuration and glucuronidation reactions in the liver. The final metabolites formed after these reactions are excreted by the kidneys. N-acetyl-p-benzoquinone imine (NAPQI), an extremely reactive intermediate, occurs after metabolization of APAP with the microsomal P-450 enzyme system (3). Overdose APAP causes cellular GSH depletion via excessive reaction between NAPQI and GSH. In this way, lipid peroxidation begins as a result of NAPQI binding to cellular proteins. These reactions lead to hepatic and renal damage (4). Although APAP toxicity has been well-defined in the liver, its effect on the kidney is not well known. The mechanisms of renal toxicity may be explained with activation of prostaglandin synthase and N-deacetylase enzymes in Cytochrome P450 (CYP450) pathway according to human and animal studies (3,5)that is, bioactivation, detoxication, chemoprevention, and chemoprotection. In addition, some pharmacological and clinical aspects are discussed briefly. A general introduction is presented on the biokinetics, biotransformation, and structural modification of paracetamol. Phase II biotransformation in relation to marked species differences and interorgan transport of metabolites are described in detail, as are bioactivation by cytochrome P450 and peroxidases, two important phase I enzyme families. Hepatotoxicity is described in depth, as it is the most frequent clinical observation after paracetamol-intoxication. In this context, covalent protein binding and oxidative stress are two important initial (Stage I).

Montelukast (MK), is an asthma drug, a selective reversible cysteinyl leukotriene-1 (CysLT1) receptor antagonist. It shows a reducing effect on airway eosinophilic inflammation in asthma (6). Wallace et al. showed that ethanol-induced gastric mucosal damages and colitis were improved by CysLT1 receptor antagonists (7). MK shows these effects with anti-inflammatory and antioxidant features. It has been stated that APAP tissue damage is closely related to increased Reactive oxygen species (ROS). Also, some studies showed that APAP-induced nephrotoxicity occurs as a result of lipid peroxidation (3).

Nitric oxide (NO) has an intercellular messenger role. It makes crucial missions like vasorelaxation and inflammation in the cell. Although important roles such as removing of pathogens and tumour cells; excessive NO converts to ROS by oxidation, causing to deterioration of cell signalling pathways and out of control inflammation (8)urinary biochemistry and urinary levels of oxalate, NO metabolites (nitrate and nitrite. One of the most important indicators of lipid peroxidation is Malondialdehyde (MDA). Glutathione (GSH) is the main intracellular antioxidant molecule. It has many crucial biological functions such as the reduction of some biologically active metabolites and the protection of the thiol part of proteins (9). Because of these features, MDA, GSH, and NO levels were used to determination of inflammatory and oxidative injury in many experimental studies.

We have shown a preventive effect of MK on gentamicin-induced nephrotoxicity in our previous experimental study (10). We consider that MK may show similar protective effect against APAP nephrotoxicity. Therefore, we examined the protective effect of MK on APAP-induced renal injury in experimental models.

MATERIAL AND METHODS

Animals and Drug Administration

Twenty-four male Wistar-Albino mouses (345-350 g) were included in the experiment. The rats were acclimated for one week before the experiment with 12 hours light and dark cycle, 20-24oC temperature and appropriate food and water. Istanbul University Animal Experiments Local Ethics Committee provided the ethical approval for the experimental study. (Date:16/01/2015. Approval no is 20) After one-week isolation period, 4 groups were randomly created as each one consists 6 rats;

Control group, only 0.9 % saline

APAP group

APAP + 0.9 % saline

APAP + MK treatment group

Normal saline was used to dissolve the APAP and it was injected intraperitoneally (i.p.) at a single dose of 1,000 mg/kg/day (3). The administration dose of APAP was based on prior studies (11). The MK dose was adjusted to 10 mg/kg by dilution with saline solution and applied by oral gavage 20 minutes after APAP injection (3).

A single 1 ml isotonic saline was administered to control group by intraperitoneally. A single dose 1000 mg/kg APAP was given to APAP group. The treatment group received MK after APAP. The other group received APAP + 0.9 % saline.

All surgical operations were done in general anaesthesia stimulated by intraperitoneal ketamine hydrochloride twenty-four hours after APAP administration. Blood samples from rats were used to evaluate biochemical parameters. Then, whole rats were sacrificed.

Kidneys were found following an abdominal mid incision and rapidly removed. Kidneys were irrigated twice with cold saline solution following separated from other tissues. One of the kidneys was stored at -80°C to evaluate tissue GSH, NO and MDA levels. Formol solution was used to preserve the remaining kidney for subsequent histopathological evaluation. Blood analysis were used to investigate urea–creatinine levels.

Histopathological Evaluation

Histopathological assessments were done according to 6 μm sections of kidney samples. Then, haematoxylin–eosin (H&E) stain was used to assess the sections under light microscopic. The criteria defined by Allen et al. were used during the semi-quantitative evaluation of the tissues in terms of scoring the severity (12). All sections were analysed in terms of tubular vacuolization, parietal hyperplasia and necrosis. While obtaining an average score, the least 50 glomerulus and proximal tubules were examined for each slide. The percentage of tubular damage was categorised as 4 group from 0 to 3. Grade 0 (none) means no changing on tubules. Grade 1 (mild) denotes tubular damages <25 %. Grade 2 (moderate) expresses tubular damage between 25-50 %. Grade 3 (severe) indicates tubular injury >50 %.

Kidney fibrosis was evaluated following Masson's trichrome stain. Specimens were categorised as 4 groups after staining. Absence of fibrosis was shown as (-). Fibrosis in <25 % of tissue (mild) was shown as (+). Fibrosis in between 25-50 % of tissue (moderate) was shown as (++). Fibrosis in >50 % of tissue (serious) was shown as (+++).

Biochemical Examinations

MDA is the final product of the lipid peroxidation. It is one of the indicators of the oxidative stress intensity. A buffer solution containing 1.5 % potassium chloride in teflon-glass was used to the homogenization of frozen kidney slides while obtaining 1:10 (w/v) whole homogenate. Since it is the reactive molecule of thiobarbituric acid, it was measured by thiobarbituric acid determination in spectrophotometer and defined as nmol/mg.

The method of Moron et al. which is based on the colour-changing at 412 nm, was used to measure reduced GSH (13). Described method of Lowry et al. was used to measure protein concentrations in tissues (14). GSH levels were expressed as nmol/mg wet tissue.

Griess test was used to assess the nitrite levels after incubating with nitrate. The absorbance was qualified at 545 nm after 30 minutes incubation.

Statistical Analysis

The values were presented as mean ± standard deviation (SD). Statistical analysis of the histopathological evaluations of the groups was performed by the chi-square test. To analyse biochemical data, ANOVA (one-way analysis of variance) test was used. The definition of significance between the two groups was done by Dunnett's multiple comparison test. Statistically significant value is $p<0.05$.

RESULTS

The degree of the tubular necrosis and biochemical results are shown in Tables 1, 2 and 3. Death or any extraordinary signs were not detected in groups. The results of the APAP and APAP + 0.9 % saline group were similar in terms of biochemical and histopathological parameters.

Tissue MDA levels in APAP alone group were significantly higher compared to control and APAP + MK groups. ($p<0.001$) This increase was prevented by MK treatment. The GSH levels were found statistically significantly lower in APAP group. However, MK treatment significantly increased the GSH levels in APAP + MK group. NO levels in APAP group were higher. However, NO levels were found significantly lower in the MK treatment group.

Serum urea and creatinine levels in APAP alone group were higher compared to both of APAP + MK and control groups. ($p< 0.001$) In the case of MK being added to APAP treatment, serum urea and creatinine levels improved.

According to histopathologic examination, there was no pathologic changing in the control group. According to light microscopic evaluation, regular morphology consisting normal glomeruli and tubules were seen in the control group (Figure 1). APAP-treated rats had obvious morphological changes such as tubuloepithelial deterioration and necrosis (grade of tubular necrosis:2–4) (Figure 2). Cortical interstitial congestion and cellular debris were determined only in the tissues of APAP-treated rats. Moderate epithelial vacuolization and tubular degeneration were found in the proximal tubules of rats treated with APAP + MK. MK treatment group had better tubular morphology and lower cellular desquamation compared to APAP group (Grade of tubular necrosis: 0-2) (Figure 3). Severe tubular vacuolization, degeneration and necrosis were seen in the tissues of APAP + 0.9 % saline group (Figure 4). According to Masson trichrome staining, statistically significant difference was not determined between groups in terms of kidney fibrosis (Table 3 and

Table1. NO, MDA, GSH levels and Kidney functions in groups

Parameters	Control	APAP	p value[a]	APAP+MK	p value[b]	APAP+ Ve
Urea (mg/dL)	33 ± 7.8	107 ± 13.9[a]	**<0.001**	42.8 ± 6.9[b]	**<0.001**	105 ± 13.4
Creatinine (mg/dL)	0.42 ± 0.1	2.08 ± 0.4[a]	**<0.001**	0.98 ± 0.09[b]	**0.013**	1.97 ± 0.4
NO (nmol/mg protein)	13.9 ± 5.1	88.3 ± 41.6[a]	**<0.001**	14.5 ± 5.7[b]	**<0.001**	83.1 ± 28.3
MDA (nmol/mg protein)	41.8 ± 10.2	83.6 ± 24.9[a]	**<0.001**	37.3 ± 19.6[b]	**<0.001**	82.4 ± 50.1
GSH (umol/mg protein)	39.1 ± 20.4	15.2 ± 3.3[a]	**<0.001**	37.6 ± 9.3[b]	**<0.001**	14.1 ± 1.7

Values are expressed as mean ± SD for six rats in each group.

[a] *Significantly different from control.*

[b] *Significantly different from APAP group ($p < 0.05$).* ***NO:*** *nitric oxide,*

MDA: *Malondialdehyde,* ***GSH:*** *glutathione,* ***APAP:*** *N-acetyl-p-aminophenol,* ***MK;*** *Montelukast,* ***Ve:*** *Vehicle*

Table 2. Semiquantitative analysis of tubular necrosis, tubular vacuolization, parietal cell hyperplasia in groups

		Tubular necrosis				Tubular vacuolization				Parietal cell hyperplasia			
	n	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
Control	6	6	0	0	0	5	1	0	0	6	0	0	0
APAP[a]	6	0	1	3	2	0	0	4	2	0	1	5	0
APAP+MK[b]	6	5	1	0	0	2	4	0	0	4	2	0	0
APAP+Ve	6	0	0	2	4	0	0	0	6	0	0	5	1

Score 0: no degeneration, ***1:*** mild degeneration, ***2:*** moderate degeneration, and ***3:*** severe degeneration
a Statistically significant difference from the control group, ***b*** Statistically significant difference from the APAP treated group and $p<0.05$. ***APAP:*** N-acetyl-p-aminophenol, ***MK:*** Montelucast, ***Ve:*** Vehicle

Table 3. Analysis of kidney fibrosis in groups

	n	(-)	(+)	(++)	(+++)
Control	6	6	0	0	0
APAP	6	3	1	2	0
APAP+MK	6	2	4	0	0
APAP+Ve	6	2	2	2	0

Score (-): no fibrosis, ***(+):*** mild fibrosis, ***(++):*** moderate fibrosis, and ***(+++):*** serious fibrosis.
No statistical difference between groups ($p>0.05$). ***APAP:*** N-acetyl-p-aminophenol, ***MK:*** Montelucast, ***Ve:*** Vehicle

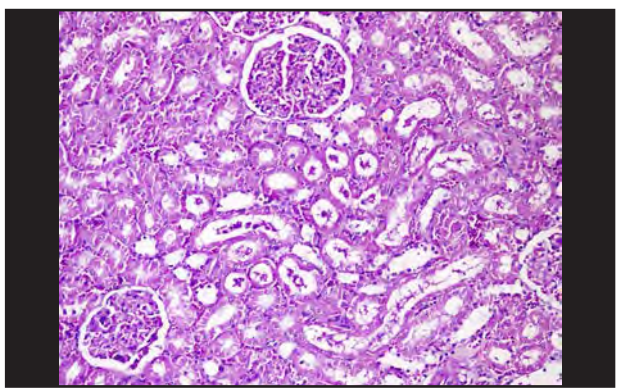

Figure 1. Normal tubules and glomeruli in kidney cortex of control group (H&E x 200)

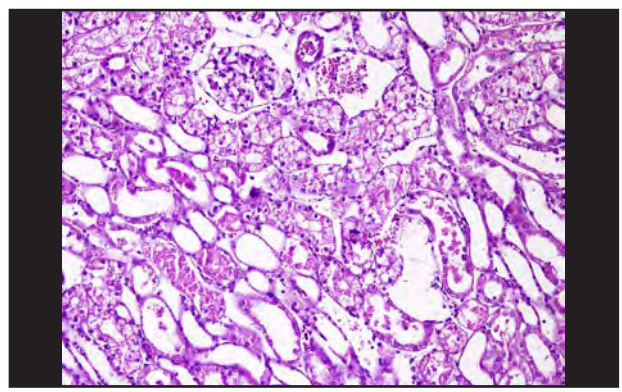

Figure 2. Severe tubular necrosis, tubular degeneration, and epithelial vacuolization in the proximal tubules of APAP group (H&E x 200).

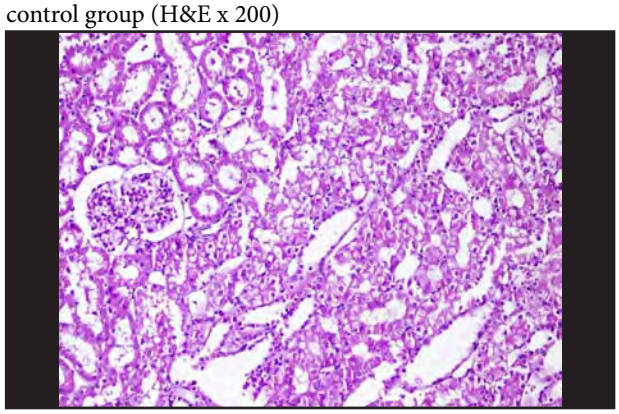

Figure 3. Mild tubular necrosis, tubular degeneration, and mild-moderate epithelial vacuolization in the proximal tubules of APAP + MK group (H&E x 200).

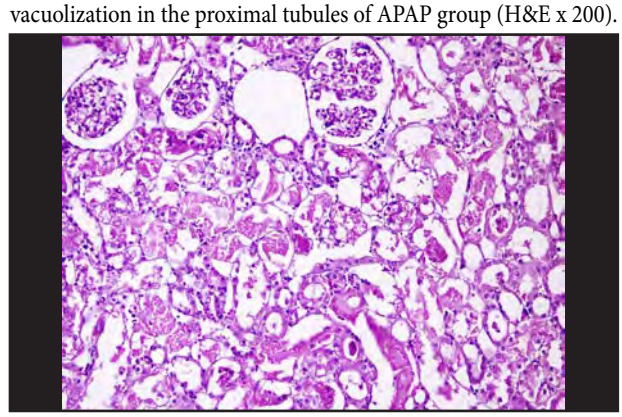

Figure 4. Severe tubular necrosis, tubular degeneration, and epithelial vacuolization in the proximal tubules of APAP+ Ve group (H&E x 200).

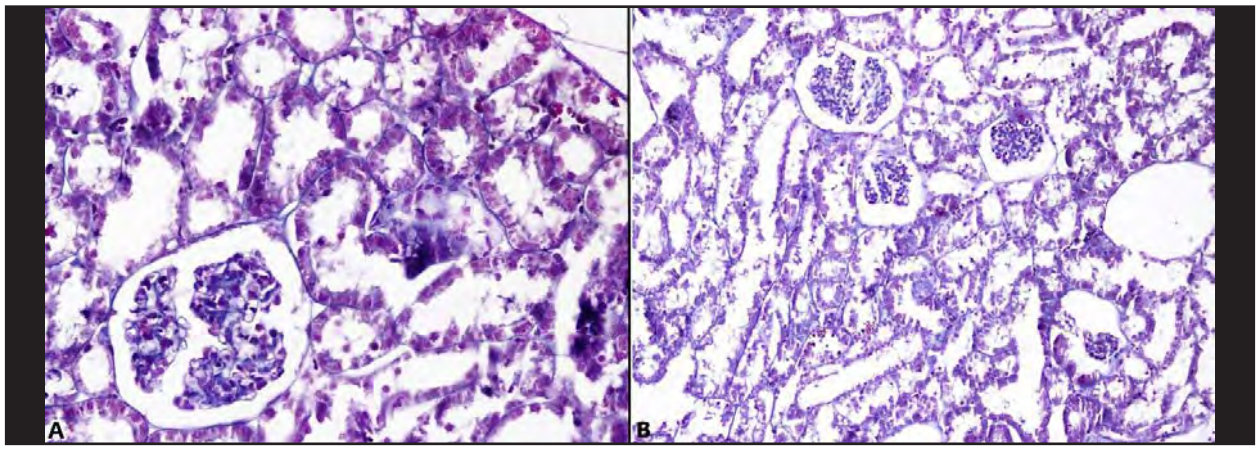

Figure 5/A. Mild fibrosis in interstitium of APAP group (Masson's trichrome x 400).

5/B. Moderate fibrosis in interstitium of APAP+MK group (Masson's trichrome x 400).

Figure 5).

DISCUSSION

Nephrotoxicity is also a crucial problem during APAP intoxication in addition to hepatotoxicity. Acute kidney injury is seen in 1-2 % of APAP overdose cases (15). Proximal tubules have been shown as a target for APAP toxicity due to absorption and secretion activities (16)acetaminophen can be toxic to the kidneys in patients who are glutathione depleted (chronic alcohol ingestion, starvation, or fasting. As APAP may induce acute kidney damage, we consider that the research of therapy of APAP induced nephrotoxicity is a notable topic. The purpose of the present study is to explore the preventive effect of MK on APAP nephrotoxicity in rats.

Although some studies showed that kidney damage begins 3-5 days after chronic use of APAP, the damage was occurred 24 hours after high dose APAP administration in some experimental studies (11). In accordance with this, we detected acute nephrotoxicity after a single dose of APAP in biochemical and histopathological findings.

Serum Blood Urea Nitrogen (BUN) and creatinine levels give us precious information about kidney functions. Increased BUN levels usually indicate the glomerular damage. Creatinine, a metabolite of creatine, is eliminated from the body via urine. Similarly, elevated creatinine levels indicate disturbed kidney functions. Cases requiring haemodialysis after APAP overdose have been reported in the literature (17). In present study, creatinine and BUN levels were found to be high in the APAP group. Our results were also in accordance with previous studies which reported enhanced urea and creatinine levels following APAP induced kidney injury (11,18)all the rats were sacrificed with a high dose of ketamine. Urea and creatinine levels were measured in the blood, and the levels of malondialdehyde (MDA. The levels were measured as lower in the MK treatment group.

Excessive oxidative activity causes cellular damage and lipid peroxidation. The last product of lipid peroxidation and one of the indicators of oxidative damage is MDA (19)as well as both nuclear and mitochondrial DNA. Melatonin achieves this widespread protection by means of its ubiquitous actions as a direct free radical scavenger and an indirect antioxidant. Thus, melatonin directly scavenges a variety of free radicals and reactive species including the hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide, peroxynitrite anion, and peroxynitrous acid. Furthermore, melatonin stimulates a number of antioxidative enzymes including superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase. Additionally, melatonin experimentally enhances intracellular glutathione (another important antioxidant. Some studies demonstrated that MK reduces the myeloperoxidase and MDA levels with

its antioxidant effect in rat models (20). Similarly, we found that MDA levels in the MK treatment group were lower than the APAP group. The primer function of GSH is the protection of the cellular components against oxidative damage. It provides the protection by supplying protein and lipid integrity in normal cellular metabolism (21). We measured a reduction in GSH levels in parallel with the increased MDA levels in the APAP group. Nitric oxide is one of the potent radicals and has been shown to have an important role in the mechanism of APAP-induced kidney injury (22). This study showed that renal NO levels in the APAP group were higher than the control and MK treatment groups.

MK, which is a selective reversible CysLT1 receptor antagonist, has been shown to regulate the oxidant-antioxidant balance and pro-inflammatory mediators in previous studies (23,24)the protective effect of montelukast (ML. We can say that MK might have a protective effect against to APAP induced kidney damage considering beneficial impacts in the levels of GSH, MDA and NO, which are indicators of oxidative damage. Furthermore, some studies indicated that MK showed reducing ischemia/reperfusion injury in various organs with angiogenic properties (25,26 ± 1, 23 ± 2, 24 ± 2 and 24 ± 4% at 24, 28, 36, 48 and 72 h after remote IPC, respectively ($P < 0.05$; $n = 826$) sham group (operation without clamping. This feature also may be related to the therapeutic effect of MK on APAP induced nephrotoxicity.

CYP-450 enzyme systems are predominantly localised in the proximal tubules of the kidney (27). Therefore, nephrotoxicity that occurs during CYP-450-mediated bioactivations is definitely localized in the proximal tubules (28). In addition, proximal tubules have been shown as a target for APAP in different studies (22,29).

This study demonstrates clear evidence of nephrotoxicity after overdose APAP administration based on histopathological findings. The most prominent histopathological change is acute tubular necrosis. The renal histological changes occurring after overdose APAP administration are also consistent with the previous study (30).

There are some limitations in our study. Other oxidative stress parameters such as catalase, superoxide dismutase and myeloperoxidase levels were not measured.

CONCLUSION

MK, a CysLT1 receptor antagonist, has protective effects on APAP-induced nephrotoxicity. It shows this effect with its free radical scavenger agent feature. Further clinical studies are needed to indicate the definite mechanism and effect of MK on APAP-induced nephrotoxicity.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Istanbul University Animal Experiments Local Ethics Committee (Approval no: 20, Date: 16/01/2015) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Ötünçtemur A, Çakır SS, Can O, Data acquisition; Can O, Eraldemir C, Çekmen M, Data analysis and interpretation; Eraldemir C, Çekmen M, Vural Ç, Can O, Drafting the manuscript; Can O, Çakır SS, Critical revision of the manuscript for scientific and factual content; Ötünçtemur A, Çakır SS, Statistical analysis; Çakır SS, Can O, Supervision; Ötünçtemur A, Eraldemir C, Çakır SS.

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An examination of relationship between overactive bladder and C-reactive protein and erythrocyte sedimentation rate

Aşırı aktif mesane ile C-reaktif protein ve eritrosit sedimantasyon hızının ilişkisi

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Özet

Amaç: Hastaların yaşam kalitesini olumsuz olarak etkileyen aşırı aktif mesanenin (OAB) kesin nedeni bilinmemektedir. Bu çalışma bugüne kadar etyolojisi tam olarak aydınlatılamayan OAB'li hastalarda inflamatuar sürece ilişkin kanıtlar sağlamak amacıyla planlandı.

Gereç ve Yöntemler: Çalışmaya OAB tanısı alan 154 kişi ile kontrol için kullanılan 131 kişi kaydedildi. Çalışma Nisan 2015 ile Nisan 2020 yılları arasında retrospektif, kesitsel olarak yapıldı. Veriler bu konuda uzman bir kişi tarafından, ilk görüşmede kaydedildi. Gruplar serumda ölçülen CRP ve ESR açısından karşılaştırıldı. İstatistiksel analizde Ki-kare testi, Bağımsız örneklemler t-testi, Mann-Whitney U testi, Pearson ve Spearman korelasyon analizleri kullanıldı. P<0.05 düzeyi istatistiksel olarak anlamlı kabul edildi.

Bulgular: Gruplar arasında ek hastalıklar açısından farklılık saptanmadı. Yaş ve BMI açısından gruplar arasında anlamlı farklılık saptandı (p<0.005). Gruplara göre CRP düzeyleri karşılaştırıldığında, OAB grubu için 0.28 [0.54] ve kontrol grubu için 0.17 [0.22] mg/dl olarak saptandı (p=0.047). ESH'nın gruplara göre dağılımı sırasıyla için 19 [30.5] ve 12.5 [13] mm/h olarak izlendi (p=0.004).

Sonuç: Bu çalışma OAB ile inflamatuar bir süreç arasındaki ilişkiyi gösteren bilgilerimize yeni kanıtlar sunmaktadır. OAB'li hastalarda CRP ve ESH düzeylerinin kontrol grubuna göre arttığı saptandı. Bu sonuçlar bize bu hastalığın temelinde inflamatuar bir sürecin olduğunu göstermektedir.

Anahtar Kelimeler: inflamasyon, aşırı aktif mesane, C-reaktif protein, eritrosit sedimantasyon hızı

Abstract

Objective: The definite cause of overactive bladder (OAB), which negatively affects the quality of life of patients, is unknown. This study aims to provide evidence for the inflammatory process in patients with OAB whose etiology has not been fully elucidated.

Material and Methods: The study included 154 people with OAB diagnosis and 131 people as controls. This study was conducted retrospectively, cross-sectionally between April 2015 and April 2020. The data were recorded at the first meeting by an expert on this subject. Groups were compared in terms of CRP and ESR measured in serum. Statistical analysis used the chi-square test, independent samples t-test, Mann-Whitney U test, and Pearson and Spearman correlation analyses. P<0.05 was accepted as statistical significance.

Results: There were no differences between the groups in terms of comorbid diseases. There were significant differences identified in terms of age and BMI between the groups (p<0.005). When groups are compared according to CRP levels, values were 0.28 [0.54] for the OAB group and 0.17 [0.22] mg/dl for the control group (p=0.047). The distribution according to ESR in the groups was 19 [30.5] and 12.5 [13] mm/h, respectively (p=0.004).

Conclusion: This study provides new evidence to the literature showing the relationship between OAB and an inflammatory process. It was determined that CRP and ESR levels were increased in patients with OAB compared to the control group. These results show us that there is an inflammatory process at the onset of this disease.

Keywords: inflammation, overactive bladder, C-reactive protein, erythrocyte sedimentation rate

The study was approved by Ordu University Ethics Committee of Clinical Researches (Approval No: 2021-54, Date: 2021/03/04). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Overactive bladder (OAB) is a pathology characterized by urgency accompanied, or not, by urine leakage, without any pathology like urinary tract infection (UTI) or diabetes. It is frequently accompanied by increased urination frequency during the day or at night (1). Despite the difficulty in identifying the definite incidence of this disease in society, it is thought that the rate is 5-10% in the general population and about 16% in young women (2). It negatively affects daily life.

Though it is frequently considered that detrusor hyperactivity causes OAB in patients, no underlying cause can be identified in many cases (3). The most important problem related to this disease is the lack of a specific diagnostic tool or marker for this disease at present. Commonly diagnosis is made by excluding other pathologies causing irritative bladder symptoms. The only objective evidence at hand is urination diaries and survey forms. Disease diagnosis may be placed fully with subjective complaints. To date, the underlying cause has not been fully understood. However, in recent times, the number of studies attracting attention to the association of OAB with inflammation has increased (4). The reason for the lack of full explanation about this disease to date may be due to the deficiency of diagnostic tests that can be used (5). A study supporting this viewpoint reported that symptoms improve when antibiotic treatment is administered even without visible infection factors in urine (6). In conclusion, inflammation may be a cause underlying this disease. These findings increased hopes of finding a specific marker for this disease.

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are markers frequently used for inflammatory events. CRP is an acute phase protein induced by proinflammatory cytokines, like interleukins. It is synthesized by liver cells in the presence of inflammatory disease (7). It is considered to be a defense against inflammatory agents in the body. Limited studies are using CRP for OAB patients and CRP levels in OAB patients are reported to be high compared to controls (8). However, data is not adequate to recommend routine use. To the best of our knowledge, there is no study in the literature about the other inflammatory marker of ESR.

This study was planned to compare the systemic inflammatory markers of CRP and ESR, accepted as prognostic markers in many diseases, in OAB patients with a control group. Our essential aim in this study is to provide evidence related to the inflammatory process for this disease with etiology not fully explained to date.

MATERIAL AND METHODS

Research Design

The study included a total of 285 sequential patients attending the urology clinic from April 2015 to April 2020 abiding by the study criteria including 148 women and 137 men.

The study was made cross-sectional with a retrospective review of data from prospectively enrolled patients. The study registered 154 people with OAB diagnosis and 131 people as controls. OAB diagnosis used urgency and increased urination frequency accompanied or not by urine leakage as criteria (1). The laboratory tests of the patients were collected at the first meeting. This diagnosis was used after excluding other underlying pathologies like UTI. If there were an underlying cause like UTI, the patient would be assessed after the treatment. Patients were assessed by an expert on this topic and prospectively registered. The control group was formed from the relatives of the patients who have any known complaint. The study was conducted in adherence to the Declaration of Helsinki. The study protocol was approved by a local ethics committee (Ordu University Clinical Research Ethics Committee, Approval Number: 2021/54, Date: 2021/03/04).

Diabetes mellitus, presence of systemic infection, chronic urinary tract infection, bladder stones, bladder cancer, neurologic diseases, and other situations that may cause OAB symptoms were used as exclusion criteria. Additionally, patients with surgical histories due to urinary incontinence or any other pelvic pathology were not included in the study. Patients with renal failure, lymphoma-myeloproliferative and hemolytic dis-

eases that may affect blood values were excluded from the study. Patient age, body mass index (BMI), waist circumference, OAB survey form, quality of life score (QoL), urinary complaints, and comorbid diseases were recorded. The forms used in the study were filled by the patient. OAB form consists of 8 questions. For each question, the patient gives points between 0-5. The total score is obtained by adding the points given to the questions (2 points added for men). Above 8 points is considered significant. For QoL, the 8th question of the IPSS inquiry form was used. Likewise, it was scored between 0 and 5. Serum c-reactive proteins and erythrocyte sedimentation rate results were recorded.

Statistical Analysis

Parameters with normal distribution are given as mean ± SD, and parameters without normal distribution are given as median ± interquartile range (IQR). The Kolmogorov-Smirnov test was used to examine the normal distribution of data. To compare the group differences, a student t-test for parametric data analysis and a Mann-Whitney-U test for nonparametric data. Correlation analysis used the Pearson test for parametric data and the Spearman chi-square test for nonparametric data. All statistical analyses were performed with the "SPSS for Windows version 20.0" program. P values <.05 were accepted as significant.

RESULTS

The study registered a total of 285 people, with 148 (51.9%) females and 137 (48.1%) males. The control group included 131 patients (46%) and the OAB group included 154 patients (54%). The control group comprised 58 women (44.3%) and 73 men (55.7%), while the OAB group comprised 90 women (58.4%) and 64 men (41.6%) (p=0.017). The mean ages in the groups were 60.97±12.29 years in the OAB group and 56.09±8.71 years in the control group (p=0.001). When groups are compared in terms of body weight, values were 82.49±14.76 and 81.02±14.63 kg in group 1 and group 2, respectively (p=0.408). In terms of BMI, values were 30.81±5.49 and 29.47±5.21, respectively (p=0.039). There were no significant differences identified between the groups in terms of comorbid diseases such as hypertension, heart disease, and diabetes (Table 1).

Comparing the groups by CRP levels, the observed values were 0.28 [0.54] in the OAB group and 0.17 [0.22] mg/dL in the control group (p= 0.047). The distribution of ESR in the groups was 19 [30.5] and 12.5 [13] mm/h, respectively (p= 0.004) (Table 2).

Table 1. Distribution of demographic characteristics

Characteristics	Groups		P-value
	OAB (Group 1)	Control (Group 2)	
Age (year)	60.9±12.2[a]	56.09±8.7[a]	0.001*
Body weight (kg)	82.4±14.7[a]	81.03±14.6[a]	0.408
BMI (kg/height[2])	30.8± 5.4[a]	29.4± 5.2[a]	*0.039**
Hypertension n (%)[b]	86 (56.6)	62 (47.7)	0.136
Dyslipidemia n (%)[b]	90 (60.4)	83 (64.8)	0.447
Heart disease n (%)[b]	33 (22.1)	19 (14.6)	0.107
Diabetes n (%)[b]	53 (34.9)	35 (26.9)	0.151
Neurologic disease n (%)[b]	20 (513.4)	13 (10)	0.377
Pulmonary disease n (%)[b]	22 (14.9)	10 (7.7)	0.062
Psychological problems n (%)[b]	41 (27.3)	35 (26.9)	0.939

*[a] = mean ± SD, [b]: Within grup, * = Statistically significant (Student's t-test)*

Table 2. Comparison of urinary complaints and inflammatory parameters in the groups

Features	LUTS Group		p-value
	OAB (Group 1)	Control (Group 2)	
CRP mg/dl	0.28 [0.54][a]	0.17 [0.22][a]	0.047*
ESR mm/h	19 [30.5][a]	12.5 [13][a]	0.004*
Frequency of daytime urination	8 [5][a]	4 [4][a]	<.001*
Frequency of nighttime urination	4[4][a]	1[1][a]	<.001*
Urine leakage n (%)	106 (99.1)	1 (0.9)	<.001*
OAB total score	14[6][a]	6[7][a]	<.001*
QoL score	1[3][a]	0[1][a]	<.001*

a*= median [IQR], * = Statistically significant (Mann- Whitney U testi)*

DISCUSSION

This study aimed to investigate whether there is a correlation between inflammatory parameters associated with many pathologies and OAB or not. The results of the study identified an association of OAB with CRP and ESR indicating that OAB is associated with the inflammatory process.

Epidemiological studies showed that urinary complaints including OAB increase with age in men and women (9). Consistent with the literature, our study results indicate that the incidence was increased in both genders by age and OAB patients had higher mean age compared to the control group. The daily life of patients is negatively affected and these problems include embarrassment, disrupted social relationships, sexual problems, and psychological problems (10).

The underlying cause has not been discovered exactly. Obesity is among the most frequently blamed causes. Lawrence et al. reported that OAB incidence increased by 2 times in obese women compared to non-obese women (11). Somestudies have found a link between obesity and OAB (12). Our results showed that the BMI in the OAB group was increased compared to the control group, compatible with the literature. The mechanism by which obesity causes urinary complaints has not been definitively revealed. In these patients, the commonly observed metabolic syndrome and related inflammatory process may trigger OAB development (13).

The present study showed that CRP and ESR increase in OAB patients compared to the control group indicating an inflammatory process as the basis of this disease. One probable reason for diagnosing this disease may be that there is no specific indication or diagnostic test for this disease. In other words, the existing inflammatory process may be missed. These patients visit the hospital with similar complaints and suffer from diseases such as UTI and bladder cancer including urgency and frequent urination. Diagnosis is made by excluding underlying pathologies. In our current practice, UTI diagnosis uses mid-flow urine cultures frequently, and >105 CFU/ml proliferation in these cultures which is accepted as significant. This test involves questions about the efficacy to show bacteria existing in the urinary tract. In a similar study by Khasriya et al., it was observed that patients with chronic urinary tract complaints for 3 years. The study found a presence of bacteria with intracellular colonization which could not be observed by classic tests. These bacteria only proliferated in sediment cultures including urothelial cells. They recommended the need for a threshold value of >102 CFU/ml for the identification of infection (5). This result indicates that the urine analysis routinely used for patients with urinary complaints is not adequate. These results were supported by Walsh et al. who reported that low-count bacteriuria frequency increased in OAB patients and that the existing infection in these patients may be overlooked due to the threshold value (14). A study observed more frequent microscopic pyuria and infected urothelial cell numbers that may be related to urinary symptoms in OAB patients compared to a control group (15). There is other evidence showing difficulties experienced in detecting the existing infection in this patient group.

A study administered combined antibiotic therapy including gram-negative and gram-positive bacteria to OAB patients and reported improved perceptions related to symptoms and bladder problems in patients after treatment (6). In OAB patients, the occurrence of low cystometric volumes may be related to increased bladder afferent sensitivity causing bladder fullness and urgency feeling (16). Proinflammatory agents occurring during inflammation may directly sensitize the afferent nerve endings (17). A study by Furuta et al. showed increased proinflammatory mediators in OAB patients (18). Neonatal bladder inflammation induced in rats resulted in OAB-like excessive response to inflammatory stimuli in adults (19). In recent times, the observation of specific microbiome presence in the bladder, as in the intestines, supports the information above. An association was reported between the known pathology of irritable bowel syndrome (IBS) and disrupted intestinal flora (20). This association may be present in the bladder with chronic urologic diseases like OAB. A study on this topic compared OAB and IC patients with known chronic bladder disease with a control group. The results of the study reported that there was variability in the bladder microbiome of patients and that OAB and IC patients had reduced lactobacilli numbers compared to the control group (21). The deficiency of Lactobacillus acidophilus was associated with an increased interstitial cystitis symptom score index and high pain score (22). Another study supporting this reported more frequent observation of the significant urinary pathogen of Proteus in lower urinary tract symptoms and OAB patients compared to a control group (5).

Briefly, the close association between inflammation and OAB is observed. The use of some markers to show this inflammatory process may contribute to diagnosis and treatment stages. When there is acute or chronic inflammation in any area of the body, inflammatory agents like interleukin-6 increase in blood. The liver releases acute phase proteins like CRP into the blood in response to this inflammatory material (7). Measurement of this material in serum provides important information related to inflammation.

CRP and ESR have frequently used laboratory tests for systemic inflammatory diseases (23). They provide important information to monitor the inflammatory process. There are limited studies investigating the association between systemic inflammatory markers like CRP and ESR with OAB. Although some studies have investigated the relationship between mainly CRP with OAB has been investigated, there is no study related to ESR to the best of our knowledge. Therefore, more studies are needed to uncover the uncertainty about this topic. In this sense, this study aims to bridge this research gap by examining the systemic dimension of the relationship between OAB and inflammation.

CRP may be considered response or defense of the body against inflammatory agents. CRP is frequently used as a marker for acute and chronic inflammatory diseases. It begins to increase 4 hours after injury and peaks within 24-72 hours. Studies associated CPR with many pathologies with an inflammation background. In a study we performed, it was identified to be associated with PSA (24). Apart from this, associations with cancer and cardiovascular diseases were shown (25). More interestingly, an association between CRP with urinary symptoms, including storage symptoms especially, was reported. A study on this topic reported a correlation between increased CPR levels with storage symptoms in males over 40 years (8). A study by Kupelian et al. supports this result. In this study, the correlation between storage symptoms with CRP was illustrated for both men and women (26).

ESR is an acute phase reactant used for a long time as a marker. Proteins like increased fibrinogen, clotting proteins, and alpha globulin determine the sedimentation rate during inflammation. Compared with ESR, CRP is a more sensitive and specific marker (27). However, ESR is known to be more effective in some situations, like low-level bone and joint infections (28). Many studies investigated its diagnostic performance. Most studies come from orthopedic surgeons. Hanada et al. compared ESR and CRP levels in osteoarthritic cases considered to involve background inflammation with a control group. Increased ESR and CRP levels were reported in the arthritis group (29). A meta-analysis investigated the specificity and sensitivity of ESR and CRP for orthopedic infections. In this study, values were 78% and 68% for ESR and 79% and 70% for CRP, respectively (23). It was reported they were beneficial for inflammatory processes in

this study. To the best of our knowledge, the correlation between ESR and OAB has not been investigated.

This study has the feature of being the first study investigating OAB with both CRP and ESR. The results of the study identified an association of OAB with CRP and ESR. These results show that the inflammatory process may be effective in the initiation or worsening of OAB disease. Overactive bladder is a pathology encompassing very complicated processes involving bladder urothelium, bladder sensory nerves, and the central nervous system. The pathology causing this disease has not been explained to date. It is important to identify the underlying causes in terms of revealing safer and more effective treatment choices. Infection beginning in the urothelium causes increased urothelial permeability and may cause proinflammatory matter in urine and the environment to pass into the detrusor. Thus, excess stimulation of sensory nerves found in the detrusor may cause OAB symptoms.

Some limitations need to be reported. First, this study is retrospective in nature. Next, CRP and ESR values were only measured once, and results obtained at different times are not known. Finally, variations after treatment are not known. However, the present study is one of the few studies assessing CRP and ESR together in OAB patients to the best knowledge. Further, the results were reflected in clinical practice and registration of adequate numbers by an expert in this topic.

CONCLUSION

This study provides a piece of evidence supporting the association between OAB and the inflammatory process. It was observed that there was a slight increase in CRP and ESR levels in OAB patients compared to the control group. These results show that the basis of this disease is the inflammatory process.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Ordu University Clinical Research Ethics Committee (Approval Number: 2021/54, Date: 2021/03/04) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design, Data acquisition, Data analysis and interpretation, Drafting the manuscript, Critical revision of the manuscript for scientific and factual content, Statistical analysis, Supervision; Benli E.

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Efficacy of combination of daily tadalafil and solifenacin in patients with storage symptom predominant lower urinary tract symptoms

Depolama semptomu baskın alt üriner sistem semptomu olan hastalarda günlük tadalafil ve solifenasin kombinasyonunun etkinliği

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Özet

Amaç: Depo semptomları baskın olan benign prostat hiperplazi hastalarında tadalafil 5mg+solifenasin 5mg kombinasyonunun alt üriner sistem semptomları (AÜSS) ve erektil fonksiyonlar açısından etkinliğini değerlendirmek.

Gereç ve Yöntemler: Ocak 2019 ile Aralık 2021 tarihleri arasında AÜSS ile başvuran ve depolama semptomları baskın olan 40 yaş üstü erkek hastalar çalışmaya dahil edildi. Hastalara günlük tadalafil 5mg ve solifenasin 5mg tedavisi başlandı. AÜSS için aşırı aktif mesane semptom skoru (OABSS), uluslararası prostat semptom skoru (IPSS) ve erektil fonksiyon için uluslararası erektil fonksiyon indeksi-erektil fonksiyon (IIEF-EF) anketleri kullanıldı. Üç günlük mesane günlüğü ile günlük idrar sıklığı, noktüri, sıkışma ve idrar kaçırma sıklığı analiz edildi. On iki hafta sonra hastaların IPSS, OABSS ve IIEF-EF skorları değerlendirildi.

Bulgular: Hastaların 12 haftalık tedavi öncesi ve sonrası semptom skorları ve mesane günlükleri karşılaştırıldığında, IPSS skorlarında (hem işeme, hem depolama, hem de toplam) anlamlı azalma (her biri için p<0,001), IIEF-EF skorlarında anlamlı artış (p<0.001) ve Qmax değer yükselmesinde anlamlı artış gözlendi. Mesane günlükleri karşılaştırıldığında, tadalafil+solifenasin tedavisi sonrası 12. ayda gündüz işeme sayısı, noktüri sayısı ve sıkışma sayısı azaldı (p<0,001).

Sonuç: Günde 5 mg tadalafil ve 5 mg solifenasin kombinasyonu, depolama semptomları baskın AÜSS/ED olan erkek hastalar için etkili ve güvenli bir tedavidir.

Anahtar Kelimeler: benign prostat hiperplazisi, depolama, tadalafil, solifenasin, erektil fonksiyon

Abstract

Objective: To evaluate the efficacy of tadalafil 5mg+solifenacin 5mg combination in terms of lower urinary tract symptoms (LUTS) and erectile functions in benign prostate hyperplasia patients with predominant storage symptoms.

Material and Methods: Male patients over the age of 40 who presented with LUTS with predominant storage symptoms between January 2019 and December 2021 were included into the study. Daily tadalafil 5mg and solifenacin 5mg treatment were started to the patients. Overactive bladder symptom score (OABSS), international prostate symptom score (IPSS) for LUTS, and international erectile function index-erectile function (IIEF-EF) questionnaires were used for erectile function. Frequency of daily urinary frequency, frequency of nocturia, urgency and urinary incontinence were analyzed with a three-day bladder diary. Twelve weeks later, IPSS, OABSS and IIEF-EF scores of the patients were evaluated.

Results: When the symptom scores and bladder diaries of the patients before and after 12 weeks of treatment were compared, significant decrease in IPSS scores (both voiding, storage and total) (p<0.001 for each), significant increase in IIEF-EF scores (p<0.001), and significant increase in Qmax value elevation was observed. When the bladder diaries were compared, the number of daytime micturitions, the number of nocturia and the number of urgency decreased in the 12th month after tadalafil+solifenacin treatment (p<0.001).

Conclusion: The combination of tadalafil 5mg and solifenacin 5mg daily is an effective and safe treatment for male patients with storage symptoms predominant LUTS/ED.

Keywords: benign prostate hyperplasia, storage, tadalafil, solifenacin, erectile function

The study was approved by Ethics Committee of University of Health and Sciences Şişli Hamidiye Etfal Training and Research Hospital (Approval No: 2089, Date: 2021/06/07). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

In aging men benign prostatic hyperplasia (BPH) is very common and it is a benign enlargement of prostate tissue and is caused by proliferation of prostate epithelial and stromal cells (1). The lower urinary tract symptoms (LUTS) associated with BPH, which greatly affect men's quality of life (QoL), include storage, voiding, and post-voidal symptoms (2). In many studies, it has been reported that nocturia, urgency, increased frequency of day and night urination, sexual dysfunction, and urge incontinence are common in men with BPH, as well as voiding symptoms (3,4).

α1-adrenergic blockers (alpha blockers), phosphodiesterase type-5 inhibitors (PDE-5 inh.), 5α reductase inhibitors (5ARI) and antimuscarinic/beta-3 adrenergic agents are used in the medical treatment of LUTS due to BPH [5,6]. With the combined use of these drugs, their efficacy increases, and their side-effect profile expands. Timing the treatment efficacy well and adjusting the doses of medical treatments to predict possible side effects increases the success of combination therapy [7].

Tadalafil, a PDE 5 inhibitor, specifically degrades cGMP and restores its smooth muscle relaxant effect. Tadalafil positively affects the lower urinary system (i) by decreasing the smooth muscle tone in the prostate, urethra, and bladder neck, (ii) by increasing the lower urinary tract blood flow by decreasing the vascular smooth muscle tone, (iii) by inhibiting the bladder afferent nerve activity (C- and Aδ-fibers). and (iv) reduction of inflammation and fibrosis through inhibition of interleukin-8 and Rho-kinase [8-10].

Solifenacin, an antimuscarinic agent, is a muscarinic receptor blocker that predominantly acts on the M3 subtype. It reduces bladder detrusor hyperactivity by suppressing acetylcholine activation [11]. As with all anticholinergic medications, dry mouth and constipation are most common side effects of solifenacin. In addition, it requires careful use in BPH patients because of the risk of voiding difficulty and increasing the post-void residual urine [12].

Currently, the study evaluating the effect with the combination of PDE5-inhibitor and antimuscarinic drugs is limited. The aim of present study was to evaluate the efficacy of tadalafil 5mg+solifenacin 5mg combination in terms of LUTS and erectile functions in BPH patients with predominant storage symptoms.

MATERIAL AND METHODS

Ethics approval of the study was obtained from the Instutional Ethical Reviewer Board, approval number 2089. Male patients over the age of 40 who presented with LUTS with predominant storage symptoms between January 2019 and December 2021 were included in the study. Demographic data of the patients were recorded. International prostate symptom score (IPSS), overactive bladder symptom score (OABSS) for LUTS, and international erectile function index-erectile function (IIEF-EF) questionnaires were used for erectile function. Frequency of daily urinary frequency, frequency of nocturia, urgency and urinary incontinence were analyzed with a three-day bladder diary. Post void residual urine volume and prostate volume (PV) (PVR) were measured by transabdominal ultrasound. Prostate specific antigen (PSA) value (ng/mL) of the patients was recorded. Maximum urine flow rate (Qmax) was evaluated with uroflowmetry.

The patients were started on daily tadalafil 5mg and solifenacin 5mg treatment. Twelve weeks later, IPSS, OABSS and IIEF-EF scores of the patients were evaluated. Bladder diary, uroflowmeter and PVR measurements were recorded. Change and satisfaction rates were compared before and after 12 weeks of treatment. Side effects observed during the treatment were noted.

Inclusion criteria: patients with mild to moderate erectile dysfunction (IIEF-EF between 12 and 21), patients with IPSS score >7, patients with Q max <15.

Exclusion criteria: PVR>50 ml, bladder neck sclerosis, neurogenic bladder, urethral stricture, active urinary tract infection, history of prostate cancer, use of 5ARI, nitrate use, history of unstable angina pectoris, history of renal hepatic failure, narrow-angle glaucoma patients, patients with myasthenia gravis.

The IPSS questionnaire is an inquiry form consisting of 7 questions [13]. The score obtained from each question in the scale is between 0-5. The total score is between 0-35 and scores of 7 and above are interpreted in favor of LUTS.

The IIEF-EF inquiry form includes questions 1-5 and 15 of the IIEF, which consists of 15 questions [14]. A maximum of 30 points can be obtained in the survey, which is organized according to five-point Likert scoring. 1st,3,5th of IPSS. While the questions are about excretion 2.,4. And 7. Questions are about the storage function. A total score of 21 and below was evaluated in favor of ED [15]. Turkish validation made by Turunç et al. [16].

OABSS is a 4 -question survey used to evaluate the extremely active bladder symptoms [17]. A total of 0-15 points can be obtained from the questionnaire and 3 points and above are indicated as OAB. Language validation was made by Culha et al. [18].

Statistical Analysis

Data analysis was done with SPSS 25.0 (IBM, USA). The homogenity of datas were evaluated with the Kolmogorov-Smirnov test. The comparison the parameters before and after the treatment performed with Paired-samples t-test and Fisher's exact test. Significant p value was determined as $p<0.05$.

RESULTS

A total of 132 patients were included in the study. Ten of them were excluded from the study because they were excluded from follow-up, and 1 patient was excluded due to intolerable side effects (constipation), and the study was terminated with 121 patients. The patients' mean age was 47.8±12.3, and the mean BMI was 27.9±8.7 kg/m2. The mean IIEF-EF score of the patients was 13.2±6.3, the mean OABSS was 8.4±2.4, the IPSS-Voiding mean was 5.3±2.2. The mean IPSS-Storage was 13.1±1.7, the mean IPSS total score was 18.4±2.6. The mean PSA value of the patients was 1.1±0.6 ng/ml (Table 1).

When the symptom scores and bladder diaries of the patients before and after 12 weeks of treatment were compared, significant decrease in IPSS scores (both Voiding, Storage and total) ($p<0.001$ for each) significant increase in IIEF-EF scores ($p<0.001$) significant increase in Qmax value elevation was observed.

When the bladder diaries were compared, the number of daytime micturitions, the number of nocturia and urgency decreased in the 12th month after tadalafil+solifenacin treatment ($p<0.001$).

In the PMR measurement, at the end of the 12th week, significantly more residual urine remained in the patients (10.0 (10-30) vs. 20.0 (10-50); $p<0.001$) (Table-2).

Treatment-related side effects were seen in 19% of the patients. Among the patients participating in the study, dry mouth developed in 9 patients (7.4%), constipation in 7 patients (5.8%), dyspepsia in 4 patients (3.3%), and muscle pain in 3 patients (2.5%). Only 1 of these patients could not tolerate the treatment due to constipation (Table-3).

Table 1. Demographic characteristics of the patients

	Mean±SD	Min-Max
Age (years)	47.8±12.3	40-79
BMI (kg/m^2)	27.9±8.7	22.2-36.4
PSA (ng/dL)	1.1±0.6	0.3-3.1
IIEF-EF	13.2±6.3	0-25
OABSS	8.4±2.4	4-14
IPSS-Voiding	5.3±2.2	1-9
IPSS-Storage	13.1±1.7	10-17
IPSS-Total	18.4±2.6	11-22
Qmax	7.3±2.3	3-12
PVR (ml)	14.9±13.2	0-40

***BMI:** body mass index, **PSA:** prostate specific antigen, **IIEF-EF:** international erectile function index-erectile function, **OABSS:** overactive bladder symptom score, **IPSS:** international prostate symptom score, **PVR:** post void residue.*

Table 2. Comparison of data before and after tadalafil + solifenacin treatment

	Before Treatment		After treatment		p value
	Mean	SD	Mean	SD	
IIEF-EF	13.2	6.3	18.9	6.7	<0.001
OABSS	8.4	2.4	3.7	3.1	<0.001
PSA (ng/dL)	1.1	0.6	1.1	0.6	0.954
IPSS-Voiding	5.3	2.2	4.4	1.8	<0.001
IPSS-Storage	13.1	1.7	8.2	3.7	<0.001
IPSS	18.4	2.6	12.6	4.1	<0.001
Qmax	7.3	2.3	8.3	2.9	<0.001
PVR (ml), median (IQR)	10 (10-30)		20 (10-50)		<0.001

IIEF-EF: *international erectile function index-erectile function,* ***OABSS:*** *overactive bladder symptom score,* ***PSA:*** *prostate specific antigen,* ***IPSS:*** *international prostate symptom score,* ***PVR:*** *post void residue*

Table 3. Side effects of the patients

Side Effects	n (%)
Dry Mouth	9 (7.4)
Constipation	7 (5.8)
Dyspepsia	4 (3.3)
Muscle Pain	3 (2.5)

DISCUSSION

The present study showed that, daily tadalafil 5mg and solifenacin 5mg treatment in male patients with storage symptoms predominant LUTS/ED had positive effects on both the LUTS symptom scores of the patients and positive effects on the bladder diary data, while it was effective in restoring erectile functions.

Guidelines recommend the addition of anticholinergic/beta 3 adrenergic agent to alpha blocker therapy in LUTS cases with predominant storage symptoms [19]. In addition, the efficacy and safety of daily use of PDE-5 inhibitors were found to be like alpha-blockers, and use of daily tadalafil 5 mg is recommended in patients with LUTS/ED [20]. In recent years, studies on the use of various combinations in the treatment of BPH/LUTS have been increasing. These combinations include treatments such as alpha blocker + 5α-reductase inhibitors (5-ARI), 5-ARI + PDE-5 inhibitors, alpha blockers, and anticholinergics. There are limited studies in the literature investigating the daily use of tadalafil and solifenacin as a safe and effective treatment [12]. In our study, tadalafil and solifenacin combination therapy was given for 12 weeks to LUTS patients with predominant storage symptoms and ED.

Tadalafil, with its mechanism of action, shows improvements in both urodynamic results and symptom scores and in monotherapy in patients with LUTS/ED. Unlike alpha-blockers, tadalafil acts to increase nitric oxide and cGMP activity, triggering detrusor muscle relaxation and eliminating functional obstruction [8,21]. In our study, significant improvements were found in the IPSS-Excretion related scores according to the initial symptoms of the patients. In addition, the significant increase in Qmax also shows the effect of tadalafil on functional obstruction.

Although the effect of alpha-blockers on LUTS-storage symptoms is not clear, it has been shown to affect storage symptoms by inhibiting urethral smooth muscle contraction [22]. Tadalafil, on the other hand, improves storage symptoms by reducing vascular smooth muscle tonicity, increasing blood flow in the pelvic region, and inhibiting affer-

ent nerves that stimulate the bladder [9,10]. In addition, its use together with solifenacin, an anticholinergic agent that inhibits bladder detrusor contractions, shows that there were significant improvements in the storage symptoms of the patients in our study. In addition, he defends the hypothesis that the decrease in the number of nocturia is also the effect of combined use.

Although the use of anticholinergics in combination with alpha-blockers has shown greater benefit for storage symptoms than alpha-blocker monotherapy, the incidence of voiding difficulty and increased residual urine is increased due to detrusor inhibition [23]. In the study of Urakami et al, they detected 16% urinary retention in the group receiving tamsulosin and solifenacin, and they found that PMR increased from 19 ml to 61 ml after 3 months of treatment [12]. In our study, although the PMR volumes of the patients receiving tadalafil and solifenacin were statistically significant (16 vs 20, $p<0.001$), no patient with clinical urinary retention was detected. This shows that the effect of tadalafil on LUTS storage functions is realized by a different mechanism than alpha-blockers and does not cause urinary retention.

Changes in nitric oxide levels in the pelvis and prostate and the neurogenic effect of this change; smooth muscle contractility, increase adrenergic tone in autonomic hyperactivity/metabolic syndrome, upregulation of the rho kinase / endothelin pathway induced by obstruction resulting in increased smooth muscle tonicity, and coexistence of ED in LUTS patients due to pelvic atherosclerosis in metabolic syndrome [24-26]. Concomitant treatment of these two symptoms by a single agent was investigated, and daily use of tadalafil was found to improve both LUTS and ED in LUTS/BPH patients [27-28]. Especially with the improvement in erectile functions, its effect on LUTS-storage symptoms at least as much as an anticholinergic makes its use widespread. It is known that tadalafil has an effect of 17-35% on IPSS scores [29]. However, this decrease is reduced in patients with predominant storage symptoms. In our study, tadalafil was used together with solifenacin, an anticholinergic, and approximately 40% improvement was achieved in the storage symptoms of the patients. In addition, a significant increase was achieved in the IIEF-EF scores of the patients.

Depending on the combined agents used, the incidence of side effects was found to be 19%. Concomitant use of tadalafil with alpha-blockers may decrease blood pressure and therefore caution should be exercised during its use [30]. However, dizziness or lightheadedness due to low blood pressure was not detected in the use of solifenacin together with tadalafil. dry mouth and constipation, which are the most common side effects, are thought to be due to solifenacin. However, only one patient was excluded from the study due to side effects.

There are some limitations of the study. The first of these is the lack of long-term follow-up of the patients. Another limitation is that tadalafil and solifenacin were not evaluated in separate groups and a comparison could not be made. The combination of tadalafil with an alpha-blocker group is also not included. Conducting the study as a single arm is also among the limitations. However, the information obtained at the end of the study will shed light on the future and will be the precursor of future randomized placebo-controlled studies.

CONCLUSION

The combination of tadalafil 5mg and solifenacin 5mg daily is a safe and effective theraphy for male patients with storage symptoms predominant LUTS/ED. Especially in patients suffering from storage functions, this combination therapy will be a good alternative if resistance is encountered in monotherapy. Prospective randomized controlled studies with large participation are needed to evaluate the efficacy of daily tadalafil+solifenacin treatment.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by University of Health and Sciences Şişli Etfal Training and Research Hospital Clinical Research Ethics Committee (Approval Number: 2089, Date: 2022/06/07) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Hacıislamoğlu A, Data acquisition; Hacıislamoğlu A, Data analysis and interpretation; Yavuzsan AH, Drafting the manuscript; Hacıislamoğlu A, Yavuzsan AH, Critical revision of the manuscript for scientific and factual content; Hacıislamoğlu A, Yavuzsan AH, Statistical analysis; Yavuzsan AH, Supervision; Hacıislamoğlu A, Yavuzsan AH.

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Original Research / Özgün Araştırma

Long-term stone-free rates after flexible URS: Does the size of DJ stent affect the outcomes

Flexible URS sonrası uzun dönem taşsızlık oranları: DJ-stentin boyutu sonuçları etkiliyor mu?

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Özet

Amaç: Bu çalışmada, kullanılan double- J (DJ) stent çapının, flexible üreteroskopik (fURS) böbrek taşı tedavisinin taşsızlık oranları ve postoperatif ağrı durumuna olası etkisini araştırdık.

Gereç ve Yöntemler: Böbrek taşı nedeniyle fURS uygulanan toplam 104 hasta çalışmaya dahil edildi. Taş tedavisi sonrası 51 hastaya 4.7 Fr DJ stent takılırken, 53 hastaya 6 Fr stent takıldı. Postoperatif 3. ayda kontrastsız bilgisayarlı tomografi ile incelenen taşsızlık durumuna ek olarak, iki grubun genel ağrı semptomları, postoperatif ilk haftayı takiben uygulanan görsel ağrı skalası ile değerlendirildi. Başarı, taşların tamamen temizlenmesi veya küçük taş parçalarının (<3 mm) varlığı olarak belirlendi.

Bulgular: İki grubun genel ağrı semptomları, görsel ağrı skalası kullanılarak ölçüldüğünde 6 Fr grubu daha öndeydi (4.02±1.10 vs 4.81±1.53, p=0.006). İki grup taşsızlık oranları açısından anlamlı fark göstermedi (%84.3 vs %74.5, p=0.264). İki grup arasında postoperatif ateş, stent migrasyonu veya acil servis ziyaretleri açısından istatistiksel olarak anlamlı bir fark bulunamadı.

Sonuç: Bu çalışma, daha büyük çaplı stentlerin hastalarda daha yüksek ağrı şikayetlerine neden olmasına rağmen, uzun süreli taşsızlık oranlarını önemli ölçüde etkilemediğini belirledi. Flexible üreteroskopik cerrahi sonrası stent seçimi söz konusu olduğunda 6 Fr yerine 4.7 Fr DJ tercih edilmelidir.

Anahtar Kelimeler: Double j stent çapı, böbrek taşı, fleksible üreterorenoskopi, taşsız

Abstract

Objective: This study's main goal was to evaluate the possible impact of different-sized double-J (DJ) stents on the pain and stone-free status following flexible ureteroscopic laser disintegration (fURS) of renal stones.

Material and Methods: A total of 104 patients who underwent fURS for kidney stones were included in our study. In 51 patients, a 4.7 Fr DJ stent was used after stone fragmentation, while in the remaining 53 cases, a 6 Fr stent was chosen. Between the two groups, general pain symptoms were evaluated using a visual pain scale at the end of the first postoperative week. The stone-free status was evaluated using non-contrast computed tomography (NCCT) after three months following surgery. Success was determined by either the complete clearance of the stones or the presence of small stone fragments (<3 mm).

Results: Using a visual pain scale, we compared the two groups' overall reports of pain (4.02±1.10 vs 4.81±1.53, p=0.006). When we looked at the stone-free rates, the two groups were not significantly different in this regard (84.3% vs 74.5%, p=0.264). We found no statistically significant difference between the two groups in terms of postoperative fever, stent migration, or visits to the emergency room.

Conclusion: In spite of the fact that larger diameter stents resulted in more pain complaints for patients, they did not alter the long-term stone-free rates appreciably, as evidenced by our findings. In order to reduce the occurrence of unpleasant symptoms, a 4.7 Fr double-j stent may be preferable over a 6 Fr stent following flexible ureteroscopic surgery.

Keywords: Double-j stent diameter, renal stones, flexible ureterorenoscopy, stone free

The study was approved by Kafkas University Ethics Committee in February 23, 2022. Approval no is 02.
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Management of symptomatic urinary stones has changed dramatically due to the advances in instrumentation and technology during the last three decades (1). Thanks to these advancements, minimally invasive treatment options, including extracorporeal shockwave lithotripsy (ESWL), flexible ureteroscopy (fURS), and percutaneous lithotripsy (PNL), have effectively replaced open surgery due to their relatively safe and successful outcomes (2). PCNL has been performed in the management of large stones (> 20 mm) with significantly higher stone-free rates (SFR) in a single session, whereas SWL and fURS have been well-performed to manage medium-sized stones (10-20 mm) due to their relatively less invasive nature with comparable success rates to PCNL (3). The European Association of Urology (EAU) Urolithiasis Guidelines acknowledge SWL and fURS as equally effective treatment methods for kidney stones smaller than 20 mm; PCNL is still indicated as the first-line treatment for stones greater than 20 mm in diameter(4).

In the last two decades, fURS has become a safe and successful treatment for medium-sized kidney stones, particularly with the advent of newer-generation flexible ureteroscopes and the practical application of the Ho-YAG laser for stone disintegration. In these stones, the safe and practical application of holmium laser lithotripsy has produced superior outcomes to that of SWL. Comparable complications and stone-free rates have been seen for these stones in comparison to PNL and SWL, two other potential management options (5).

However, based on the department's established clinical practice and the surgeon's option, a ureteric DJ stent may be placed to drain the affected upper urinary tract. Stenting has been demonstrated to avoid ureteral blockage caused by post-procedure mucosal edema, clots, and stone fragments. In addition, it decreases pain and reduces the risk of renal functional degradation by maintaining an open lumen (6,7). In spite of these benefits, side effects such as lower urinary tract symptoms (LUTS), sexual dysfunction, poor work performance, flank and/or body discomfort, and hematuria may occur after DJ insertion (8). Studies examining the advantages and disadvantages of stents based on stent diameter (particularly 4.7-5 French (Fr) and 6 Fr DJ stents) indicated that stents with smaller diameters were better tolerated with less pain and patient discomfort. Additionally, several investigations have suggested that relatively tiny stents may be more prone to upward migration (9). To our knowledge, however, there is not enough information in the literature to make a conclusion about the potential impact of various DJ stent diameters on long-term stone-free status following fURS.

The study being presented compares post-fURS complications dependent on stent size and evaluates whether ureteral stents have an effect on long-term stone-free rates.

We have shown a preventive effect of MK on gentamicin-induced nephrotoxicity in our previous experimental study (10). We consider that MK may show similar protective effect against APAP nephrotoxicity. Therefore, we examined the protective effect of MK on APAP-induced renal injury in experimental models.

MATERIAL AND METHODS

Between October 2020 and February 2022, 105 uncomplicated fURS procedures were conducted at our clinic to treat kidney stones. This study program contained the data from these procedures. All participants gave their consent in writing after being fully informed. Our investigation was authorized by the local ethics committee of our institute (Approval file number: 80576354-050-99/44). The Declaration of Helsinki and the ethical guidelines for human experimentation established by the regional ethics council were followed in every instance. All patients underwent low-dose non-contrast computerized tomography (NCCT) and kidney-ureter-bladder radiography (KUB) as part of their preoperative evaluation in addition to blood and urine analyses (including a culture sensitivity test). Patients with acute renal failure, a history of ureteral stenosis, or bilateral stones were not included in the study. A further exclusion criterion was the insertion of a DJ stent prior to surgery. Patients with urinary tract infections were treated with antibiotics prior to surgery. Patients were prospectively divided into two groups based on the stent diameters following fragmentation. One group consisted of pa-

tients who had received a 4.7 Fr DJ stent, and the other consisted of patients who had received a 6 Fr DJ stent.

During a Surgical Procedure

Second-generation cephalosporins were administered 30 minutes prior to the surgery as the appropriate antibiotic for prophylaxis. All procedures were performed under general anesthesia. In the lithotomy position, a 0.038 Fr guide wire was implanted into the renal pelvis via a 9.5 Fr semi-rigid ureteroscopy under fluoroscopic guidance. The pelvicalyceal system was evaluated by retrograde pyelography. A ureteral access sheath (9.5/11.5 Fr, Cook Medical, Bloomington, IN) was placed under fluoroscopy. The collecting system was entered with a 7.5 Fr fiber optic flexible ureteroscope (Storz FLEX-X2). To disintegrate stones, we utilized a holmium laser equipped with a 273 fiber and used high energy-low frequency settings (1-1.2 J and 6-10 Hz). After laser lithotripsy was completed, stone particles smaller than 2 mm were left for spontaneous passage. A nitinol basket (ZeroTipTM; Cook Urological Inc.) was used to retrieve fragments greater than 3 mm. All patients were subsequently implanted with two different-sized DJ stents (4.7 F and 6 F) after the operation. On the first postoperative day, KUB was used to assess the location of the stents. Antibiotics and nonsteroidal anti-inflammatory drugs were administered to all patients after surgery. Patients were only given access to nonsteroidal anti-inflammatory drugs for a total of three days. This method was used to ensure that the analgesic medicine wouldn't affect the pain assessment at the end of the first postoperative week.

Postoperative Follow-up

One week after their operations, the patients were seen in the outpatient clinic for follow-up evaluations. In addition to answering questions about their symptoms, patients were also asked to rate their pain on a 10-cm visual analog scale (VAS). Following three weeks after the procedure, all DJ stents were extracted. Stone-free status was assessed using low-dose, non-contrast computed tomography after three months following surgery. For this purpose, success was defined as either the complete absence of remaining fragments or the presence of very small stone fragments (<3 mm).

Statistical evaluations were performed using SPSS 22.0. (SPSS Inc, Chicago, IL, USA). The normality of the distribution between groups was evaluated using the Kolmogorov-Smirnov test. The normally distributed means were compared using a Student t-test on independent samples. The Mann-Whitney U test was used to compare non-normally distributed means. The Chi-square or Fisher's exact test was employed for categorical variable analysis. A p-value of 0.05 or lower was considered statistically significant.

RESULTS

Our sample size was 104 patients. The 4.7 Fr group consisted of 51 patients, while the 6 Fr group comprised 53 patients. Mean age (51.18±16.23 vs 55.19±15.30, p=0.354) and gender distribution were found to be similar between the two groups Preoperative evaluations showed no statistically significant differences in the prevalence of diabetes mellitus, Charlson Comorbidity Indexes, or ASA scores between the two groups. Again, there was no discernible difference in terms of number, lateralization, pelvicalyceal position, or opacity of stones between the two groups. Further, there was no significant difference between the groups with regard to the presence/grade of hydronephrosis, the infundibulopelvic angle, or the use of anticoagulants. When comparing the two groups before and after surgery, there was no discernible difference in hemoglobin or creatinine levels. Table 1 provides demographic and laboratory results for the two groups.

Hospital stay, fever, emergency room visits, and stent migration rates were comparable between the two groups in the postoperative period. While VAS scores were recorded for both groups, the 6 Fr group had a much higher mean value (4.02±1.10 vs 4.81±1.53, p=0.006). Third-month stone-free rates after surgery were comparable between the groups, which is an important parameter (84.3 % vs 74.5 %, p=0.264). Postoperative follow-up data of the patients are given in Table 2.

DISCUSSION

After the endoscopic treatment of reno-ureteral stones, a ureteral stent is placed in a certain percentage of patients in order to prevent ureteral obstruction caused by stone fragments, edema, or clots. Also,

Table 1. Patient characteristics and laboratory findings

		4.7 Fr		6 Fr		p
Gender	Male	28	54.9%	34	64.2%	0.339
	Female	23	45.1%	19	35.8%	
Age (years)		51.1	±16.2	55.1	±15.3	0.354
ASA score	ASA- 1	28	54.9%	23	43.4%	0.168
	ASA- 2	20	39.2%	23	43.4%	
	ASA-3	3	5.9%	7	13.2%	
Diabetes		3	5.9%	5	9.4%	0.499
Charlson Index [median (IQR)]		1	(0-2)	2	(1-3)	0.104
Stone Lateralization	Right	21	41.2%	28	52.8%	0.236
	Left	30	58.8%	25	47.2%	
Stone Location	Pelvic	31	60.8%	39	73.6%	0.91
	Lower	5	9.8%	3	5.7%	
	Middle	0	0%	2	3.8%	
	Upper	1	2.0%	5	9.4%	
	Multicalyxal	14	27.5%	4	7.5%	
Stone Size (mm)		11.2	±4.3	12.8	±5.7	0.200
Opacity	Opac	34	66.7%	31	58.5%	0.392
	Non-opac	17	33.3%	22	41.5%	
Stone Number	Single	33	64.7%	36	67.9%	0.730
	Multiple	18	35.3%	17	32.1%	
Hydronephrosis		14	27.5%	17	32.1%	0.560
Infundibulopelvic Angle (°)		46.0	±13.0	48.8	±12.6	0.326
Preop hg (gr/dL)		14.2	±1.7	13.9	±1.8	0.266
Preop cr (mg/dL)		0.97	±0.35	1.08	±0.94	0.649
Postop hg (gr/dL)		14.0	±1.9	13.9	±1.6	0.592
Postop cr (mg/dL)		0.88	±.25	0.93	±0.31	0.416
Anticoagulant use		4	7.8%	9	17.3%	0.150
Alfa Blocker Use		3	5.9%	9	17.0%	0.078

ASA: American Society of Anesthesiologists. ***hg:*** *hemoglobin. cr: creatinine.* ***Postop:*** *postoperative.* ***Preop:*** *preoperative.*

Table 2. Postoperative follow-up data

	4.7 Fr (n=51)		6 Fr (n=53)		p
Hospital Stay	2.2	±.0.8	2.4	±1.8	0.412
PO Fever	4	7.8%	3	5.6%	0.658
VAS Score	4.0	±1.1	4.8	±1.5	0.006
Emergency Service Admission	2	3.9%	5	9.4%	0.264
Stent Migration	3	5.8%	1	1.8%	0.292
Stone Free Rate (PO 3. month)	43	84.3%	40	74.5%	0.264

PO: *Post-operative*

it reduces pain and preserves kidney functions (6,7). However, DJ-stent insertion is not routinely recommended in guidelines because it prolongs the operation time and brings additional cost and morbidity. The ultimate decision is left to the operating surgeon (10). Reported study outcomes clearly demonstrate that majority of urologists prefer stenting after fURS to manage small residing fragments and possible edema formation in the ureter due to the ureteral access sheath. A global study reported that the rate of stenting after kidney stone treatment with fURS was 80% (11).

Patients with DJ-stents face problems such as poor quality of life (QoL), lower urinary tract symptoms (LUTS), and body pain during the early postoperative period. In a meta-analysis, it has been well shown that the 6 Fr DJ-stent caused higher pain than smaller-sized stents (12). In the same study, patient ratings on the ureteral stent symptom score (USSQ) were lower for LUTS, general health, and additional problems, when the stent diameter was smaller. In contrast to the study cited above, we employed VAS to measure the degree of pain experienced by individuals after DJ implantation. As a result, our patients who had 6 Fr stents in situ, complained of higher pain throughout the surgical first week of follow-up, and it was consistent with the results of the mentioned meta-analysis. In contrast to our findings, a prior study comparing two stent types (5 Fr vs 6 Fr) with respect to postoperative pain using the VAS score, found no significant difference between the two groups (13).

Our study's primary objective was to assess the potential impacts of two different-sized stents on the patients' final stone-free status after three months of surgery. The long-term stone-free status of patients who underwent fURS treatment for kidney stones was unaffected by the insertion of 4.7 Fr or 6 Fr DJ. The emergency department admission rate was lower in the 4.7 Fr group, even though this difference was not statistically significant. Similar to this, we showed that the rate of stent migration was higher in the DJ group with the smaller diameter, but this difference did not reach the criteria for statistical significance. Our findings were supported by a previous study comparing the migration rates of 4.8 Fr and 6 Fr stents. Small-diameter stents were also more likely to migrate in this study (14).

No statistically significant difference in the incidence of postoperative fever between the two groups could be demonstrated in a randomized prospective study comparing 4.6 Fr and 6 Fr DJ-stents, and the findings of this study largely complied with ours regarding postoperative fever rates (15).

NCCT is regarded as the gold standard for estimating stone-free rates following fURS. In addition, it has been determined that 90 days postoperatively would be the optimal time for this scan (16). In the majority of studies examining the effect of different stent diameters on stone-free rates, postoperative NCCT was not routinely performed, in contrast to our study. This is one of our work's strengths (15,17,18).

LIMITATIONS

Our study's primary and most significant drawback is that it wasn't carried out in a prospective, randomized manner. Our study is retrospective even though stent size was randomly given to all patients included. Another restriction that seems to present is the small number of patients. A further drawback is the absence of a control group of patients who had the operation but were not inserted a DJ-stent. Another restriction is the fact that we were unable to compare the two groups using the USSQ questionnaire. Despite this, numerous studies, including a series of meta-analyses, have thoroughly assessed the effects of various-sized stents on irritative symptoms, quality of life, and other problems. The main goal of our study was to compare how stent size affected rates of final stone-free rates in the 3rd postoperative month. As a result, not using the USSQ score might not be considered a significant restriction.

CONCLUSION

Our findings indicated that a 6 Fr DJ catheter would be less advantageous than a 4.7 Fr one in terms of postoperative pain, which has an impact on patients' quality of life. Furthermore, it has been shown that the incidence of complications, such as fever and migration, is comparable in both groups. Based on our

findings, a smaller stent (4.7 Fr.) may be beneficial with the same stone-free but lower pain rates after surgeries. However, we believe that more randomized controlled trials with larger sample sizes are needed for this area.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Kafkas University Local Ethics Committee (Approval no: 02, Date: 2022/02/23) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design, Data acquisition, Data analysis and interpretation, Drafting the manuscript, Critical revision of the manuscript for scientific and factual content, Statistical analysis, Supervision; All authors contributed to this study equally.

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Can a single-layer of renorrhaphy be applied with hemostatic agent in robot-assisted laparoscopic nephron-sparing surgery applied to complex renal tumors?

Kompleks renal tümörlerde uygulanan robot yardımlı laparoskopik nefron koruyucu cerrahide hemostatik ajan eşliğinde tek kat renorrafi uygulanabilir mi?

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Özet

Amaç: Kompleks renal tümör nedenli robotik parsiyel nefrektomi uygulanan hastalarda hemostatik ajan eşliğinde tek kat renorrafi ile çift kat renorrafi kullanımı sonuçlarının karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Ağustos 2017–Şubat 2021 tarihleri arasında kompleks renal tümör (PADUA skoru≥10) nedenli robotik parsiyel nefrektomi uygulanan 51 hasta retrospektif olarak çalışmaya dahil edilmiştir. 36 hastada çift kat renorrafi(Grup 1), 15 hastada FloSeal® (Baxter Medical, Fremont, CA) hemostatik ajan eşliğinde tek kat renorrafi (Grup 2) uygulanmıştır. Pre- ve post-operatif serum kreatinin, glomerüler filtrasyon hızı ve hemoglobin düzeyleri, cerrahi ve sıcak iskemi süreleri, dren ve hastanede kalış süreleri, komplikasyonlar değerlendirildi.

Bulgular: Hastaların ortalama yaşı 50 olup kadın/erkek oranı 18/33'dü. Grup 1 ve Grup 2 ortalama PADUA skorları sırasıyla 11 ve 10.47 hesaplandı. Pre-, post-operatif 1.gün ve 6.ay ortalama serum kreatinin değerleri Grup 1'de sırasıyla 1.02, 1.15 ve 1.09 mg/dL olup Grup 2'de 0.93, 1.02 ve 0.90 mg/dL'idi. Pre-, post-operatif 1.gün ve 6.ay ortalama GFR değerleri Grup 1 'de sırasıyla 91.47, 77.31 ve 81.90 mL/dk/1.73m2 olup Grup 2'de 92.07, 84.93 ve 90.73 mL/dk/1.73m2 'idi. Pre- ve post-operatif hemoglobin değerleri de karşılaştırıldı. Operasyon ve sıcak iskemi süreleri sırasıyla Grup 1'de 118 ve 23 dk iken Grup 2'de 101 ve 13 dk olarak kaydedildi. Gruplar arasında dren ve hastanede kalış süreleri açısından anlamlı

Abstract

Objective: To compare outcomes of single-layer renorrhaphy suturing and hemostatic agent application with double-layer renorrhaphy among complex renal tumors.

Material and Methods: 51 patients who underwent robotic partial nephrectomy due to complex renal tumors (PADUA score ≥10) between August 2017 and February 2021 were retrospectively enrolled. A double-layer renorrhaphy was applied in 36 patients (Group 1), and a single-layer renorrhaphy plus hemostatic agent FloSeal® (Baxter Medical, Fremont, CA) was applied in 15 patients (Group 2). Pre- and post-operative serum creatinine, glomerular filtration rate, hemoglobin levels, surgical and warm ischemia time, drainage, hospital stay duration, as well as complications were all evaluated.

Results: Group 1 and Group 2 mean PADUA scores were 11 and 10.47, respectively. The mean preoperative, postoperative 1st day and 6th month serum creatinine were 1.02, 1.15 and 1.09 mg/dL in the Group 1 and were 0.93, 1.02 and 0.90 mg/dL in the Group 2, respectively. The mean preoperative, postoperative 1st day and 6th month glomerular filtration rates were 91.47, 77.31 and 81.90 mL/min/1.73m2 in the Group 1 and were 92.07, 84.93 ve 90.73 mL/min/1.73m2 in the Group 2, respectively. Operation and warm ischemia time were 118min and 23min in the Group 1, and 101min and 13 min in the Group 2, respectively. There was no significant difference between groups in terms of drain removal time and hospital stay. Periop-

The study was approved by Ethics Committee of Şişli Memorial Hospital (Approval No: 2021/09, Date: 26.02.2021). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

fark izlenmedi. Perioperatif sadece Clavian I ve II komplikasyonlar izlendi. Takipte herhangi nüks izlenmedi.

Sonuç: Robotik parsiyel nefrektomi uygulanan PADUA skoru 10-11 arasındaki kompleks tümörlerde hemostatik ajan eşliğinde tek kat renorrafi güvenle uygulanabilir.

Anahtar Kelimeler: robotik parsiyel nefrektomi, nefron koruyucu cerrahi, renorrafi, kompleks renal tümör

erative only Clavien I and II complications were observed with no recurrence during the follow-up.

Conclusion: A single-layer of renorrhaphy plus hemostatic agent application can be safely applied in complex renal tumors with a PADUA score between 10-11 undergoing robotic partial nephrectomy.

Keywords: robotic partial nephrectomy, nephron sparing surgery, renorrhaphy, complex renal tumor

INTRODUCTION

Nephron sparing surgery (NSS) commonly known as partial nephrectomy (PN), is currently the standard surgical intervention for small renal tumors (cT1, <7cm) (1). Increasing surgical skills with the aid of accurate case selection, NSS may be performed even for selected cT2 (>7cm) renal cortical tumors (2). One of the most important goals is to preserve maximum renal function during the postoperative term. On average there is a 20% renal function loss in kidneys after NSS due to ischemia and nephron loss during reconstruction (3). Thus creating challenging conditions for urologists. Some common surgical skills preferably used to diminish kidney damage are; supplying hypothermia, limited warm ischemia including zero or segmental ischemia, early unclamping (3).

During the last decade, robotic NSS has become the preferred technique among experienced laparoscopists due to lower ischemia times and shorter learning curve (4). Suturing of the tumor floor and renal parenchyma are essentials for hemostasis. In order to decrease the ischemia time and diminish nephron damage, single-layer renorrhaphy seems to be the most common method (5). During renorrhaphy (parenchymal) suturing in order to accelerate operation time while decreasing the ischemia time, certain hemostatic agents seem to be effective to prevent complications and nephron loss (6).

The aim of this study is to compare single-layer renorrhaphy plus hemostatic agent with double-layer renorrhaphy among complex renal tumors (PADUA score ≥ 10) in terms of both safety and effectiveness.

MATERIAL AND METHODS

Following the hospital's ethical committee approval (approval number 26022021/09), a total of 51 patients with complex renal cortical tumors that underwent robotic NSS between August 2017 and February 2021 were retrospectively collected. Complex renal cortical tumors were defined according to the PADUA classification (10-14) preoperatively by advanced radiologic imaging (7). All patients had preoperative standardized computerized tomography (CT) or magnetic resonance imaging (MRI) scans with adequate and correct enhancement protocols. All renorrhaphy sutures were performed with 3-0 V-lock™(V-20 Taper 6" 15cm ½ 26mm, Covidien Inc., Mansfield, MA, USA). Sliding clip renorrhaphy technique with hem-o-lock clips was performed in all procedures (8). Considering the renal parenchymal hemostasis and reconstruction patients were classified in two groups. The group 1 (n=36) consisted of double-layer 3-0 V-lock™ renorrhaphy sutures and the group 2 (n=15) was consisted of single-layer 3-0 V-lock™ renorrhaphy sutures plus hemostatic agent FloSeal® (Baxter Medical, Fremont, CA) application. Total surgery and warm ischemia time (WIT), pre- and post-operative hemoglobin levels (g/dL), pre- and post-operative creatinine levels (mg/dL), pre- and post-operative glomerular filtration rate (GFR) (mL/min/1.73m^2), total drainage (mL), hospitalization and drain removal times (day) were all recorded. The GFR values were calculated with MDRD formulazation.

Inclusion-exclusion Criterias

Patients with <10 cm renal cortical tumors (PADUA score ≥10) who underwent robot assisted laparoscopic NSS were included. Among them, patients with previously impaired renal functions and with a history of coagulopathy disorder were all excluded.

Surgical Technique

All the robotic NSS procedures were performed by

a robotic surgery trained surgeon with more than 500 case experience. According to tumor location opponent side lateral flex decubitus nephrectomy position was given to each patient. Patients prepped and draped in a regular fashion. The Da Vinci Xi robotic system (Intuitive Surgical, CA, USA) was docked with active 3 robotic arms. Three 8 mm robotic trocars were placed as in triangular manner. A 12 mm assistance trocar placed on midline superior to umbilicus. Taking in consideration the upper pole right kidney tumors in certain cases, an extra 5 mm assistance trocar was placed in the midline inferior to the xiphoid. On the left robotic arm bipolar fenestrated grasper, on the right robotic arm monopolar scissor and needle-holder were placed. The ascendant/descendant colonic segments were all medialized and access to retroperitoneal area was sustained. The kidney and tumor areas were all prepared for NSS. Bulldog clamp was used in each case during the warm ischemia. 3-0 V-lock™(V-20 Taper 6" 15cm ½ 26mm, Covidien Inc., Mansfield, MA, USA) sutures and sliding Hem-o-lock clips were used during the renorrhaphy steps. FloSeal® (Baxter Medical, Fremont, CA) was used as hemostatic agent. The tumor with its own Gerota's fat tissue were all placed inside an Endo bag. A Jackson-Pratt drain was placed at the end of each intervention.

Statistical Analysis

The data analyzed by GraphPad Prism version 9 (GraphPad Software, California, USA). The Shapiro-Wilk test was used for the normality and the distribution of variables. One-way ANOVA test used to compare GFR values across times in both group 1 and group 2 seperately. Multiple comparisons adjusted by the Tukey test. Adjusted p values are given in the Table 2. Friedman test and Dunn's multiple comparison test were used for the comparison of creatinine values across timelines in both group 1 and group 2 seperately. Numerical variables were compared using independent samples t-test or a Mann-Whitney U test. A $p < 0.05$ value was considered statistically significant.

RESULTS

The mean age of patients was 50 years, and the female/male ratio was 18/33 in the study cohort. Group 1 and Group 2 mean PADUA scores were 11 and 10.47, respectively. The mean pre-, post-operative 1st day and 6th month serum creatinine values were 1.02, 1.15 and 1.09 mg/dL in the Group 1 and were 0.93, 1.09 and 0.92 mg/dL in the Group 2, respectively (Table 2). In Group 1, there were significant differences in between pre- and post-operative serum creatinine levels ($p<0.05$) whereas there was no significant difference in between the post-operative 1st day and 6th month serum creatinine levels ($p=0.1377$). In Group 2, there was a significant difference in between pre- and post-operative serum creatinine levels ($p<0.05$) and a significance was relevant between the post-opreative 1st day and 6th month serum creatinine level ($p=0.0002$) (Table 2). The mean pre-, post-operative 1st day and 6th month glomerular filtration rates were 91.47, 77.31 and 81.90 mL/min/1.73m^2 in Group 1 and were 92.07, 84.93 ve 90.73 mL/min/1.73m^2 in Group 2, respectively.

Table 1. Comparison of the study groups

	Group 1 (n=36)	Group 2 (n=15)	p value
Age	51.44 ± 14.958	46.73 ± 14.074	0.302
Tumor size (cm)	5.53 ± 1.7269	4.93 ± 1.6586	0.258
PADUA score	11 ± 0.793	10.47 ± 0.516	**0.021**
Operation time (min)	118.19 ± 28.212	101.33 ± 14.573	**0.034**
WIT (min)	23.39 ± 7.299	13.07 ± 7.601	**0.00**
Bleeding (mL)	172.78 ± 68.603	114 ± 31.122	**0.003**
Duration of drain (days)	2.11 ± 0.465	2.13 ± 0.516	0.881
Duration of hospital stay (days)	2.97 ± 0.506	2.73 ± 0.594	0.151

Data given as Mean ± SD. ***Group 1****: Double-layer renorrhaphy suture,* ***Group 2:*** *Single-layer renorrhaphy suture, + hemostatic agent,* ***N:*** *number of patients,* ***WIT:*** *Warm ischemia time,* ***min:*** *minutes,* ***mL:*** *Milliliter, cm: centimeter.*

Table 2. The comparison of preopertive, post-operative early and at 6th months serum creatinine and GFR

Study Groups		Serum Creatinine	p value	GFR	p value
1 (N=36)	Preoperative [a]	1.022 ± 0.637	**0.0003** [a,b]	91.47 ±33.88	**<0.0001** [a,b]
	Postoperative [b]	1.158 ± 0.619	0.1377 [b,c]	77.31 ± 25.94	0.279 [b,c]
	Postoperative 6th month [c]	1.096 ± 0.628	**0.04** [a,,c]	81.90 ±27.58	**0.011** [a,c]
2 (N=15)	Preoperative [x]	0.938 ± 0.306	**0.003** [x,y]	92.07±28.11	0.117 [x,y]
	Postoperative [y]	1.093 ± 0.326	**0.0004** [y,z]	84.93±28.59	**0.024** [y,z]
	Postoperative 6th month [z]	0.922 ± 0.288	>0.999 [z,x]	90.73±26.28	0.814 [z,x]

Data presented as mean ± standard deviation (Mean ± SD). ***Group 1:*** *Double-layer renorrhaphy suture,* ***Group 2:*** *Single-layer renorrhaphy suture + hemostatic agent,* ***N:*** *Number of patients,* ***GFR:*** *Glomerular filtration rate.*
One-way ANOVA test used to compare GFR values across times in both group 1 and group 2. Multiple comparisons adjusted by the Tukey test. Adjusted p values are given in the Table. Friedman test and Dunn's multiple comparison test were used for the comparison of creatinine values across timelines. Adjusted p values are given in the Table.

Table 3. The distribution of pathology results among groups

	Group 1 (N=36)	Group 2 (N=15)
Malignant (N=42)		
Clear cell RCC	24	9
Papillary RCC		
Type 1	1	3
Type 2	3	-
Chromophobe RCC	1	1
Benign (N=9)		
Oncocytoma	4	-
Renal adenoma	-	1
Angiomyolipoma	2	-
Simple cortical cyst	1	1
Pathology stage (N=42)		
pT1a	12	4
pT1b	13	8
pT2a	3	1
pT2b	-	-
pT3a	1	-

Group 1: *Double-layer renorrhaphy suture,* ***Group 2:*** *Single-layer renorrhaphy suture + hemostatic agent,* ***N:*** *Number of patients,* ***RCC:*** *Renal cell carcinoma.*

Table 4: The distribution of complications according to Clavian-Dindo classification

	Group 1 (N=36)	Group 2 (N=15)
Grade I		
Antipyretics	2/36 (5.5%)	1/15 (6.6%)
Grade II		
Blood transfusion	1/36 (2.7%)	0/15 (0%)

Group 1: *Double-layer renorrhaphy suture,*
Group 2: *Single-layer renorrhaphy suture +hemostatic agent,* ***N:*** *Number of patients.*

There were significant differences in between pre- and post-operative 1st day and 6th months GFR in Group 1 (p=<0.0001). In Group 2, post-operative 1st day and 6th months GFR also showed significant difference (p=0.0246) (Table 2). During pre-, post-operative 1st day and 6th month controls there were no significant difference among serum creatinine levels and GFR in between groups (p>0.05). The mean pre- and post-operative hemoglobin values were 13.4 and 12.4 g/dL in Group 1 while they were 14.3 and 13.6 g/dL in Group 2, respectively (p>0.05). There was a significant difference in between the operation and WIT in between the groups (p<0.05) (Table 1). No significant difference was observed between groups in terms of drain removal and hospital stay. Perioperative only Clavian I and II complications as fever and blood transfusion were observed and listed on Table 4. The distribution of pathology results was listed on Table 3. No recurrence of any tumor was observed during the follow-up among both groups.

DISCUSSION

During the last decades the interest and preference of robot assisted laparoscopic NSS has been increased among urologists in the scope of minimal invasive surgery to lower complications rates, better surgical outcomes and shorter hospital stay (9). Besides the successful resection of tumor during NSS renal reconstructions to preserve renal function and to decrease complication rates are other key factors. Several renorrhaphy techniques such as early unclamping, segmental clamping, tumor enucleation, usage of hemostatic agents are some of the techniques utilized during renal reconstruction via NSS.

Sliding-clip renorrhaphy has become as universal standardized technique among urologists (10). Williams at el. demonstrated that omitting collecting system repair during robotic NSS a single-layer sliding-clip renorrhaphy decreases WIT without altering complications (11).

Shatagopam et al. compared single and double-layer renorrhaphy techniques in their literature review (12). The resected renal parenchymal volume and WIT are important parameters for renal function; however, recently renal reconstruction is also gaining importance for preserving renal functions (13). Bahler et al. showed that volume loss can be decreased by modifying the renorrhaphy technique (14). According to their study the single and double-layer renorrhaphy groups were consisted of 15 and 30 patients respectively. There were significant renal volume loss and GFR decrease between the groups whereas no differences in blood loss or complications. The median nephrometry scores were 6 while only in one patient with complex tumor (nephrometry score 10-12) single-layer renorrhaphy was performed (14). In another study Porpiglia et al. included a total of 50 patients with PADUA scores >8 (15). According to their results there were no significant differences considering serum creatinine and GFR in between the single and double-layer groups. However post-operative 3rd month renal scan demonstrated significant difference in between groups (15).

Antonelli et al. showed that adding hemostatic agents as FloSeal or TachoSil to renorrhaphy during NSS among clinical stage cT1a - cT1b tumors does not provide better surgical outcomes(16). However, Wille et al. evaluated a total of 102 patients underwent laparoscopic NSS (tumor sizes 0.5-8.5 cm) followed to collecting system repair the hemostasis was sustained only with FloSeal (17). Li et al. also demonstrated that laparoscopic NSS can be completed by usage of hemostatic agents as FloSeal or Tisseel on 31 patients with mean tumor size 2.9 cm (1.8-6.3 cm) and mean RENAL nephrometry score 6.3 (4-7) without intracorporeal suturing (6).

According to our results Group 2 where we used FloSeal, showed significantly lower PADUA scores, less WIT, operation time and bleeding. Post-operative transfusion was performed in only 1 of the patients who underwent double-layer renorrhaphy. There was a significant difference in terms of amount of drainage (p=0.003). We can say that patients who underwent a single-layer of renorrhaphy are the cases that do not have any expectation of bleeding. Also, in Group 2 preservation of renal function on long term seems to be better than in Group 1 (Figure 1). The post-operative 1st day and 6th months GFR in Group 2 showed significant difference. However, in Group 1

the post-operative 1st day and 6th months results did not differ (Table 2). During tumor resection, clipping of the vessels feeding the tumor, removal of the tumor with enucleation, and an effective single-layer suturing can better options to preserve kidney functions in the long term.

To the best of our knowledge this is the first study only evaluating the single-layer renorrhaphy among complex renal tumors with PADUA score ≥10. Comparison of pre- and post-operative scintigraphy evaluation is missing which may be a main limitation. Further studies including long term scintigraphy evaluations are needed.

CONCLUSION

In terms of lowering WIT and preserving long term kidney function, selected complex renal cortical tumors with PADUA score between 10-11 seem to be safely and successfully operated with single-layer renorrhaphy plus a usage of hemostatic agents by experienced robotic surgeons.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Şişli Memorial Hospital Ethics Committee (Approval Number: 26.02.2021/09) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Binbay M, Data acquisition; Aydoğan TB, Data analysis and interpretation; Aydoğan TB, Binbay M, Drafting the manuscript; Aydoğan TB, Critical revision of the manuscript for scientific and factual content; Binbay M, Statistical analysis; Aydoğan TB, Supervision; Binbay M.

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Original Research / Özgün Araştırma

Effect of large prostate volume on perioperative, oncological and functional outcomes after robotic radical prostatectomy: A retrospective clinical study

Büyük prostat hacminin robotik radikal prostatektomi sonrası perioperatif, onkolojik ve fonksiyonel sonuçlar üzerine etkisi: Retrospektif klinik çalışma

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Özet

Amaç: Bu çalışmada büyük prostat volümünün Robot yardımlı radikal prostatektomi (RARP) uygulanan prostat kanserli hastalarda cerrahi, onkolojik ve fonksiyonel sonuçlara etkisinin değerlendirilmesini amaçladık.

Gereç ve Yöntemler: Bu çalışmada prostat kanseri nedeniyle tek cerrah tarafından RARP uygulanan hastalar 75 cc'nin üzerinde büyük prostat hacmi (Grup-1) ve 75 cc'nin altında prostat hacmi (Grup-2) olmak üzere iki gruba ayrılmış ve bu iki grup retrospektif olarak karşılaştırılmıştır. Hastalar 12 aylık takip süresince değerlendirildi.

Bulgular: Yaş, preoperatif PSA seviyesi, klinik evre dağılımları , Gleason skoru, D'Amico risk sınıflaması, cerrahi öncesinde potens ve kontinans değerlendirmesi açısından iki grup arasında anlamlı fark yoktu (p>0.05). Operasyon süresi grup 1 ve 2'de sırasıyla 169.9 ± 62.5 dakika ve 145.6 ± 56.1 dakika saptandı ve Grup 1'de anlamlı olarak daha yüksekti (p = 0.02). Grup 1 ve 2'de sırasıyla 17 (%35) ve 2 (%3) hastaya mesane boynu rekonstrüksiyonu yapıldı ve grup-1'de istatiksel anlamlı olarak yüksekti (p = 0.001). Grup 1 ve Grup 2'de üretral kateter çıkarıldıktan sonra tam kontinans ve potens oranları 1 yıllık takip süresince benzerdi (p > 0.05). 6. ay ve 1. yılda biyokimyasal nüks oranları Grup 1 ve Grup 2'de benzer izlendi (p > 0.05).

Sonuç: Büyük prostat hacmine sahip prostat kanserli hastalarda RARP daha uzun operasyon süresi ile sonuçlanır ve mesane boynu rekonstruksiyonu gerekebilir. Ancak deneyimli cerrahlar tarafından gerçekleştirilen operasyonlarda büyük prostat hacminin cerrahi, fonksiyonel ve onkolojik sonuçlara olumsuz etkisi yoktur.

Anahtar Kelimeler: robotik cerrahi işlemler, prostatektomi, prostat, organ büyüklüğü

Abstract

Objective: In this study, we aimed to evaluate the effect of large prostate volume on surgical, oncological and functional outcomes in prostate cancer patients who underwent Robot-assisted radical prostatectomy (RARP).

Material and Methods: In this study, patients who underwent RARP due to prostate cancer by a single surgeon were divided into two groups as large prostate volume over 75 cc (Group-1) and prostate volume less than 75 cc (Group-2), and these two groups were compared retrospectively. Patients who were followed up for 12 months were assessed.

Results: There was no significant difference between the two groups in terms of age, preoperative PSA level, clinical stage distributions, Gleason score, D'Amico risk classification, preoperative potency and continence assessment (p>0.05). The operative time was 169.9 ± 62.5 minutes and 145.6 ± 56.1 minutes in Groups 1 and 2, respectively, and was significantly higher in Group 1 (p= 0.02). Bladder neck reconstruction was performed in 17 (35%) and 2 (3%) patients in Groups 1 and 2, respectively, and it was statistically significantly higher in Group-1 (p=0.001). After removal of the urethral catheter in Group 1 and Group 2, full continence and potency rates were similar during the 1-year follow-up (p >0.05). Biochemical recurrence rates at 6 months and 1 year were similar in Group 1 and Group 2 (p >0.05).

Conclusion: In prostate cancer patients with large prostate volume, RARP results in longer operative time and bladder neck reconstruction may be required.. However, in operations performed by experienced surgeons, large prostate volume does not have a negative effect on surgical, functional and oncological outcomes.

Keywords: robotic surgical procedures, prostatectomy, prostate, organ size

The study was approved by University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital Ethical Committee, (Decision No: 2021/482).
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

When the cancers observed in men are examined, prostate cancer is the second most common cancer type and the fifth leading cause of cancer-related deaths (1). Prostate specific antigen (PSA) as a screening test has become widespread in most countries, and with this, patients are beginning to be diagnosed and treated at an earlier stage (2). Prostate hyperplasia is a general condition that increases in prevalence with aging in men (3). With PSA screening tests, prostate cancer is also detected in the patients with large prostates, and the rate of cancer patients with large prostate volumes is increasing compared to the period before PSA was used (4).

Radical prostatectomy (RP) is the current gold standard curative treatment option in organ-confined prostate cancer, which includes the removal of the entire prostate and, if possible, aims to preserve continence and erectile functions (5).

The relationship between prostate volume and the degree of prostate cancer, functional and oncological results in the post-surgical period, and biochemical recurrence were examined and it was stated in the literature that progression was observed more frequently in the group of patients with small prostate volumes after surgery and prostate volume could be a predictive criterion for biochemical recurrence (6,7). In RP operations for large prostates, there are disadvantages such as limitation of mobility, difficulty in visualization, and the risk of adversely affecting functional and oncological results after the operation, especially in the patient group with narrow pelvis structure (8,9).

With the introduction of robot-assisted laparoscopic radical prostatectomy (RARP) after 2000, the Da Vinci robotic system has provided advantages such as similarity to wrist movements, three-dimensional image, microscopic magnification, ease in dissection and anastomoses, and has had a very common usage area (10).

In this study, we aimed to consider the effect of large prostate volume on perioperative, oncological and functional outcomes in the patients with RARP, which is frequently performed in our clinic.

MATERIAL AND METHODS

In this retrospective study, 256 patients between March 2016 and March 2018 were examined. RARP was applied to all patients. The study was conducted in our urology clinic after the approval of the ethics committee. History of prostate surgery (Transurethral or transvesical prostatectomy) and abdominal surgery was determined as the exclusion criteria. Prostate cancer patients with an enlarged median lobe of the prostate that median lobe larger than 1 cm in diameter were excluded from the study. Forty-eight patients who met the inclusion criteria of 75 cc and above were identified, and these patients were identified as having a large prostate volume and 51 consecutive patients who met the inclusion criteria among the patients below 75 cc were included in the study and formed the normal prostate volume group. The patients included in the study in both groups were operated by the same surgeon (V.T) who had sufficient experience and completed the learning curve (11). The Frankfurt technique described by Wolfram et al. was used as the surgical technique (12).

All patients underwent Multiparametric Magnetic Resonance Imaging (MpMR) of the prostate before the operation. According to the D'amico classification, the patients in the intermediate and high risk groups were examined with whole body bone scintigraphy. RARP was performed on the patients without adjacent organ invasion or distant metastasis. Nerve sparing method was not applied in the high risk group and in the cases with high tumor burden. A nerve-sparing technique was used in all other patients. Extended pelvic lymph node dissection was performed in the patients in the intermediate and high risk groups.

Before the operations, the demographic information of the patients, (age, body mass index (BMI)), preoperative PSA value, clinical stage, biopsy Gleason score, international prostate symptom score (IPSS), prostate size, the risk group they are included according to D'Amico risk classification was retrospectively scanned and noted according to the data of our clinic. Preoperative MpMR images were used for prostate size measurement. The patients with 75 cc and above were determined to have large prostate volume and the patients below 75 cc formed the other group.

To monitor functional results before RARP, a five-item international index of erectile function (IIEF-5) was applied for each patient for potency evaluation. Those who scored above 17 were considered normal (13). In addition, the preoperative patients were asked whether they had urinary incontinence. All of the patients included in the study consisted of fully continent patients. The patients were examined in terms of functional results in our outpatient clinic during the postoperative follow-up period. (7th day, 1st month, 3rd month, 6th month, 12th month, for the first year, after urethral catheter removal). Penile rehabilitation was routinely performed with catheter removal after surgery, and phosphodiesterase 5 inhibitors were used in patients. To evaluate the erectile function, the patients were asked if they could reach penile stiffness enough to allow penetration during sexual intercourse in the postoperative 6th and 12th months. Those who responded positively were considered potent. For the evaluation of continence, which is another functional condition, the patients were asked about their urinary incontinence status at the postoperative 1st week, 1st month, 6th month and 12th month. Three options were offered in response to this question. The group with no urinary incontinence and no need to use pads was the first option, and the group who rarely had urinary incontinence, incontinence with stress and only occasionally used pads for safety made up the second option. The third option was composed of the patients who had urinary incontinence and routinely needed to use one or more pads a day.

In all RARP cases, perioperative blood loss amount, total operation time, console time, anastomosis time, whether nerve-sparing technique was applied, bladder neck reconstruction requirement, postoperative hospital stay, urethral catheter removal time, pathological stage, Gleason score and surgical margin positivity data was recorded. This clinical study was conducted in accordance with the Principles of the Declaration of Helsinki.

Statistical Method

Mean, standard deviation, minimum maximum median, frequency and ratio values were used in the descriptive statistics of the data. The Kolmogorov Smirnov test was used to measure the distribution of variables. Mann-Whitney u test and independent sample t test were used in the analysis of quantitative data. Chi-square test was used in the analysis of qualitative data, and fischer test was used when the chi-square test conditions were not met. SPSS 22.0 software was used in the analyses.

RESULTS

In our study consisting of 99 patients, prostate volume was measured above 75 cc in 48 patients (group 1) and below 75 cc in 51 patients (group 2).

In the age, BMI, preoperative PSA value, clinical stage pathology examination, there was no statistically significant difference between Gleason score, preoperative IPSS and IEFF values of the two groups ($p > 0.05$) (Table -1).

Operation time, console time and urethrovesical anastomosis (UVA) time were found to be statistically and significantly longer in group 1 compared to group 2 ($p = 0.020$, $p= 0.021$, $p=0.007$). The amount of bleeding, catheterization time, and hospital stay were similar between the two groups ($p > 0.05$). The data on perioperative findings are given in Table-2.

There was no statistically significant difference between the two groups in terms of nerve-sparing procedure, surgical margin positivity, lymph node dissection rate, and biochemical recurrence ($p > 0.05$). Bladder neck reconstruction was performed in 17 patients (35%) in Group-1, and in 2 patients (3%) in Group-2. Bladder neck reconstruction rate was statistically significantly higher in group-1 compared to group-2 ($p = 0.001$).(Table 3).

In the examination of the complications, pulmonary embolism was seen in 1 patient in group-1 and urethral stenosis was seen in 2 patients in group-1, which was considered in Clavien 3-4 group. Minor complications grouped as Clavien 1-2 developed in 4 patients in group-1, while they were observed in 3 patients in group-2 and were not found to be statistically significant. ($p=0.233$) Major complications grouped as Clavien 3-4 developed in 3 patients in group-1, but not in group-2. It was not found statistically significant ($p=0.371$). Complications are listed in Table -4.

The postoperative functional evaluation is stated in Table-5. There was no significant difference in continence rates between the two groups at the 1st week, 1st month, 3rd month, 6th and 12th months after catheter

Table1. Patient demographic characteristics

		Prostate Volume > 75 cc				Prostate Volume ≤ 75 cc				p
		Ave.±SD /n-%		Med (Min-Max)		Ave.±SD/n-%		Med (Min-Max)		
Age		62.1 ±	5.1	62	53-71	61.0 ±	5.6	61	45-71	0.464
BMI (kg/m2)		27.3 ±	1.7	27	24-32	27.5 ±	1.7	27	25-30	0.688
ASA Score	I	16	34%			14	27%			0.509
	II	29	59%			36	71%			
	III	3	7%			1	2%			
Preop PSA		8.1 ±	4.9	7	1-27	9.0 ±	5.0	7	4-25	0.465
Prostate Weight		91.0 ±	16.1	83	75-130	45.0 ±	13.4	45	20-71	0.000
Clinical Stage	T1c	41	86%			39	76%			0.295
	T2a	7	14%			12	24%			
Preop IPSS	Mild	16	34%			15	29%			0.465
	Modarate	12	24%			8	16%			
	Severe	20	41%			28	55%			
Preop IIEF-5	≥17	34	72%			27	53%			0.087
	<17	14	28%			24	47%			
D'Amico Risk Classification	Low	28	59%			21	41%			0.133
	Intermediate	18	38%			29	57%			
	High	2	3%			1	2%			
Preop Gleason Score		6.2 ±	0.4	6	6-7	6.4 ±	0.5	6	6-7	0.173
Specimen Gleason Score		6.1 ±	0.4	6	6-7	6.4 ±	0.6	6	6-8	0.038

Mann-whitney u test / Chi-square test
***Ave. ±SD**: Average ± Standart Deviation; **PSA**: prostate-specific antigen; **ASA**: American Society of Anesthesiologists; **BMI**: body mass index ; **IPSS:** International Prostatism Symptom Score; **IEFF:** International Index of Erectile Function*

Table 2. Perioperative and postoperative data

	Prostate Volume > 75 cc				Prostate Volume ≤ 75 cc				p
	Ave.±SD		Med (Min-Max)		Ave.±SD		Med (Min-Max)		
Operation Time (min)	169.9 ±	62.5	170	130-360	145.6 ±	56.1	140	110-355	**0.020**
Console Time (min)	125.3 ±	43.3	125	100-320	106.0 ±	33.6	100	80-300	**0.021**
UVA Time (min)	34.3 ±	8.7	33	20-50	22.1 ±	7.1	24	17-45	**0.007**
Perioperative Hemorrhage (ml)	124.1 ±	44.1	105	75-300	110.5 ±	33.5	100	50-200	0.163
Catheterization time(day)	10.0 ±	0.7	10	8-12	10.1 ±	1.4	10	7-14	0.571
LOS (day)	4.5 ±	1.7	4	4-14	4.5 ±	1.8	4	4-14	0.472

*Mann-whitney U test **UVA:** Urethrovesical anastomosis; **LOS:** Length of Hospital Stay*

Table 3. Perioperative technique and postoperative oncological data

		Prostate Volume > 75 cc		Prostate Volume ≤75 cc		p
		n	%	n	%	
NVB Saved	Unilaterally	0	0%	1	2%	
	Bilaterally	43	90%	47	92%	0.466
	None	5	10%	3	6%	
Positive Surgical Margin	Negative	45	93%	45	88%	0.485
	Positive	3	7%	6	12%	
PLND	Bilaterally	0	0%	4	8%	0.291
	None	48	100%	47	92%	
Bladder Neck Reconstruction	No	31	65%	49	97%	0.001
	Yes	17	35%	2	3%	
Biochemical Recurrence	Yes	46	97%	50	98%	0.296
	No	2	3%	1	2%	

Chi-square test/ Mann-whitney u test
NVB Saved: *neurovascular bundle saved ;* ***PLND*** *: Pelvic Lymph Node Dissection*

Table 4. Complication rates

	Prostate Volume > 75 cc	**Prostate Volume < 75cc**	**p**
	n(%)	**n(%)**	
Minor Clavien 1-2			0.233
Anastomosis leakage	2 (4.2%)	1 (2 %)	
Urinary Tract Infection	1 (2.1%)	0 (0 %)	
Ileus	0 (0%)	1 (2 %)	
Bleeding	1 (2.1%)	1(2 %)	
Major Clavien 3-4			0.371
Pulmonary emboli	1 (2.1%)	0 (0%)	
Urethral stricture	2 (4.2%)	0 (0%)	
Totals	7 (14.6%)	3 (6%)	

Table 5. Functional outcomes

		Prostate Volume > 75 cc		**Prostate Volume ≤ 75 cc**		**p**
		n	**%**	**n**	**%**	
Urinary Continence Status 7.Days	Complete	16	33%	15	29%	
	Mild	21	45%	32	63%	0.879
	Incontinent	11	23%	4	8%	
Urinary Continence Status 1.Months	Complete	16	33%	30	59%	
	Mild	28	58%	21	41%	0.986
	Incontinent	4	10%	0	0%	
Urinary Continence Status 3.Months	Complete	28	58%	37	73%	
	Mild	19	40%	14	27%	0.784
	Incontinent	1	3%	0	0%	

Urinary Continence Status 6.Months	Complete	34	70%	43	84%	0.505
	Mild	13	28%	8	16%	
	Incontinent	1	3%	0	0%	
Urinary Continence Status 1.Year	Complete	43	88%	45	88%	0.545
	Mild	4	10%	6	12%	
	Incontinent	1	3%	0	0%	
Potency 6.Months	Yes	13	28%	10	20%	0.411
	None	35	72%	41	80%	
Potency 1.Year	Yes	34	70%	22	43%	0.657
	None	14	30%	29	57%	

Chi-square test

removal (p >0.05). When the potency was examined, the results were found to be similar between the two groups at the 6th and 12th months, no statistically significant difference was observed (p >0.05).

DISCUSSION

Robotic surgery for radical prostatectomy may have advantages such as facilitating dissection and achieving better functional results. However, the patients with larger prostates may experience difficulties as vision and mobility in the pelvis are affected (8). The effect of prostate size on functional and oncological outcomes after RP is discussed as a controversial issue. Despite many publications on this subject, no clear results could be obtained. In the meta-analysis examining prostate volume with oncological and functional results in the literature, it was seen that prostate volume sizes were different in different studies and there was no clear cut-off value. (14).

Large and small for prostate volume is not a clear definition. In the literature, the threshold value varies between 40 and 100 cc (15). In this study, the results of RARP applied in patients with prostates larger than 75 cc, which we accept as the threshold value, and prostates with normal volume were compared.

In the publications investigating the relationship between prostate volume and oncological outcomes, Allaparthi et al. reported that large prostate volume (PV) has a significant positive effect on pathological features, positive surgical margin rate, and biochemical recurrence-free survival (16). These results are similar to those of Moschini et al. and demonstrated that larger PV is an independent predictor for favorable disease traits (17). In these studies, it should not be ignored that prostate biopsies performed due to high PSA values in the patients with large PV with PSA elevation associated with diffuse benign prostatic hyperplasia potentially have better oncologic results by detecting earlier tumor stages (4). When the cases with localized prostate cancer are examined, it has been stated that the large amount of prostate tissue surrounding the cancerous lesion facilitates dissection and provides an advantage in terms of surgical margin negativity in the surgery of large-volume prostates (14). In our study, the mean preoperative PSA values, pathology results and D'amico risk classifications were similar between the two groups. When analyzed in this way, we found that there was no significant difference in positive surgical margin and biochemical recurrence rates between the two groups.

In the literature, Hirasawa et al. stated that as the prostate size increases, the amount of perioperative bleeding increases due to wider resection margins and increased vascularization and Kim et al. reported that the operation times are longer in RARPs with large PV (18,19). In our results, operation time and console time were found to be significantly longer in RARP cases with large PV, but there was no significant difference in the amount of bleeding.

As the prostate size increases, more dissection of the bladder neck may be required, resulting in a larger defect in the area to be anastomosed at the bladder

neck. In such cases, the bladder neck is anastomosed to the urethral stump using additional techniques (20). Yasui et al. published that patients with large prostate had longer anastomosis time, but this was not statistically significant (21). In our study, the UVA time and the necessity of bladder neck reconstruction were significantly higher in the group with large prostate.

Functional outcomes of RP are primarily evaluated depend on erectile function and continence status. Conservation of erectile and urinary functions is related to the nerve sparing procedure (22). Galfano et al. stated that there was no significant difference in 1-year potency ratios according to prostate volumes in the patients who underwent RARP (23). In our study, bilateral nerve-sparing procedures were applied to a large extent in both groups, and we found that large prostate volume did not have a negative effect on potency ratios at 1-year follow-up. It has been reported in the literature that there is a trend towards better early continence after RARP in the patients with small prostate volumes. However, it should be noted that the definition of continence is different between studies and the parameters and query forms used in the evaluation of continence are not standardized (14). On the other hand, Yasui et al. stated in their study that PV has no effect on the recovery of urinary functions after RARP (21). Although the literature contains contradictions in the relationship between prostate volume and functional results in the patients undergoing RARP, the continence rates were not significantly different between the two groups in our study, both in the early period and at the end of the first year.

The limitation of our study is its retrospective design and the fact that it was conducted with a relatively small number of patients.

CONCLUSION

RARP can be considered a more challenging operation in the patients with large prostates, due to having difficulties such as a long operation time and the need for bladder neck reconstruction. However, the prostate size does not have a negative effect on the oncological and functional outcomes in the procedures performed by experienced surgeons.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by University of Health Sciences, Dr. Sadi Konuk Training and Research Hospital Ethical Committee (Decision No: 2021/482) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Sungur U, Evren İ, Gürbüz N, Taşçı Aİ, Data acquisition; Kargı T, Karadağ S, Polat H, Data analysis and interpretation; Ekşi M, Evren İ, Tuğcu V, Drafting the manuscript; Sungur U, Gürbüz N, Critical revision of the manuscript for scientific and factual content; Kargı T, Hacıislamoğlu A, Polat H, Statistical analysis; Ekşi M, Karadağ S, Supervision; Sungur U, Evren İ, Hacıislamoğlu A,Gürbüz N, Taşçı Aİ.

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Original Research / Özgün Araştırma

Impact of urethrovesical anastomotic leakage after robotic radical prostatectomy on early postoperative continence

Robotik radikal prostatektomi sonrası üretrovezikal anastomoz kaçağının erken postoperatif kontinans üzerine etkisi

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Özet

Amaç: Bu çalışmada robot yardımlı radikal prostatektomi (RYRP) uygulanan hastalarda üretrovezikal anastomoz kaçağı (UAK) ve ilişkili faktörleri ve bunun erken kontinans üzerine etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu retrospektif analizde Şubat 2017 ile Haziran 2022 tarihleri arasında RYRP uygulanan 81 hastanın verileri değerlendirildi. Ameliyat sonrası yedinci günde hastalarda UAK olup olmadığını belirlemek için sistografi çekildi. UAK'ye yol açabilecek faktörleri araştırmak için tek ve çok değişkenli analizler yapıldı. Ameliyattan 6-12 hafta sonra hastalarda kontinans oranları kaydedildi.

Bulgular: Toplamda 25 hastada (%31) UAK vardı; 12'si (%15) hafif, 8'i (%10) orta ve 5'i (%6) ileri derecedeydi. Dren/serum kreatinin oranının >1,5 olması ve prostat hacminin >53 cm^3 olması UAK'yi öngörmede hem tek değişkenli hem de çok değişkenli analizlerde anlamlı bulundu (sırasıyla p=0,017 ve p=0,046). Postoperatif ikinci veya üçüncü günde dren çıkışı 100 ml'den fazla olan 36 hastanın sekizinde (%22) yüksek dren/serum kreatinin oranı (>1,5) vardı ve bunların yedisinde (%88) UAK vardı. Erken dönem takip verilerine göre UAK'lı hastaların 9 (%36)'sında, UAK'sız hastaların ise 20 (%37)'sinde inkontinans saptandı (p=0,959).

Sonuç: Sistografi, RYRP sonrası anastomoz kaçağını tespit etmede etkili bir yöntemdir. Büyük prostat hacmi (>53 cm^3) ve yüksek postoperatif dren/serum kreatinin oranı (>1.5) UAK ile ilişkili bulunmuştur. UAK'ın erken kontinans üzerinde etkisi gözlenmemiştir.

Anahtar Kelimeler: anastomoz kaçağı, idrar kaçırma, robot yardımlı, prostatektomi, sistografi

Abstract

Objective: This study aimed to assess the urethrovesical anastomotic leakage (UAL) and associated factors in patients who underwent robot-assisted radical prostatectomy (RARP) and its effect on early continence.

Material and Methods: The data of 81 patients who underwent RARP between February 2017 and June 2022 were evaluated in this retrospective analysis. On the seventh postoperative day, we performed a cystography to determine whether the patients had UAL. Uni- and multivariate analyses were done to investigate the factors that could lead to UAL. Continence rates were recorded in patients at 6-12 weeks after surgery.

Results: Overall 25 patients (31%) had UAL; of them 12 (15%) were mild, eight (10%) were moderate, and five (6%) were extensive. A drain/serum creatinine ratio >1.5 and a prostate volume >53 cm^3 were determined to be significant in predicting UAL in both the uni- and multivariate analyses (p=0.017 and p=0.046, respectively). On the postoperative second or third day, of the 36 patients who had drain output greater than 100 ml, eight (22%) had a high drain/serum creatinine ratio (>1.5), seven (88%) of which had UAL. According to the early period follow-up data, incontinence was prevalent in 9 (36%) of the patients with UAL and 20 (%37) of the patients without UAL (p=0.959).

Conclusion: Cystography is an effective method for detecting leakage after RARP. A large prostate volume (>53 cm^3) and a high postoperative drain/serum creatinine ratio (>1.5) were found to be associated with UAL. UAL had no effect on early continence.

Keywords: anastomotic leak, cystography, prostatectomy, robot-assisted, urinary incontinence

The study was approved by Koç University Ethical Committee, (Decision No: 2022.449.IRB1.175, Date: 2022/12/06).
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Urethrovesical anastomotic leakage (UAL) is one of the possible early complications in patients undergoing radical prostatectomy (RP) for prostate cancer. Until recently, radical prostatectomy was performed using the open method, and most of the studies on UAL were conducted in the open RP era. In these studies, especially the anastomosis part of open surgery was seen as an important predictor among the factors that caused UAL (1, 2). Recently, robot-assisted radical prostatectomy (RARP) has become increasingly popular and the most widely used method. One of the points that robot assistance is most utilized is urethrovesical anastomosis. In addition to providing a better view, the comfort created by the robot arms in a narrow space such as the Retzius space can facilitate urethrovesical anastomosis (3).

The clinical significance of UAL in prolonged catheterization time, peritonitis, ileus, need for intra-abdominal drain placement, prolongation of time to continence, and urethral stricture has been demonstrated by many studies (4, 5).

While in some centers the Foley catheter is removed based on the creatinine level of the drain output, in other centers the catheter can be taken out on the specified day without any control. Cystography, on the other hand, is one of the most effective diagnostic methods for UAL (2). However, cystography to evaluate urethrovesical anastomosis is not a routine practice in many centers. While failing to perform cystography can lead to the underdiagnosis of anastomotic leakage, performing it on all patients, on the other hand, is not cost-effective and may cause overdiagnosis.

In this study, we aimed to reveal the incidence and severity of UAL, and its effect on early continence in patients who underwent RARP and indicate the associated risk factors.

MATERIAL AND METHODS

After the approval of the ethics committee (2022.449. IRB1.175), the data of 92 patients who underwent RARP followed by cystography between 2017 and 2022 were evaluated in this retrospective analysis. Patients with regular follow-up data were included in the study. Of them, 11 patients were excluded from the study since their cystographies were performed in another center that did not meet our standards for cystography. The remaining 81 patients were included in the study.

Variables including demographic and perioperative data were recorded. The cystography findings at the end of the first week and the continence statuses between the 6th and 12th weeks were noted.

All surgeries were performed by a single surgeon (MDB) who had fifteen years of experience in robotic surgery, using the transperitoneal approach, utilizing the da Vinci Surgical System (Intuitive Surgica, Sunnyvale, CA, USA). The posterior reconstruction of urethrovesical anastomoses was performed using the Rocco technique. Then, the anastomosis was completed using the 3.0 STRATAFIX™ Spiral PGA-PCL sutures over a 22 Fr Foley catheter using the Van Velthoven technique, starting at the six o'clock position. At the end of the operation, a drain was placed in the minor pelvis.

All patients were scheduled for cystography on the postoperative seventh day. The patients were given 150 ml of contrast material through the Foley catheter during cystography. Oblique and anteroposterior images were obtained under C-arm fluoroscopy. Anastomotic leakage was categorized according to Han's classification. Moderate and extensive leakage were both considered major leakage (6). The Foley catheters were removed from patients with mild leakage at the end of cystography. In case of moderate and extensive leakage, cystography was performed again on the 14th day, and if there were no or mild leakage, the urethral catheter was removed. The same technique was performed on day 21 and day 28 if the leakage persisted with the same severity. The continence statuses of the patients were evaluated between the 6th and 12th weeks. According to the recommendation of the International Continence Society (ICS), any level of involuntary urine leakage was considered urinary incontinence (UI) (7).

Statistical Method

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) were used to describe the continuous variables. The conformity of the continuous variables to the normal distribution was examined using the Shapiro-Wilks test. Univariate

evaluation between leakage/non-leakage groups and minor/major leakage groups were analyzed with the Univariate Logistic Regression Analysis. The statistical evaluation was followed by using Multivariate Logistic Regression Analysis, by including the independent variables, which are found as statistically significant in univariate analysis.

The statistical significance level was determined as $p<0.05$. Analyses were performed using MedCalc® Statistical Software v.19.7.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021) and IBM IBM SPSS Statistics for Windows, v.28.0. (IBM Corp., Armonk, NY, USA).

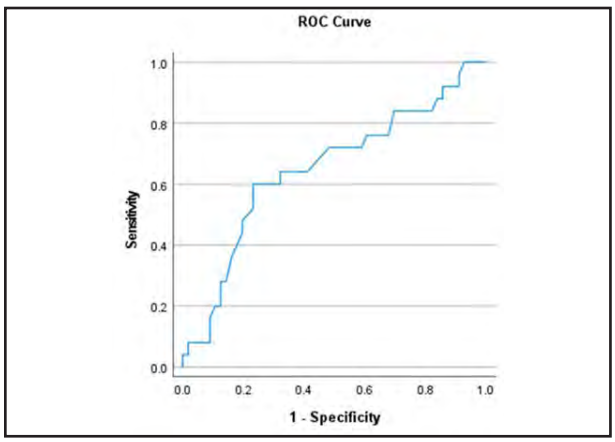

Figure 1. Area under the ROC curve for prostate volume in predicting urinary leakage

RESULTS

Demographic data and perioperative findings of the patients are summarized in Table 1. UAL was observed in 25 (31%) of the patients that underwent cystography at the end of the first week. Of them, 12 (15%) had mild, 8 (10%) moderate, and 5 (6%) extensive leakage.

The area under the curve (AUC) for prostate volume in predicting UAL was 0.649, with a cut-off value of 53 cm^3 (p=0.002) (Figure 1). Table 2 shows the univariate analysis results of the patients with and without UAL. UAL was observed more frequently in patients with a prostate volume greater than 53 cm^3 and patients with a drain/serum creatinine ratio above 1.5. In multivariate analysis, a prostate volume >53 cm^3 and a drain/serum creatinine ratio >1.5 were found to be significant predictors of UAL (p=0.046 and p=0.018, respectively).

On the second and third postoperative days, creatinine was measured in the drain fluid of seven patients with a mean drain output between 100-200 ml and 29 patients with a mean drain output above 200 ml. The mean drain fluid output was 339±206 ml. The drain/serum creatinine ratio was >1.5 in eight (22%) of the patients whose drain creatinine levels were measured. Seven (88%) patients with drain creatinine measurement had UAL.

Table 1. Demographic characteristics and perioperative data of the patients

Age, years	63(57.5-69.5)
BMI, kg/m²	28.1±3.6
Number of patients with diabetes	18 (22.2%)
Number of patients with previous prostate surgery	6 (7.4%)
PSA level (range), ng/mL	6.4 (4.8-9.5)
Prostate volume, cm^3	49.4±20.2
Duration of operation, minutes	200(180-235)
Number of patients with nerve sparing	76 (93.8%)
Number of patients with lymph node dissection	56 (69.1%)
Blood loss, mL	100(50-200)
Length of hospital stay, days	3(3-4)
Leakage	
None	56 (69.1%)
Mild	12 (14.8%)
Moderate	8 (9.9%)
Extensive	5 (6.2%)

Data are given as mean±SD for normal distributed data, med(IQR) for non-normally distributed data.

Table 2. Univariate analysis results of the demographic data in the diagnosis of urethrovesical anastomosis leakage

	Leakage - (n=56)	Leakage + (n=25)	p	OR	95% CI
Age, years	62(57-68)	66(58-70)	0.376	1.03	0.97-1.09
BMI, kg/m²	27.7(24.8-29.7)	29(26.2-30.6)	0.615	1.03	0.91-1.12
Number of patients with diabetes	14 (25%)	4 (16%)	0.372	0.57	0.17-1.95
Number of patients with previous prostate surgery	5 (8.9%)	2 (8%)	0.873	0.87	0.16-4.82
PSA level, ng/mL	6.2(4.7-9.5)	7(5.3-10.8)	0.821	1.01	0.96-1.06
Number of patients with a prostate volume >53 cm³	10 (17.8%)	12 (48%)	**0.002**	**4.96**	**1.80-13.67**
Duration of operation, minutes	195(180-227.5)	210(167.5-265)	0.073	1.01	0.99-1.01
Number of patients with nerve sparing	52 (92.8%)	24 (96%)	0.592	1.85	0.20-17.41
Number of patients with lymph node dissection	41 (73.2%)	15 (60%)	0.093	0.43	0.16-1.15
Number of lymph nodes	28(21.5-40.5)	21(16-31)	0.133	0.96	0.90-1.01
Blood loss, mL	100(77.5-200)	100(50-175)	0.554	0.99	0.99-1.01
Drain output, ml	120(52.5-281.5)	90(50-290)	0.456	1.00	0.99-1.01
Number of patients with a drain/ serum creatinine ratio >1.5†	1 (4.2%)	7 (58.3%)	**0.003**	**32.2**	**3.2-323.7**
Length of hospital stay, days	3.5(3-4)	3(3-4)	0.754	1.05	0.76-1.46

BMI: body mass index, PSA: prostate-specific antigen.
**Data are given as mean±SD for normal distributed data, med(IQR) for non-normally distributed data.*
†The drain/serum creatinine ratio was evaluated on a total of 36 patients.
Significant p values are written in bold.

Table 3. Univariate analysis results of the demographic data in the diagnosis of major urethrovesical anastomosis leakage

	No or minor leakage (n=68)	Major leakage (n=13)	p	OR	95% CI
Age, years	63(57.3-69)	63(57.5-70.5)	0.962	0.99	0.93-1.07
BMI, kg/m²	27.7(25-29.7)	29(27.2-32.1)	0.124	0.13	0.97-1.34
Number of patients with diabetes	17 (25%)	2 (15%)	0.198	0.25	0.03-2.07
Number of patients with previous prostate surgery	5 (7.4%)	1 (7.7%)	0.883	0.85	0.093-7.69
PSA level, ng/mL	6.1(4.7-9.4)	7.2(6.2-11.4)	0.625	1.01	0.95-1.07
Number of patients with a prostate volume >53 cm³	18 (26.5%)	8 (61.5%)	**0.002**	**9.26**	**2.29-37.5**
Duration of operation, minutes	200(180-233.8)	210(152.5-255)	0.993	1.00	0.99-1.01
Number of patients with nerve sparing	64 (94.1%)	12 (92.3%)	0.804	0.75	0.08-7.31

Number of patients with lymph node dissection	49 (72.1%)	7 (53.8%)	0.119	0.38	0.12-1.28
Number of lymph nodes	27(19.5-37)	21(16-39)	0.823	0.99	0.93-1.06
Blood loss, mL	100(55-200)	100(50-225)	0.523	0.99	0.99-1.00
Drain output, ml	107.5(50-273.8)	250(50-385)	0.094	1.00	1.0-1.01
Number of patients with a drain/serum creatinine ratio >1.5†	4 (14%)	4 (50%)	**0.044**	**6.00**	**1.05-34.32**
Length of hospital stay, days	3(3-4)	3(3-7)	0.298	1.22	0.84-1.77

BMI: body mass index, PSA: prostate-specific antigen.
**Data are given as mean±SD for normal distributed data, med(IQR) for non-normally distributed data.*
†The drain/serum creatinine ratio was evaluated on a total of 36 patients.
Significant p values are written in bold.

Table 4. Multivariate analysis results of the variables for leakage and major leakage

	Multivariate analysis					
	No leakage vs leakage			No/minor leakage vs major leakage		
	p	OR	95% CI	p	OR	95% CI
Prostate volume >53 cm³	**0.046**	6.468	1.033-40.494	0.149	5.214	0.647-41.988
Drain/serum creatinine ratio >1.5	**0.017**	20.456	1.725-242.55	0.061	6.259	0.891-1568

CI: confidence interval, OR: odds ratio.
Significant p values are written in bold.

In the comparison of patients with major leakage and those with no/minor leakage, having a prostate volume >53 cm^3 and a drain/serum creatinine ratio >1.5 were significant in univariate analysis but not in multivariate analysis (Table 3 and Table 4).

The urinary catheters of three patients with moderate UAL among 13 patients with a major UAL were removed on the seventh day. In the remaining 10 patients, cystography was repeated at the end of the second week. While leakage with the same severity was observed in one patient, no/mild leakage was observed in the rest. The catheters of the patients who were not observed to have major leakages at the second week follow-up were removed, while the catheter of the only remaining patient was removed after the leakage regressed at the third week follow-up.

While full continence was prevalent in 16 (64%) of the patients with UAL at the 6th and 12th week follow-ups, the rate of patients using one pad a day was 5 (20%) and the rate of patients who did not prefer to use pads was also 4 (16%). Full continence was prevalent in 35 (63%) of the patients without UAL. In this group, the rate of patients using one pad a day was 13 (23%), while the rate of patients who did not use pads was 8 (14%) (p=0.959).

DISCUSSION

The current study, in which we investigated UAL in patients undergoing RARP, revealed several noteworthy findings. First, we could demonstrate that prostate volume is a determinant in urinary incontinence. In addition, we found urinary anastomosis leakage to be higher in patients with a prostate volume >53 cm^3. Cormio et al. also found that prostate volume is the most effective factor in predicting UAL. In their study, the cut-off value for prostate volume was reported as 40 cc (8). In patients with a large prostate volume, the distance between the remaining urethra and bladder is

expected to be large, which in turn may lead to difficulty in bringing the urethra closer to the bladder. Techniques for both supporting anastomosis and preventing postoperative incontinence have been described in previous studies. Some of the common techniques include Rocco stitches, advanced reconstruction of vesicourethral support (ARVUS), and total anatomical reconstruction described by Porpglia et al. (9-11). We apply the Rocco method as a standard in all our cases. With this method, a tension-free posterior support and a tension-free vesicourethral anastomosis are provided. Previous studies have shown that posterior support facilitates vesicourethral anastomosis and reduces UAL rates (12, 13).

Second, we showed an association between the drain creatinine value and UAL. In our study, drain creatinine was measured in 36 patients (44%) whose drain fluid was observed to work excessively on the second or third postoperative day (>100 ml). Lymph node dissection was performed in two-thirds of the operated patients in our series, while the mean number of lymph nodes removed was 29. As a result, drain creatinine was measured to differentiate between lymphatic drainage and anastomotic leakage. Our study has shown that a drain fluid/serum creatinine ratio above 1.5 is a predictor of UAL. In a limited number of previous studies, various cut-off values between 1.2 and 2 have been proposed to predict UAL (14-16).

In previous studies, the effects of factors such as age, body mass index, diabetes, the duration of operation, the amount of intraoperative bleeding, and the number of dissected lymph nodes on UAL have been shown (4, 17). However, we could not establish a significant relationship between these factors and UAL.

Third, in our study, the incidence of UAL was 31%. The prevalence of UAL has been reported to vary between 4% and 33% in previous studies, which shows that our result is within the limits reported in the literature (2, 18-20). Although the surgical technique and patient characteristics are important, the method used for evaluating anastomotic leakage may also have an impact on the potential causes that affect UAL rates. During the imaging performed with a C-arm X-ray, the contrast medium can be given through the Foley catheter as a drop infusion with gravity or directly by a catheter tip syringe. Using a catheter tip syringe may result in a faster and more pressurized delivery than the other, which may affect leak detection rates (4). The difference between drip infusion cystography and fast-filling cystography may be the subject of other research.

Besides the studies showing the relationship of UAL with postoperative urinary incontinence, the literature holds other studies showing that even major UAL does not affect continence (4, 21, 22). Varkarakis et al. showed that there was no difference in the continence rates at the third, sixth, and 12th month controls between patients with and without UAL (20). In Tohi et al.'s study, the effect of UAL on urinary incontinence was determined only in the early period (3rd month) (23). In our study, we evaluated the continence status in the early period (6 to 12 weeks) and found that only 36% of the patients with UAL and 37% without UAL had incontinence. These rates are consistent with those from the previous studies (4, 20-22).

Our study had some limitations. First, it had a retrospective design. Second, the results of the study include the results of a single surgeon's operation. For this reason, the surgeon's ability, which is one of the factors that may affect UAL, could not be the subject of this study. Third, the fact that the number of patients with UAL was not high may have affected the results statistically. Fourth, the drain creatinine level was measured only in patients with a high drain output; we could not assess the remaining patients' drain/serum creatinine rates.

CONCLUSION

Cystography is an effective method to detect anastomotic leakage after RARP. Despite the routine Rocco sutures, UAL was more common in patients with large prostate volumes (>53 cm^3). We also found that a high postoperative drain/serum creatinine ratio (>1.5) was associated with UAL. Our study confirms that UAL had no effect on early urinary continence.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Koç University Ethical Committee (Decision No: 2022.449.IRB1.175, Date:2022/12/06) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Kılıç M, Balbay MD, Data acquisition; Kılıç M, Madendere S, Tekkalan FB, Köseoğlu E, Data analysis and interpretation; Kılıç M, Eden BA, Balbay MD, Drafting the manuscript; Kılıç M, Madendere S, Balbay MD, Critical revision of the manuscript for scientific and factual content; Kılıç M, Madendere S, Balbay MD, Statistical analysis; Eden BA, Supervision; Balbay MD.

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Original Research / Özgün Araştırma

The applicability of laparoscopic adrenalectomy and our experience at a secondary health institution

İkinci basamak devlet hastanesinde laparoskopik adrenalektomi uygulanabilirliği ve deneyimlerimiz

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Özet

Amaç: Laparoskopi eğitiminin yaygınlaşması, ileri düzey laparoskopik girişimlerin ikinci basamak sağlık kuruluşlarında da yapılabilmesine olanak tanımıştır. Biz laparoskopiye yeni başlayan kliniğimizde transperitoneal laparoskopik adrenalektomi deneyimlerimizi paylaşmayı amaçladık.

Gereç ve Yöntemler: Ekim 2012 ve Nisan 2019 arası laparoskopik transperitoneal adrenelektomi yapılan otuz hasta çalışmaya dahil edildi. Retrospektif olarak yapılan değerlendirmede; cinsiyet, yaş, beden kitle endeksi, adrenal kitle karakteristikleri, hormonal aktivitesi,operasyon süresi,kanama durumu, transfüzyon ihtiyacı, final patoloji ve komplikasyon oranları incelendi.

Bulgular: Ortalama kitle boyutu 48.5±23 milimetre ve ortalama operasyon süresi 70.2±21.6 dakika olarak bulundu. Peroperatif ortalama kanama miktarı 41±48.8 cc olarak bulunurken sadece 2 hastada transfüzyon ihtiyacı görüldü. Ortalama hastanede yatış süresi ise 1.3±0.88 gün olarak bulundu. Vakaların hiçbirinde açık tekniğe dönüş gerekmedi ve 2 hastada transfüzyon ihtiyacı dışında major komplikasyon yaşanmadı.

Sonuç: Transperitoneal laparoskopik adrenelektomi cerrahisi, yeterli eğitim sonrasında uygun hastalarda ikinci basamak hastanelerde de düşük komorbidite ve mortalite oranları ile güvenle uygulanabilir.

Anahtar Kelimeler: laparaskopi, transperitoneal, adrenalektomi, deneyim, açık cerrahi

Abstract

Objective: Since the laparoscopy education had became widespread, the advance laparoscopic procedures can be performed even at secondary public hospitals. In this study, we aimed to present our experience of the first seven years of laparoscopic transperitoneal adrenalectomy.

Material And Methods: the study included 30 patients with laparoscopic transperitoneal adrenalectomy (LA) performed from October 2012 to April 2019. The retrospective assessment investigated age, sex, body mass index, adrenal mass characteristics, hormonal activity, operation duration, hemorrhage status, transfusion requirements, final pathology and complication rates.

Results: Mean age was 54.3±11.5 years and mean body mass index was 25.6±2.7 kg/m2. Mean mass size was 48.5±23 mm and mean operation duration was 70.2±21.6 minutes. Mean peroperative hemorrhage amount was 41±48.8 cc, while only 2 patients required transfusion. Mean hospitalization duration was 1.3±0.88 days. None of the laparoscopic cases was converted to open surgery, and no major complications such as death recorded.

Conclusion: Transperitoneal laparoscopic adrenalectomy (LA) surgery may be performed safely after adequate training for appropriate patients with low morbidity and mortality.

Keywords: laparoscopy, adrenalectomy, experience, open surgery, transperitoneal

The study was approved by Memorial Bahçelievler Hospital Ethical Committee, (Decision No: 2022-63, Date: 2022/07/27).
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Open adrenalectomy has been the most popular surgical technique for adrenal pathologies, and is performed for nearly a century, starting in the late 19th century to 20th. In this technique adrenal glands are totally resected transabdominally or retroperitoneally, which may cause complications due to its invasive nature, effecting surgical results (1,2).

Recently, with the developments in laparoscopic techniques, minimally invasive adrenalectomy mostly replaced open surgery due to having fewer complications, thus open technique was preserved only for tumors bigger than 8 cm such as feochromositoma, and for cortical adrenal cancers with higher risk of local invasion (1-3).

Laparoscopic adrenalectomy (LA) was first performed in 1992 (4). Many approaches like transperitoneal, lateral retroperitoneal and posterior retroperitoneal approach have been defined for laparoscopic adrenalectomy.

Laparoscopy is an advanced surgical procedure yielding satisfactory outcomes with better cosmesis and acceptable mortality and morbidity rates including decreased hemorrhage, shorter hospitalization duration, lower complication rates (5-7). However it is not a 'zero complication' technique, that is, it requires high skill and experience level and the limited excess to the equipments limits its widespread usage (2,8-10). Although, open surgery may be used for advanced-stage malignancies and large tumors, the most common complications of open surgery are wound and pulmonary infections, hematoma, sepsis, and thrombosis (11,12).

Laparoscopic surgery as being an advanced surgery requiring high skill level and experience, has a learning curve that is reported in the literature to be stabilized between 20 and 40 surgical cases. (13-15).

In this study, we aimed to present our experience of the first seven years of laparoscopic transperitoneal adrenalectomy, which we performed after having an experience of laparoscopic nephrectomy cases of more than 55. Final outcome, peroperative data and complication rates were assessed.

MATERIAL AND METHODS

The study included 30 patients with laparoscopic transperitoneal LA performed from October 2012 to April 2019. The data retrospectively assessed are, age, sex, body mass index, adrenal mass dimensions, hormonal activity, operation duration, mean blood loss, and transfusion requirement, rates of conversion to open technique, histopathological results and intraoperative and postoperative complications, mortality rate. Hormonally active tumors or tumors bigger than 4 cm, increasing of dimensions during follow up, any suspicion of malignancy in radiological imaging were the main surgical indications.

Diagnosis of adrenal tumors is established by computerized tomography and magnetic resonance imaging. During diagnosis and treatment of hormone-active adrenal tumors, consultation was requested with the endocrinology department and care was coordinated with the endocrinology department before and after the operation.

All procedures were performed under general anesthesia. A semi-flank positioning (on the left or right side) of the patient is facilitated. By bending the operating table 20-30 degrees at 4-5 cm superior to the iliac crest, the highest level of distance was maintained between the iliac crest and the lower ribs (Figure 1). Usually three or four ports (Two 10-mm ports for the camera and right hand and one or two 5-mm ports for other instruments) were used during the procedure (Figure 2). Nasogastric tube and Foley catheter should also be applied. After dissection of the adrenal gland, the adrenal vein was identified (Figure 3) and sealed using Liga-Sure or with a Harmonic Scalpel or by clipping (Figure 4). The adrenal mass was dissected carefully again using the Liga-Sure or a Harmonic Scalpel (Figure 5). The specimen was retrieved totally in an specien retrieval bag (Figure 6).

The blood loss was assessed as the blood level in the suction machine. The surgery time starting from the first incision for the camera port to its closure.

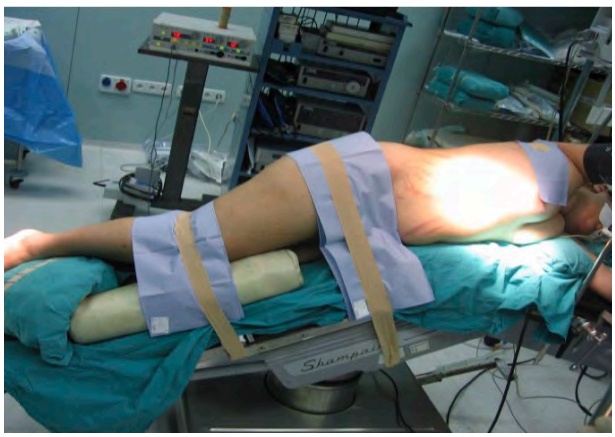


Figure 1. Surgical position during right adrenalectomy

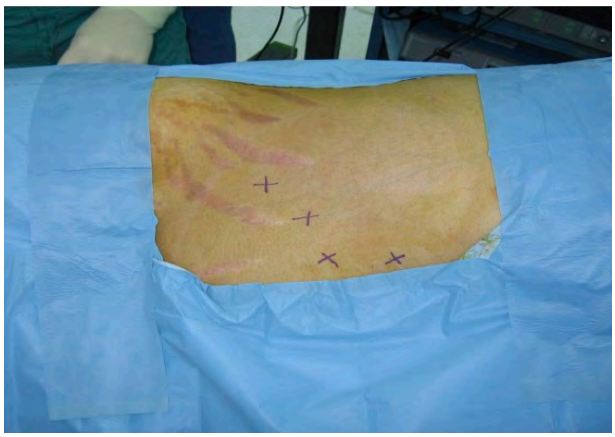


Figure 2. Port placement for right adrenalectomy

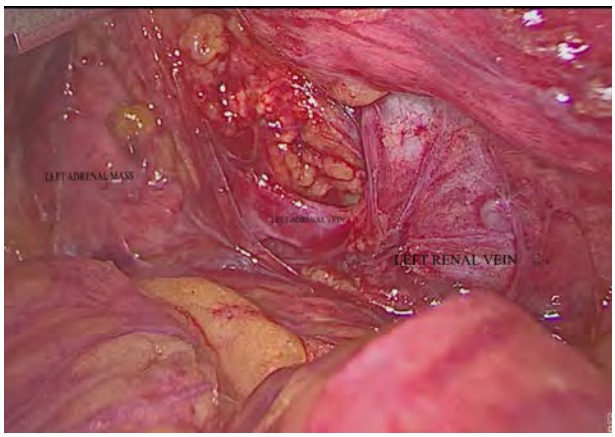


Figure 3. The identification of the left adrenal vein and renal vein

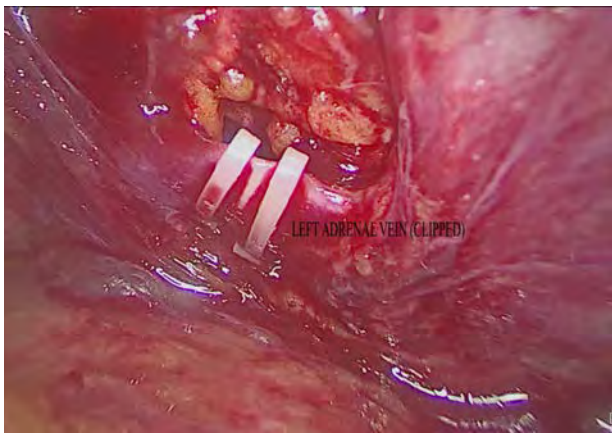


Figure 4. Clipping the left adrenal vein

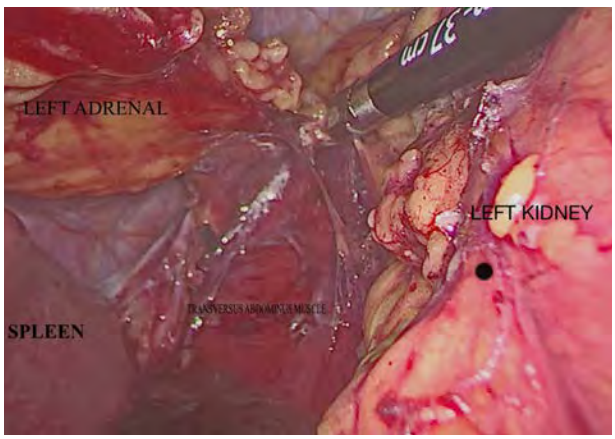


Figure 5. Dissection of the left adrenal gland

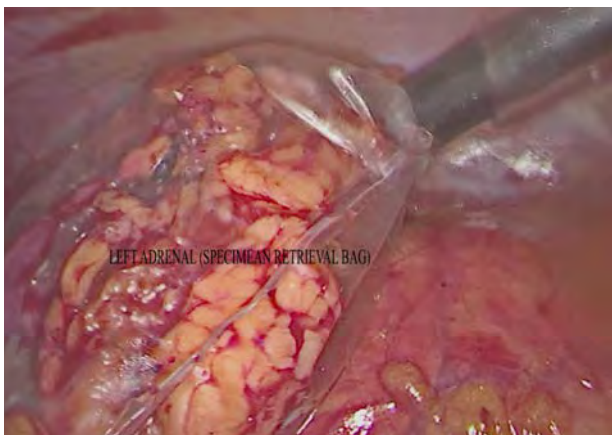


Figure 6. Retrieval of the adrenal gland within the bag

RESULTS

The study included a total of 30 patients comprising 6 men (20%) and 24 women (80%). Mean age was 54.3±11.5 (30-72) years and mean body mass index was 25.6±2.7 kg/m^2 (22-33). Mean mass size was 48.5±23 (28-100) mm and mean operation duration was 70.2±21.6 (40-130) minutes.

Half of patients had adrenal mass on the right (n:15), while the other half had adrenal mass on the left (n:15). Only one of the operated patients had hormonal activity and final pathology was pheochromacytoma. Histopathological evaluation revealed that; 17 patients had cortical adenoma, 4 patients have myelolipoma, 4 patients have adrenal cyst, 2 patients have 1 patient had ganglioneuroma, 1 patient had granulomatous infection, and 1 patient had pheochromocytoma (Graphic 1).

Mean perioperative hemorrhage amount was 41±48.8 (10-250) cc and only 2 patients required transfusion. Mean hospitalization duration was 1.3±0.88 (1-5) days. None of the cases is converted to open surgery (Table 1).

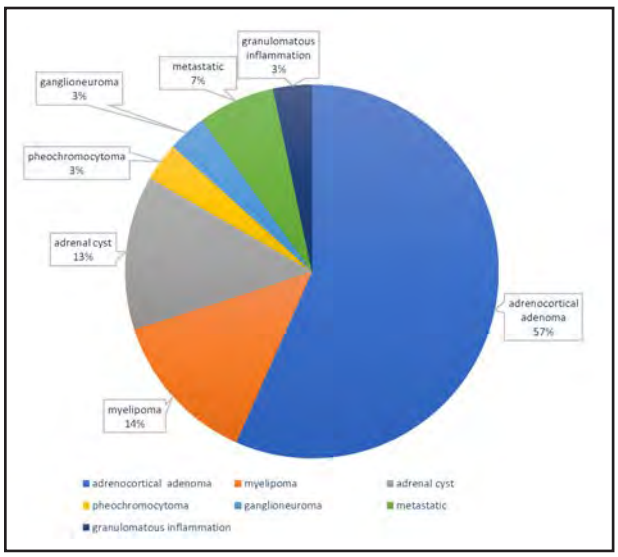
Table1. Demographic features and parameters

Patient (n=30)	
Gender(M/F)	6/24
Site (R/L)	15/15
Hormonal activity	1 patient (3,3%)
Mean age	54.3±11.5 years
Mean body mass index	25.6±2.7 kg/m^2
Mean size of the mass	48.5±23 mm
Mean operation duration	70.2±21.6 minutes
Need of transfusion	2 patients (6.66%)

DISCUSSION

This study summarizes the seven-year LA results of a single surgeon after experience of laparoscopic nephrectomy of 55 cases (Y.İ.Ç.).

All patients included are either referred from an endocrinologist or primarily diagnosed in our clinic and referred to endocrinology for hormonal evaluation. Adrenal benign tumors with hormone secretion and tumors with malignancy suspicion are main indications for open adrenalectomy.



Graphic 1. Histopathological diagnosis

In the classical open surgical technique, a large incision in the flank area up to 25 cm is performed. Commonly 12th costa is removed for better visualization (16,17).

Laparoscopic adrenalectomy (LA) technique is first reported in 1992 and has become the popular surgical approach for adrenal tumors (4). Laparoscopy is an advanced surgical procedure yielding satisfactory outcomes with better cosmesis and acceptable mortality and morbidity rates including decreased hemorrhage, shorter hospitalization duration, lower complication rate.

Open adrenalectomy requires large incision with increased risk of wound and pulmonary infection, sepsis, longer recovery time, higher intra and postoperative complications (2,10,18-20).

Postoperative retroperitoneal hemorrage may result in hypovolemic shock requiring re-surgery for exploration of the hemorrage localization. intraoperative hemostasis is an important step in open adrenalectomy (21).

The surgeon may decide planned open adrenalectomy preoperatively or may convert to open technique during the laparoscopic surgery.

The indications for conversion to open surgery during laparoscopy are, perioperative visualization of the invasion to vascular structures, to adjacent tissues or lymphadenopathy that can't be detected in radiological imaging. An other indication is that,

larger or adherent tumor that can't be removed en-bloc causing risk of tumor seeding. Al-Jalabneh et al, compared open surgery with LA and reported that there was a significant blood loss, operative time and hospital stay difference in favor of LA in their study (22).

In our series, transperitoneal laparoscopic adrenalectomy is preferred due to familiarity of the surgeon to transperitoneal approach which was performed with low complication rates and no mortality.

In the literature LA is suggested for tumors smaller than 8 cm (23-25). However, Boylu et al., reported successful results of LA for tumors to 12 cm (26). A case of 18 cm tumor is reported to be successfully removed by LA (27). In the present study, tumors with sizes 10 cm or less were operated laparoscopically.

Although some guidelines recommending laparoscopic surgery for tumors smaller than 6 cm, (15), Oneil et al., suggested open technique in cases with tumor invasion, trombus, and lesions bigger than 10 cm (28).

However, in a recent study in 2020, Fiori et al., have proposed that laparoscopy yields excellent results for large lesions (up to 12–14cm) without radiological signs of malignancy, in experienced hands (29).

Although this study subjectifies laparoscopic surgery, it should be noted that open adrenalectomy has a current role and should be used in cases of bigger adrenal tumors, in tumors with radiologically suspicion of malignancy or evidence of local invasion in computerized tomography, that is expected to be adrenocortical cancer (ENSAT III) staging system (European Network for the Study of Adrenal Tumors)(30).

Lack of equipment, high expenses in more technological approaches and limited sources of trained and skilled mentors limits the surgeons to start to laparoscopic approach especially in developing countries.

It is reported that the learning curve for LA stabilizes between the 20th and 40th surgery (13-15). The training should include therotical knowledge in anatomy and instrumentation followed by practice. The previous experience with other procedures of the learning surgeon and the experience and shoulder to shoulder mentoring of the mentor is important

If the surgeon has experience in laparoscopic techniques such as nephrectomy, prostatectomy, LA becomes easier to apply. A surgeon in a center with more cases for minimally invasive techniques earns the ability and performs better. Guebbels et al., described that learning to operate faster is possible where a more experienced is learning from the experienced (31).

In the literature the importance of training starting from theorotical, simulator assitance, and higher volume of assistance with the mentor, utilizes the key to a succesful LA performance. In the literature it is reported that there was no difference in surgery time of residents when compared to attending surgeons, which is discussed as selecting basic cases for residents and switching of the operator when face with an obstacle. This shows the importance of patient selection.

This study shows that the training and education in laparoscopy leads surgeons and patients to better and less invasive surgeries with lower morbidity, which will improve results, decrease complications.

According to a comparison of transperitoneal and retroperitoneal laparoscopic adrenalectomy published in the 2018 Cochrane database, the mean operation duration for transperitoneal laparoscopic adrenalectomy was between 59.7±18.6 to 271.6±46.9 minutes. When investigated in terms of mortality rates, mortality developed in 1 patient out of a total of 75 in three studies included in the meta-analysis. Mean hemorrhage amount displayed variability from 16.3±25.4 to 406.6±138 cc. In 4 studies included in the meta-analysis and out of a total of 110 patients, 1 patient converted to open surgery (32). When these results are investigated, it appears our data are consistent with the literature.

The greatest limitations of our study can be listed as the retrospective design, lack of follow-up results, lack of duration until oral intake, lack of duration to mobilization, and not determining comorbidities.

CONCLUSION

This study provides important conclusions for the surgeons beginning to LA which may be performed safely with low morbidity and mortality rates, especially in second step hospitals where laparoscopic techniques are less frequently used.

Conflict of Interest

The author declare to have no conflicts of interest.

Financial Disclosure

The author declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Memorial Bahçelievler Hospital Ethical Committee (Decision No: 2022-63, Date:2022/07/27) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Data acquisition; Data analysis and interpretation; Drafting the manuscript; Critical revision of the manuscript for scientific and factual content; Statistical analysis; Supervision; Çömez Yİ.

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Original Research / Özgün Araştırma

Male partner characteristics providing support for HPV vaccination of married women

Evli kadınların HPV aşısına destek sağlayan erkek partner özellikleri

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Özet

Amaç: Partnerlerine HPV aşısı olması konusunda destek veren erkeklerin özelliklerini değerlendirmek.

Gereç ve Yöntemler: Kadın hastalıkları polikliniğine başvuran tüm evli kadınlar (<26 yaş) ve eşleri çalışmaya katılım açısından değerlendirildi. Hastaların ve erkek partnerlerin tüm özellikleri kaydedildi. Tüm erkek katılımcılar, HPV ve HPV aşısı hakkında on ifade içeren bir anket formunu yanıtladı. Erkek katılımcılar, eşlerinin HPV aşısını desteklemelerine ve desteklememelerine göre iki gruba ayrıldı.

Bulgular: Toplamda 92 erkek partneri için HPV aşısını desteklerken, 144 erkek HPV aşısına karşı çıktı (destek oranı: %39). Ortalama evlilik yaşı, eğitim durumu ve aylık gelir eşlerine HPV aşısını destekleyen erkekler lehine anlamlı olarak yüksekti. Dindar olduğunu belirtenlerin oranı aşı karşıtı grupta anlamlı olarak daha yüksekti. Aşı ile ilgili güvenlik endişeleri (%27,8), aşının maliyeti (%26,4) ve HPV aşısının etkinliğine dair inanç (%26,4) HPV aşısına karşı çıkmanın en yaygın nedenleriydi. Çok değişkenli regresyon analizinde evlilik yaşı ≥25, lise ve üniversite eğitim düzeyi, aylık gelirin yüksek olması ve kendini dindar olarak tanımlamamanın HPV aşısı destek oranını artırdığını ortaya koydu.

Sonuç: Bu çalışmada evlilik yaşı, eğitim düzeyi, aylık geliri ve HPV anketi puanı yüksek olan erkeklerin eşlerinin HPV aşısı olmalarını anlamlı olarak daha fazla destekledikleri bulunmuştur. Buna karşılık, kendilerini dindar olarak tanımlayan erkekler, eşlerinin aşı olmasını önemli ölçüde daha az destekliediler.

Anahtar Kelimeler: aşı, bağışıklık, genital siğil, human papilloma virüs, rahim ağzı kanseri

Abstract

Objective: To evaluate the characteristics of men who support their partners in getting the HPV vaccine.

Material And Methods: All married women (< 26 years) who were admitted to the gynecology outpatient clinic and their husbands were evaluated for participation in the study. Patients' and all characteristics of male partners were recorded. All male participants answered a survey form including ten statements about HPV and HPV vaccination. Male participants were divided into two groups according to their support or lack of support for HPV vaccination of their wife.

Results: In total, 92 men supported HPV vaccination for their partners and 144 men opposed HPV vaccination (support rate: 39%). The mean marriage age, education status and monthly income were significantly higher in favor of men who support HPV vaccination for their wives. The rate of those who stated they were religious was significantly higher in the anti-vaccine group. Safety concerns about vaccine (27.8%), cost of vaccine (26.4%) and belief about HPV vaccine effectiveness (26.4%) were most common reasons for opposing HPV vaccination. Multivariate regression analysis revealed marriage age ≥25 years, education level of high school and university, higher monthly income and not self-identification as religious increased the HPV vaccine support rate.

Conclusion: The present study found that men with higher marriage age, higher educational level, higher monthly income, and higher score on the HPV survey were significantly more supportive of their spouses getting the HPV vaccination. In contrast, men who identified themselves as religious had significantly less support for their wife being vaccinated.

Keywords: vaccine, immunity, genital wart, human papilloma virus, cervical cancer

The study was approved by Ethics Committee of University of Bezm-i Alem (Approval No: 2022/183, Date: 2021/10/21). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Human papilloma virus (HPV) infection is the most frequently diagnosed sexually transmitted disease, and previous studies revealed that almost 75% of sexually active women encounter HPV during their lifespan (1). Although most HPV cases are asymptomatic, it is well-known that HPV may result in anal warts, anal dysplasia, oral and pharyngeal cancers, and gynecological malignancies (2). Vaccines were developed to prevent HPV complications, and the efficiency and safety of the quadrivalent HPV (HPV - 6, 11, 16, and 18) vaccine for prevention of cervical intraepithelial neoplasia, cervical cancer, vaginal and vulvar malignancies was proven by numerous studies (3). The Centers for Disease Control and Prevention (CDC) suggest routine HPV vaccination at the age of 11 or 12 years (also, vaccination can be done at age nine), and for all women up to age 26 years if not adequately vaccinated before (4).

Previous studies stated that HPV vaccination rates in women have not reached the desired level. Numerous reports investigated the possible factors affecting rejection of the HPV vaccination by women. Yeganeh and colleagues analyzed factors about accepting HPV vaccination in adolescents, and the authors stated that positive opinions about HPV vaccine safety, maternal pap-smear positivity, educational programs about HPV, and ethnicity affected vaccine acceptance (5). In a meta-analysis, which including three original articles, Santhanes et al. found vaccine cost, low knowledge about HPV infection and cervical cancer, and lack of positive recommendations by professional health care providers had negative impacts on HPV vaccine acceptance by women (6).

Previous studies analyzed the possible factors affecting HPV vaccination, but to our knowledge, there are not enough studies on the role of male partner characteristics on HPV vaccine acceptance in women, we aimed to clarify male partner characteristics providing support for HPV vaccination of women.

MATERIAL AND METHODS

The present study was conducted prospectively between January 2022 and July 2022. Informed consent was obtained from all women and their partners, and the study was performed in accordance with Helsinki Universal Declaration of human rights. All married women who were admitted to the gynecology outpatient clinic and their husbands were evaluated for participation in the study. The cut-off age for women was 26 years for HPV vaccination according to the CDC; thus, women ≥26 years and their partners were not included in the study. Also, if any of the couples were diagnosed or treated for HPV infection and HPV-related cancer, they were excluded from the study. Other exclusion criteria were, presence of female and/or male sexual dysfunction, allergy to HPV vaccine, presence of immunodeficiency disorder(s), presence of pregnancy, belong to a religion other than Islam, and presence of active sexually transmitted infection and/or urinary infection.

All characteristics of male partners including age, presence of any chronic disease, age of first sexual intercourse, marriage age, education status, monthly income, and self-identification as religious were recorded. Also, opinions of male partners about HPV vaccination for their wives were noted (who supported vaccination and who opposed vaccination). Participants who were undecided about HPV vaccination were not given any guidance. Lastly, all male participants answered a survey form including ten statements about HPV and HPV vaccination accompanied by a doctor. These statements were 'HPV is a virus', 'HPV can be transmitted sexually', 'HPV vaccine is administered to treat the infected patient', 'HPV is associated with some types of cancer', 'HPV infects only men', 'antibiotics are used to treat HPV', 'HPV vaccine is a single dose vaccine', 'HPV can cause genital warts', 'HPV can be transmitted from mother to baby during pregnancy', and 'HPV can be transmitted by blood transfusion'. Participants got one point for each correct answer (range from zero to ten, worst to best).

Study Group

Male participants were divided into two groups according to their support or lack of support for HPV vaccination of their wife. Groups were compared according to women's age, male demographic characteristics and male knowledge about HPV and HPV vaccine. Multivariate analysis was done to identify male factors for opposing HPV vaccination for women.

Statistical Analysis

The Statistical Package for the Social Sciences version 22 (SPSS IBM Corp., Armonk, NY, USA) program was used for statistical analysis. Shapiro-Wilk test and Q-Q plots were done to identify normality of variable distribution. Independent Student t-test was used for normally distributed parameters. Quantitative variables are presented as mean ± standard deviation. Categorical values were analyzed using the $\chi 2$ test or Fisher's exact test. Multivariate analysis was done to identify male factors associated with supporting HPV vaccination of women. The data were evaluated at 95% confidence level and p value ≤0.05 was considered statistically significant.

RESULTS

In the study period, 236 men with mean age 28.3±4.7 years were enrolled into the study. The mean age of women was 22.4±3.5 years old. In total, 92 men supported HPV vaccination for their partners (support rate: 39%). Age of first sexual intercourse and marriage age were 22.0±3.8 years and 23.9±3.8 years, respectively. Only 20.8% of men finished university and 23.3% of participants finished high school. A total of 98 (41.5%) men described themselves as religious. The mean points for the HPV survey was 5.1±2.6 for the study population. Participant characteristics are summarized in Table 1.

No significant differences were found between the groups with regards to mean age, mean partner age, presence of chronic disease and age at first sexual intercourse, respectively (p= 0.125, p= 0.317, p= 0.914 and p= 0.315). However, mean marriage age was significantly higher in men supporting HPV vaccination (25.0±3.6 years *vs* 23.2±3.9 years, p= 0.001). Also, education status and monthly income were significantly higher in favor of men who support HPV vaccination for their wives (p= 0.004 and p= 0.007). Points on the HPV survey were 6.4±2.0 for men who support vaccination and 4.3±2.7 for men who oppose vaccination (p= 0.001). The rate of those who stated they were religious was significantly higher in the anti-vaccine group (30.4% *vs* 54.9%, p= 0.007). Safety concerns about vaccine (27.8%), cost of vaccine (26.4%) and belief about HPV vaccine effectiveness (26.4%) were most common reasons for opposing HPV vaccination (Table 2).

Table 1. Demographic characteristics of 236 men

	n:236
Age (years)*	28.3±4.7
Age of partner (years)*	22.4±3.5
Presence of chronic disease	53 (22.5%)
Age at first sexual intercourse*	22.0±3.8
Marriage age	23.9±3.8
Education status	
Illiterate or Elementary school	59 (25.0%)
Middle school	73 (30.9%)
High school	55 (23.3%)
University	49 (20.8%)
Monthly income	
Minimum wage	75 (31.8%)
2 x Minimum wage	76 (32.2%)
3 x Minimum wage	85 (36.0%)
Self-identification as religious	98 (41.5%)
Points on the HPV questionnaire	5.1±2.6

***HPV:** Human papilloma virus*

Table 2. Comparison of parameters between groups

	Accepted (n:92)	Rejected (n:144)	P value
Age (years)*	27.7±5.0	28.6±4.4	0.125
Age of partner (years)*	22.7±3.4	22.2±3.6	0.317
Presence of chronic disease	21 (22.8%)	32 (22.2%)	0.914
Age at first sexual intercourse*	21.7±3.9	22.2±3.7	0.315
Marriage age*	25.0±3.6	23.2±3.9	***0.001***
Education status			
Illiterate or Elementary school	15 (16.3%)	44 (30.6%)	***0.004***
Middle school	24 (26.1%)	49 (34.0%)	
High school	31 (33.7%)	24 (16.7%)	
University	22 (23.9%)	27 (18.7%)	
Monthly income			
Minimum wage	19 (20.6%)	56 (38.9%)	***0.007***
2 x Minimum wage	31 (33.7%)	45 (31.2%)	
3 x Minimum wage	42 (45.6%)	43 (29.9%)	
Self-identification as religious	28 (30.4%)	79 (54.9%)	***0.007***
Points on the HPV questionnaire*	6.4±2.0	4.3±2.7	***0.001***
Reason for not accepting the vaccine			
Not safe, side effects	-	40 (27.8%)	
Costly	-	38 (26.4%)	
No benefits	-	38 (26.4%)	
Religious reasons	-	14 (9.7%)	
Others	-	14 (9.7%)	

mean ± standard deviation,* ***HPV:* *Human papilloma virus*

Table 3. Multivariate analysis of factors associated with men's support for HPV vaccination of their wife

	Univariate analysis	Multivariate analysis		
		Odds ratio	95% CI	P value
Marriage age (<25 or ≥25)	***0.001***	3.049	1.496-6.214	***0.002***
Education status				
Illiterate or Elementary school	***0.004***	Ref.	Ref.	Ref.
Middle school		1.380	0.532-3.584	0.508
High school		3.939	1.431-10.845	***0.008***
University		3.497	1.205-10.146	***0.021***
Monthly income				
Minimum wage	***0.007***	Ref.	Ref.	Ref.
2 x Minimum wage		2.837	1.120-7.185	***0.028***
3 x Minimum wage		4.188	1.663-10.548	***0.002***
Points on HPV questionnaire (<5 or ≥5)	***0.001***	8.361	3.793-18.427	***0.001***
Self-identification as religious (yes or no)	***0.007***	8.890	2.716-29.100	***0.001***

CI: *Confidence interval*

Supplement 1. Questions asked to measure men's knowledge about HPV and HPV vaccine

	n:236
HPV is a virus.	176 (74.6%)
HPV can be transmitted sexually.	144 (61.0%)
The HPV vaccine is administered to treat the infected patient.	112 (47.4%)
HPV is associated with some types of cancer.	102 (43.2%)
HPV infects only men.	98 (41.5%)
Antibiotics are used to treat HPV.	149 (63.1%)
HPV vaccine is a single dose vaccine.	155 (65.7%)
HPV can cause genital warts.	177 (75.0%)
HPV can be transmitted from mother to baby during pregnancy.	91 (38.6%)
HPV can be transmitted by blood transfusion	90 (38.1%)

** 1 point for each correct answer*

Multivariate regression analysis revealed marriage age ≥ 25 years and education level of high school and university increased the HPV vaccine support rate 3.049 times, 3.939 times and 3.497 times, respectively (p= 0.002, p= 0.008 and p= 0.021). Also, higher monthly income was associated with higher HPV vaccine acceptance in comparison with minimum wage (p= 0.028 and p= 0.002). Self-identification as religious significantly decreased the support rate for vaccination (p= 0.001). Lastly, higher points on the HPV survey were significantly associated with supporting HPV vaccination (p= 0.001).

DISCUSSION

Factors affecting individual rejection of the HPV vaccine are still a hot topic in gynecology. Spouses support for each other is known to be critical in health-related matters. Thus, we investigated male opinions about HPV vaccination in women, and found that only 39% of men supported HPV vaccination for their wives. Also, we found that higher marriage age, higher educational level, higher monthly income, and higher score on the HPV survey were significantly associated with increased support for HPV vaccination of women. In contrast, being religious had a negative impact on men's support for HPV vaccination.

Previous reports emphasized the importance of knowledge about vaccines in acceptance of vaccine administration. Nickel and colleagues investigated 179 parents of daughters aged between 9 and 17 years and found significant correlation between higher knowledge about HPV vaccine and vaccine acceptance rate (7). In another study, Dursun et al. analyzed women's knowledge of HPV and HPV vaccination, and the authors found that 55% of participants had no knowledge about HPV and HPV vaccination. However, they stated that after intensive information, 70% of patients accepted HPV vaccination (8). Although people use many sources to have medical information, they may not reach enough information (9). In our study, almost half of men had no idea about HPV and HPV vaccination, and our study showed that society should be informed about HPV and HPV vaccines by professional health institutions. In addition, our results revealed that men who were more supportive of their spouses about the HPV vaccine had significantly higher knowledge level about HPV and HPV vaccine.

Educational level is crucial while understanding disease pathophysiology and prevention. Rosenthal and colleagues analyzed factors affecting HPV vaccine acceptance in adolescents and found that parents with university education level had a higher HPV vaccine acceptance rate than parents with high school education level (10). In another study, Constantine et al. investigated the HPV vaccine acceptance of 552 individuals, and the authors found higher HPV vaccine acceptance rates in individuals with higher education level (11). For the first time, we analyzed

the impact of men's educational level on support for HPV vaccination of women. Men with high school and university education level were more supportive about their wives receiving the HPV vaccine. In addition, there was a positive correlation between higher monthly income and HPV vaccine support. In our country, the government does not pay for HPV vaccination, and patients receive the HPV vaccine at their own expense. This may explain why low-income men are opposed to their spouses getting vaccinated.

To our knowledge, no study has evaluated the impact of marriage age on HPV vaccine acceptance. However, some studies investigated the role of age on HPV vaccine acceptance. Jones and Cook investigated 138 men and 202 women, and the authors found that individuals aged 18–19 years were 5.4 times more likely to accept the HPV vaccine than individuals aged 22–32 years (12). In another study, Jaspers et al. stated that an increase in age by one year was associated with a decrease in vaccine acceptance by 6.6% (13). In contrast, higher marriage age in men was associated with higher support for vaccination in our study. We believe that gaining self-confidence, economic independence and freedom from family pressure after marriage in developing countries may have led to this result.

Even though the present study is the first to investigate the impact of male characteristics on HPV vaccination support for women, our study has some limitations. First of all, the present study was a survey study, and participant answers could be affected by many internal and external factors. To prevent this, all participants answered questions in a quiet room without time constraints. Also, in case of any disruption, the participant was supported by a professional health worker. Secondly, the study evaluated a certain period and administered in a single centre. Individual opinions could change over time. Lastly, the present study identified only barriers affecting men's support of HPV vaccination; finding solutions to these problems may be the subject of future studies.

CONCLUSION

Our study demonstrated that only two out of five men supported their wife receiving HPV vaccination. Moreover, the present study found that men with higher marriage age, higher educational level, higher monthly income, and higher score on the HPV survey were significantly more supportive of their spouses getting the HPV vaccination. In contrast, men who identified themselves as religious had significantly less support for their wife being vaccinated. We believe that our study findings could be used in studies to increase the acceptance of the HPV vaccine.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Bezm-i Alem University Ethics Committee (Approval Number: 2021/183, Date: 2021/10/21) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Ergül A, Data acquisition; Ergül A, Data analysis and interpretation; Çağlar U , Drafting the manuscript; Ergül A, Çağlar U, Critical revision of the manuscript for scientific and factual content; Ergül A, Çağlar U, Statistical analysis; Çağlar U, Supervision; Ergül A.

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Original Research / Özgün Araştırma

Determining the learning curve for robot-assisted radical perineal prostatectomy in surgeons familiar with robotic retropubic prostatectomy

Robotik retropubik prostatektomiye aşina cerrahlar için robot yardımlı perineal prostatektomi için öğrenme eğrisi

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Özet

Amaç: Robot yardımlı transperitoneal radikal prostatektomi ameliyatını rutin olarak gerçekleştiren cerrahlar için Robot yardımlı laparoskopik perineal prostatektomi (Robotik RPP) ameliyatının öğrenme eğrisinin belirlenmesi

Gereç ve Yöntemler: Tek cerrah tarafından gerçekleştirilen ilk 120 Robotik RPP vakasının perioperatif verileri değerlendirildi. Operasyon zamanı, tahmini kan kaybı, postoperatif yatış süresi, komplikasyonlar ve pozitif cerrahi sınır olmak üzere perioperatif tüm veriler derlendi. Olgular operasyon zamanlarına göre dört gruba ayrıldılar; 1–30. olgular (Grup 1), 31–60.olgular (Grup 2), 61–90.olgular (Grup 3) and 91-120. olgular (Grup 4).

Bulgular: Hastaların yaş ortalaması 61.4 (46-73) yıl ve PSA seviyeleri 8.4 (2-32) idi. Ortalama operasyon süresi 143.2 dakika iken cerrahi süresi progresif olarak zamanla azalmıştır. (Grup 1'den grup 4'e ; P<001). Ortalama konsol zaman 90.6 dakika iken grup 3 ve 4 arasında anlamlı bir fark bulunmuştur. (p=0.047). Ortalama hastane yatış süresi 1.6 gün iken 60.vakadan sonra anlamlı bir şekilde azalmaya başlamıştır. Katater çıkarılma zamanı Grup 4 için anlamlı bir şekilde daha kısa idi (P1vs4=0.012). Gruplar arasında patolojik evre, pozitif cerrahi sınır ve komplikasyonlar açısından anlamlı bir fark yoktu.

Sonuç: Bu çalışma ile deneyimli robotik cerrahlar için Robotik RPP ameliyatında yeterliliğinin 90 vakadan sağlanabileceğini sonucuna varılmıştır.

Anahtar Kelimeler: prostatektomi, robot yardımlı, perineal, öğrenme eğrisi, prostat kanseri

Abstract

Objective: To investigate the learning curve for robot assisted laparoscopic radical perineal prostatectomy (robotic RPP) for surgeons who already perform transperitoneal robot assisted laparoscopic radical prostatectomy.

Material and Methods: A total of initial 120 robotic RPP cases were analyzed for perioperative data from single surgeon performing to determine the learning curve. Perioperative all data are collected including operation time, estimated blood loss, postoperative length of stay, complications and positive surgical margin results. The consecutive patients were classified into four groups: cases 1–30 (Group 1), cases 31–60 (Group 2), cases 61–90 (Group 3) and cases 91-120 (Group 4).

Results: Median age of 61.4 (46-73) years and PSA level was 8.4 (2-32). Mean operative time was 143.2 minutes, and the length of surgery progressively decreased over time (from group 1 to group 4; P<001). Mean console time was 90.6 minutes and significant differences was found group 3 vs. 4 (p=0.047). The mean length of stay was 1.6 days, and significantly decrease after 60 cases over time (P<0.001). Mean removal of the urethral catheter significantly earlier in group 4 (P1vs4=0.012). There was no statistically significant difference between the groups with respect to pathologic tumor Gleason score, positive surgical margine of the specimen and complications.

Conclusions: This study suggests that surgical qualification for robotic RPP can be obtained at least after 90 cases for an experienced robotic surgeon.

Keywords: prostatectomy, robot-assisted, perineal, learning curve, prostate cancer

The study was approved by Memorial Bahçelievler Hospital Ethical Committee, (Decision No: 2022-63, Date: 2022/07/27).
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

Prostate cancer (PCa) is reported to be the second common cancer among men (1) with organ-confined disease rates up to 90% through the last decade. The surgical options vary and develop as with the developments in technology along with the popularity robot-assisted approaches gained. Radical perineal prostatectomy (RPP) is the main technique for removal of prostate as defined by Hugh Hampton Young in 1905 (2). Radical retropubic prostatectomy (RRP) technique is respectively described by Walsch and those 2 techniques reveal the same anatomic relationship, success rate in cancer control besides preserving the parasympathetic and sympathetic nerves that control penile erection and ejaculation (3). RRP is accepted as the preferred approach for radical prostatectomy (RP) for years. Minimal invasive surgery for prostate cancer has developed with the advent of robotic platforms at the beginning of new millennium (4,5). Overall learning curve for robotic-assisted laparoscopic surgery was recorded comparable until >150 cases (6).

Although RPP had advantages as decrease in morbidity, in hospital costs, in hospitalization duration with shorter operation time, it has lost its popularity with the developments of robotic platforms (7). However RPP became preferred technique again during the last two decades due to increased interest in nerve sparing techniques and facility of performing lymphadenectomy (8). In light of those developments Laydner et al., as the first researchers who describing the robotic RPP technique in a cadaveric model, published their clinical experience in 2016 (9,10).

In the present study, we aim to examine the learning curve of a high volume robotic surgeon with no previous experience at robotic RPP at a single center.

MATERIAL AND METHODS

This study is approved by Local Ethical Committee of Bakirkoy Sadi Konuk Training and Research Hospital, and written informed consent is obtained from all patients. Retrospective data of 120 patients operated by single surgeon (VT), between November 2016 and February 2020 included in the study. Experienced surgeon has robotic experience over 1500 cases and more than 20 cases of RPP under supervision of highly experienced surgeon who defined the first technique of robot-assisted RPP. The patients are divided into 4 groups, as patients 1 to 30 included in Group 1; patients between 31-60 in Group 2; patients between 61 and 90 in Group 3 and patients between 91 and 120 are included in Group 4. Patients' age, body mass index (BMI), American Society of Anesthesiologists anesthetic/surgical risks class (ASA), prostate-specific antigen (PSA) levels, PSA density, biopsy percentage, Gleason score, and the clinical stage of the patients are recorded. Patients treated for prostate cancer, neoadjuvant or adjuvant hormonal therapy were nor included in the study.

The preoperative and postoperative PSA levels and Gleason scores, hospitalization duration, skin to skin operative time, estimated blood loss, complications, the status of surgical margin, and the presence of capsular penetration are accepted as primary outcome variables.

Statistical Analysis

Categorical data were presented as numbers and percentages. Data for continuous variables are presented as mean and standard deviation. The Shapiro-Wilk test was used to determine whether the distributions of continuous variables were normal. Mean differences between more than two related groups of normally distributed data were compared with ANOVA, while the Kruskal-Wallis Test was used to compare non-normally distributed data. The frequencies of categorical variables were compared using Fisher›s exact test. Statistical significance was considered when p value was<0.05. In normally distributed data, Bonferroni correction was used in pairwise comparison of more than two groups with statistically significant differences. In non-normally distributed data, Tamhane's correction was used in pairwise comparison of more than two groups with statistically significant differences. Statistical analysis was performed using Statistical Package of Social Sciences version 21 (IBM SPSS Statistics; IBM Corp.,

Armonk, NY).

RESULTS

The median age of the patients was 61.4 (46-73) years, the median prostate size was 50.2 ml (15-100), the median preoperative PSA was 8.4 (2-32) and the median preoperative Gleason score was 6 (6-8). Table 1 lists the baseline demographic characteristics and surgical data.

The mean operative time was 143.2 minutes (between 110 and 255 minutes), and the surgery time observed to be decreased from group 1 to group 4 (P<001). Mean console time was 90.6 minutes (range, 55-155 minutes), progressively decreased and significant differences was found group 3 vs. 4 (p=0.047). The mean hospitalization duration was 1.6 days (range, 1-4 days). The length of hospitalization time is found to be significantly decreased after 60 cases (P<0.001). Mean removal of the urethral catheter was 7.2 days (range, 6-25 days) and significantly earlier in group 4 (Group 1 vs Group 4=0.012). The difference in the results of the pathological tumor Gleason score and positivity of the surgical margin were not statistically significant between the groups. Pelvic lymph node dissection was performed in 12 patients since they are accepted as having high risk of node involvement according to Partin nomogram. A mean of 14.6 ± 1.7 lymph nodes were resected and 4 patients are found to have lymph node metastasis.

According to Clavien-Dindo classification overall grade 2 and 3 complications rate was 14% (11.7%), and no significant decrease in the complication rate is observed as the surgeon's experience increased (Groups 1, 2, 3, and 4; 16.7%, 6.7%, 16.7%, and 6.7%, respectively; P=0.450) No grade 4 and 5 complications were seen. In 4 patients wound infection and wound dehiscence were detected and repaired primarily. In 3 patients postoperative fever which responded to antipyretics is detected. In 4 patients urinary leakage occurred which is treated with prolonged urethral catheterization. Three patients are diagnosed to have

Table 1. Demographic data and clinical parameters

Number of patients	120
Age (year)	
Mean ± SD	61.4 ± 6.7
Median (range)	62 (46-73)
BMI	
Mean ± SD	28.0 ± 2.2
Median (range)	28 (23-35)
PV (ml)	
Mean ± SD	50.2 ± 17.4
Median (range)	48 (15-100)
PSA(ng/dl)	
Mean ± SD	8.4 ± 5.6
Median (range)	7 (2-32)
Gleason skor	
Mean ± SD	6.2 ± 0.4
Median (range)	6 (6-8)
MpMRI PIRADS, n(%)	
PIRADS 1	10 (8.3)
PIRADS 2	31 (25.8)
PIRADS 3	23 (19.2)
PIRADS 4	54 (45.0)
PIRADS 5	2 (1.7)

Clinical stage, n(%)	
T1c	12 (10.0)
T2a	12 (10.0)
T2b	31 (25.8)
T2c	65 (54.1)
ASA score, n(%)	
ASA 1	5 (4.2)
ASA 2	96 (80.0)
ASA 3	19 (15.8)
Operation time (min)	
Mean ± SD	143.2 ± 17.8
Median (range)	140 (110-255)
Console time (min)	
Mean ± SD	90.6 ± 14.0
Median (range)	90 (55-155)
Blood loss (ml)	
Mean ± SD	67.1 ± 13.6
Median (range)	65 (45-120)
LOS (day)	
Mean ± SD	1.58 ± 0.69
Median (range)	1 (1-4)
Removal of catheter time (day)	
Mean ± SD	7.2 ± 2.3
Median (range)	7 (6-25)
Return to job time (day)	
Mean ± SD	10.5 ± 2.8
Median (range)	10 (7-30)

***SD:** standart deviation; **BMI:** body massindex; **PV:** prostate volume; **LOS:** lenght of stay*

Table 2. Comparison of patients' characteristics according to time

Variables	**1st 30**	**2nd 30**	**3rd 30**	**4th 30**	**P value**
Number of patients	30	30	30	30	
Mean age ± SD, year	61.5 ± 7.0	60.4 ± 7.8	61.8 ± 6.5	62.2 ± 5.5	0.752*
Age (year) Mean ± SD	61.5 ± 7.0	60.4 ± 7.8	61.8 ± 6.5	62.2 ± 5.5	0.752*
Mean BMI ± SD	28.3 ± 2.0	27.3 ± 2.4	27.8 ± 2.3	28.7 ± 2.2	0.102*
Mean PV ± SD (ml)	42.3 ± 14.0	58.6 ± 21.0	49.1 ± 17.4	50.8 ± 12.8	0.015¥ 1 vs 2 0.006
Mean PSA(ng/dl)	6.3 ± 2.4	9.1 ± 6.4	10.8 ± 8.1	7.6 ± 2.2	0.045¥ 1 vs 3 0.035
Mean GS score ± SD	6.4 ± 0.5	6.2 ± 0.4	6.2 ± 0.4	6.3 ± 0.4	0.353¥

GS at biopsy, n(%)					
6 7 8-10	19 (63.3) 10 (33.3) 1 (3.3)	24 (80.0) 6 (20.0) 0 (0.0)	24 (80.0) 6 (20.0) 0 (0.0)	21 (70.0) 9 (30.0) 0 (0.0)	0.487&
Mean MpMRI score± SD	3.06 ± 1.08	2.96 ± 1.06	3.16 ± 1.05	3.03 ± 1.06	0.908*
MpMRI Score, n(%)					
PIRADS 1 PIRADS 2 PIRADS 3 PIRADS 4 PIRADS 5	3 (10.0) 6 (20.0) 8 (26.7) 12 (40.0) 1 (3.3)	3 (10.0) 8 (26.7) 6 (20.0) 13 (43.3) 0 (0.0)	2 (6.7) 7 (23.3) 6 (20.0) 14 (46.7) 1 (3.3)	2 (6.7) 10 (33.3) 3 (10.0) 15 (50.0) 0 (0.0)	0.925&
Clinical stage, n(%)					
T1c T2a T2b T2c	3 (10.0) 5 (16.7) 7 (23.3) 15 (50.0)	3 (10.0) 6 (20.0) 5 (16.7) 16 (53.3)	2 (6.7) 0 (0.0) 13 (43.3) 15 (50.0)	4 (13.3) 1 (3.3) 6 (20.0) 19 (63.3)	0.091&
ASA score, n(%)					
Asa 1 Asa 2 Asa 3	0 (0.0) 26 (86.7) 4 (13.3)	0 (0.0) 21 (84.0) 4 (16.0)	2 (6.7) 20 (66.7) 8 (26.7)	3 (10.0) 25 (83.3) 2 (6.7)	0.133&
Mean OT ± SD (min)	157.0 ± 28.6	140.0 ± 7.3	140.5 ± 5.9	135.6 ± 10.8	<0.001¥ 1 vs 2 0.021 1 vs 3 0.025 1 vs 4 0.003
Mean CT ± SD (min)	96.8 ± 23.2	90.5 ± 6.4	90.8 ± 4.7	84.5 ± 11.4	0.041¥ 3 vs 4 0.047
Mean BL ± SD (ml)	68.1 ± 13.4	70.5 ± 15.7	67.6 ± 12.9	62.3 ± 11.1	0.121*
Mean LOS ± SD (day)	2.0 ± 0.7	1.6 ± 0.7	1.4 ± 0.5	1.2 ± 0.4	<0.001* 1 vs 3 0.001 1 vs 4<0.001
Removal of UC ± SD (day)	8.2 ± 2.8	7.2 ± 3.4	7.1 ± 0.9	6.3 ± 0.6	0.021* 1 vs 4 0.012
Return to job time ± SD (day)	11.3 ± 3.7	10.6 ± 3.8	10.3 ± 1.0	10.0 ± 1.2	0.179¥
SM, n(%) Negative Positive	 27 (90.0) 3(10.0)	 29 (96.7) 1 (3.3)	 27 (90.0) 3 (10.0)	 26 (86.7) 4 (13.3)	 0.685&
Comlication, n(%)					
Positive Negative	5 (16.7) 25 (83.3)	2 (6.7) 28 (93.2)	5 (16.7) 25 (83.3)	2 (6.7) 28 (93.3)	0.450&
Mean RP specimen GS score ± SD	6.5 ± 0.7	6.2 ± 0.4	6.7 ± 0.5	6.5 ± 0.5	0.121*
GS at RP, n(%)					
6 7 8-10	16 (53.3) 12 (40.0) 2 (6.7)	19 (63.3) 11 (36.7) 0 (0.0)	9 (30.0) 20 (66.7) 1 (3.3)	14 (46.7) 15 (50.0) 1 (3.3)	0.110&

***SD,** standart deviation; **BMI,** body massindex; **PV,** Prostate volume; **GS,** Gleason score; **OT,** Operation time; **CT,** Console time; **BL,** Blood loss; **LOS,** Lenght of stay; **UC,** Urethral Catheter; **SM,** Surgical margine; **RP,** Radical prostatectomy*
** One way ANOVA; **¥** Kruskal Wallis test; **&** Fisher's Exact Test*

transient neurological deficit in the lower extremity due to exaggerated lithotomy position which improved by time (Table 2).

DISCUSSION

In 1905, although it was first described technique in the surgical treatment of PCa, RPP, which was not performed commonly for a century, resurgenced again in the early 2000s. Having less blood loss, lower pain after the operation, shorter hospitalization time and more rapid recovery were the main advantages of the RPP when compared to RRP (11). The others are having shorter learning curve (11) and the less surgical complexity in patients who experienced prostate or bladder surgery (12). RPP provides relatively convenient anatomical approach to the prostate with a small incision. However, in RPP, the surgeon may have ergonomic issues during operation due to the superior position of the prostate as per surgeon, and those challenges may have inhibited its utilization. The application of the robotic system to RP, utilized to reduce the above mentioned difficulties in conventional RPP (13). Robotic surgery is actually a validated treatment option for localized prostate cancer. Lower blood loss, lower blood transfusion need and early continence were reported to be the main advantages of robotic surgery. Improved cosmetic appearance and shorter recovery time also served to higher patient acceptance of robotic procedures.

The Robotic prostatectomy technique has also developed rapidly with different approaches where robotic RPP is a more recent developed technique. After Kaouk et al., first described the robotic RPP technique in a cadaveric model, they reported their first clinical experience and concluded that combining robotic technology with RPP, eliminated narrow and deep operative field observed in open RPP and provided a magnified 3D view of the periprostatic tissues (10). Tugcu et al. reported early results of 95 patients who underwent robotic RPP. Median operation duration was 140 min, the console time was 90 min and the mean blood loss was 67.4 ml. Positive surgical margins were detected in 8.4% of the patients. Immediate continence rate was 41% , in the first month it was 78%, in the third month it was 87% and at the first year 91%. Complication rate was 11.6% and they reported no grade 4 and 5 complication. The authors concluded that robotic RPP is an effective surgical technique which can be utilized in the treatment of localized prostate cancer regardless of prostate size, and it can be applied in patients with a history of abdominal surgery, where pelvic lymph node dissection may be performed through the same incision (14).

The learning curve is a one of the prominent problem in surgery, where the surgical procedure is often more difficult and slow to perform, associated with a higher risk of complications and low performance due to the inexperience of the surgeon. If a basic assessment is made, the learning curve is mainly a theoretical concept, because this is a subject of research rarely present in residency programs and urologic literature. A minimum of 60 surgery cases are required to attain proficiency (15). With improvement in the techniques performed, structured training programs are developed to provide safe and effective training of surgeons with no previous experience of open or laparoscopic surgery (16) On the other hand, surgeons with robotic experience will also have a short learning curve, because they already have a certain competence and proficiency of the instruments. For this reason, the learning curve of robotic surgery is generally shorter than that of laparoscopic surgery. Patel et al., reported that after 20-25 cases, the surgeon could perform the surgery on his own. In this study, the robotic surgery team consisted of a trained laparoscopic surgeon and an experienced open surgery surgeon (17). Kouok et al., published their initial data of the robot assisted laparoscopic radical perineal prostatectomy using new robotic single port platform by Da Vinci System. They reported that the new system had encouraging results (18). In our series, an experienced surgeon in robotic surgery, performed all the operations. The articles In the surgical literature about learning curve, report that the most typical approach to exhibit the relationship between the experience and the outcome is to categorize, such as dividing 100 or 120 cases into three to four equal groups respectively and then draw conclusions by making comparison between groups (19). Similarly, in our study, we divided 120 patients into 4 equal and

consecutive groups and compared them with each other. Surgical time was shortened in each group, but console time was significantly less only in the 4th (in patients between 90 and 120) group compared to the 3rd group. While the duration of hospitalization was significantly less after the 60th patient, the duration of catheter removal was significantly earlier after the 90th patient. There was no statistically significant difference between the groups in terms of surgical margin positivity and complications. With these results, we can conclude that surgical parameters in robotic RPP improved after the 90th case. This duration seems longer when compared to other robotic prostatectomy methods. A multi-centric study (LAPPRO trial) with inclusion of total 2672 clinical localized PCa patients treated with RARP, reported outcomes regarding incontinence and erectile function, claims that incontinence was stable all through the learning period, and erectile function preserved in 38% in the first 74 cases while the percentage increased to 53% after 300 cases (20). It would not be wrong to think that this situation is due to the narrowness of the working area and encountering more difficulties than the standard procedure. However, the fact that surgical margins and complications are not different between all groups; one may conclude that experienced surgeons can be adapted to this difficult surgical procedure in a short time. The main limitations of our study are the lack of urinary incontinence and erectile function data.

CONCLUSION

In conclusion this study demonstrates that surgeons with significant experience in robotic surgery are able to provide successful surgical outcomes in short time comparable to standard methods in robotic RPP.

Conflict of Interest

The author declare to have no conflicts of interest.

Financial Disclosure

The author declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Memorial Bahçelievler Hospital Ethical Committee (Decision No: 2022-63, Date:2022/07/27) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Çömez Yİ, Balcı M, Tuğcu V, Data acquisition; Çömez Yİ, Sökmen D, Şeker KG, Tuğcu V, Data analysis and interpretation; Çömez Yİ, Balcı M, Drafting the manuscript; Çömez Yİ, Balcı M, Tuğcu V, Critical revision of the manuscript for scientific and factual content; Çömez Yİ, Tuğcu V, Statistical analysis; Balcı M, Supervision; Çömez Yİ, Sökmen D, Şeker KG, Tuğcu V.

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Demographic characteristics of Turkish kidney donors and the impact of donor-recipient relationship on postoperative outcomes: A single-center experience

Türk böbrek donörlerinin demografik özellikleri ve alıcı ile verici akrabalık ilişkisinin postoperatif parametrelere etkisi: Tek merkez deneyimi

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Özet

Amaç: Son Dönem Böbrek Yetmezliği (SDBY) hastalarına uygulanabilecek en etkili tedavi yöntemi böbrek transplantasyonudur (KTx). Canlı vericiden yapılan böbrek nakillleri, tamamen sağlıklı bir insanın ameliyata dahil edilmesi nedeniyle özellikli bir cerrahidir. Biz de bu retrospektif çalışmada, donör nefrektomi (DNx) yapılan Türk donörlerde, verici ile akrabalık derecesinin postoperatif sonuçlara etkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmaya sol DNx yapılan toplam 297 hasta dahil edildi. Çalışmaya dahil edilen hastalar verici ile akrabalık derecelerine göre 6 ayrı gruba ayrılarak istatistiksel değerlendirmeye tabi tutuldu : böbrek vericisi anneler olan 69 DNx vakası grup-1'e, babalar olan 29 vaka grup-2'ye, eşlerden yapılan 70 donör nefrektomi vakası grup-3'e, kardeşlerden yapılan 68 vaka grup-4'e, çocuklardan yapılan 31 vaka grup-5'e ve 2. derece ve daha uzak akrabalardan yapılan 30 DNx vakası grup-6'ya dahil edildi. Hastalara ait yaş, cinsiyet, eğitim seviyesi, operasyon süresi (ST), postoperatif 1. gün Vizüel Analog Skala (VAS) ağrı skoru, hastanede yatış süresi ve Quality of Life (QoL) verileri retrospektif incelenerek kaydedildi.

Bulgular: Donörlerin akrabalık derecesine göre dağılımına bakıldığında, donör nefrektomi operasyonunun en sık eşlere (%23.57), annelere (%23.23) ve kardeşlere (%22.9) uygulandığı görülmektedir. Donörlerin %59.26'sının kadın olduğu ve çoğunluğunun (%67.68) orta öğrenim ve üzeri bir eğitim seviyesine sahip olduğu saptanmıştır. Gruplar arasında VAS skorları, hastanede kalış sü-

Abstract

Objective: Kidney transplantation (KTx) is the most effective treatment option for patients with end-stage renal disease (ESRD). Live donor kidney transplantation is unique as it involves healthy individuals who undergo a major surgery. This retrospective study seeks to investigate the effect of donor–recipient relationship on postoperative outcomes in Turkish donors undergoing laparoscopic donor nephrectomy (DNx).

Material and Methods: The study was conducted with a total of 297 patients who underwent left DNx. The patients included in the study were divided into six different groups based on the degree of relationship with the recipients: Sixty-nine cases of DNx involved mothers as kidney donors classified into group-1, 29 cases involving fathers into group-2, 70 cases involving spouses into group-3, 68 cases involving siblings into group-4, 31 cases involving children into group-5, and 30 cases involving second-degree and more distant relatives into group-6. Patients' data including age, sex, education level, duration of surgery (ST), Visual Analog Scale (VAS) pain score at postoperative day 1, length of hospital stay (HS), and Quality of Life (QoL) were retrospectively analyzed and recorded.

Results: The groups had significant differences in terms of VAS scores, HS, and QoL-MS. Posthoc analysis was performed to find out which groups had significant differences. Results showed that group-1 had significantly lower VAS scores than group-2, group-3, and group-6. HS was significantly long in group-3 and group-6. QoL-MS

The study was approved by Ethics Committee of University of Health and Sciences Bakırköy Dr.Sadi Konuk Training and Research Hospital (Approval No: 2023-01-35, Date: 2022/11/04). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

resi ve Qol-Mental Skor açısından anlamlı farklılık izlenmiştir.

Sonuç: Canlı böbrek donörlerinin alıcı ile akrabalık dereceleri, postoperatif erken dönemde psikolojik sağlıkları üzerinde etkili olmakta ve muhtemelen bu yolla da VAS skorlarını ve hastanede kalış sürelerini etkilemektedir. Böbrek donasyon sürecinden en az etkilenen vericilerin anneler olduğu söylenebilir.

Anahtar Kelimeler: böbrek; transplantasyon; canlı böbrek donörü; alıcı-verici akrabalık derecesi

was significantly lower in group-2 and group-6 than the other groups.

Conclusion: The degree of relationship of living kidney donors to recipients influences their psychological health in the early postoperative period and probably affects VAS scores and length of hospital stay. It can be argued that mothers are the group of donors least affected by the kidney donation process.

Keywords: kidney; transplantation; live donor; donor-recipient relationship

INTRODUCTION

Kidney transplantation (KTx) is the most effective treatment option for patients with end-stage renal disease (ESRD). KTx relieves ESRD patients of both the psychological and socioeconomic burden of dialysis. However, living-donor kidney transplant surgery involves not only recipients but also donors as a group of patients. Patients undergoing donor nephrectomy have two healthy kidneys, usually have no major health problems and do not benefit functionally from the surgery they choose to undergo. In most cases, these patients volunteer to donate their organ for a close family member.

Experiences with patients undergoing nephrectomy show that patients undergoing donor nephrectomy (DNx) may have a different postoperative psychological state compared to patients undergoing nephrectomy for a disease (nonfunctioning kidney, tumor, etc.). These differences cause patients to perceive usual postoperative processes differently and feel anxiety, have more need for analgesics and longer hospital stays. Some studies have shown the impact of surgery on patients' psychological state as well as the effect of patients' emotional state on surgery and postoperative outcomes (1,2).

In 2020, 2,494 kidney transplants were performed in 78 centers in Turkey, making this the second most common transplantation after bone marrow transplant (3). More than 80% of kidney transplants in Turkey are performed using organs from living donors, and this means that it is crucial to investigate how living donors perceive the transplantation process and how their degree of relationship with the recipient affects this perception.

This retrospective study sought to investigate the effect of donor–recipient relationship on postoperative outcomes in Turkish donors undergoing DNx.

MATERIAL AND METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee (İstanbul Gelişim University, 2023-01-35). It involved a retrospective evaluation of patients' data.

The data of 353 patients who underwent DNx between January 2016 and December 2021 in our center was reviewed retrospectively. Patients were excluded if they were unrelated to the recipient, underwent DNx for paired transplantation, were foreign nationals, did not have sufficient data for statistical analysis, failed to present for regular follow-up examinations, or if their data were not readily available. Thus, the study was conducted with a total of 297 patients who underwent left DNx. The patients included in the study were divided into six different groups based on the degree of relationship with the recipients and statistically evaluated. Sixty-nine cases of DNx involved mothers as kidney donors classified into group-1, 29 cases involving fathers into group-2, 70 cases involving spouses into group-3, 68 cases involving siblings into group-4, 31 cases involving children into group-5, and 30 cases involving second-degree and more distant relatives into group-6.

Patients' data including age, sex, education level, duration of surgery (ST), Visual Analog Scale (VAS) pain score at postoperative day 1, length of hospital stay (HS), and Quality of Life (QoL) were retrospectively analyzed and recorded. ST was defined as the time from establishing pneumoperitoneum to extraction of graft. QoL scores were evaluated using "the medical outcomes study short form-12 (SF-12)," which was routinely administered for patients who presented for follow-up at week one. Patients' physical (QoL-PS) and mental (QoL-MS) scores were evaluated separately (4,5).

Surgical technique : In our center, all donor nephrectomies were performed by a single surgeon with the full laparoscopic donor nephrectomy technique. Before nephrectomy, a 7-8 cm Pfannenstiel incision was prepared for graft extraction while the patient was in the supine position. The patient was then placed in lateral decubitus position for laparoscopic nephrectomy. LDN were performed through three subcostal 5mm laparoscopy ports. After completion of donor nephrectomy, a 12 mm port was inserted through the opening at the end of the previously prepared Pfannenstiel incision, and the renal arteries and vein were severed separately with laparoscopic vascular staplers advanced through the 12mm port. The Pfannenstiel incision was opened completely including the peritoneum and the graft was extracted. The extraction incision was sutured subcuticularly after the layers were properly closed. The port entrance holes were also sutured subcuticularly.

Statistical Analysis

Statistical analyses were performed using the software SPSS version 25.0. Variables were analyzed for normality of distribution using histogram plots and the Kolmogorov–Smirnov test. Descriptive analyses were presented using mean, standard deviation, median and IQR values. Non-normally distributed (nonparametric) variables were analyzed using the Kruskal–Wallis Test for comparisons of more than two groups, and using the Mann–Whitney U Test for comparisons between two groups. Statistical significance was set at $p < 0.05$.

RESULTS

Table-1 shows the demographic characteristics of the patients. Distribution of donors by degree of relationship shows that donor nephrectomy was most commonly performed on spouses (23.57%), mothers (23.23%), and siblings (22.9%). 59.26% of the donors were female and the majority (67.68%) had secondary education and above.

Table-2 presents the distribution of demographic characteristic by groups. Since the groups were composed of participants with different degrees of relationship, demographic characteristics were not statistically analyzed for comparison purposes.

Table-3 presents data relating to DNx surgery. The groups had significant differences in terms of VAS scores, HS, and QoL-MS. Posthoc analysis was performed to find out which groups had significant differences. Results showed that group-1 had significantly lower VAS scores than group-2, group-3, and group-6 (Figure-1). HS was significantly long in group-3 and group-6 (Figure-2). QoL-MS was significantly lower in group-2 and group-6 than the other groups (Figure-3).

Table 1. Patients' demographic data.

		n	%
Groups	Group-1	69	(23,2)
	Group-2	29	(9,7)
	Group-3	70	(23,5)
	Group-4	68	(22,9)
	Group-5	31	(10,4)
	Group-6	30	(10,1)
Sex	Male	121	(40,7)
	Female	176	(59,2)
Education	No	36	(12,1)
	Primary	60	(20,2)
	Secondary	155	(52,1)
	High school	46	(15,4)
Age	Mean±SD	48,4±12,8	
	Median (IQR)	48 (38-59)	

***SD:** Standard deviation, **IQR:** Interquartile Range*

Table-2. Demographic data by groups.

	n	Group-1		Group-2		Group-3		Group-4		Group-5		Group-6	
		%	n	%	n	%	n	%	n	%	n	%	
Sex	Male			29	(100,0)	25	(35,7)	40	(58,8)	10	(32,2)	17	(56,6)
	Female	69	(100,0)			45	(64,2)	28	(41,1)	21	(67,7)	13	(43,3)
Edu.	No	15	(21,7)	5	(17,2)	7	(10,0)	4	(5,8)			5	(16,6)
	Primary	27	(39,1)	5	(17,2)	14	(20,0)	8	(11,7)	2	(6,4)	4	(13,3)
	Secondary	21	(30,4)	15	(51,7)	38	(54,2)	45	(66,1)	20	(64,5)	16	(53,3)
	High school	6	(8,7)	4	(13,7)	11	(15,7)	11	(16,1)	9	(29,0)	5	(16,6)
Age	Mean±SD	58,2±9,5		54,6±10,2		49,3±11,2		42,5±10,9		34,4±8,2		46,1±11,7	
	Median (IQR)	60 (51-64)		55 (48-60)		50 (39-57)		40 (35,5-47,5)		35 (28-40)		43,5 (35-56)	

***SD:** Standard deviation, **Edu:**Education, **IQR:** Interquartile Range*

Table 3. Data relating to the surgery

		Group-1	Group-2	Group-3	Group-4	Group-5	Group-6	p
ST	Mean±SD	42,2±5,7	41,6±4,9	42,2±5,1	42,2±5	43,4±5,5	43,1±4,7	0,719
	Median (IQR)	42 (38-46)	42 (38-44)	42 (38-46)	42 (38-45,5)	44 (40-46)	44 (40-45)	
VAS	Mean±SD	3±1,4	5,1±1,6	3,8±1,3	3,5±1,5	3,5±1,3	4,8±1,9	**<0,001**
	Median (IQR)	3 (2-4)	5 (4-6)	4 (3-5)	3 (2-5)	4 (3-4)	5,5 (3-6)	
HS	Mean±SD	1,3±0,5	1,4±0,6	1,7±0,9	1,2±0,5	1,3±0,5	1,7±0,7	**<0,001**
	Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-1)	1 (1-2)	2 (1-2)	
QoL-PS	Mean±SD	51,5±7,9	51,4±8,8	48,6±9,8	48±10,8	48,9±10,6	49,3±10,1	0,708
	Median (IQR)	55,9 (46,1-56,4)	55,9 (54,8-56,4)	54,8 (43,5-56,4)	54,8 (43,5-56,4)	54,8 (43,5-56,4)	55,9 (36,8-56,4)	
QoL-MS	Mean±SD	56±9,4	43,6±15,3	51,2±13,6	53±12,6	54±11,8	41,2±13,8	**<0,001**
	Median (IQR)	58,9 (55,9-59,8)	37,9 (33,2-59,8)	57,9 (46,1-59,8)	58,4 (51,1-60,8)	58,9 (55,9-60,8)	37,9 (33,2-55,9)	

***SD:** Standard deviation, **IQR:** Interquartile Range, **ST:** Surgery time, **VAS:** Visual analog scale,*
***HS:** Length of hospital stay, **QoL-PS:** Quality of life-physical score, **QoL-MS:** Quality of life-mental score*

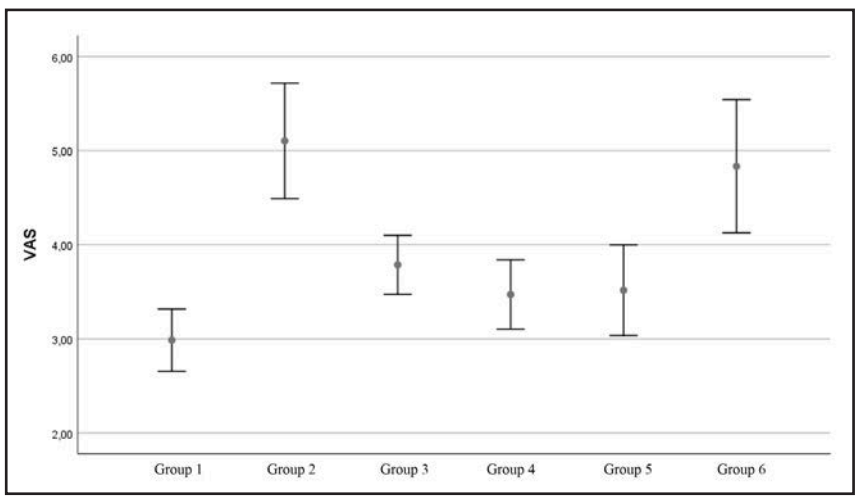

Figure 1. Visual Analog Scale (VAS) scores by groups

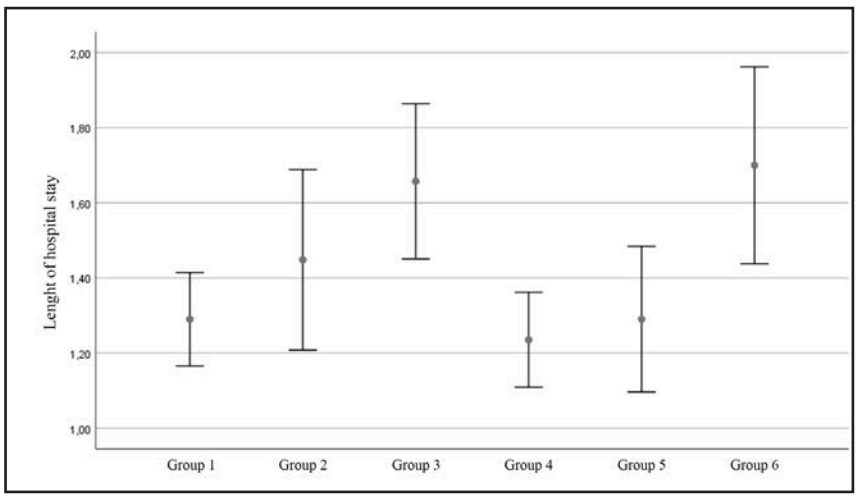

Figure 2. Length of hospital stay by groups.

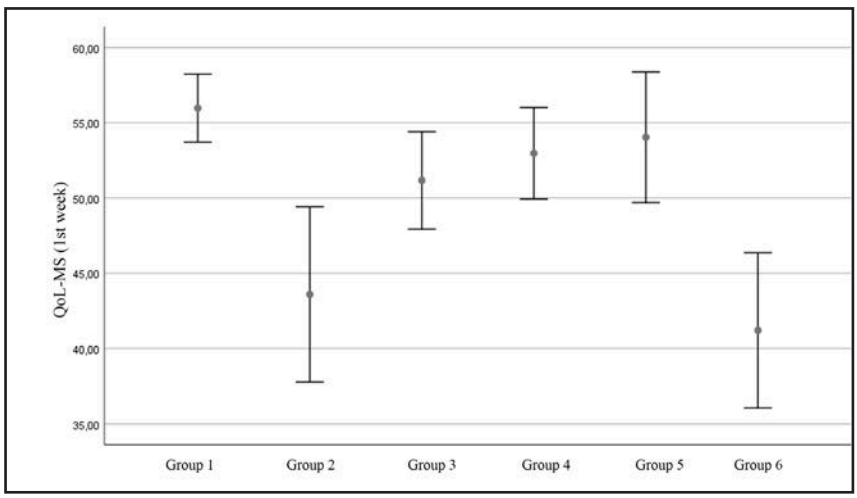

Figure 3. Quality of Life-Mental Scores (QoL-MS) by groups

DISCUSSION

Distribution of the living kidney donors based on relation to recipients in this study shows that spouses ranked first as donors with 23.57%, followed by mothers (23.23%) and siblings (22.90%). These data are in sharp contrast with previous studies. Messersmith et al. reported that most donors were siblings (41%), followed by parents (18%), while spouses ranked fourth with 8.9% (6). Similarly, Frade et al. also reported that most donors were siblings with 62.5%, followed by parents with 34.4% (7). The differences in the distribution of donors' biological relationship to recipients in previous studies may be due to various factors such as sociocultural characteristics, concept of family, education level, or income status, which vary across societies. As for education level, most kidney donors in our study were high school graduates (secondary education) with 52.1%. It is extremely difficult to make comparisons on this parameter as countries have vastly different levels of education and national education systems. For example, a US-based study reported that more than 97% of kidney donors had a high school diploma or higher (6).

KTx contributes to the physical and psychosocial capacity of the patient with ESRD in the postoperative period and thus improves the QoL and life expectancy (8,9). Due to the low rate of cadaveric kidney transplantation in Turkey, living organ donation is

mostly used in kidney transplantation. This requires paying attention to the problems experienced by both kidney donors and recipients in the postoperative period. When postoperative care and monitoring focuses solely on assessing organic changes due to the surgery, it may lead to a disregard of the psychosocial changes that the organ donor may experience during and after the donation process. Understanding whether the degree of relationship with the recipient might affect potential negative outcomes is crucial, and can help prepare donors for the donation process in the preoperative period. Rodrıgue et al. investigated this subject and showed that patients who were concerned about their future kidney health before donation remained concerned after donation as well (10).

A large number of studies have been conducted on the mood changes and QoL of living kidney donors in the postoperative period. The dominant view in most studies is that donors experience no adverse physical effects. However, studies have reported different results in terms of the psychosocial effects associated with the donation process (7,11,12,12,13,14,15,16). We believe that studies should focus not only on the psychosocial problems that kidney donors may experience during the rest of their lives, but also on the association of these problems with donor–recipient relationship. Our study found no difference between the groups in terms of QoL-PS, which is in line with the literature; whereas, QoL-MS was significantly lower in group-2 and group-6. Although limitations in our data prevent any comparisons with preoperative values, the low QoL-MS in group-2 may be explained by fathers' concern of incompetence related to their status in the family and society. On the other hand, donors in group-6, unlike other groups, did not have a homogeneous degree of relationship to recipients, and this makes it difficult to comment on the association of donor–recipient relationship with low QoL-MS scores in group-6. However, one possible explanation is that a more distant degree of donor–recipient relationship may be causing donors to have a decreased sense of psychological comfort associated with donating a kidney.

Another issue worth mentioning is the sex distribution of kidney donors. In our series, the majority of kidney donors were women (59.26% vs. 40.74%), which is consistent with previous studies. An article investigating this subject put forward a number of reasons why living kidney donors are predominantly women. These reasons include in particular psychosocial and economic factors (17). Overall, it is known that mothers outnumber fathers, wives outnumber husbands, and daughters outnumber sons as living kidney donors (18). Our study found similar results. Our observations led us to think that this is due to the socioeconomic status of men in Turkish society. Men have the primary role in providing for the family, especially in terms of livelihood in Turkish society, and this may be the main reason why men are reluctant to become kidney donors. Some studies have revealed that kidney donation led to a financial loss and this loss was more prominent in donors with low household income (19, 20). Musol et al. evaluated the role of gender in living kidney donation and reported that women related to recipients considered kidney donation as a natural process and donated organs with an optimistic attitude and disregard for their own health. The same study emphasized that wives considered kidney donation as a way to avoid assuming the role of caregiver for their husbands and to protect their children (21).

VAS scores at postoperative day one in our study were significantly lower in group-1. The highest VAS score was in group-2. QoL-MS comparison between groups showed that group-1 also has the highest QoL-MS score. These data suggest that mothers are less affected by the kidney donation process in psychological terms. Lower VAS scores without any difference in QoL-PS scores may be explained by better psychological motivation of the mothers. Our clinical observations suggest that mothers donate kidneys with a more altruistic approach.

Finally, the length of hospital stay was significantly long in group-3 and group-6. We often observe that spouses donating a kidney are reluctant to be discharged for concerns over own care while their spouses are hospitalized or in order to spend more time with their spouses. This is likely to be reflected in the statistical analysis. On the other hand, the group composed of

distant relatives had long hospital stays, combined with high VAS scores and low QoL-MS values, which can be attributed to the concerns of these patients over their overall health.

In general, it can be said that the lowest VAS score after donor nephrectomy is observed in mothers, the shortest hospital stay in siblings, and the lowest QoL-MS score in fathers and distant relatives. The main limitation of this study is its retrospective design. Being a single-center study and focusing on early postoperative parameters can be counted as other limitations.

CONCLUSION

The degree of relationship of living kidney donors to recipients influences their psychological health in the early postoperative period and probably affects VAS scores and length of hospital stay. It can be argued that mothers are the group of donors least affected by the kidney donation process. In the preoperative period, donors should be evaluated for these aspects and, if necessary, referred to psychological support, which may help prevent potential negative outcomes in the postoperative period.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by University of Health and Sciences Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (Approval Number: 2023-01-35, Date: 2022/11/04) and written informed consent was received from all participants. The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

Conception and design; Açıkgöz O, Altınel M, Data acquisition; Açıkgöz O, Altınel M, Data analysis and interpretation; Altınel M, Drafting the manuscript; Açıkgöz O, Critical revision of the manuscript for scientific and factual content; Açıkgöz O, Statistical analysis; Açıkgöz O, Altınel M, Supervision; Açıkgöz O, Altınel M.

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Authors must include relevant keywords (3-6) on the line following the end of the abstract The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

For the international authors, submission of Turkish title, Turkish abstracts and Turkish keywords are not required. These will be provided by the editorial office.

Manuscript

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be explained clearly in parentheses following the definition and custom abbreviations should not be used.

Statistical analysis is usually necessary to support results in original articles. Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Whenever a product, software, or software program is mentioned in the main text, product information (including state in the USA) must be given in parentheses, including the product name, product manufacturer, city of production, and country of the company.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the discussion section before the conclusion paragraph.

Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies.

Letter to the Editor discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." The text should be unstructured.

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text. The symbols used must be nomenclature used standards.

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All pages of the manuscript should be numbered at the bottom center, except for the title page. Papers should include the necessary number of tables and figures to provide better understanding.

Limitations for each manuscript type;

Type of Article	Abstract	Text (Word)	References	Table	Figure
Original Article	250 Structured	3000	30	6	5
Review Article	250 Unstructured	4000	50	6	5
Case Reports	250 Unstructured	2000	10	1	3
Letter to the Editor	No abstract	1000	5	1	1

Original Research Articles should include subheadings below;

- Title (both Turkish and English)
- Abstract (both Turkish and English)
- Keywords (both Turkish and English)
- Introduction
- Material and Methods
- Results
- Discussion
- Conclusions
- Figures and Tables Legend
- References

Case Reports should include subheadings below;

- Title (both Turkish and English)
- Abstract (unstructured, both Turkish and English)
- Keywords (both Turkish and English)
- Introduction
- Case Presentation
- Discussion and Conclusion
- Figures and Tables Legend
- References

Review Article should include subheadings below;

- Title (both Turkish and English)
- Abstract (unstructured, both Turkish and English)
- Keywords (both Turkish and English)
- Main text
- Conclusion
- Figures and Tables Legend
- References

For systematic reviews, authors must adhere to the PRISMA guidelines.

Letters to Editor should include subheadings below;

- Title
- Keywords
- Main text
- Figures and Table Legend
- References

Figures and Tables

Figures, graphics, and photographs should be submitted as separate files (in JPEG format) through the submission system.

The files should not be embedded in a Word file of the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system.

Images should be numbered by Arabic numbers to indicate figure subunits.

Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends.

The minimum resolution of each submitted figure should be 300 DPI.

Figures or illustrations must not permit the identification of patients and written informed consent for publication must be sought for any photograph.

Figure legends should be listed at the end of the main document.

Tables should embed in the main document or should be submitted as separate files but if tables are submitted separately please note where it is suitable in the main text. All tables should be numbered consecutively in the order they are used to within the main text. Tables legends should be listed at the end of the main document.

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References

While citing publications, preference should be given to the latest, most up-to-date publications. Authors should avoid using references that are older than ten years. All the references should be written according to the Vancouver reference style. The references used in the article must be written in parenthesis, at the end of the sentences. References should be numbered in the order they appear in the text and listed in the same order in which they are cited in the text. Be consistent with your referencing style across the document.

References must contain surnames and initials of all authors, article title, name of the journal, the year and the first and last page numbers. If there are more than 6 authors, an abbreviation of "et al." should be used for the authors out of the first three. Journal titles should be abbreviated according to Index Medicus.

You must add the DOI (Digital object identifier) at end of each reference.

For Examples;

Article in journal: Tasci A, Tugcu V, Ozbay B, et al. Stone formation in prostatic urethra after potassium-titanyl-phosphate laser ablation of the prostate for benign prostatic hyperplasia. J Endourol. 2009;23:1879-1881.

For Books: Günalp İ. Modern Üroloji. Ankara: Yargıçoğlu Matbaası, 1975.

Chapters in books: Anderson JL, Muhlestein JB. Extra corporeal ureteric stenting during laparoscopic pyeloplasty. Philadelphia: W.B. Saunders, 2003; p. 288-307.

For website; Gaudin S. How moon landing changed technology history [serial online]. 2009 [cited 2014 June 15]. Available from: http://www.computerworlduk.com/in-depth/it-business/2387/how-moon-landing-changed-technology-history/

For conference proceeding; Anderson JC. Current status of chorion villus biopsy. Paper presented at: APSB 1986. Proceedings of the 4th Congress of the Australian Perinatal Society, Mothers and Babies; 1986 Sep 8-10; Queensland, Australian. Berlin: Springer; 1986. p. 182-191.

For Thesis; Ercan S. Venöz yetmezlikli hastalarda kalf kası egzersizlerinin venöz fonksiyona ve kas gücüne etkisi. Süleyman Demirel Üniversitesi Tıp Fakültesi Spor Hekimliği Anabilim Dalı Uzmanlık Tezi. Isparta: Süleyman Demirel Üniversitesi; 2016.

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Manuscript Retraction: For any other reason authors may withdraw their manuscript from the journal with a written declaration.

Revisions

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial period is over.

AFTER ACCEPTANCE

Accepted manuscripts are copy-edited for grammar, punctuation, and format. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested. The journal owner and the editorial board are authorized to decide in which volume of the accepted article will be printed. Authors may publish their articles on their personal or corporate websites by linking them to the appropriate cite and library rules.

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PEER REVIEW PROCESS

The Double-Blind Peer Review Process

1. Submission of Paper

The corresponding author submits the paper via Dergipark online system to the journal (http://dergipark.gov.tr/journal/1455/submission/start).

2. Editorial Office Assessment

Editorial Office checks the paper's composition and arrangement against the journal's Author Guidelines to make sure it includes the required sections and stylizations. The quality of the paper is not assessed at this point.

3. Appraisal by the Editor-in-Chief

The Editor-in-Chief assigns submission to Section Editor to see through the editorial process. Section Editor checks that the paper is appropriate for the journal and is sufficiently original and interesting. If not, the paper may be rejected without being reviewed any further.

4. Invitation to Reviewers

The Section Editor sends invitations to individuals he or she believes would be appropriate reviewers. As responses are received, further invitations are issued, if necessary, until the required number of acceptances is obtained – commonly this is 2.

5. Response to Invitations

Potential reviewers consider the invitation as anonymous against their own expertise, conflicts of interest and availability. They then accept or decline. If possible, when declining, they might also suggest alternative reviewers.

6. Review is Conducted

The reviewer sets time aside to read the paper several times. The first read is used to form an initial impression of the work. If major problems are found at this stage, the reviewer may feel comfortable rejecting the paper with-out further work. Otherwise they will read the paper several more times, taking notes so as to build a detailed point-by-point review. The review is then submitted to the journal, with a recommendation to accept or reject it – or else with a request for revision (usually flagged as either major or minor) before it is reconsidered.

7. Journal Evaluates the Reviews

The Section Editor considers all the returned reviews before making an overall decision. If the reviews differ widely, the editor may invite an additional reviewer so as to get an extra opinion before making a decision.

8. The Decision is Communicated

The Section Editor sends a decision email to the author including any relevant reviewer comments as anonymous.

9. Next Steps

If accepted, the paper is sent to language Editor. If the article is rejected or sent back for either major or minor revision, the Section Editor should include constructive comments from the reviewers to help the author improve the article. At this point, reviewers should also be sent an email or letter letting them know the outcome of their review. If the paper was sent back for revision, the reviewers should expect to receive a new version, unless they have opted out of further participation. However, where only minor changes were requested this follow-up re-view might be done by the Section Editor.

- After these;
- Copyedit submission
- Layout
- Corrections
- Publishing the submissions on the web page as early print
- Creating issues
- Organize Table of Contents
- Publishing the issue on the web page and printing hardcopy.

We are applying the same steps on The Double-Blind Peer Review Process when we got the in-house submission.

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