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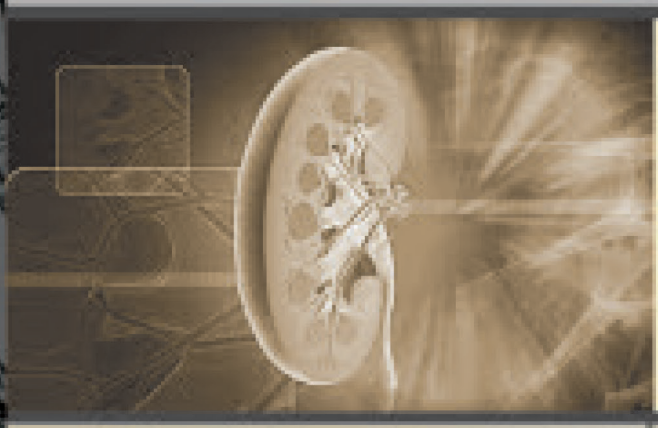

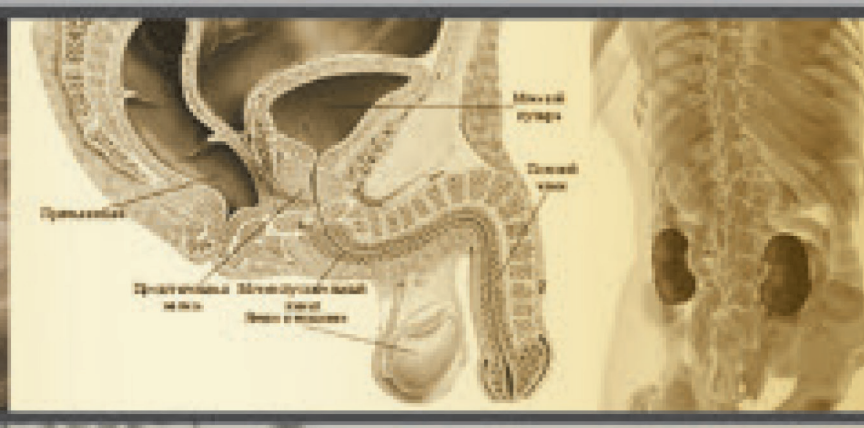

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Ghoneim IA, Miocinovic R, Stephenson AJ, Garcia JA, Gong MC, Campbell SC, Hansel DE, Fergany AF. Neoadjuvant systemic therapy or early cystectomy? Singlecenter analysis of outcomes after therapy for patients with clinically localized micropapillary urothelial carcinoma of the bladder. Urology 2011;77:867-870.

2. Organization as Author

Yaycioglu O, Eskicorapci S, Karabulut E, Soyupak B, Gogus C, Divrik T, Turkeri L, Yazici S, Ozen H; Society of Urooncology Study Group for Kidney Cancer Prognosis. A preoperative prognostic model predicting recurrence-free survival for patients with kidney cancer. Jpn J Clin Oncol 2013;43:63-68.

3. Complete Book

Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012.

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 2012, pp 1257-1323.

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5. Abstract

Nguyen CT, Fu AZ, Gilligan TD, Kattan MW, Wells BJ, Klein EA. Decision analysis model for clinical stage I nonseminomatous germ cell testicular cancer. J Urol 2008;179:495a (abstract).

6. Letter to the Editor

Lingeman JE. Holmium laser enucleation of the prostate-If not now, when? J Urol 2011;186:1762-1763.

7. Supplement

Fine MS, Smith KM, Shrivastava D, Cook ME, Shukla AR. Posterior Urethral Valve Treatments and Outcomes in Children Receiving Kidney Transplants. J Urol 2011;185(Suppl):2491-2496.

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Original Researches

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Case Reports

ORIGINAL RESEARCH
Endourology

Doi: 10.4274/jus.galenos.2020.3113
Journal of Urological Surgery, 2020;7(3):158-165

Should the Double-J Stent Be Removed Endoscopically after a Ureteroscopic Stone Surgery?

Üreteroroskopik Taş Cerrahisinden Sonra Double-J Stent Endoskopik Yolla Çıkarılmalı mı?

Önder Çınar[1], Mustafa Suat Bolat[2], Kemal Öztürk[2]

[1]Zonguldak Bülent Ecevit University Faculty of Medicine, Department of Urology, Zonguldak, Turkiye
[2]Samsun Gazi Hospital, Clinic of Urology, Samsun, Turkiye

What's known on the subject? and What does the study add?

Urologists mostly prefer to use Duuble-J (JJ) stents to provide better postoperative comfort for their patients without an extraction string. Our findings showed that removal of the JJ stent with its extraction string with lower treatment costs and complications does not adversely affect surgical outcomes, and has higher patient comfort.

Abstract

Objective: Ureterorenoscopic stone surgery (USS) is the primary method of ureteral stone treatment. Double-J (JJ) stenting is an integral part of a USS, and most urologists prefer to use it without an extraction string. The probable reason for such preference could be the lack of reliable and sufficient data on JJ stent use with an extraction string.

Materials and Methods: A total of 177 patients who underwent USS were divided into four groups: Group 1 men (JJ stent was manually removed), group 2 men (JJ stent was cystoscopically removed), group 3 women (JJ stent was manually removed), and group 4 women (JJ stent was cystoscopically removed). We investigated the impact of two different JJ stent removal techniques on pain perception, lower urinary tract symptoms (LUTS), depressive symptomatology, complications, and cost.

Results: Compared to groups 1 and 3, the mean surgery times were higher in groups 2 and 4 (p=0.001). Preoperative LUTS scores were similar in all groups (p>0.05). Postoperative pain scores in groups 3 and 4 were similar (p=0.06), but they were lower in group 1 than in group 2 (p=0.004). Postoperative Beck depression inventory scores were lower in groups 1 and 3 (p<0.02). The total cost of USS was 28.5% higher in groups 2 and 4 compared to groups 1 and 3.

Conclusion: It is concluded that JJ stent removal with an extraction string is a reliable method with low treatment costs that does not adversely affect surgical outcomes.

Keywords: Cost effectivity, Double-J stent, Extraction string, Ureterorenoscopy, Pain

Öz

Amaç: Üreterorenoskopik taş cerrahisi, üreter taşı tedavisinin temel yöntemidir. Double-J (JJ) stent, taş cerrahisinin ayrılmaz bir parçasıdır ve çoğu ürolog ipsiz JJ stent kullanmayı tercih etmektedir. Bu tercih, büyük olasılıkla, ipli JJ stent kullanımı hakkında güvenilir ve yeterli veri bulunmamasından kaynaklanmaktadır.

Gereç ve Yöntem: Üreterorenoskopik taş cerrahisi uygulanan toplam 177 hasta grup 1 erkeklere (ipli JJ stent, manuel olarak çıkarıldı), grup 2 erkek (ipsiz JJ stent sistoskopik olarak çıkarıldı), grup 3 kadınlara (ipli JJ stent, manuel olarak çıkarıldı) ve grup 4 kadınlara (ipsiz JJ stent sistoskopik olarak çıkarıldı) sınıflandırıldı. İki farklı JJ stent çıkarma tekniğinin ağrı algısı, alt idrar yolu semptomları (AÜSS), depresif semptomlar, komplikasyonlar ve maliyet üzerindeki etkisini araştırdık.

Bulgular: Grup 1 ve 3 ile karşılaştırıldığında, ortalama ameliyat süresi grup 2 ve 4'te daha yüksekti (p=0,001). Preoperatif AÜSS skorları tüm gruplarda benzerdi (p>0,05). Postoperatif 3. ve 4. gruplardaki ağrı skorları benzerdi (p=0,06), ancak grup 1'de grup 2'den düşüktü (p=0,004). Postoperatif Beck depresyon envanteri skorları 1. ve 3. gruplarda daha düşüktü (p<0,02). Üreterorenoskopik taş cerrahisinin toplam maliyeti grup 1 ve 3'e kıyasla grup 2 ve 4'te %28,5 daha yüksek olarak saptandı.

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Sonuç: JJ stentin ipli şekilde manuel oarak çıkarılmasının düşük tedavi maliyetleriyle güvenilir bir yöntem olduğu sonucuna ulaştık. JJ stentlerin ipli kullanımı cerrahi sonuçları olumsuz yönde etkilememektedir.
Anahtar Kelimeler: Maliyet etkinliği, Double-J stent, Ekstraksiyon ipi, Üreterorenoskopi, Ağrı

Introduction

Stone incidence varies depending on geographical, climatic, ethnic, dietary, and genetic factors with a prevalence rate of 1-14% (1). Medical expulsive treatment (MET), shock wave lithotripsy (SWL), and ureterorenoscopic stone surgery (USS) are the primary methods used in ureteral stone treatment. The evolution of smart and advanced technological instruments has led to a higher preference for endoscopic surgery for the removal of ureteral stones (2). The USS is one of the most investigated surgical techniques in terms of its efficacy and complications and Double-J (JJ) stenting is an integral part of this technique. JJ stents are placed in 60-80% of patients after ureteral or renal stone surgery to prevent urinary obstruction (3). Urologists tend to use JJ stents without extraction strings, despite their benefits, due to their anticipation of risks such as infection, string irritation, or dislocation of the JJ stent, and possibly due to the lack of data on the use of JJ stents with extraction string (4).

The cost of ureteral stone treatment continues to increase national health expenditures significantly. At the beginning of the 1980s, the financial burden associated with urinary stones was reported to be less than $900 million in the United States. This figure increased to $5.3 billion in 2014 (5). In addition to the direct cost of ureteral stone surgery, almost one in seven patients are readmitted to the hospital due to complications and face further indirect costs (6). The costs of endoscopic ureteral laser surgery have been reported to be $1,425 per case (7) and $926-$3,520 (8-10) in the United States and European countries, respectively. According to the repayment policy of the Turkish Social Security Institution, the official cost of endoscopic ureteral stone treatment is $154.9 for a JJ stentless procedure and an additional $45.1 for stent removal.

Despite the revolution in JJ stent technology, stent-related morbidity is still the primary concern, as the ideal stent has not been produced yet. The lack of published studies providing sufficient data and the continued use of JJ stents without extraction strings by urologists encouraged us to conduct the present study.

The removal of the JJ stent with or without an extraction string may have an impact on postoperative outcomes and treatment costs. In this study, we aimed to investigate the impact of two different JJ stent removal techniques on pain perception, depressive symptomatology, complications, and cost.

Materials and Methods

This retrospective study was conducted between January and October 2018 using a two-center and two-arm design, which was approved by the Ethics Committee of the Zonguldak Bülent Ecevit University (12/10/2018-33479383). A written consent form was obtained from all participants.

Inclusion criteria for JJ stent with and without extraction string

Adult men and women with the unilateral ureteral stone disease who had failed MET and could not pass the stone with SWL.

Exclusion criteria

Patients with an untreated urinary tract infection, uncorrected bleeding diathesis, bilateral ureteral stones, urogenital tumors, a neurogenic bladder, pregnancy, urogenital malformations (i.e., horseshoe kidney or pelvic kidney), renal insufficiency, renal transplantation, or pregnancy were excluded. Pediatric patients and participants who were taking antidepressant therapy for a psychogenic disorder were also excluded.

Study design

Of the 196 patients, 177 were included in this study. Nineteen patients were excluded due to incomplete data. Random sampling was performed by tossing up a coin. Of the 131 men included in the study, 40 were identified as group 1 (JJ stents were manually removed), and the remaining 91 as group 2 (JJ stents were cystoscopically removed). Out of the 46 women included in the study, 19 were identified as group 3 (JJ stents were manually removed) and 27 as group 4 (JJ stents were cystoscopically removed). The patients were given antispasmodic drugs when needed for stent-related irritative symptoms and pain control.

JJ stent insertion and removal techniques

After ureteral stone surgery, 4.7 French JJ stents were cystoscopically placed under the guidance of fluoroscopy, and thus, the distal end of the extraction strings exited the external urethral meatus and it was secured to the radix penis or mons pubis in groups 1 and 3, respectively (Figure 1a, b).

JJ stents without extraction strings were cystoscopically placed into ureters under the guidance of fluoroscopy in groups 2 and 4 following the USS. The patients in groups 1 and 3 were warned and educated about hygienic practices to take care of their distal extraction strings, and their JJ stents were manually removed.

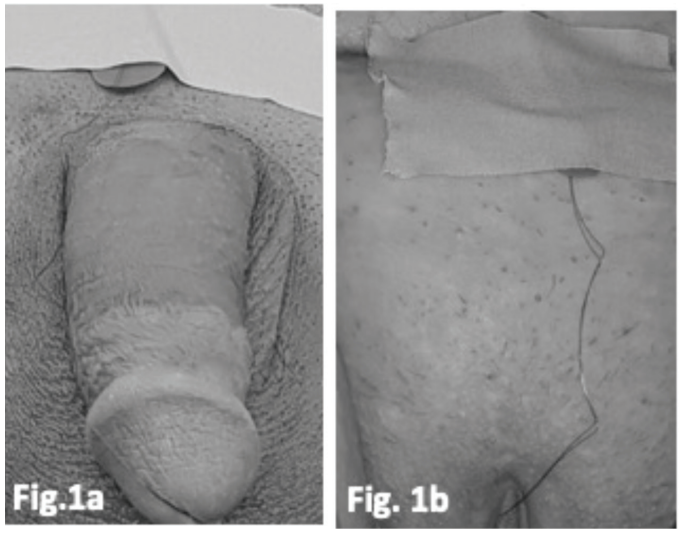

Figure 1. a, b. Distal end of the extraction strings were secured to the radix penis or mons pubis

The JJ stents were endoscopically removed in patients in groups 2 and 4 under sterile conditions using local anesthesia.

Primary outcome measures

1. Men and women with LUTS
2. Pain perception during JJ stent removal
3. Cost of intervention

Secondary outcome measures

1. Depressive symptoms
2. Complications

Measurement tools

In men, LUTS were evaluated using the Turkish validated international prostate symptom score (IPSS) and was based on the answer to seven questions concerning urinary symptoms. The questions allowed the patient to choose one out of six answers indicating the severity of a particular symptom. Each answer was assigned a point from 0 to 5, and the total score was from 0 (asymptomatic) to 35 (the worst). Total scores were grouped into three categories: mild (symptom score ≤7), moderate (symptom score within the range of 8-19), or severe (symptom score ≥20) (8).

Pain perception level due to ureteral colic was identified using an 11-point numeric rating scale (NRS) score (0= no pain, 10= unbearable pain) (9). Post-operative NRS scores were recorded as the perceived pain during the removal of JJ stents in the groups.

Micturition changes in women and men were evaluated using Turkish validated international consultation on incontinence questionnaire-female lower urinary tract symptoms (ICIQ-FLUTS) and male lower urinary tract symptoms (ICIQ-MLUTS) questionnaires that assess the prevalence of 13 urinary symptoms and their impact on daily life (10). Eleven symptoms were rated using a score from 0 ("never") to 4 ("all the time"). The daytime frequency was measured using a score from 0 ("1-6 times") to 4 ("≥13 times"). Nocturia was measured using a score from 0 ("0 times") to 4 ("≥ 4 times"). Impact on the daily life of each symptom was scored on a scale from 0 ("not at all") to 10 ("a great deal").

Depressive symptoms of the participants in each group were assessed using the Beck depression inventory (BDI), which is one of the most commonly used tools for the self-rated measurement of emotional, cognitive, somatic, and motivational components (11). BDI scores were classified as none (<13 pts), minimal-moderate (14-19), moderate–severe (20-29), and severe (30-63).

Preoperative urine cultures were obtained from all participants regardless of their grouping. Non-contrast enhanced computerized tomography scans localized the stones in patients and revealed the sizes of the stones. Because the JJ might affect stent-related symptoms, it was confirmed that the distal end of the JJ stent did not cross the midline using the postoperative kidney-ureter-bladder (KUB) X-ray.

All the aforementioned questionnaires were then applied to all participants included in the study before grouping. Following the initial evaluation, men and women were divided into four groups: group 1 (men whose JJ stents with extraction strings were manually removed by a urologist without an additional endoscopic procedure, n=40); group 2 (men whose JJ stents without extraction strings were removed with an additional cystoscopy, n=91); group 3 (women whose JJ stents with extraction strings were removed manually without an additional cystoscopy, n=19); and group 4 (women whose JJ stents without extraction strings were removed with an additional cystoscopy, n=27). On the day of JJ stent removal, all patients were invited to the clinic for reassessment using the aforementioned instruments.

Treatment costs for both removal techniques

According to the repayment price policy of the Turkish Social Security Institution, the official cost of an endoscopic ureteral stone treatment is $154.9 per patient. For a JJ stent without an extraction string placed after the surgery, the cystoscopic removal of the JJ stent costs an additional $44.1 (Table 1).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Science (SPSS 21.0 for Windows; SPSS Inc., Chicago, Illinois, USA) and presented as mean ± standard deviation (SD) and frequency (%). A comparison of preoperative and postoperative data was performed using an independent sample test and a

Table 1. Demographic and clinical variables of men in the groups			
	Group 1	**Group 2**	**p-value**
Patients n, (%)	40 (30.5)	91 (69.5)	–
Age (years, mean ± SD)	44.5±12.3	46.4±13.5	0.33
BMI* (kg/m^2)	27.6±3.4	27.3±3.0	0.77
Comorbidity (n, %) 0 1 2 ≥3	 37 (92.5) 2 (5) 1 (2.5) –	 79 (86.8) 9 (9.9) 3 (3.3) –	0.62
Marital status (n, %) Married Single Divorced	 39 (97.5) 1 (2.5) –	 83 (91.2) 7 (7.7) 1 (1.1)	–
Stone burden (mm^2, mean ± SD)	78.1±55.8	82.2±60.4	0.17
Stone location (n, %) Upper ureter Middle ureter Lower ureter	 9 (22.5) 7 (17.5) 24 (60.0)	 39 (42.9) 30 (32.9) 22 (24.2)	–
Previous shock wave lithotripsy (n, %) Yes No	 1 (2.5) 39 (97.5)	 3 (3.3) 88 (96.7)	0.14
Treatment cost per patient (USD**)	154.9	199	–
Stent stay period (days, mean ± SD), (min-max)	6.4±3.9 (5-11)	13.6±11.2 (8-25)	**0.02**
Surgery time (min, mean ± SD)	43.7±12.1	58.0±15.4	**0.001**
Complications (n, %) Urinary infection requiring antibiotic treatment JJ stent displacement String irritation	 1 (2.5) 1 (2.5) 1 (2.5)	 2 (2.2) – –	0.91
*BMI: Body mass index, **USD: United States Dollar, JJ: Double-J			

paired sample test for men and the Mann-Whitney U test for women. A value of p<0.05 was considered as significant.

Results

The demographic data of groups 1 to 4 such as the mean age, gender, body mass index (BMI), comorbidities, marital status, location and burden of the stone, and history of previous SWL are summarized in Tables 1 and 2. For men and women, the mean ages, BMI, history of previous SWL, and comorbidities were similar (p>0.05). JJ stent insertion with extraction string rates were 30.5% in men, 41.3% in women, and 33.3% in total. The mean surgery times were significantly higher in groups 2 and 4 compared to those in groups 1 and 3 (p=0.001), although the stone sizes were similar (p>0.05) (Tables 1, 2).

The mean preoperative and postoperative IPSS scores were 9.7±7.0 and 8.5±7.5 in group 1 (p=0.71) and 8.9±5.7 and 10.9±6.3 in group 2 (p=0.001), respectively. Groups 1 and 2 showed similar mean postoperative IPSS scores (p>0.05) (Table 3).

The mean preoperative and postoperative voiding, storage, and incontinence subdomains of the MLUTS and MLUTS impact on daily life scores were similar in groups 1 and 2 (p>0.05). For group 2, only the mean storage subdomain of MLUTS increased (p=0.001), whereas the other subdomains were similar (p>0.05). Preoperative MLUTS and MLUTS impact on daily life scores were similar between groups 1 and 2, as in the postoperative period (p>0.05) (Table 3). The mean preoperative and postoperative voiding, storage, and incontinence subdomains of the FLUTS and FLUTS impact on daily life scores were similar in groups 3 and 4 (p>0.05) (Table 4).

The mean postoperative NRS scores were 2.3±1.5 and 4.0±2.5 in groups 1 and 2, respectively (p=0.004) (Table 3). For women, the mean postoperative NRS scores were 3.0±2.8 and 4.2±2.3 in groups 3 and 4, respectively (p=0.06). The mean postoperative NRS score was significantly lower in group 1 than in group 2 (p=0.004) (Table 4).

The mean preoperative and postoperative BDI scores were 10.5±6.8 and 6.6±5.7 in Group 1 (p=0.04); 12.3±9.7 and 10.8±8.3 in Group 2 (p=0.20) (Table 3); 12.7±7.4 and 7.0±3.5 (p=0.02) in Group 3; and 14.6±9.4 and 14.0±8.4 in Group 4 (p = 0.86), respectively (Table 4). Groups 1 and 2, and groups 3 and 4 had similar preoperative BDI scores (p>0.05). The mean postoperative BDI score was significantly lower in group 1 than

Table 2. Demographic and clinical variables of women in the groups			
	Group 3 (n=19)	**Group 4 (n=27)**	**p-value**
Age (years, mean ± SD)	48.7±15.9	51.3±15.4	0.52
BMI* (kg/m²)	28.2±4.3	28.7±3.6	0.21
Comorbidity (n, %) 0 1 2 ≥3	 15 (78.9) 2 (10.5) 2 (10.5) –	 21 (77.7) 4 (14.8) 1 (3.7) 1 (%3.7)	0.66
Marital status (n, %) Married Single Divorced	 17 (89.5) 2 (10.5) –	 24 (89.9) 3 (11.1) –	–
Stone burden (mm², mean ± SD)	77.9±49.0	84.4±57.0	0.09
Stone location (n, %) Upper ureter Middle ureter Lower ureter	 4 (21.1) 5 (26.3) 10 (56.6)	 16 (59.3) 3 (11.1) 8 (29.6)	–
Previous shock wave lithotripsy (n, %) Yes No	 1(5.3) 18 (94.7)	 4 (14.8) 23 (85.2)	0.43
Treatment cost per patient (USD**)	154.9	199	–
Surgery time (min, mean ± SD)	37.5±13.0	53.5±15.6	**0.001**
Stent stay period (days, mean ± SD), (min-max)	5.7±2.8 (3-8)	11.6±8.2 (8-23)	**0.01**
Complications (n, %) Urinary infection requiring hospitalization Incontinence due to JJ stent displacement String irritation External meatal erosion	 2 (10.5) 1 (5.2) 1 (5.2) 1 (5.2)	 2 (7.4) – – –	0.82
*BMI: Body mass index, **USD: United states dollar			

Table 3. Preoperative and postoperative changes in men								
	Group 1 (n=40)			**Group 2 (n=91)**			**Group 1 vs group 2**	**Group 1 vs group 2**
	Preoperative	**Postoperative**	**p-value**	**Preoperative**	**Postoperative**	**p-value**	**(Preoperative) p-value**	**(Postoperative) p-value**
IPSS*	9.7±7.0	8.5±7.5	0.71	8.9±5.7	10.9±6.3	**0.001**	0.51	0.10
M-LUTS** Voiding Storage Postmicturition	 6.3±3.4 4.0±2.8 2.9±1.9	 7.0±5.8 5.4±5.1 3.0±1.8	 0.31 0.26 0.36	 5.9±4.1 3.6±2.8 2.6±1.7	 5.8±4.3 4.5±3.5 2.8±1.7	 0.44 **0.001** 0.14	 0.63 0.64 0.50	 0.34 0.43 0.62
M-LUTS BOTHER Voiding Storage Postmicturition	 18.4±11.7 13.5±10.8 7.8±6.3	 15.8±14.1 19.2±15.7 6.1±5.9	 0.81 0.17 0.73	 13.7±12.0 13.5±11.6 7.2±6.7	 13.2±13.0 13.0±12.8 6.1±5.4	 0.14 **0.001** 0.48	 0.08 0.54 0.52	 0.44 0.10 0.68
NRS***	–	2.3±1.5	–	–	4.0±2.5	–	–	**0.004**
BDI⁺	10.5±6.8	6.6±5.7	**0.04**	12.3±9.7	10.8±8.3	0.20	0.35	**0.02**
*IPSS: International prostate symptom index, **M-LUTS: Male lower urinary tract symptom, *NRS: Numerical rating scale, ⁺BDI: Beck depression inventory								

in group 2 (p=0.02). Similarly, the mean postoperative BDI score was significantly lower in group 3 than in group 4 (p=0.004).

Postoperative urinary tract infection rates were 5.0%, 2.2%, 10.5%, and 7.4% in groups 1, 2, 3, and 4, respectively. Other complications are listed in Tables 1 and 2.

Discussion

JJ stenting is frequently applied after USS to provide urinary drainage (4). Unless removed, JJ stents may cause LUTS predominantly due to irritation of trigone rich in neurogenic innervation (12-14). Although the IPSS questionnaire was

Table 4. Preoperative and postoperative changes in women

	Group 3 (n=19)			Group 4 (n=27)			Group 3 vs group 4	Group 3 vs group 4
	Preoperative	Postoperative	p-value	Preoperative	Postoperative	p-value	(Preoperative) p-value	(Postoperative) p-value
F-LUTS**								
Voiding	6.8±4.5	4.9±3.5	0.58	6.0±4.2	6.2±3.9	0.30	0.75	0.22
Storage	4.8±3.6	5.0±3.9	0.31	4.4±2.4	3.0±1.7	0.42	0.49	0.15
Postmicturition	5.5±4.0	4.0±2.1	0.56	3.1±2.4	7.1±6.2	0.99	0.16	0.33
F-LUTS BOTHER								
Voiding	15.6±15.1	12.3±11.5	0.68	14.5±11.3	14.2±11.4	0.47	0.74	0.33
Storage	11.6±10.2	9.8±8.9	0.95	10.5±8.0	9.6±6.7	0.20	0.94	0.74
Postmicturition	13.5±11.8	8.8±5.4	0.47	10.4±8.6	16.8±13.7	0.20	0.55	0.32
NRS*** score	–	3.0±2.8	–	–	4.2±2.3	–	–	0.06
BDI& score	12.7±7.4	7.0±3.5	**0.02**	14.6±9.4	14.0±8.4	0.86	0.84	**0.004**

**F-LUTS: Female lower urinary tract symptoms, ***NRS: Numeric rating scale, &BDI: Beck depression Inventory

initially considered for questioning prostate-related symptoms, today it is used to evaluate several pathologies. Urologists are familiar with the IPSS questionnaire because it is easy to use. However, the ICIQ-MLUTS questionnaire provides more comprehensive data for all LUTS subdomains such as voiding, storage, and postmicturition (15). We investigated the impact of JJ stenting on postoperative LUTS using the IPSS and the ICIQ-MLUTS questionnaires in men and observed no significant differences between groups 1 and 2. As expected, postoperative IPSS and only the storage subdomain score of the ICIQ-MLUTS increased in group 2 compared to preoperative levels (p=0.001). This finding can be explained by the trigonal irritation of the JJ stent due to a relatively longer JJ stent dwell-time than group 1 (Table 1). A shorter JJ stent indwell time was associated with mild complications only, and a higher complication rate was reported as JJ stenting time increased (16). The daily workload for clinicians and the need for an additional session for cystoscopic stent removal in group 2 were the main causes of longer JJ stenting periods. Group 1 patients had a shorter JJ dwell-time because they had the option to immediately remove their stents during outpatient admission, a finding consistent with previous reports (17). Although an increased rate of a urinary infection may be expected in patients whose JJ stents were inserted with extraction string, similar infection rates were reported (18). In consistent with previous reports, no significant difference was observed in the risk of infection both in men and women in the present study (p>0.05). Both an irritation secondary to extraction string and an incomplete accidental stent dislodgement were observed only in one patient each. No additional intervention was required for these patients, and they were told to remove their JJ stents slowly by pulling off the string. Our opinion is that, although the number of patients was very low, JJ stenting with extraction string may not be suitable for patients with ureteral perforation, higher upper urinary infection, and after endopyelotomy.

In women, similar findings were found in terms of ICIQ-FLUTS scores (Table 4). Both females and males reported an increase in postoperative LUTS scores, and the use of JJ stents with extraction strings did not cause this increase.

The patients' expectations of pain and the occurrence of pain during stent removal remain to be the primary factors affecting their future decisions to receive another ureteral stone surgery (19). Using the NRS, we found a significantly lower postoperative pain score in group 1 compared to group 2 (p=0.004). This finding was consistent with previous reports (4). Although the difference in mean postoperative NRS scores between groups 3 and 4 was not statistically significant, this finding could be explained by the fact that the number of cases was relatively lower for female patients than for male patients and also the shorter length of the urethra in women than in men (p=0.06).

JJ stents should be removed as early as possible to minimize LUTS. Despite their best efforts, urologists may forget to remove the JJ stents, which may result in major complications such as encrustation, fragmentation, urinary obstruction, or even renal failure (20). Moreover, removal of a complicated JJ stent could result in a 7-fold increase in treatment costs (21). Using JJ stents with extraction strings eliminates all these risks.

Emotional stress in patients may increase during the removal of a JJ stent with an additional cystoscopy. Patients usually expect postoperative JJ stent removal to be a painful procedure, possibly due to their previous experiences relating to urinary stone disease. A majority of the patients stated that cystoscopic removal of the JJ stent would be a painful procedure. Indeed, at the beginning of the study, we observed that participants in groups 1 and 3 were happy with the information that their JJ stents would be manually removed. To prove this, we measured depressive symptoms for each groups pre- and postoperatively and found significantly lower postoperative BDI scores in groups 1 and 3.

Although the repayment and pricing policies of different insurance systems vary among countries, an additional endoscopic procedure is one of the main factors worldwide that raises treatment costs after ureteroscopic surgery. The total cost of the surgery was 28.5 % higher in groups 2 and 4 compared to groups 1 and 3 in the study. According to the Turkish Social Security Institution, the official cost of endoscopic ureteral stone treatment is approximately $200 per patient with the additional cost of cystoscopic JJ stent removal included. In a report, the cost of treatment was reported to be $243 and $185 for cystoscopic and manual removal, respectively (22). A combined 10,500 patients underwent USS in the United Kingdom in 2014, which was 86% higher compared to the number of USS patients in 2007, possibly due to increased prevalence of metabolic syndrome (23). The presence of overweight status, one of the components of metabolic syndrome, supports the increasing prevalence of stone disease over the globe. In this respect, it is foreseeable that a considerable part of the world's population will be candidates for USS due to ureter stones. Today, JJ stents are used in approximately 80% of the USS patients, but only 1/3 of the stents are placed with extraction strings. In parallel to the prevalence of urolithiasis reaching 16%, there is a significant increase in annual USS (24). The present study clearly showed that the use of JJ stents with extraction strings could reduce the cost of treatment by 28.5% per patient.

Regardless of groupings, JJ stents were safely removed with its extraction strings in the outpatient setting. In group 1, one patient had a urinary infection requiring hospitalization, and two patients had external meatal hyperemia due to stent displacement for one patient and string irritation for the other patient. Only two patients had urinary infections requiring hospitalization, one had incontinence due to stent displacement, and one had meatal erosion due to string irritation in group 3. These are minor complications that can easily be managed (Tables 1, 2).

This study has shifted our projection in favor of using JJ stents with extraction strings, and our findings support that the use of the JJ stents with extraction strings does not adversely affect the patients' comfort.

Conclusion

Urologists mostly prefer to use JJ stents to provide better postoperative comfort to their patients. The decision on the use of a JJ stent is usually based on the preference of urologists rather than the patient and is generally placed and removed without an extraction string. The lack of sufficient data is the main reason for the removal of a JJ stent without an extraction string in urology practice. Our findings showed that removal of the JJ stent with its extraction string is a reliable method with a lower treatment cost, higher patient comfort, and acceptable minor complications. Using JJ stents with extraction strings does not adversely affect surgical outcomes.

Ethics

Ethics Committee Approval: This retrospective study was conducted between January and October 2018 using a two-center and two-arm design, which was approved by the Ethics Committee of the Zonguldak Bülent Ecevit University (12/10/2018-33479383).

Informed Consent: A written consent form was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Ç., M.S.B., K.Ö., Concept: Ö.Ç., M.S.B., Design: Ö.Ç., M.S.B., Data Collection or Processing: Ö.Ç., M.S.B., Analysis or Interpretation: Ö.Ç., M.S.B., Literature Search: Ö.Ç., M.S.B., Writing: Ö.Ç., M.S.B.

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Kidney Stone Treatment in the Anomalous Kidney with Retrograde Intrarenal Surgery: A Matched Pair Analysis

Anomalik Böbrek Taş Tedavisinde Retrograd İntrarenal Cerrahi: Çift Eşleştirilmiş Analiz

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What's known on the subject? and What does the study add?

Retrograde intrarenal surgery (RIRS) is a recently popular treatment method for kidney stones. But in anomalous kidney stones, RIRS may be challenging due to impaired urine drainage and changed anatomic structure. There are studies about RIRS in anomalous kidney stone treatment. But our study shows collectively the experience of RIRS in different types of anomalies.

Abstract

Objective: To show our retrograde intrarenal surgery (RIRS) experience in anomalous kidney stones and compare its safety and efficiency with normal kidney stones.

Materials and Methods: Between 2012 and 2018, patient data was reviewed retrospectively and 1700 procedures were taken into consideration. Forty-seven anomalous kidney stones were included in the study (group A). In these patients, 18 had calyx diverticulum, 12 had horseshoe kidney, 8 had ureteral duplication, 2 had ectopic kidneys, 1 had malrotation, and 1 had bifid pelvis. After making a matched pair analysis, 47 normal kidney stones with similar demographic and stone characteristics were included in our study (group N). Demographic, stone, intraoperative and postoperative data were recorded. We compared these groups regarding efficiency and safety.

Results: Average scope time, hospitalization time, and postoperative double J-stent rate were higher in group A. The difference was statistically insignificant (p>0.05). Ureteral access sheath usage was higher in group N, though the difference was statistically insignificant (p=0.63). Stone-free rates and success rates were higher in group N though the difference was not statistically significant (p>0.05). The rate of complications was statistically significantly higher in group A (p=0.02).

Conclusion: RIRS can be used in the management of anomalous kidney stones. It is an efficient and safe method. Prospective and larger patient numbered studies are needed.

Keywords: Anomalous, Matched pair, RIRC

Öz

Amaç: Anomalik böbrek taşlarında retrograd intrarenal cerrahi (RİRC) deneyimimizi göstermek ve normal böbrek taşları ile güvenlik ve etkinliğini karşılaştırmaktır.

Gereç ve Yöntem: 2012-2018 yılları arasında veriler retrospektif olarak tarandı. Bin yedi yüz işlem değerlendirildi. Kırk yedi anomalik böbrek taşı çalışmaya alındı (grup A). Bunlardan 18'inde kaliks divertikülü, 12'sinde atnalı böbrek, 8'inde üreteral duplikasyon, 2'sinde ektopik böbrek, birinde malrotasyon ve birinde bifid pelvis mevcuttu. Çift eşleştirilmiş analiz sonrası benzer özelliklere sahip 47 normal böbrek taşı çalışmaya alındı (grup N). Demografik, taş, intraoperatif ve postoperatif veriler kaydedildi. Gruplar etkinlik ve güvenilirlik açısından karşılaştırıldı.

Bulgular: Ortalama skopi süresi, hastanede kalış süresi ve postoperatif Double-J stent oranı A grubunda yüksekti. Aradaki fark istatiksel olarak anlamsızdı (p>0,05). Üreteral akses kılıf kullanımı N grubunda yüksekti. Aradaki fark istatiksel olarak anlamsızdı (p=0,63). Taşsızlık ve başarı oranı N

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grubunda yüksekti. Aradaki fark istatistiksel olarak anlamlı değildi. Komplikasyon oranı A grubunda istatiksel olarak anlamlı şekilde yüksekti (p=0,02).
Sonuç: RİRC anomalik böbrek taş tedavisinde kullanılabilecek etkin ve güvenilir bir yöntemdir. Prospetif ve yüksek sayılı çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Anomalik, Çift eşleştirilmiş, RIRC

Introduction

Kidney anomalies are seen in 300-1000 births (1,2). Impaired urine drainage increases stone formation in anomalous kidneys (2,3). Stone management is important in anomalous kidneys. Shock wave lithotripsy (SWL) is a method used in management. SWL is a non-invasive method with stone clearance rate of 67.8% (54%-82%) (4), but impaired urine drainage and changed anatomic structure may worsen stone clearance (5). Another method for management is percutaneous nephrolithotomy (PNL). PNL is the first choice for treatment of stones >2 cm in size, but serious complications can be encountered by using this process. It has a success rate of approximately 87.5%. The position of the patient and complications (pneumothorax, hemorrhage, nephro-pleural fistula) are disadvantages of PNL (6). The other management options are laparoscopic pyelolithotomy and laparoscopy-assisted PNL. These methods are more invasive than endoscopic methods (7). Retrograde intrarenal surgery (RIRS) was firstly used in the late 20th century, and its usage increased with advanced technology (8,9). The development of flexible ureteroscope size and deflection technologies expanded RIRS usage areas (10-14). Serious complications are rarely seen in RIRS method (15,16). RIRS can be used for the treatment of anomalous kidney stones. In our study, we aimed to show our RIRS experience in anomalous kidney stones and compare its safety and efficiency with normal kidney stones.

Materials and Methods

Between 2012 and 2018, data collected was reviewed retrospectively and 1700 procedures were taken into consideration. For anomalous kidney stones, 47 procedures were included in the study. In these patients, 18 had calyx diverticulum (CD), 12 had horseshoe kidney (HSK), 8 had ureteral duplication, 2 had ectopic kidney (EK), 1 had malrotation (M), and 1 had bifid pelvis. For non-anomalous kidney stones, 47 procedures were selected and enrolled. The anomalous procedures were divided into groups according to stone size 5-10 mm, 11-15 mm, 16-20 mm, 21-25 mm, 26-30 mm, 31-35 mm, 36-40 mm, 41-45 mm, 46-50 mm, and 51-55 mm. The similar number of procedures were selected from the non-anomalous procedures randomly. The randomization was made similarly for the criteria such as stone laterality, stone number and stone localization. Patients were informed about treatment methods. Treatment method was chosen according to patient and surgeon choice.

Common blood count, serum biochemical values, bleeding and coagulation profile, urine analysis and urine culture were obtained for all patients preoperatively. All urine cultures were provided preoperative sterile. Different radiological methods were used kidney-ureter-bladder graphy (KUBG), ultrasonography (US), intravenous urography, and/or computerized tomography. For non-opaque stones, the stone diameter was measured with the US. For opaque stones, KUBG was used. In multiple stones, the sum of the longest diameters of each stone was defined as stone diameter. Informed consent was taken from all patients before the operation. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Surgical Procedure

Parenteral antibiotic was applied one hour before operation. RIRS operation was applied under general anesthesia in the lithotomy position. Semi rigid renoscopy was applied, and the hydrophilic guide wire was inserted into the ureter under fluoroscopic control. Ureteral access sheath (UAS) (9.5 French (Fr)/11.5 Fr or 11/13Fr (Elite Flex, Ankara, Turkiye) was placed over the guidewire under fluoroscopic control. Unless UAS placed, flexible ureterorenoscope (Flex-X^2; Karl Storz, Tutlingen, Germany) was placed over the guidewire. And renal access was supplied. Lithotripsy was made with 200-micron holmium laser probe (Holmium:Yttrium Aluminum Garnet (Ho-YAG) Laser:Dornier Meditech; Munich,Germany). Lithotripsy was performed with 8-10 Hertz frequency and 1.2-1.5 joule power. Dusting and fragmentation methods were used according to surgeon's choice. Double-J (DJ) stent was placed due to intraoperative conditions (bleeding, residual fragments, etc). DJ stent was taken under sedation three weeks later. All calyxes were controlled with flexible ureteroscope under fluoroscopic control at the end of the operation. To evaluate success, KUBG was used for opaque stones; the US was used for non-opaque stones on the postoperative first day. The patients were followed for six months. Being stone free or having <3 mm residual fragment on intraoperative and postoperative controls (first day and month) were described as successful. In case of being unsuccessful second procedure was planned three weeks later. Complications were evaluated according to Clavien-Dindo classification.

Statistical Analysis

Data was analyzed using the Statistical Package for Social Sciences (SPSS 16.0, Chicago). One Sample Kolmogorov-Smirnov test was applied to numeric variables. Numeric variables that are normally distributed were reported in mean ± standard deviation. The distribution was not normal for the variables except age, body mass index (BMI) due to the p-values <0.05. Student's t-test was used to compare numeric variables while discrete variables were analyzed using Pearson's chi-square test. Mann-Whitney U test was used to compare categorical variables while p-values <0.05 were considered statistically significant. Quantitative variables analyzed include age and BMI. Qualitative variables analyzed include sex, stone laterality, stone localization, access sheath usage, DJ stent usage, complication rate, previous surgery history, preoperative DJ stent usage, anticoagulant usage, success, and residual fragment rates.

Results

Ninety-four procedures were included in our study, and were divided into two groups: Anomalous group (group A) and non-anomalous group (group N). For demographic and stone characteristics, there was no statistically significant difference for age, BMI and gender between two groups. Previous surgery history, anticoagulant usage, stone laterality and stone localization were similar between two groups (Table 1). Stone burden was statistically insignificantly higher in Group N. Preoperative DJ stent usage and stone number was higher in group N but the difference was not statistically significant (p>0.05) (Table 1).

For intraoperative and postoperative data, average operation time, average scope time, hospitalization time and postoperative DJ stent rate were higher in group A. The difference was insignificant (p>0.05). UAS usage was insignificantly higher in group N. Stone-free rate and success rate were higher in group N, though the difference was not statistically significant (p=0.18). For complications, the complication rate was statistically significantly higher in group A (p=0.02) (Table 2). Most of the complications were minor complications.

Discussion

Stone formation risk increases in anomalous kidneys and stone management is an important issue (2,3). RIRS can be used in the management of anomalous kidney stones due to its new technology and rare serious complication rate (10-17). In our study, we aimed to report our RIRS experience in patients who have anomalous kidney stones and compare this experience with normal kidney stones. Ninety-four procedures were included in our study.

In our study, the largest patient group was in CD group. CD is an abnormal cavity that has no draining papilla that is related with renal collecting system through the narrow diverticula neck (18). PNL is the most used method for stone management in CD patients. In this method, diverticula can be reached through percutaneous access. Diverticular urothelium can be fulgurated. If draining infundibulum is found, it can be fulgurated and incised or dilated with nephrostomy tube. 75-100% success rate is reported (19-21). In RIRS procedure, stone fragmentation and diverticula neck incision can be made with laser. Combining with SWL, success rate is about 90%. If accessible diverticula neck is present, RIRS can be used for especially <2 cm sized upper and mid pole stones treatment (18). In our study, the success rate was 72%. The average stone size was 17.94 mm.

HSK is the most frequent congenital genitourinary anomaly. It is observed in 1 in every 400 births. The kidney stone is present in 20% of HSK patients (2,3). One of the methods used for kidney stone management in HSK patients is SWL. Limited urine drainage and excessive stone-skin distance decrease success of SWL (22). PNL is the most used method, but serious complications can be seen (5). RIRS is an another treatment method. In 2005, Weizer et al. (1) reported 75% stone-free rate in HSK patients who have <2 cm sized kidney stones. No complication reported (1). In 2010, Molimard et al. (23) reported 53% stone-free rate in 17 HSK patients. The average stone size was 16 mm. In another

Table 1. Demographic and stone characteristics

	Group N (n=47)	Group A (n=47)	p
Age (years) (± SD)	42.72±15.52	47.72±17.90	0.317
Gender (M/F)	31/16	32/15	0.826
BMI (kg/m^2) (± SD)	24.78±4.21	25.63±4.47	0.724
Previous surgery history (n, %)	22 (46.8)	23 (48.9)	0.836
Anticoagulant usage (n, %)	0	1 (2.1)	0.315
Preoperative DJ stent usage (n, %)	3(6.4)	6 (12.8)	0.293
Stone laterality (R/L) (n)	21/26	20/26	0.599
Stone number (n) (± SD)	1.51±0.90	1.53±0.85	0.883
Stone burden (mm) (± SD)	17.38±10.48	16.87±10.64	0.802
Stone localization (n, %)			0.999
Upper calyx (n, %)	8 (17)	9 (19.1)	-
Lower calyx (n, %)	12 (25.5)	12 (25.5)	-
Mid calyx (n, %)	8 (17)	8 (17)	-
Pelvis (n, %)	9 (19.1)	9 (19.1)	-
Multicaliceal (n, %)	5 (10.6)	5 (10.6)	-
Proximal ureter (n, %)	5 (10.6)	4 (8.5)	-

M/F: Male/Female, BMI: Body Mass Index, DJ: Double-J, SD: Standard deviation, mm: milimeter

Table 2. Intraoperative and postoperative data			
	Group N (n=47)	**Group A (n=47)**	**p**
Average operation Time (min ± SD)	44.65±15.42	52.12±23.65	0.086
Average scopy time (Sc ± SD)	36.10±28.34	46.85±44.84	0.282
Postoperative DJ stent, n (%)	33 (70.2)	34 (72.3)	0.820
Uretheral access sheath usage, n (%)	36 (76.6)	34 (72.3)	0.636
Average hospitalization time (± SD) (day)	1.08±0.41	1.27±1.22	0.401
Success, n (%)	41 (87.2)	36 (76.6)	0.18
Stone-free	40 (85.1)	32 (68.1)	-
Residuel fragment (<3 mm)	1 (2.1)	4 (8.5)	-
Residuel fragment (≥3 mm)	6 (12.8)	11 (23.4)	-
Complication rate, n (%)	6 (12.8)	15 (31.92)	0.026
Intraoperative complication			
Mucosal injury, n (%)	2 (4.3)	1 (2.1)	-
Bleeding, n (%)	1 (2.1)	2 (4.3)	-
Perforation, n (%)	1 (2.1)	0	-
Postoperative complication			
Minor complication			
Fever (Clavien I), n (%)	1 (2.1)	3 (6.4)	-
Bleeding (Clavien I), n (%)	5 (10.6)	2 (4.3)	-
Urinary tract infection (Clavien II), n (%)	3 (6.4)	0	-
DJ stent migration (Clavien IIIb), n (%)	2 (4.3)	0	-
Min: Minutes, Sec: Seconds, DJ: Double-J, SD: Standard deviation, mm: Milimeter			

study, 60% stone-free rate was reported in 20 HSK patients. The average stone size was 17.8±4.5 mm, the average operation time was 40.5±11.2 minutes (min), the average scopy time was 29.4±14.8 seconds (sc). Minor complication was seen in 5 patients but no major complication was seen (15). In our study, 15 procedures were made in 12 patients. The average stone size was 17.93 mm; the average operation time was 49 min, the average scopy time was 43.8 sc. and the stone-free rate was 83.33 %. Eryildirim et al. (24) reported that RIRS and PNL were safe and effective treatment methods for renal stones with HSK.

EK is seen in 1 in every 2200 to 3000 births. The anterior positioning of the renal pelvis, high insertion of the ureter and renal vascularization impair calyx drainage, increase stone formation risk. Injury risk of aberrant veins, neighboring abdominal organs and nerves make surgery difficult in EK patients (25). Demirkesen et al. (26) reported 38% stone-free rate in EK patients after 3 session of SWL. Talic (27) reported 82% stone-free rate in 14 EK patients. In another study, 75% stone-free rate for RIRS was reported in 4 SWL failed EK patients. Tortuous ureter makes renoscope difficult in EK (25). In our study, there were 2 EK patients. None of these patients was stone free and intraoperative complications were observed.

M is a rare condition and occurs due to dystopia and abnormal blood circulation. EK and HSK anomalies usually accompany with anterior rotation (28). There are rare number of studies about kidney stone management in M patients. Mosavi-Bahar et al. (29) reported 81% success rate with no major complication in 5 M patients. Binbay et al. (30) reported 77.3% success rate in 44 M patients of 6 centers. In our study, 100% success was achieved in one patient after 2 sessions with no minor and major complication seen.

RIRS and PNL are the most popular methods used in anomalous kidney stone treatment. In a study comparing RIRS and PNL for the treatment of anomalous kidney stones, Singh et al. (31) reported an algorithm-based approach. This approach was shaped according to factors like stone size, stone location, spatial calyceal orientation and the pelvicalyceal drainage system. In our study, we aimed to show our RIRS experience in kidney stones with different renal anomalies.

Demographic and stone characteristics such as age, gender, BMI, previous surgery history, anticoagulant usage, preoperative DJ stent usage, stone number, laterality and localization were similar between the two groups.

When we examine intraoperative and postoperative data, average operation time, scopy time, hospitalization time, postoperative DJ stent rate and success rate were similar between the two groups.

The complication rate was statistically significantly lower in group N. Impaired urine drainage and changed anatomic structure could explain this finding (2). For group A, complications were seen in 15 of 47 procedures with 13 minor and major complications. Major complications were seen in CD and HSK patients, and we did not compare the subgroups.

The instruments used in RIRS are costly and was a major disadvantage and shortcoming. Also, they may deteriorate according to the surgeons experience and the number of procedures. In our study, only one flexible ureterorenoscope was used for the procedures.

RIRS may affect renovascular hemodynamics (32). In our study, we found that RIRS has almost similar efficiency in anomalous kidney stones when compared with normal kidney stones. Meanwhile in anomalous kidney stones, more complications can be seen due to impaired anatomy and urine drainage (2). No serious complication was recorded in the normal and anomalous kidney stones groups. The small sample size could explain these findings.

Study Limitations

Retrospective nature and low patient number were the limitations of our study. Prospective and larger sample sized studies are recommended.

Conclusion

RIRS can be used in the management of anomalous kidney stones. It is an efficient and safe method. Prospective and larger sample sized studies are needed to support this idea.

Ethics

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

Informed Consent: Informed consent was taken from all patients before the operation.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.S., M.Ç.Ç., I.G.K., A.L.S., A.N.K., Design: H.U.Ö., A.A., Ö.B., İ.G.K., Data Collection or Processing: S.S., M.C.C., H.U.Ö., Analysis or Interpretation: M.Ç.Ç., A.A., Ö.B., İ.G.K., A.L.S., Literature Search: S.S., H.U.Ö., M.Ç.Ç., Writing: S.S., M.Ç.Ç., H.U.O., A.N.K.

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Comparison of Pain Scores During Retrieval of Ureteral Stents Using Rigid Cystoscope Versus Rigid Ureteroscope in an Office Setting: A Prospective Study

Bir Ofis Ortamında Rijit Sistoskop ile Rijit Üreteroskop Kullanılarak Üreteral Stentlerin Alınması Sırasında Ağrı Skorlarının Karşılaştırılması: Prospektif Bir Çalışma

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What's known on the subject? and What does the study add?

Many patients, especially males, complain of severe pain and discomfort during stent removal using rigid cystoscope in office setting which can largely be attributed to the longer length of urethra, enlarged prostate and bigger calibre of rigid cystoscope. We employed reduction in the caliber of the retrieving instrument by using rigid ureteroscope which is easily available in every urologist's armamentarium. Though a couple of studies have employed rigid ureteroscope for stent retrieval, no study has studied male patients exclusively. Our study compares stent retrieval with rigid cystoscope and rigid ureteroscope in office setting making it an affordable and dependable method.

Abstract

Objective: Ureteral stents inserted to prevent obstruction to the flow of urine need to be removed after they serve the purpose of their insertion. The most commonly practiced method for stent removal is using a rigid cystoscope in an office setting. However, it is quite painful and may require general anesthesia especially in males. Due to their small caliber, rigid ureteroscope can reduce patient discomfort during ureteral stent retrieval procedure. In this study, we compared the pain scores during ureteral stent retrieval using a rigid cystoscope and a rigid ureteroscope.

Materials and Methods: A prospective study was conducted with 64 male patients with ureteral stents who were divided into two groups. Group A had 36 patients who underwent stent retrieval with rigid cystoscope while group B had 28 patients who underwent with rigid ureteroscope. Pain experienced during the procedure and during the first void thereafter were recorded using visual analog scale.

Results: The patients who underwent stent retrieval using rigid cystoscope (mean 7.05±1.21) had a significantly higher ($p<0.0001$) pain score compared to those who underwent it using rigid ureteroscope (mean 2.57±1.04). The pain scores during the first void after the procedure as reported by patients in groups A and B were 6.58±1.27 and 3.03±0.96 ($p<0.0001$), respectively.

Conclusion: Rigid ureteroscopic stent retrieval is a less painful, safe, and dependable method, with a reduced requirement for postoperative analgesics as compared to rigid cystoscopic stent retrieval.

Keywords: Rigid cystoscope, Rigid ureteroscope, Ureteral stents, Stent retrieval

Öz

Amaç: İdrar akışının tıkanmasını önlemek için yerleştirilen üreteral stentler, yerleştirilme amacına hizmet ettikten sonra çıkarılmalıdır. Stentin çıkarılması için en sık uygulanan yöntem, muayenehane koşullarında rijit bir sistoskop kullanmaktır. Bununla birlikte, oldukça ağrılıdır ve özellikle erkeklerde genel anestezi gerektirebilir. Küçük kalibreleri nedeniyle, rijit üreteroskop, üreter stent ekstraksiyon prosedürü sırasında hastanın rahatsızlığını azaltabilir. Bu çalışmada, rijit bir sistoskop ve rijit bir üreteroskop kullanarak yapılan üreter stent ekstraksiyonu sırasındaki ağrı skorlarını karşılaştırdık.

Gereç ve Yöntem: Üreteral stentli 64 erkek hasta iki gruba ayrılarak prospektif olarak değerlendirildi. Grup A, rijit sistoskop ile stent ekstraksiyonu yapılan 36 hasta; grup B ise rijit üreteroskop ile stent ekstraksiyonu yapılan 28 hastadan oluşmakta idi. İşlem sırasında ve sonrasındaki ilk idrar çıkışı sırasında yaşanan ağrı görsel analog skala kullanılarak kaydedildi.

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Bulgular: Rijit sistoskop kullanılarak stent ekstraksiyonu yapılan hastalar (ortalama 7,05±1,21), rijit üreteroskop kullanılarak stent ekstraksiyonu yapılanlara göre anlamlı olarak daha yüksek (p<0,0001) ağrı skoruna sahipti (ortalama 2,57±1,04). A ve B gruplarındaki hastalar tarafından bildirilen işlem sonrası ilk idrar çıkışındaki ağrı skorları sırasıyla 6,58±1,27 ve 3,03±0,96 (p<0,0001) idi.
Sonuç: Rijit üreteroskopik stent ekstraksiyonu, rijit sistoskopik stent ekstraksiyonuna kıyasla postoperatif analjeziklere daha az ihtiyaç duyulan, daha az ağrılı, güvenli ve güvenilir bir yöntemdir.
Anahtar Kelimeler: Rijit sistoskop, Rijit üreteroskop, Üreteral stentler, Stent çıkarımı

Introduction

Ureteral Double-J stents are the most commonly used device in urological practice and are primarily used to maintain the patency of the ureter. Ureteral stents are used to relieve obstruction, which can occur due to various intrinsic and extrinsic etiologies during treatment of ureteric injuries and after ureteral anastomosis (1). Prophylactic ureteral stenting may also be done prior to extracorporeal shock wave lithotripsy and pelvic surgeries (1). Ureteral stent placement is associated to some degree of morbidity in the majority of patients in the form of generalized urinary discomfort, urinary tract infection and encrustation (2-4). The stents need to be removed after the purpose of their placement is served.

The most commonly practiced method for stent removal in an office setting is by the use of a rigid cystoscope (5). Many patients especially males complain of severe pain and discomfort during such procedure, which can largely be attributed to the longer length of urethra in males, enlarged prostate and bigger caliber of rigid cystoscope (6). Various methods like administering of general anesthesia, use of periprocedural analgesics and use of flexible cystoscope have been suggested to reduce the pain and discomfort associated during stent retrieval (6-8). Modifications in the stent design such as magnetic stents and biodegradable stents have been employed to obviate the need for endoscope for stent removal; however their use has not been widely accepted (9,10). Another suggested method is to reduce the caliber of the cystoscope to reduce the pain. One such scope is a rigid ureteroscope, which is present in the armamentarium of all urologists. We conducted a prospective study to compare the post-procedural pain scores using a visual analog scale (VAS), after ureteral stent retrieval in male patients using rigid cystoscope and a rigid ureteroscope.

Materials and Methods

Patient Cohort

This prospective study was conducted from January to June 2018 after approval from the Institutional Ethics Committee (MDC/DOME/498 dated 11-23-2017) of JNMC Institutional Ethics Committee on Human Subjects Research, J. N. Medical College, Belagavi). The patients with residual stones, active urinary infection, history of sepsis, renal failure, bilateral ureteral stents, and migrated stents were not eligible for the study. A total of 82 adult male patients, with unilateral Double-J uretral stents, were assessed for eligibility for the study and 64 patients were enrolled for randomization (Figure 1).

All patients were assessed by the kidney, ureter, and bladder radiograph prior to the procedure.

Using random number table method, patients were divided into two groups, which were based on the method of stent retrieval. Group A comprising 36 patients who had their stents retrieved using a 17 Fr rigid cystoscope (Karl Storz, Tuttlingen, Germany) with grasping forceps. Group B consisted of 28 patients who had their stent retrieved using an 8.0/9.8 Fr rigid ureteroscope (Richard Wolf, Knittlingen, Germany) and grasping forceps.

Procedure and Data Collection

The stent retrieval procedures were performed by a single urologist to minimize the errors or biases. A written consent was obtained from all the participants after explaining the procedure in their vernacular language. A single dose of second-generation cephalosporin antibiotic was administered intravenously before the procedure. The stents were retrieved after putting the patients in lithotomy position and instilling 15 mL of 2% lignocaine jelly into the urethra. The stent was retrieved with grasping forceps using rigid cystoscope in the patients randomized to group A and rigid ureteroscope in the patients randomized to group B. The duration of stent placement, laterality of stent, indication for stent placement, postprocedure pain score, and pain during first void, after the procedure were assessed in each patient. The VAS was used by each patient at the end of the procedure to mark his subjective perception of pain during the procedure and during the first void after the procedure. Other urinary complains such as hematuria, frequency, and urgency as reported by the patients were documented. All the patients were discharged home within 1 h of postprocedural voiding.

Statistical Analysis

A sample size of 62 patients was calculated using comparing two proportion formulas. It was estimated to yield 80% power (type II or beta error of 0.20%) to detect a difference of 15% or more between two groups, allowing 5% of type I error. Totally, 64 patients were enrolled in the study. Statistical analysis was done using SPSS Software Version 20. Univariable analysis was

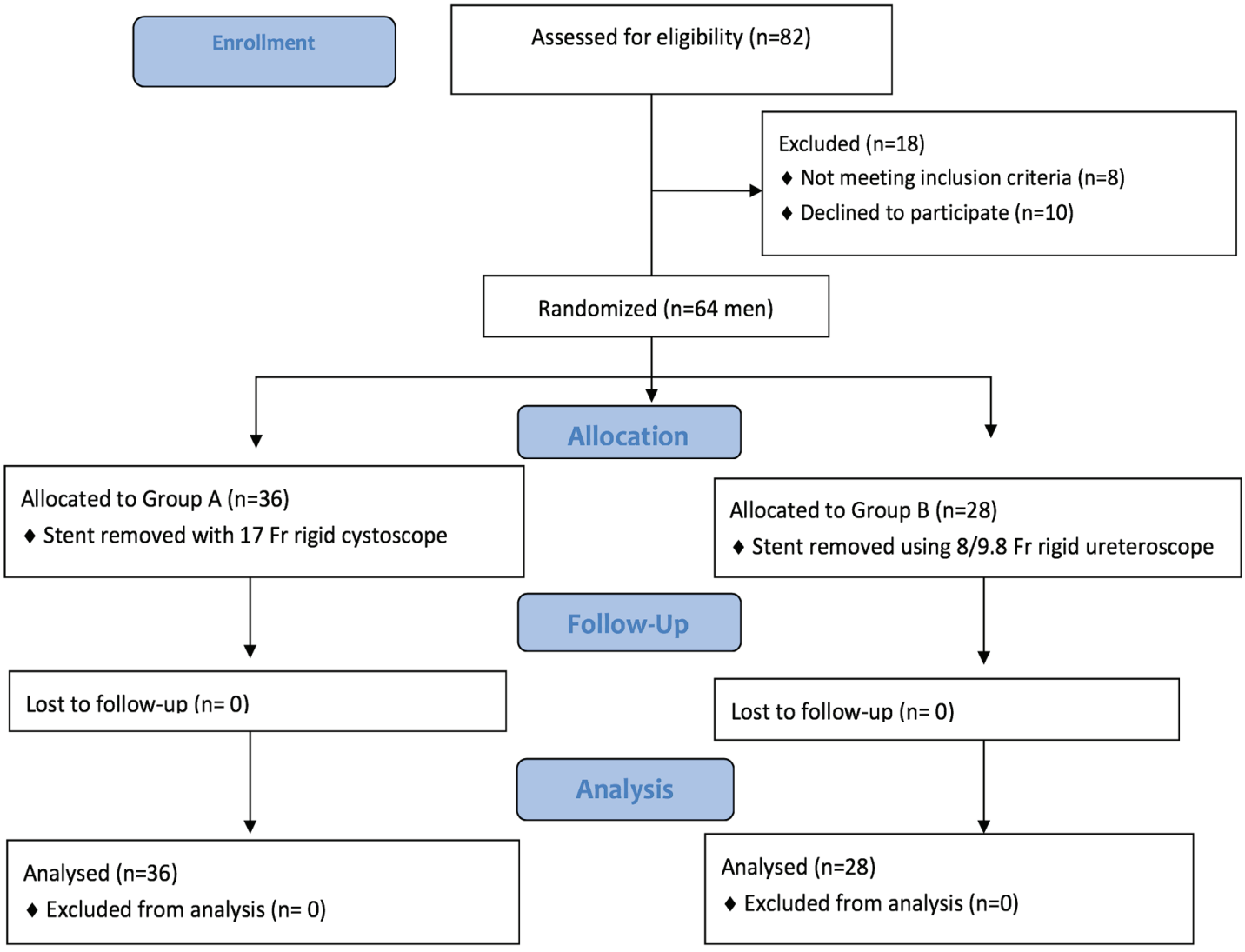

Figure 1. CONSORT statement

performed using Pearson χ^2 statistics and Fischer's Exact test for categorical data. P values <0.05 were considered significant.

Results

The two groups were compared with regards to age, laterality of stent, indications for stent placement, and duration of the stent (Table 1). The highest indication for stent placement in our study was ureteroscopic lithotripsy (59.37%) followed by percutaneous nephrolithotomy cases (20.31%). The mean duration of stent placement in group A and B was 22.69±17.13 and 25.01±16.87 days, respectively. Stent-related symptoms (hematuria, frequency, urgency, and dysuria) were reported in 31 patients (48.43%). All the ureteral stents were successfully retrieved, using either of the scopes, in both groups.

The reported mean VAS pain score during the stent retrieval using rigid cystoscope was significantly higher than that of rigid ureteroscope (Table 2). Also the pain experienced during the first void after the procedure was higher in group A. Of the total number of patients, seven (10.93%) required analgesia after stent retrieval, six of whom belonged to group A, having postprocedure VAS pain score more than 7. In five cases, oral paracetamol 650 mg and the two other cases injectable analgesic medications were administered to the patients. In each group, one of the patient reported mild hematuria during the first void after the procedure. Two patients in group A and one patient in group B complained of urgency and frequency after the procedure. None of the patients were reported suffering from

Table 1. Patient characteristics		
Variables	**Rigid cystoscope**	**Rigid ureteroscope**
No. of cases	36	28
Mean age ± SD	43.9±13.3	39.21±15.3
Laterality (right / left)	14/22	16/12
Duration of stent (mean ± SD)	22.69±17.13	25.01±16.87
Bothersome stent-related symptoms	17	14
Indications for stenting		
Ureteroscopy	24	14
PCNL	07	06
ESWL	02	04
Obstructive uropathy	02	01
Pyeloplasty	01	03
Analgesic requirement postprocedure	06	01

PCNL: Percutaneous nephrolithonom, ESWL: Ekstra corporeal shock wave lithotripsy, SD: Stardard deviation

Table 2. Postprocedure visual analog scale pain score in two groups			
Variables	**Rigid cystoscope**	**Rigid ureteroscope**	**p value**
VAS pain score (mean ± SD)	7.05±1.21	2.57±1.04	<0.0001
Pain during first void postprocedure (mean ± SD)	6.58±1.27	3.03±0.96	<0.0001

VAS: visual analog scale, SD: Stardard deviation

fever or retention of urine after stent removal.

Discussion

Stent placement and subsequent removal results in higher procedural costs than when it is not used. In an uncomplicated ureteroscopy (URS) placement of a stent do not have any advantage and in fact may add to the morbidity (11,12). However, majority of urologists place a stent after uncomplicated URS in the hope of reducing the visits to the emergency department by such unstented patients (13).

Newer stents incorporate extraction strings made of fine suture material secured to the distal end of the stent, which is visible at the urethral meatus.

The extraction strings avoid the need to repeat cystoscopy for stent removal. However, most of the urologists remove stent extraction strings prior to their insertion due to the concerns over perceived risks, such as increased LUTS from string irritation, stent dislodgement, infection, stent retention due to patients forgetting to remove stents, broken strings, and lack of strong evidence relating to its safety and tolerability (14).

In developed countries, flexible cystoscope is used to retrieve ureteral stents in office setting (1,15). Since flexible cystoscopes are expensive and less readily available in developing countries, rigid cystoscopes are routinely employed for removal of ureteral stents in office setting (8).

Owing to the larger caliber of rigid cystoscope, which can induce pain while insertion and during the procedure, several other factors make this method more difficult, especially in male patients, including longer urethra and prostatic enlargement (6). Söylemez et al. (15) described the use of rigid ureteroscope to retrieve ureteral stents as an alternative that may be less painful as compared to rigid cystoscope.

We have been routinely using rigid cystoscopic and ureteroscopic method for retrieval of ureteral stents in our center. In this study, we found out that post-procedural VAS pain scores for patients whose ureteral stents were retrieved using rigid ureteroscope (2.57±1.04) were less as compared to rigid cystoscopy group (7.05±1.21; p<0.0001).

Patients also reported pain on VAS during first void postprocedure in our study, which were 6.58±1.27 in cystoscope group versus 3.03±0.96 in ureteroscope group (p<0001). Söylemez et al. (15) also reported that the mean operative pain scores were significantly higher in patients undergoing stent retrieval using rigid cystoscope than rigid ureteroscope group (p<0.01).

Kim et al. (6) conducted a study on rigid cystoscopic ureteral stent retrieval using analgesics [Intravenous (IV) ketorolac, midazolam] and sedation (IV propofol) to assess procedural pain and postprocedure satisfaction of patients. VAS pain score of 8 for IV ketorolac group, score of 5 for midazolam group and no procedural pain in propofol group noted. Use of midazolam and propofol needs observation in the postprocedure period, especially in patients with comorbid illnesses, which also adds to cost of overall hospital visit.

Single dose of Rofecoxib, a non-steroidal anti-inflammatory drug (NSAID) was studied in a prospective, double-blind, placebo-controlled trial by Tadros et al. (16) in 22 patients undergoing cystoscopic stent retrieval. The authors concluded that in placebo group, postoperative VAS score ≥7 (severe pain) was found in 55% of the patient and required postprocedure narcotic analgesics, whereas a single dose of Rofecoxib prevented severe pain in NSAID arm during post- operative procedure. Oral NSAID (Diclofenac) use was also evaluated by Karthikeyan et al. (8) in a double-blind, placebo-controlled trial in 121 patients undergoing ureteral stent retrieval using cystoscope. VAS pain score during procedure, at first void, and 24 h postop was assessed, and authors concluded that use of oral diclofenac significantly reduced pain with minimal side effects (8).

In a study by Söylemez et al. (15), the mean pain scores, irritative voiding symptom scores and hematuria were not statistically significant in patients undergoing stent retrieval using flexible cystoscope and rigid ureteroscope. They concluded that stent retrieval using rigid ureteroscopy is safe, cost effective, and widely usable method (17).

It is evident from this current study that the postprocedure VAS pain scores and discomfort were significantly less along with less discomfort using a smaller caliber scope for stent retrieval. Only one patient in the rigid ureteroscopy group required postoperative analgesia as compared to six patients in the rigid cystoscopy group.

Study Limitations

The limitations of our study include the relatively small sample size and a single-center study, which will have an unavoidable inherent bias. It would be more ideal to conduct a prospective study with a larger sample size in a multi-center setup. Also, we have not assessed the cost effectiveness in either group.

However, it is safe to conclude that use of smaller caliber scope for stent retrieval can be a viable and less painful alternative to conventional rigid cystoscopic stent retrieval.

Conclusion

In the present study, use of the ureteroscope method for ureteral stent retrieval was less painful, safe, effective, and dependable method. Other advantages include wider availability, cost effective, and proficiency of urologists with its use. This helps in reducing the procedural discomfort and the use of postoperative analgesics among the patients.

Ethics

Ethics Committee Approval: This prospective study was conducted from January to June 2018 after approval from the Institutional Ethics Committee (MDC/ DOME/498 dated 11-23-2017) of JNMC Institutional Ethics Committee on Human Subjects Research, J. N. Medical College, Belagavi).

Informed Consent: Taken in the vernacular language spoken by the patient (Kannada, Marathi and Hindi).

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.I.N, S.H.N., Concept: S.I.N, S.H.N., Design: S.I.N, S.H.N., Data Collection or Processing: S.I.N, S.H.N., Analysis or Interpretation: S.I.N, S.H.N., Literature Search: S.I.N, S.H.N., Writing: S.I.N, S.H.N.

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

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Postoperative Fever and Systemic Inflammatory Response Syndrome after Ureteroscopy for Stone Disease in the Geriatric Population: Risk Factors and Determinants

Geriatrik Popülasyonda Taş Hastalığı için Uygulanan Üreterorenoskopi Sonrası Gelişen Postoperatif Ateş ve Sistemik Enflamatuvar Cevap Sendromu: Risk Faktörleri ve Belirleyiciler

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What's known on the subject? and What does the study add?

Endoscopic procedure should be kept as short as possible in geriatric patients, and indications for postoperative Double-J catheter placement should be reduced as much as possible.

Abstract

Objective: The purpose of this study was to determine the perioperative risk factors for postoperative fever (POF)/systemic inflammatory response syndrome (SIRS) among geriatric patients after semi-rigid ureterorenoscopy with laser lithotripsy (RURSLL).

Materials and Methods: We retrospectively reviewed data of 139 procedures from 129 consecutive geriatric patients who had undergone RURSLL for stone disease in our department. Preoperative and intraoperative characteristics between patients with and without POF/SIRS were compared using univariate analyses. The significant variables on univariate analyses were included in a multivariate logistic regression analysis to evaluate the risk factors associated with POF/SIRS following RURSLL.

Results: Twenty-nine (21%) patients had POF/SIRS after RURSLL. Patients were found with higher percentage of comorbidities, body mass indices, and lower estimated glomerular filtration rates. On univariate analysis, positive preoperative urine culture, stone size, operation time, and the presence of postoperative double-J (DJ) stent were found to be significant variables (p=0.004; p=0.016; p=0.01; p=0.01, respectively). On multivariate analysis, positive preoperative urine culture [odds ratio (OR): 8.36; 95% confidence interval (CI): 2.20-31.79; p=0.002) and postoperative DJ stent insertion (OR: 6.14; 95% CI: 1.16-32.57; p=0.033) were found to be the most significant dependent variables.

Conclusion: We found that positive preoperative urine culture and postoperative DJ stent insertion were the most important determinants for infectious complications after RURSLL in geriatric population. So, the procedure should be kept as short as possible, and indications for postoperative DJ catheter insertion should be reduced as much as possible.

Keywords: Postoperative fever, Systemic inflammatory response syndrome, Ureterorenoscopy, Geriatric

Öz

Amaç: Çalışmanın amacı geriatrik hastalarda semi-rijit üreterorenoskopi (URS) sonrası postoperatif ateş/sistemik enflamatuvar cevap sendromu (SIRS) için perioperatif risk faktörlerini belirlemektir.

Gereç ve Yöntem: Kliniğimizde taş hastalığı nedeniyle uygulanan 129 ardışık geriatrik hastaya uyguladığımız 139 prosedüre ait veriler retrospektif olarak incelendi. Postoperatif ateş/SIRS olan ve olmayan hastalar arasında ameliyat öncesi ve ameliyat sonrası özellikler tek değişkenli analizler kullanılarak karşılaştırıldı. Risk faktörleri çok değişkenli lojistik regresyon analizine tek değişkenli analizlerde anlamlı değişkenler dahil edilerek değerlendirildi.

Bulgular: Yirmi dokuz (%21) hastada postoperatif ateş/SIRS gelişti. Komplikasyon gelişen hastalarda daha yüksek komorbidite yüzdesi, vücut kitle indeksleri ve daha düşük tahmini glamerüler filtrasyon oranları gözlendi. Tek değişkenli analizde pozitif preoperatif idrar kültürü, taş boyutu,

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operasyon süresi ve postoperatif double-st stent varlığı anlamlı bulundu (p=0,004; p=0,016; p=0,01; p=0,01). Çok değişkenli analizde ise pozitif preoperatif idrar kültürü [Olasılık oranı (OR): 8,36 %95 Güven aralığı (CI): 2,20-31,79; p=0,002] ve postoperatif Double-J stent yerleştirilmesi (OR: 6,14; % 95 CI: 1,16-32,57; p=0.033) en anlamlı bağımsız değişkenler olarak izlendi.
Sonuç: Ameliyat öncesi pozitif idrar kültürü ve postoperatif DJ stent yerleştirilmesi geriatrik popülasyonda URS sonrası enfeksiyöz komplikasyonlar için en önemli belirleyicilerdir. Bu nedenle geriatrik hastalarda prosedür mümkün olduğunca kısa tutulmalı ve postoperatif DJ stent yerleştirme endikasyonları mümkün olduğunca azaltılmalıdır.
Anahtar Kelimeler: Postoperatif ateş, Sistemik enflamatuvar cevap sendromu, Üreterorenoskopi, Yaşlı

Introduction

According to a published data, the number of older persons-aged 60 years or more-has increased substantially in recent years and is projected to exceed 2 billion by 2050 (1). With the increasing population in this age group, the prevalence of urolithiasis is expected to increase 10%-12% (2). The elderly people will have limited function in different organ systems, and aging-related comorbidities will cause problems in perioperative and/or postoperative follow-up after therapeutic approaches (3). In addition, impairment of cardiopulmonary and renal functions may lead to increase in perioperative complication rates associated with significant operations (4).

The least invasive treatment option in the management of upper urinary tract stones included extracorporeal shock wave lithotripsy (ESWL). Erstwhile, ESWL was recommended as a first-line treatment for the treatment of kidney stones smaller than 20 mm (5). Flexible ureterorenoscopy (FURS) has been shown to be a viable alternative for these patients because of advances in ureterorenoscopy (URS) (6). Albeit FURS is highlighted in the modern literature, rigid URS (RURS) is commonly preferred for distal and proximal ureteral stones. Current literature has shown that RURS is a safe and efficacious choice for proximal ureteral calculi (7,8). While RURS cannot be used in renal stones because of its limited maneuverability and tough access to middle and lower calyces, it can reach the kidney with ease in some cases. Besides, RURS has the superiority of larger working channel and equipment. In addition, better images can be achieved because of the higher irrigation flow. A standout among the most widely recognized complications prompting unplanned hospitalizations is postoperative fever (POF) or systemic inflammatory response syndrome (SIRS) (9-12). Latest analyses show that 3.4%-14.2% of emergency department visits are caused by POF (13,14). More than 40% of patients with fever are admitted to hospital (15). After RURS, SIRS affects in 8.1% of patients (16). Early recognition and timely administration of medicine for POF/SIRS are important to avoid sepsis development that conveys a mortality rate of 28.3%-41.1% (17). Few investigations have inspected an assortment of patient and surgical features trying to distinguish people with high risk. The aim of this research was to define POF/SIRS predictors for stone disease especially in the geriatric population after rigid ureterorenoscopy with laser lithotripsy (RURSLL).

Materials and Methods

After the approval of the ethics committee (protocol number: 2019-84-22/05, date: 22.05.2019), we retrospectively analyzed the collected data of 926 patients who underwent 1163 RURSLL between June 2004 and November 2018 in our clinic. Informed consent was obtained before oparation from all individual participants included in the study.

Investigation was carried out with cross-checking the data by using electronic operating notes, laboratory files, and hospital discharge documents. Patients with missing information or out of geriatric age group were excluded from the study. In the gathering, 251 patients were present. At long last, 129 appropriate patients were enrolled for our study.

Stone size and stone-free state (SFS) were routinely evaluated by ultrasound and/or simple kidney-ureter-bladder radiography. All patients' urine were regularly cultivated, and this was handled before RURSLL if the result was positive.

All ureteroscopic procedures were performed with antibiotic prophylaxis under general anesthesia in the lithotomy position. Ureteric dilation is not a standard practice in the unit. Before navigating the ureter, a standard sensor tip guide wire (Zip Wire, Boston Scientific, Marlborough, MA, USA) is routinely embedded into the affected ureteric orifice with a 20 F cystoscope (Karl Storz). 9.5 F rigid Wolf ureteroscopes were used. The irrigation fluid was heated to core body temperature in order to prevent intraoperative heat loss. Stones were broken with a holmium-yttrium-aluminum garnet laser [Versa PulseHolmium Powersuite 100 W or 20 W Lumenis (UK) Ltd., Elstree, UK] utilizing a 500-u3 fiber at 15 W laser control (1,200-1,400 mJ and 8-12 Hz frequency). Choice to embed a Double-J (DJ) ureteric stent was made by the operator relying upon the length of operation, the grade of ureteric edema, and magnitude of the manipulation.

SFS was precised both endoscopically at the end of the operation and radiologically preceding discharge of the patients. SFS has been described as <2-mm-size fragments (16-18).

The primary outcome was POF or SIRS and identified 7 days after RURSLL. SIRS was defined as the occurrence of at least two of the following criteria: fever >38°C, pulse >90 beats/minute, respiratory rate >20 breaths/minute or $PaCO_2$ <32

mmHg, or white blood cell count >12,000/mm^3, <4,000/mm^3, or >10% bands. Since many postoperative patients fulfill these requirements, we restricted the result to clinically important POF/SIRS defined as instant postoperative admission, hospital readmission, or emergency visit within 7 days. Manual chart analysis was conducted to verify that patients met POF or SIRS requirements.

Demographic characteristics included age, gender, body mass index (BMI), estimated glomerular filtration rate (eGFR), and the Charlson comorbidity index including age. Earlier, urologic and stone procedures were identified. Preoperative characteristics included stone laterality, largest stone size, stone location, presence of positive preoperative urine culture, presence of multidrug resistant (MDR) positive urine culture, and presenting. At the conclusion of the RURSLL, intraoperative characteristics included surgery duration and stent placement. Types of bacteria in preoperative cultures of patients with and without POF/SIRS were examined.

Statistical Analysis

Perioperative characteristics between patients with and without POF or SIRS were compared using univariate Mann-Whitney test, chi-square, or Fisher's Exact test. All significant factors associated with POF/SIRS following RURSLL with $p<0.05$ on univariate analyses were then included in a multivariate logistic regression analysis with a backward stepwise approach to select the significant ones. SPSS software version 19.0 (IBM, Armonk, NY, USA) was used for analysis with $p<0.05$ being considered statistically significant.

Results

Among the 129 patients who underwent 139 procedures, the male-female ratio was 1.68:1 with a mean age of 69.9 years. The mean Charlson comorbidity index score of 129 patients was 2.7±0.8. Anatomical abnormality was found in 7/129 (5.4%) patients. Mean cumulative stone size of patients was 13±6.2 (range: 5-30 mm) and 23 (16.7%) with multiple stones. Forty-two cases (30.4%) had been stented preoperatively. The place of the index stone was 29.7% in the upper ureter, 17.4% in the middle ureter, 39.9% in the lower ureter, and 4.3% in the renal pelvis. Of the 19/129 (13.8%) patients with positive urine culture, 11 (8%) had preoperative MDR infection, of which *Escherichia coli* and *Enterococcus species* represented as the most common pathogens. These were managed with the suitable antibiotics according to sensitivity and microbiology advice, and scheduled URS was performed upon verification of sterile urine. The SFR after the first URS was 98 (71%). Of the rest of the patients, 31 required a subsequent operation and 9 required a third strategy to be stone free. Accordingly, the final SFR was 99%, requiring 1.34 procedures per patient to be stone free. One hundred three (76.4%) had ureteric stent placed at the end of the procedure. The average hospital stay duration was 4.4 days (range: 2-13). Within the 139 procedures, 29 (21%) were complicated with fever/SIRS (case group).

In the case group, patients had a larger median stone size compared to control group patients, although this difference was small and median stone size was 13 mm (p=0.016) for both groups. In five cases with evidence of pyonephrosis, in nine cases with severe hydronephrosis, and in the remaining majority (n=28) to allow passive ureteral dilation to facilitate the passage of URS preoperative DJ stents (n=42, 30.4% of 139) were inserted. Postoperative DJ stents were placed in 63 cases (61.2%) to ease the passage of stone fragments, whereas DJ stents were needed in all cases with intraoperative complications (n=40, 63.5%) including mucosal damage of ureter (n=26.65%) and mucosal bleeding (n=14.35%). There were no catastrophic ureteral injuries in any patient, such as avulsion or perforation. Patients in the case group were susceptible to have a positive preoperative non-MDR urine culture (31% vs 9.2%, p=0.004) and MDR urine culture (20.7 vs 4.6%, p=0.011). By and large, after RURSLL, 29 (21%) procedures experienced postoperative infectious complications. Of the 29 infectious complicated procedures, 4 (13.8%) had pyuria and 25 (86.2%) had SIRS (Table 1).

Postoperative POF/SIRS after RURSLL were seen in 20 of 120 (16.67%) patients with negative preoperative urine cultures, 3 of 8 (37.5%) patients with preoperative non-MDR urine cultures, and 6 of 11 (54.54%) patients with preoperative MDR urine cultures. In particular, 68.4% (13/19) of positive preoperative urine cultures of patients in whom POF/SIRS developed consisted of gram-negative pathogens. No patient experienced sepsis.

On multivariate analysis, positive preoperative urine culture (OR: 8.364, 95% CI: 2.2–31.79; p=0.002), operation time (OR: 1.03, 95% CI: 1.01-1.04; p=0.002), postoperative DJ stent insertion (OR: 6.138, 95% CI: 1.15-32.56; p=0.033), and BMI (OR: 1.15, 95% CI: 1.03-1.29; p=0.016) were found to be significant with the dependent variable as the postoperative infectious complications after controlling for stone size, eGFR, and positive preoperative MDR urine culture (Table 2).

Discussion

We examined a single-institution contemporary arrangement of patients undergoing RURSLL for the management of ureteral calculi at any level. Our goal was to figure out which demographic, preoperative, and intraoperative characteristics were the best predictors of POF/SIRS in the geriatric age gathering. We found that the strongest predictors of POF/SIRS after RURSLL for stone disease were longer surgical times,

Table 1. Demographic as well as perioperative characteristics of patients and by Post operative fever/Systemic inflammatory response syndrome

Variable	Total cohort (n=139)	POF/SIRS (n=29)	Control (n=110)	p
Age in years, median (IQR)	69.9±5,6	70.8±5.9	69.75±5.5	**0.364**
Gender, female, %	48 (36.2%)	13 (50%)	35 (33%)	**0.129**
Body mass index, kg/m² (IQR)	25.6±4.5	27.8±4.8	25±4.2	**0.003**
ACCI	2.7±0.8	2.9±0.6	2.7±0.9	**0.021**
eGFR, mL/min				**0.034**
>60	67 (48.6%)	9 (31%)	58 (53.2%)	
<60	71 (51.4%)	20 (69%)	51 (46.8%)	
Stone size, mm, median (IQR)	13±6.2	15.5±5.7	12.4±6.2	**0.016**
Stone number, median (IQR)				**0.263**
Single	115 (83.3%)	22 (75.9%)	93 (85.3%)	
More than one	23 (16.7%)	7 (24.1%)	16 (14.7%)	
Stone location:				**0.645**
Upper ureteral	41 (2.7%)	8 (27.6 %)	33 (30.3%)	
Middle ureteral	24 (17.4%)	3 (10.3%)	21 (19.3%)	
Distal ureteral	55 (39.9%)	13 (44.8%)	42 (38.5%)	
Multiple	12 (8.7%)	4 (13.8%)	8 (7.3%)	
Renal pelvis	6 (4.3%)	1 (3.4%)	5 (4.6%)	
Preoperative Double-J stent, %	42 (30.4%)	8 (27.6%)	34 (31.2%)	**0.708**
Positive preoperative urine culture, %	19 (13.8%)	9 (31%)	10 (9.2%)	**0.004**
Positive preoperative MDR urine culture, %	11 (8%)	6 (20.7%)	5 (4.6%)	**0.011**
History of previous stone treatment, %				**0.82**
None	70 (52.2%)	14 (48.3%)	58 (53.2%)	
Extracorporeal shock wave lithotripsy	25 (18.1%)	6 (20.7%)	19 (17.4%)	
Ureterorenoscopy	18 (13%)	5 (17.2%)	13 (11.9%)	
Percutaneous nephrolithotomy	10 (7.2%)	1 (3.4%)	9 (8.3%)	
Open surgery	7 (5.1%)	1 (3.4%)	6 (5.5%)	
Multiple modalities	6 (4.3%)	2 (6.9%)	4 (3.7%)	
Operation time, minutes, median (IQR)	69.7±26.9	81.6±34.7	66.6±23.6	**0.01**
Preoperative double-J stent, %	42 (30.4%)	8 (27.6%)	34 (31.2%)	**0.708**
Postoperative double-J stent, %	103 (76.4%)	27 (93.1%)	76 (69.7%)	**0.01**
Hospitalization time, days, median (IQR)	4.4±2.4	4.7±2.7	4.3±2.3	**0.342**
Presence of residual fragments, %	40 (29%)	8 (27.6%)	32 (29.9%)	**0.852**
Renal anatomical anomaly, %	7 (5.1%)	1 (3.4%)	6 (5.5%)	**0.654**
Hydronephrosis, %				**0.15**
None or mild	96 (69.6%)	17 (58.6%)	79 (72.5%)	
Moderate or severe	42 (30.4%)	12 (41.4%)	30 (27.5%)	

ACCI: Charlson comorbidity index including age, eGFR: Estimated glomerular filtration ratio, IQR: Interquartile range

medical complexity, and positive preoperative urine cultures. This is one of the largest investigations in this age gathering analyzing risk factors for POF/SIRS after RURSLL.

Stone disease is an increasing, expensive chronic condition and seeks medical advice (18,19). URS is an alternative for treatment of stones <1 cm and has grown exponentially over the past decades (20-22). Although URS complications are rare, POF is the most common complication that requires more emergency visits and unplanned admissions (10,13,23,24). Tantamount to revealed rates, we discovered that 6.9% of URS cases were either seen in the emergency unit or readmitted for POF/SIRS (25). Our outcomes expand on earlier investigations of POF, SIRS, and other post-URS infectious complications. In spite of the fact that no standard description of post-URS infectious complications exists, medical complexity, longer operative time, and preoperative pyuria, or positive culture have all been noted

Table 2. Multivariate logistic regression analysis of variables associated with Post operative fever/Systemic inflammatory re sponse syndrome after semi-rigid ureterorenoscopy with laser lithotripsy

Multivariate analysis	OR	95% CI	p
Body mass index	1.15	1.03-1.29	**0.016**
ACCI	1.67	0.96-2.89	**0.068**
Positive preoperative urine culture	8.36	2.20-31.79	**0.002**
Operation time	1.03	1.01-1.05	**0.002**
Postoperative Double-J stent	6.14	1.16-32.57	**0.033**

ACCI: Charlson comorbidity index including age, OR: Odds ratio, CI: Confidence interval

as hazard factors in studies utilizing an assortment of outcome definitions. In 1,325 cases from the Clinical Research Office of the Endourological Society (CROES) URS Global Study Database, female gender and medical complexity were found to be the predictive factors of POF or urinary tract infection (UTI), even in the lack of a positive preoperative urinary culture (26). Another research confirmed these results in 927 URS procedures, 286 of which were carried out in females. The authors observed an important distinction between males (1%) and females (3%) in the incidence of febrile UTI (27). While it is not apparent why females are more likely to experience infectious complications after URS, this may be due to the short urethral length or ambient bacteria. However, we could not see such a distinction in gender in our research.

Similar to other research, we discovered that POF/SIRS requires longer operation time. Owing to stone characteristics, operation time can be a proxy for surgical complexity (28). Kuroda et al. (29) created a model based on a cohort of 972 patients to anticipate URS operation time. Preoperative stenting, stone volume, Hounsfield units, specialist experience, gender, and small-sized sheaths anticipated longer operation times. We think that most of the preoperative and intraoperative features in our research were insignificant as they contribute to longer surgical time jointly. Other research showed the association between longer operation times and POF. A research of 550 patients showed that URS operation times of more than 120 minutes were correlated with unplanned infection yields, although the confidence intervals were wide, probably owing to the small number of results (23).

In debates on the hazards and advantages of urological procedures, aging and medical complexity are significant factors (30). In 11,719 patients from the CROES URS Global Study Database, the writers observed that elderly, medically complicated, and anticoagulant users were more likely to have postoperative complications (3.5%), 75% of which were fever, UTI, or other problems (31). In a cohort of 276 URS, patients with two or more comorbidities were at a greater risk of readmission, and readmission was substantially related with hypertension or asthma/chronic obstructive pulmonary disease (24). In our cohort study, as it included the geriatric community, the mean comorbidity index was 2.7. On the other hand, like other research, however, the mean CCI score in the POF/SIRS group was considerably higher.

Positive preoperative urine culture was the most important modifiable predictor from our cohort. Multiple studies discovered that preoperative pyuria or positive urine cultures were correlated with URS-related infectious complications, although lower cohort sizes ranged from 100 to 500 patients. The biggest cohort had 532 patients and discovered that 3.8% had infectious problems with the risk factors including preoperative bacteriuria, hydronephrosis, and foreign bodies in the urinary tract (32). In another cohort of 153 patients, 18.3% experienced febrile UTI, and one of the most important factors was preoperative pyuria (33). These findings correspond with those of Margel et al. who discovered that 19 of 75 (25%) percutaneous nephrolithotomy-treated patients with a positive stone culture had sterile urine, and urine culture sensitivity to predict stone colonization was only 30% (34). Moreover, antibiotic prophylaxis used in this study did not eliminate the risk of infection after FURSLL in 30 of 433 (6.9%) patients with negative preoperative urine cultures. Indeed, in the CROES-URS Global Study, Martov et al. (26) showed that rates of postoperative UTI and fever were not reduced by preoperative antibiotic prophylaxis in patients who underwent URS for ureteral stones (n=1141) or kidney stones (n=184). Possible reasons for these results might be that urine cultures may not correctly represent the pathogens responsible for the infection found in the upper urinary tract or in infected stones and may not be able to thoroughly penetrate the infected stone (35). A declaration of best practice by the American Urological Association (AUA) proposes perioperative antimicrobial prophylaxis for all patients undergoing URS owing to the hazard of bacteremia from stone manipulation and upper tract endoscopy (36).

Stent insertion is an efficient technique for acute drainage of hydronephrotic or pyonephrotic kidneys (37). In contrast, it may be the long-term cause of the infection. Several trials revealed colonization rates of ureteral stents from 44% to 69% and bacteriuria rates from 21% to 29.9%. Because of bacterial colonization of DJ stents (38), mild fever, UTI, and even sepsis can be seen. POF was observed in 22 (25%) patients who had

no preoperative fever in a research undertaken with 87 patients who had DJ stent insertion following urgent intervention (n=34) or elective intervention (n=53). Fever was observed in 56% of patients who had stent insertion after emergency intervention, while it was present in only 6% of patients who had stent insertion after elective intervention. Therefore, stent insertion was revealed to significantly increase the risk of fever after emergency intervention (39). In another research, 26 of the 48 patients underwent URS due to distal ureteral stone was placed with DJ stent, and 22 patients were followed up without a stent. In just one patient who had DJ stent insertion, urosepsis was discovered and the distinction was not significant (40). A comparable research found that there was no association between fever and stent insertion (41). Ibrahim et al. (42) prospectively evaluated 110 stent patients and 110 non-stent patients in their big sequence. Fever developed in 8 (7.3%) patients and UTIs found in 5 (4.5%) patients in the stent group, whereas fever occurred in 10 (9.1%) instances and UTIs occurred in 7 (6.4%) instances in the non-stented group. Even though there was no significant distinction between the groups, fever and infection in the unstented group were slightly higher. In this study, after RURSLL, we discovered fever rates in the stented group were significantly higher. We could not interpret whether our results depended on age because only the geriatric age population was included in our research group. This complication can be caused by medical complexity, which should be studied.

For asymptomatic individuals, it is not our normal practice to acquire urine cultures regardless of symptoms before URS similar to AUA guidelines that suggest urinalysis alone (20). The perioperative antibiotic is tailored to the bacterial organism and susceptibility, according to the results of the antibiogram. A 3-day regimen of antibiotic with genitourinary coverage (e.g., cephalexin) or 5-7 days of nitrofurantoin is our postoperative regimen. Some patients still develop infectious complications in spite of this standard approach. In order to comprehend the pathophysiology and how to decrease the hazard of this complication, further study is required.

Study Limitations

Our study has some built-in limitations. First, this is a retrospective observational study in a gathering of geriatric patients who underwent RURSLL. Second, there is no standard definition of infectious complications, and we concentrated on POF/SIRS, which results in expensive use of health care. Third, no complete data on stone compound, stone culture, and urine culture of the upper urinary tract were available. Finally, we did not consider the possible effect of intraoperative fluid irrigation pressure on postoperative infectious complications.

Conclusions

In this research of RURSLL among geriatric population, we discovered that the most important predictors of POF/SIRS were longer operation times, positive preoperative urine cultures, and postoperative insertion of DJ stent. These data indicate that the procedure should be kept as short as possible, and the indications for postoperative DJ catheter insertion should be reduced as much as possible in geriatric patients. This information will assist suppliers to identify the high-risk people and guide them on assessment of risk factors to reduce the rate of POF/SIRS. Future studies will concentrate on how to protect at-risk patients from infectious complications.

Ethics

The study were approved by the Bulent Ecevit University Faculty of Medicine, Department of Urology Local Ethics Committee (protocol number: 2019-84-22/05, date: 22.05.2019).

Informed Consent: Informed consent was obtained before oparation from all individual participants included in the study.

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Authorship Contributions

Surgical and Medical Practices: R.G., E.D.D., Concept: R.G., E.D.D., Design: R.G., E.D.D., Data Collection or Processing: R.G., E.D.D., Analysis or Interpretation: R.G., E.D.D., Literature Search: R.G., E.D.D., Writing: R.G., E.D.D.

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ORIGINAL RESEARCH
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Global Publication Outcomes in Retrograde Intrarenal Surgery and Turkiye's Effectiveness: A Bibliometric Analysis between 1980 and 2019

Retrograd İntrarenal Cerrahide Global Yayın Sonuçları ve Türkiye'nin Etkinliği: 1980-2019 Yılları Arasında Bibliyometrik Analiz

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What's known on the subject? and What does the study add?

Bibliometric analysis on retrograde intrarenal surgery. This study is the first study that makes a holistic analysis of the articles about this issue. One of the notable findings of this study is that Turkiye is among the world countries that produced the highest number of publications about this issue and the hospitals where this technique is used most are located in Turkiye.

Abstract

Objective: Urinary system stone disease is a very common health problem that affects 2 to 3% of people and causes serious complications when it is not treated. The prevalence of renal stones has been increasing worldwide and surgical methods have changed over time. However, there is no comprehensive bibliometric analysis of the retrograde intrarenal surgery (RIRS) method in the literature. This study aimed to conduct a bibliometric analysis of all articles regarding RIRS published between 1980 and 2019.

Materials and Methods: The literature search was performed using only the following keywords: "RIRS" and "flexible ureterorenoscopy/flexible ureteroscopy", in the "title" part of the search. Using this search method, all the articles published between 1980 and 2019 on this topic were accessed and downloaded from the Web of Science database, and the articles were analyzed using bibliometric methods.

Results: Totally, 1378 publications were found as a result of the literature search, of which 619 were articles. We noted that there has been a rapid increase in the number of publications, especially from the year 2011. Turkiye was found to be the most productive country with regard to RIRS. The journals that contributed most to the literature were: Journal of Endourology, Urology, Journal of Urology, Urolithiasis, and World Journal of Urology.

Conclusion: One of the notable findings of this study is that Turkiye is among the world countries that produced the highest number of publications with regard to this topic and that the hospitals where this technique is used the most are located in Turkiye.

Keywords: Retrograde intrarenal surgery, RIRS, Flexible ureterorenoscopy, Bibliometric analysis, Trends

Öz

Amaç: Üriner sistem taş hastalığı, insanların %2 ila 3'ünü etkileyen ve tedavi edilmediğinde ciddi sorunlara neden olan çok yaygın bir sağlık sorunudur. Renal taşların prevalansı dünya çapında artmaktadır ve cerrahi yöntemler zaman içinde değişmiştir. Bununla birlikte, literatürde retrograd intrarenal cerrahi (RIRC) yönteminin kapsamlı bir bibliyometrik analizi yer almamaktadır. Bu çalışma 1980 ve 2019 yılları arasında yayınlanan RIRC ile ilgili tüm makalelerin bibliyometrik analizini yapmayı amaçlamaktadır.

Gereç ve Yöntem: Literatür taraması sadece aramanın "başlık" kısmında "RIRC" ve "esnek üreterorenoskopi/esnek üreteroskopi" anahtar kelimeleri kullanılarak yapıldı. Bu arama yöntemi kullanılarak 1980-2019 yılları arasında bu konu hakkında yayınlanan tüm makalelere erişildi ve Web of Science veritabanından indirildi. Makaleler bibliometrik yöntemler kullanılarak analiz edildi.

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Bulgular: Literatür taraması sonucunda toplam 1378 yayın bulundu. Bu yayınlardan 619'u makaleydi. Özellikle 2011 yılından bu yana yayın sayısında hızlı bir artış olmuştur. Türkiye'nin RIRS konusunda en verimli ülke olduğu tespit edildi. Literatüre en fazla katkıda bulunan dergiler Journal of Endourology, Urology, Journal of Urology, Urolithiasis, and World Journal of Urology olarak bulundu.
Sonuç: Bu çalışmanın dikkate değer bulgularından biri de Türkiye'nin bu konuda en fazla sayıda yayın yapan dünya ülkeleri arasında olması ve bu tekniğin en çok kullanıldığı hastanelerin Türkiye'de bulunmasıdır.
Anahtar Kelimeler: Retrograd intrarenal cerrahi, RIRS, Fleksibıl üreterorenoskopi, Bibliometrik analiz, Trends

Introduction

Urinary system stone disease encompasses the kidneys, ureter, bladder, and urethral calculus. It is a commonly encountered health problem affecting 2-3% of people and causes serious complications when it is not treated. The retrograde intrarenal surgery (RIRS) technique performed under general anesthesia is done using a thin instrument, 3 mm in diameter (flexible renoscopy), with a light source that enables monitoring with an optic fiber by passing from the urethra (urinary canal) and bladder (urinary bladder) to the path that connects kidneys and bladder (ureter), in order to break the stone located within the kidney. Renal stone is broken using a laser power source that can pass through renoscopy and the big stone parts are taken out after the breaking procedure; the fragments that are now in powdered form are removed from the kidney (1,2).

Today, RIRS enables the successful treatment for most small or medium size renal stones, without any need for open surgery or percutaneous nephrolithotomy (PCNL). This method makes it possible to access the kidney from the abdominal wall without needing to open any holes; renoscopy that could be bent by entering from the urinary canal and laser enable the complete breaking and removal of the stones. Using this method, patients could be discharged from the hospital in a shorter period and begin to live as before (3-5).

The treatment of renal stones has recently undergone significant changes. The treatment options include open surgery, as well as the less invasive PCNL, extracorporeal shock wave lithotripsy (ESWL), and RIRS (6). With the increase in surgical experience, RIRS has become an important and acceptable treatment option for renal stones for all age groups, stone sizes, and localizations (7).

Bibliometric analyses enabled the identification of the most effective and top-cited studies and journals, through the statistical analysis of articles published with regard to a specific topic, specific research field, journal, or a country (8-11). They also enabled us to explore the collaborations between countries, authors, and institutions.

Bibliometric studies involve the investigation of the relationship between publication productivity and various factors possible (12-15). There have been several bibliometric studies in the medical field in recent years. The value of bibliometric studies has been increasing as a result of the increased number of publications in literature day by day (16).

The prevalence of renal stones has been increasing worldwide (5,17), and surgical methods have changed over time. However, there is no comprehensive bibliometric analysis of this method in the literature This study aimed to conduct a bibliometric analysis of all the articles regarding RIRS published between 1980 and 2019.

Material and Methods

The literature review was done using the following keywords: "RIRS" and "flexible ureterorenoscopy/flexible ureteroscopy/FURS), in the "title" part of the search. [Access codes: (title: (retrograde intrarenal*) or title: (flexible uretero*) or title: (RIRS) or title: (FURS) timespan: 1980-2019. indexes: SCI-Expanded, A&HCI, SSCI, CPCI-S, BKCI-S, CPCI-SSH, BKCI-SSH, ESCI) and access date: August 01, 2020]. Through this search, all the articles that were published between 1980 and 2019 on this topic were accessed and downloaded from the Web of Science (WoS) database. The articles were analyzed using bibliometric methods. VOSviewer (Version 1.6.13) package program was used for the bibliometric web visualizations. The world map was drawn using an online web site (http://lert.co.nz/map/).

Results

Totally, 1378 publications were found as a result of the literature search, of which 619 were articles, 544 were Meeting Abstracts, 109 were Editorial Materials, 53 were Reviews, 33 were Letters, 19 were Proceedings Papers, and 20 were other publications (Early Access, Correction, Book Chapter, Note). This study included the bibliometric analysis of 619 publications only; all of which were articles. Of these articles, 90.3% were English (n=559), and the others were French (n=34), Spanish (n=22), Turkish (n=3), and Korean (n=1).

The 619 articles accessed received 8518 citations (without self-citations 5549) in total, and the mean citation number per article was found to be 13,76, while the H-index of all the articles was 44.

Active Research Areas

The top 10 research areas of the published articles included Urology and Nephrology (515: 83.2%); General Internal medicine (35); Surgery (30); Experimental Medicine Research (25); Multidisciplinary Sciences (11); Pediatrics (10); Pharmacology and Pharmacy (4); Radiology, Nuclear Medicine, and Medical Imaging (3); Anatomy Morphology (2); and Biotechnology Applied Microbiology (2).

Development of Publications

The distribution of the articles is demonstrated in Figure 1. The increase in the number of articles has been significant since 2011, and a notable increase was found after the year 2014.

Active Countries

A total of 51 countries had made publications on this topic; Figure 2 demonstrates the rank order of 23 countries that produced the highest number of articles. The network map of international collaborations between the 30 countries that produced a minimum of three publications is displayed in Figure 3.

Active Authors

Table 1 presents the top 25 authors producing the highest number of publications about this issue.

Active Organizations

The top active organizations involved and organizations that produced the highest number of publications are demonstrated in Table 2.

Active Journals and Citation Analysis

Table 3 presents the active journals producing the highest number of publications regarding this topic. The number of citations and the number of citations per article are shown in the last column of Table 3. The Citation network visualization map among the journals is given in Figure 4.

Most Cited Articles

Table 4 displays the top 15 articles that had received the highest number of citations (18-32).

Co-citation Analysis

A total of 4484 publications were cited in the references section of the 619 published articles. The studies receiving the highest number of citations were those conducted by Dindo, 2004 (Citation: 88) (33); Breda, 2009 (Citation: 80) (21); Breda, 2008 (Citation: 69) (20); Traxer, 2013 (Citation: 65) (18); and Bozkurt, 2011 (Citation: 58) (25). There were 33 articles that received citations at least 30 times. The density map of these articles is shown in Figure 5.

Trend Topics

There were 697 different keywords in the 619 articles. Figure 6 shows the network map of the cluster analysis results conducted with 71 keywords that were used in minimum of four different articles. The network map of trend words analysis is given in Figure 7.

Discussion

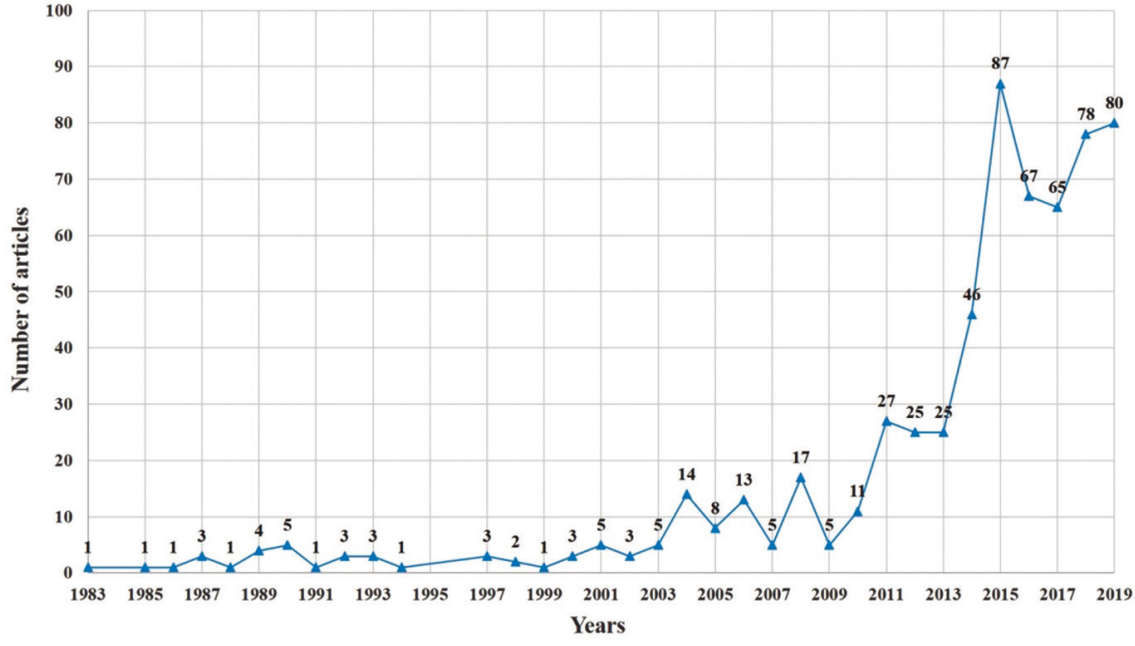

Figure 1. Distribution of articles published on retrograde intrarenal surgery by years

Table 1. Active authors on retrograde intrarenal surgery

Authors	RC	%
Traxer	46	7.431
Resorlu	23	3.716
Unsal	20	3.231
Atis	15	2.423
Bagley	15	2.423
Binbay	15	2.423
Bozkurt	15	2.423
Caskurlu	15	2.423
Proietti	15	2.423
Giusti	13	2.100
Ozgor	13	2.100
Tepeler	12	1.939
Doizi	11	1.777
Matsuzaki	11	1.777
Monga	11	1.777
Muslumanoglu	11	1.777
Lechevallier	10	1.616
Sener	10	1.616
Yao	10	1.616
Zeng	10	1.616
Cho	9	1.454
Clayman	9	1.454
Ito	9	1.454
Ozyuvali	9	1.454
Preminger	9	1.454

RC: Record count C: Number of citation

In line with the increase in the importance of RIRS, the importance of the number of publications and citations has also increased. Particularly, the number of publications has increased rapidly since 2011, and it has reached approximately 80 articles in recent years. Turkiye was found to be the most productive country with regards to RIRS. Although the publication productivity of developed countries such as the USA, China, France, United Kingdom, Germany, Italy, Spain, and Japan reveals that publication productivity is closely related to financial power; it is also important to note the contribution of countries such as Turkiye, India, Brazil, Chili, and Romania.

The analysis performed to detect the collaboration between the countries showed that the collaborations were in clusters of geographical location. Developing or undeveloped countries could be encouraged to create collaborations on this issue topic.

The journals that had the highest contribution to the literature were Journal of Endourology, Urology, Journal of Urology, Urolithiasis, and World Journal of Urology. As per the total number of citations, the Journal of Endourology, Urology,

Table 2. Active organizations-enhanced and organizations on retrograde intrarenal surgery

Organizations-enhanced	RC	%	Organizations	RC	%
Sorbonne Universite	47	7.593	University Paris 06	17	2.746
Assistance Publique Hopitaux Paris Aphp	46	7.431	Guangzhou Med University	16	2.585
Hopital Universitaire Tenon Aphp	45	7.270	Kecioren Training Res Hospital	16	2.585
Ankara Kecioren Training Research Hospital	23	3.716	Hop Tenon	15	2.423
Diskapi Yildirim Beyazit Training Research Hospital	21	3.393	Thomas Jefferson University	15	2.423
Istanbul Medeniyet University	19	3.069	Gazi University	14	2.262
Istanbul Haseki Training Research Hospital	17	2.746	Istanbul Medeniyet University	12	1.939
Guangzhou Medical University	16	2.585	Bezmialem Vakif University	11	1.777
Jefferson University	15	2.423	Bozok University	11	1.777
Gazi University	14	2.262	Yokohama City University	11	1.777
University of California System	13	2.100	Ankara Numune Training Res Hospital	10	1.616
Ankara Numune Training Research Hospital	12	1.939	Duke University	10	1.616
Bezmialem Vakif University	12	1.939	Haseki Training Res Hospital	10	1.616
Istanbul Goztepe Training and Research Hospital	12	1.939	University Health Science	10	1.616
Seoul National University Snu	12	1.939	University Wisconsin	10	1.616
Vita Salute San Raffaele University	12	1.939	Washington University	9	1.454
Bozok University	11	1.777	Ankara University	8	1.292
Ministry of Health Turkiye	11	1.777	Capital Med University	8	1.292
Yokohama City University	11	1.777	Seoul Natl University	8	1.292
Aix Marseille Universite	10	1.616	University Tubingen	8	1.292
Duke University	10	1.616	Asklepios Hospital Barmbek	7	1.131
Seoul National University Hospital	10	1.616	Cent S University	7	1.131
University of Wisconsin Madison	10	1.616	Huazhong University Sci Technol	7	1.131
University of Wisconsin System	10	1.616	Karabuk University	7	1.131
Eberhard Karls University of Tubingen	9	1.454	Medeniyet University	7	1.131

RC: Record count C: Number of citation

Journal of Urology, and BJU International were the effective journals. The journals receiving the highest number of citations per article were European Urology, Journal of Urology, BJU International, Urology, and Urological Research. Researchers could be recommended to consider these journals for studies that they would like to receive more citations. As for the journals addressing Turkiye, the notable journals were the Journal of Urological Surgery and Turkish Journal of Urology.

The articles with the highest total number of citations included the articles entitled "Prospective Evaluation and Classification of Ureteral Wall Injuries Resulting from Insertion of a Ureteral Access Sheath During RIRS" written by Traxer and Thomas (18) and "Ureteral access sheath provides protection against elevated renal pressures during routine flexible ureteroscopic stone manipulation" written by Auge et al. (19). Apart from these studies, the top-cited articles according to the average number of citations included the studies entitled "Flexible Ureteroscopy and Laser Lithotripsy for Multiple Unilateral Intrarenal Stones" and "Flexible ureteroscopy and laser lithotripsy for single intrarenal stones 2 cm or greater - Is this the new frontier?" by Breda (20,21), respectively. The top-cited Turkish study entitled "RIRS Versus Percutaneous Nephrolithotomy in the Management

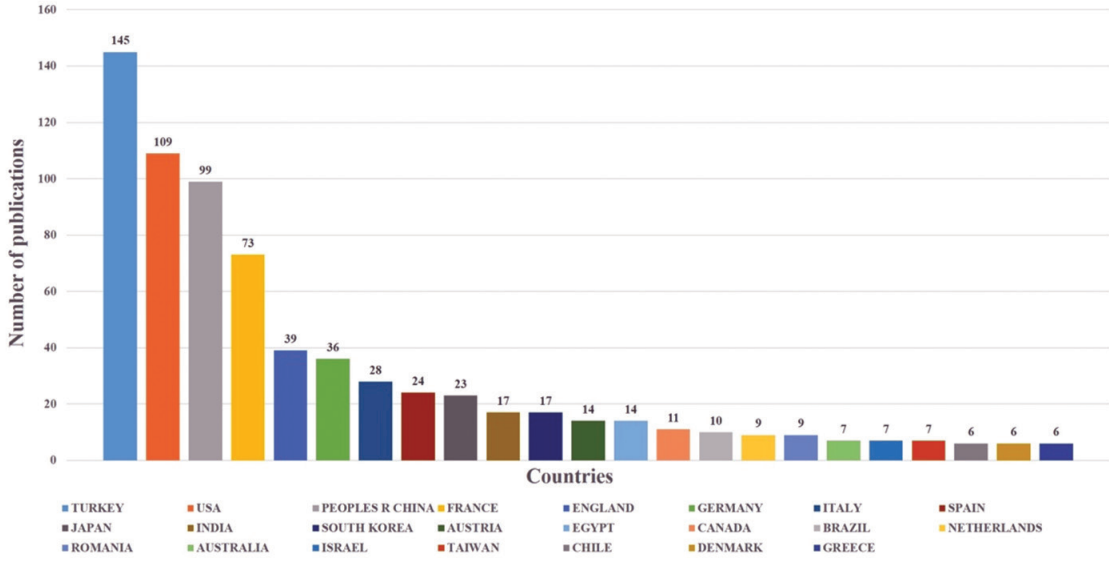

Figure 2. World map on the distribution of world countries producing publications on retrograde intrarenal surgery

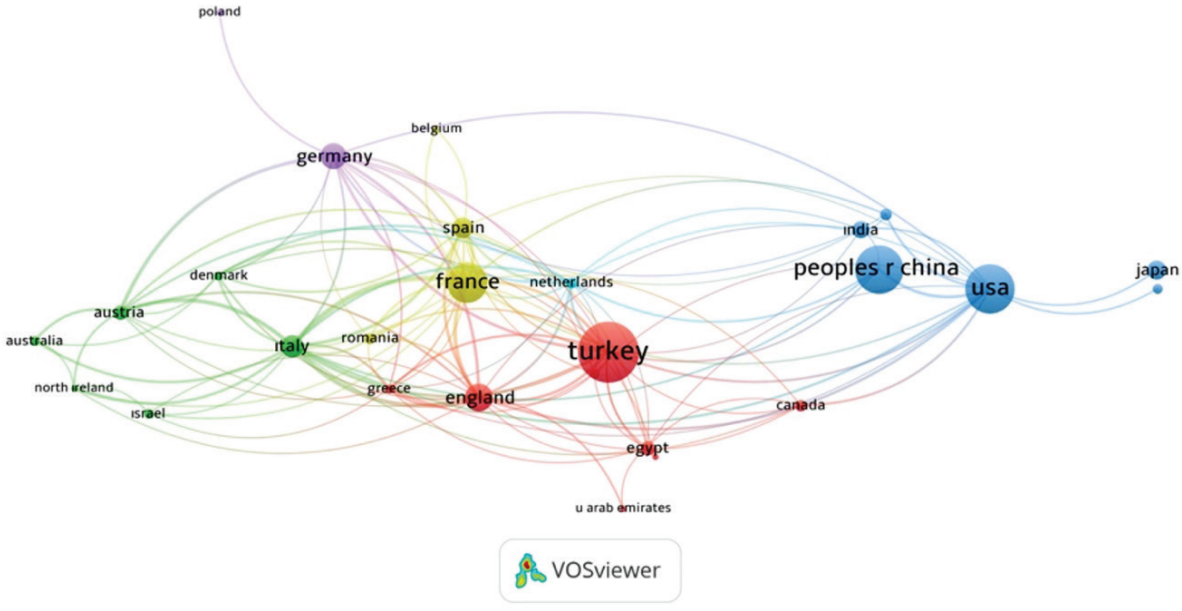

Figure 3. Network visualization map showing the international collaboration of countries on retrograde intrarenal surgery Footnote: Colors indicate clustering

Table 3. Active journals on retrograde intrarenal surgery

Journals	RC	%	C	AC
Journal of Endourology	114	18.417	2195	19.3
Urology	49	7.916	1213	24.8
Journal of Urology	37	5.977	1789	48.4
Urolithiasis	34	5.493	426	12.5
World Journal of Urology	34	5.493	445	13.1
Progres En Urologie	33	5.331	126	3.8
Urologia Internationalis	21	3.393	171	8.1
BJU International	19	3.069	548	28.8
Urology Journal	19	3.069	73	3.8
Actas Urologicas Espanolas	13	2.100	78	6.0
International Braz J Urol	13	2.100	77	5.9
International Journal of Clinical and Experimental Medicine	13	2.100	38	2.9
Archivos Espanoles De Urologia	10	1.616	7	0.7
Turkish Journal of Urology	9	1.454	24	2.7
Journal of Pediatric Urology	8	1.292	19	2.4
Arab Journal of Urology	7	1.131	11	1.6
BMC Urology	7	1.131	17	2.4
Urological Research	7	1.131	168	24.0
Archivio Italiano Di Urologia E Andrologia	6	0.969	20	3.3
CUAJ Canadian Urological Association Journal	6	0.969	37	6.2
European Urology	6	0.969	364	60.7
International Urology and Nephrology	6	0.969	34	5.7
Central European Journal of Urology	5	0.808	34	6.8
International Journal of Urology	5	0.808	78	15.6
Journal of Urological Surgery	5	0.808	0	0.0

RC: Record count C: Number of citation AC: Average citation per article

of Lower-Pole Renal Stones with a Diameter of 15 to 20 mm" was written by Bozkurt et al. (25) in the Journal of Endourology.

According to the co-citation analysis results, the studies conducted by Dindo et al. (33), Breda et al. (20,21), Traxer et al. (18), and Bozkurt et al. (25) were cited the most in the references sections of the articles. Researchers interested in RIRS are recommended to first read these studies.

Keyword analyses indicated eight different clusters, and the cluster centers included RIRS, flexible ureteroscopy, ureteroscopy, and urolithiasis. While previous percutaneous nephrolithotomy and ureteroscopy topics were searched, especially after the year 2000, laser and RIRS topics were searched, which is considered to be as a result of using holmium laser in RIRS operations in 1995.

Study Limitation

The limitation of the present study is that it did not search the PubMed and Scopus databases. WoS database was preferred, as the journals with a high impact factor are indexed there and it is a more reliable database in terms of citations (11,34,35).

Conclusion

With the increase of the importance of RIRS, a less invasive technique for the treatment of urinary system stone diseases, the present study is the first of its kind study to conduct a holistic analysis of the articles on this issue. The study is believed to guide physicians, academics, and students in studying RIRS, on topics such as effective journals, top-cited studies, trend topics, and the most productive countries. One of the notable findings of this study is that Turkiye is among the world countries that had the highest number of publications on this topic and the hospitals where this technique is used are mostly located in Turkiye.

Ethics

Ethics Committee Approval: This article does not contain any studies with human participants or animals performed by any of the authors.

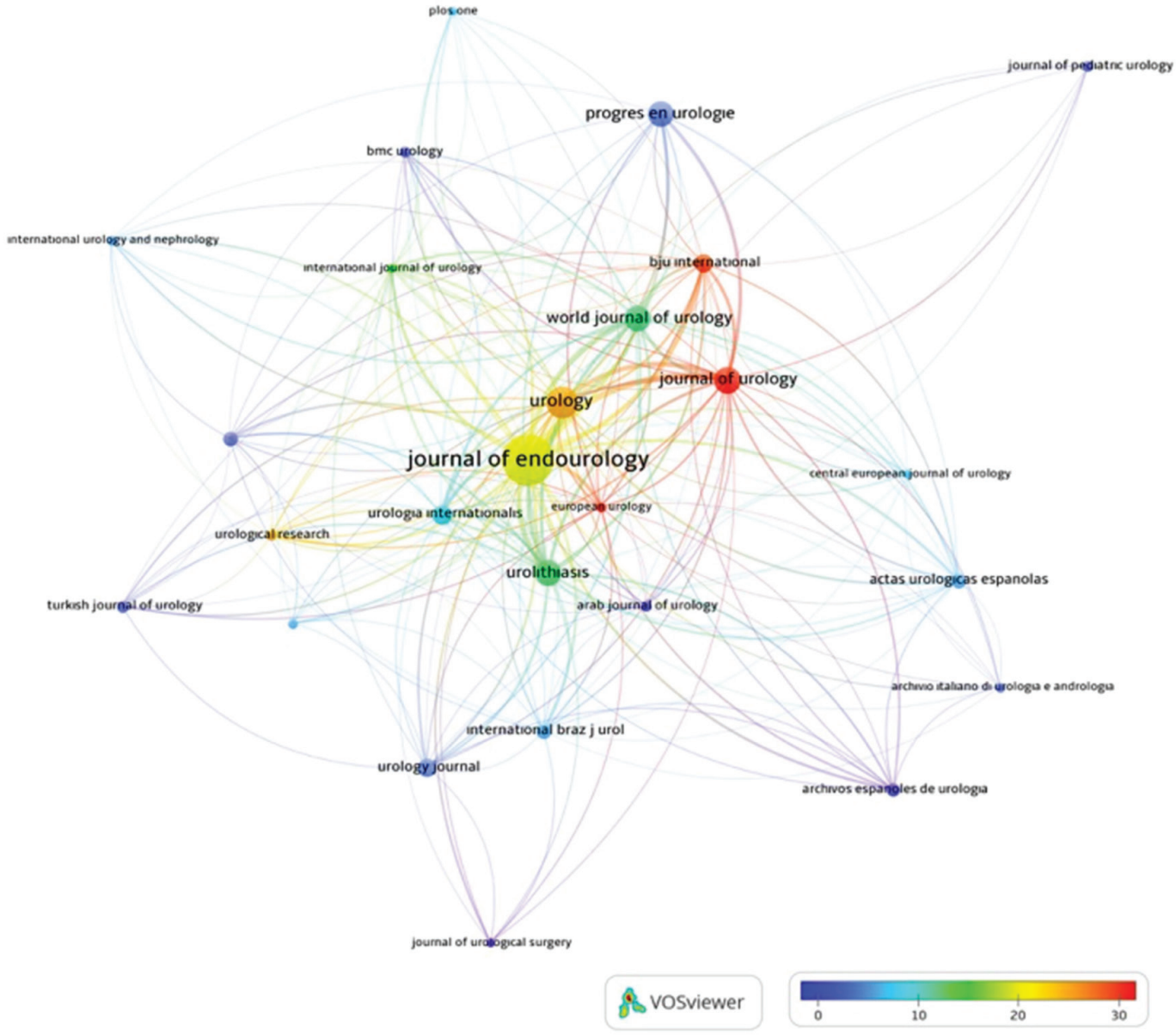

Figure 4. Network visualization map of citation analysis of active journals producing publications on retrograde intrarenal surgery
Footnote: Number of receiving citations increases from blue to red

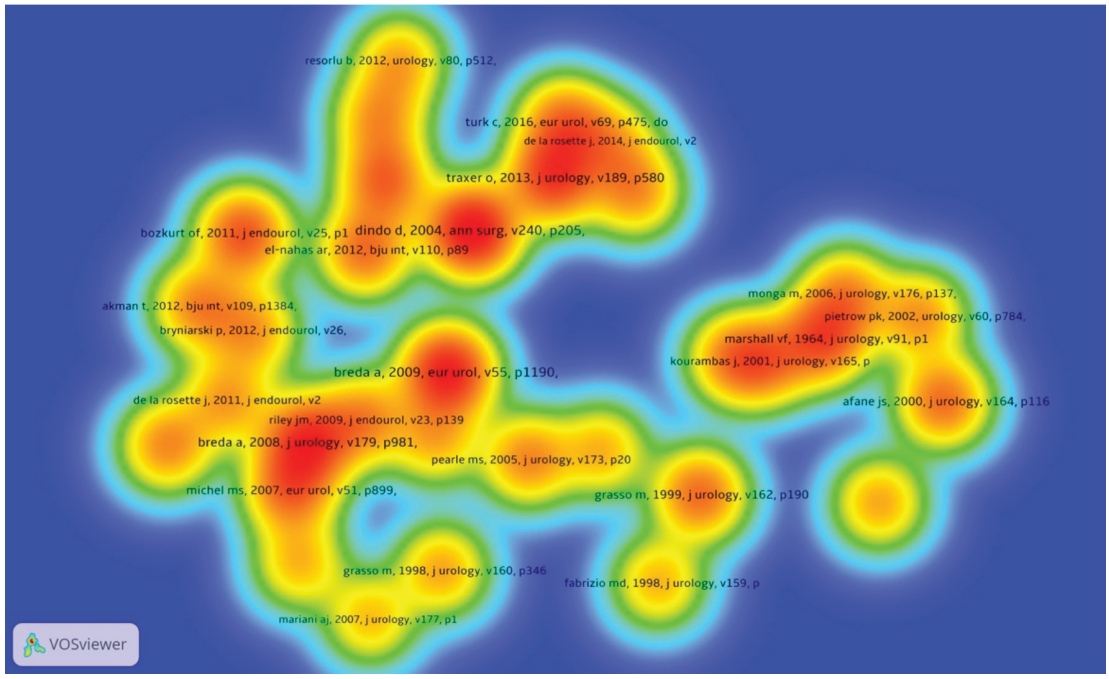

Figure 5. Density map of co-citation analysis in references on retrograde intrarenal surgery
Footnote: Number of receiving citations increases from blue to red

Table 4. Top 15 most cited articles according to total citations on retrograde intrarenal surgery

No	Article	Author	Journal	PY	TC	AC
1	Prospective Evaluation and Classification of Ureteral Wall Injuries Resulting from Insertion of a Ureteral Access Sheath During Retrograde Intrarenal Surgery	Traxer and Thomas (18)	Journal of Urology	2013	202	25.25
2	Ureteral access sheath provides protection against elevated renal pressures during routine flexible ureteroscopic stone manipulation	Auge et al. (19)	Journal of Endourology	2004	151	8.88
3	Flexible ureteroscopy and laser lithotripsy for single intrarenal stones 2 cm or greater - Is this the new frontier?	Breda et al. (20)	Journal of Urology	2008	142	10.92
4	Flexible Ureteroscopy and Laser Lithotripsy for Multiple Unilateral Intrarenal Stones	Breda et al. (21)	European Urology	2009	141	11.75
5	Flexible ureteroscopes: A single center evaluation of the durability and function of the new endoscopes smaller than 9Fr	Afane et al. (22)	Journal of Urology	2000	121	5.76
6	Small diameter, actively deflectable, flexible ureteropyeloscopy	Grasso and Bagley (23)	Journal of Urology	1998	121	5.26
7	Management of lower pole renal calculi: shock wave lithotripsy versus percutaneous nephrolithotomy versus flexible ureteroscopy	Preminger (24)	Urological Research	2006	99	6.6
8	Retrograde Intrarenal Surgery Versus Percutaneous Nephrolithotomy in the Management of Lower-Pole Renal Stones with a Diameter of 15 to 20 mm	Bozkurt et al. (25)	Journal of Endourology	2011	97	9.7
9	Flexible Ureterorenoscopy and Holmium Laser Lithotripsy for the Management of Renal Stone Burdens That Measure 2 to 3 cm: A Multi-Institutional Experience	Hyams et al. (26)	Journal of Endourology	2010	93	8.45
10	Techniques to maximize flexible ureteroscope longevity	Pietrow et al. (27)	Urology	2002	90	4.74
11	Flexible ureterorenoscopy versus extracorporeal shock wave lithotripsy for treatment of lower pole stones of 10-20 mm	El-Nahas et al. (28)	BJU International	2012	88	9.78
12	Flexible Ureteropyeloscopy - Diagnosis And Treatment In The Upper Urinary-Tract	Bagley et al. (29)	Journal of Urology	1987	88	2.59
13	Durability of flexible ureteroscopes: A randomized, prospective study	Monga et al. (30)	Journal of Urology	2006	84	5.6
14	Lower-pole caliceal stone clearance after shockwave lithotripsy, percutaneous nephrolithotomy, and flexible ureteroscopy: Impact of radiographic spatial anatomy	Elbahnasy et al. (31)	Journal of Endourology	1998	83	3.61
15	Safety and efficacy of flexible ureterorenoscopy and Holmium : YAG lithotripsy for intrarenal stones in anticoagulated cases	Turna et al. (32)	Journal of Urology	2008	82	6.31

PY: Publication year, TC: Total citation, AC: Average citations per year

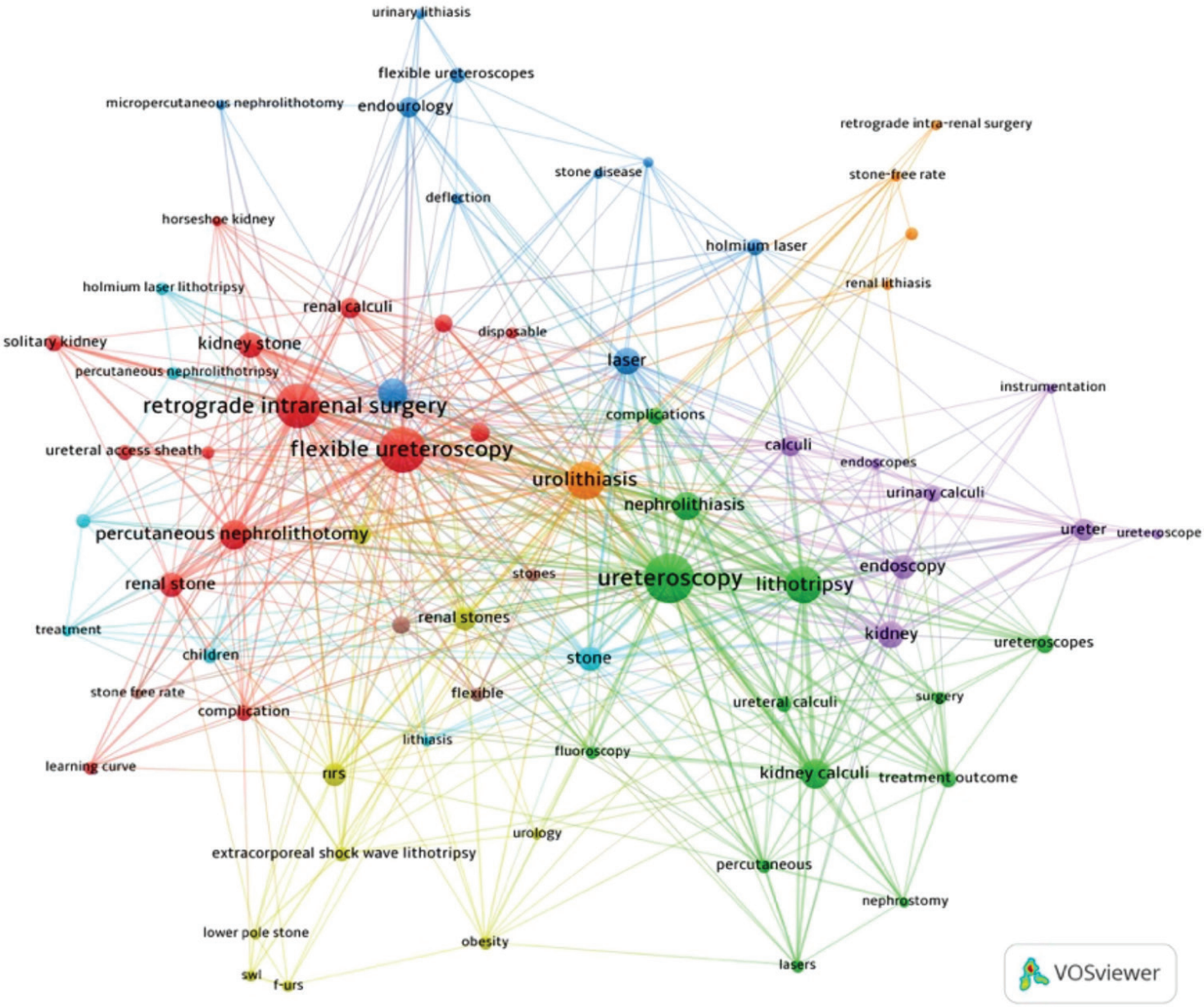

Figure 6. Network visualization map showing cluster analysis results based on keyword analysis on retrograde intrarenal surgery
Footnote: Colors indicate clustering

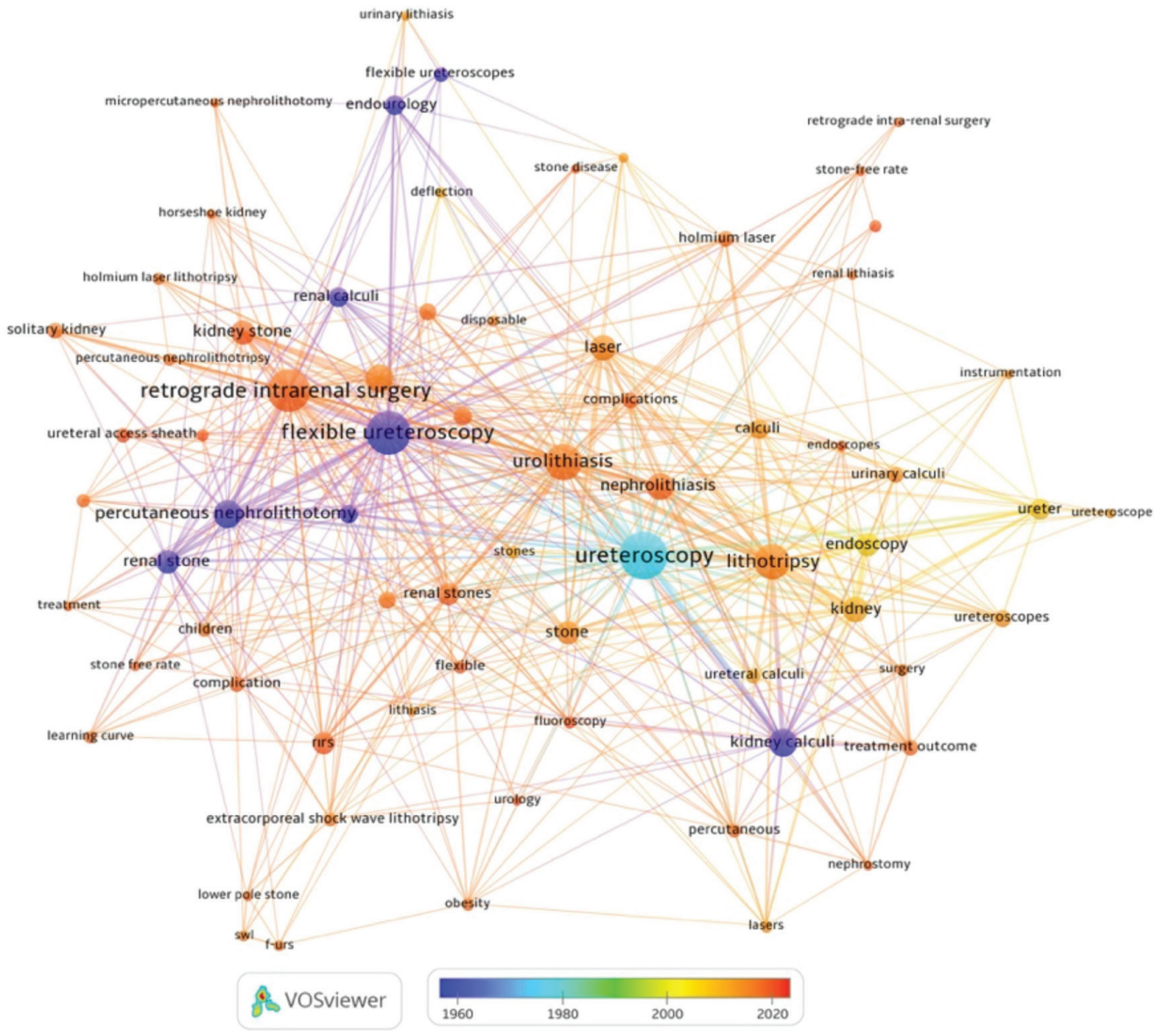

Figure 7. Network visualization map showing current trends based on keyword analysis results on retrograde intrarenal surgery
Footnote: Updates increases from blue to red

Informed Consent: For this type of study formal consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.M.B., M.E., Design: M.M.B., M.E., Data Collection or Processing: M.E., E.D., Analysis or Interpretation: M.E., E.D., Literature Search: M.E., E.D., Writing: M.M.B., M.E.

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

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Early Period Evaluations after Varicocelectomy: Semen Analysis and Spontaneous Pregnancy Rates

Varikoselektomi Sonrası Erken Dönemde Sperm Parametrelerinin ve Spontan Gebelik Oranlarının Değerlendirilmesi

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What's known on the subject? and What does the study add?

Patients should wait at least 6 months after varicocele surgery and should not immediately apply to assisted reproductive techniques as the spontaneous pregnancy rates will increase with improvement in sperm parameters. Thus avoiding both economic cost and a possible invasive intervention.

Abstract

Objective: The objective of this study is to evaluate and compare the sperm parameters and spontaneous pregnancy rates of patients with varicocele and primary infertility at three and six months after surgery.
Materials and Methods: We retrospectively evaluated the sperm parameters of 134 male patients who presented with clinical varicocele and primary infertility between July 2016 and May 2019. All the patients underwent microscopic inguinal varicocelectomy. We compared the sperm parameters (count, movement, and morphology) and spontaneous pregnancy of the patients preoperatively, and at three and six months postoperatively.
Results: In total, 134 patients with a mean age of 26.2 (20-38) years underwent the surgery. We found an increase in all the sperm parameters in the third and sixth months postoperatively. We also examined the differences among the sperm parameters in the third month and sixth month, and found a significant increase in the sperm count and motility at six months ($p<0.001$). The postoperative third-month pregnancy rates were 2.9% (n=4) and 26.8% (n=36) in the sixth month.
Conclusion: The improvement in sperm parameters in the third month after varicocele operation continued and increased by the postoperative sixth month. Therefore, patients with varicocele and primary infertility should be aware that the rate of spontaneous pregnancy could increase within six months and should wait for at least that period before applying for assistive reproductive techniques.
Keywords: Microscopic subinguinal varicocelectomy, Spermiogram, Varicocele

Öz

Amaç: Primer infertilitesi ve klinik varikoseli olan hastalarda varikoselektomi sonrası 3. ve 6. aylarda sperm parametrelerini karşılaştırdık ve spontan gebelik oranlarını değerlendirdik
Gereç ve Yöntem: Haziran 2016 - Mayıs 2019 tarihleri arasında üroloji polikliniğine gelen primer infertilitesi ve klinik varikoseli olan toplam 134 hastayı retrospektif olarak değerlendirdik. Tüm hastalara mikroskobik subinguinal varikoselektomi yapıldıktan sonra sperm parametreleri (sayı, hareket, morfoloji) ve spontan gebelik oranları preoperatif dönem ve postoperatif 3. ve 6. aylar değerlendirildi ve karşılaştırıldı.
Bulgular: Yüz otuz dört hastaya varikoselektomi yapıldı ve yaş ortalaması 26,2 (20-38) idi. Tüm sperm parametreleri 3. ve 6. ayda yükselmişti. Postoperatif 3. ve 6. ay karşılaştırıldığında sperm sayı ve hızında anlamlı derecede yükselme mevcuttu ($p<0,001$). Postoperatif 3. ay gebelik oranı %2,9 (n=4) iken postoperatif 6. ayda bu oran %26,8 (n=36) idi.
Sonuç: Varikoselektomi sonrası 3. ayda düzelen ve artış gösteren sperm parametreleri 6. ayda da yükselmeye devam etti. Primer enfertilite ile birlikte

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klinik varikoseli olan hastaların yardımcı üreme tekniklerine başvurmadan önce en azından 6 ay sonra sperm parametrelerindeki yükselmeye bağlı olarak yüksek oranda spontan gebelik ihtimali mevcuttur.
Anahtar Kelimeler: Mikroskopik subinguinal varikoselektomi, Spermiyogram, Varikosel

Introduction

Varicocele is a disease that causes the abnormal dilatation of testicular veins and, consequently, impaired spermatogenesis and infertility. It is also known to be the most common correctable cause of male infertility. Varicocele is found in up to 15% of the adult male population and occurs in 35% of men with primary infertility. Animal and human studies have demonstrated that varicocele is associated with a progressive and time-dependent decline in the testicular function. Further damage to the testes can be prevented by varicocele repair, and it will result in a positive outcome of spermatogenesis and increased leydig cell function in a large percentage of men (1). Microsurgical varicocelectomy is the gold standard of surgical treatment for clinical varicocele.

Although sperm parameters have been shown to improve after varicocelectomy, many fertility specialists want to learn the time which is best for improving the semen parameters after surgery (2). Few studies have shown an increase in sperm parameters, especially in patients with severe oligospermia after varicocele surgery (3). Spontaneous pregnancies are observed in patients with varicocele after surgery due to an increase in the sperm parameters. Nevertheless, no exact time has been defined for the maximal sperm parameters after varicocelectomy. The objective of this study is to compare the sperm parameters of patients with primary infertility and varicocele, preoperatively, and at the third and sixth months, postoperatively. This study further aims to determine the spontaneous pregnancy rates at these times.

Materials and Methods

We retrospectively evaluated 134 patients with clinic varicocele who underwent microscopic subinguinal varicocelectomy at our hospital from July 2016 to May 2019. All the patients were infertile couples who had presented at our hospital for urological evaluation including physical examination, semen analysis, and detailed anamnesis. The couples included in the study were those who had not achieved pregnancy despite regular sexual intercourse for at least one year. The obstetrics and gynaecology department evaluated all the female partners. and we excluded all the female causes of infertility. The parameters studied in the males included semen volume, number, motility, and morphology of sperm, preoperatively, and at three and six months postoperatively. The presence of varicocele was diagnosed by a physical examination in a temperature-controlled room at over 23˚C under adequate illumination. Scrotal doppler ultrasound was performed on all the patients to exclude other testicular pathologies (such as tumor, epididymitis). In all the patients, preoperative semen analysis was performed by using two different semen specimens, each obtained by masturbation at least three weeks preoperatively and three and six months after varicocele treatment according to the recommendations of World Health Organization (2010). The duration of sexual abstinence was three to four days in all the patients. The interval between the two sample collections had to be more than seven days and less than three weeks. Semen analysis was performed manually and included the measurement of the volume of ejaculation and determination of sperm concentration, motility, and morphology according to the criteria of World Health Organization (4). We excluded the patients aged more than 40 years, were smokers, having or had hereditary disorders, genetic abnormalities such as Klinefelter syndrome or Y-chromosome microdeletion, primary hormonal disorders, ongoing use of medication that may affect fertility, subclinical varicocele, recurrent varicocele, complications of testicular atrophy, a history of testicular tumor and chemotherapy-radiotherapy, or azoospermia (obstructive or non-obstructive).

Surgical Technique

Subinguinal microsurgical varicocelectomy was performed under general anesthesia with a subinguinal incision of approximately 2-3 cm. First, the spermatic cord was suspended and dissected under microscopic magnification (Leica Microsystems©). Next, the spermatic fascia was incised. Thereafter, the testicular artery and vas were safeguarded. All the internal spermatic veins were ligated. Importantly, testicular lymphatics and the vasal vein were preserved. The testis was delivered, and the external spermatic perforators were ligated. Then, gubernaculum veins were transfixed. Finally, the testis was re-positioned into the scrotum before the closure of wound.

Statistical Analysis

To assess normal distribution, we analyzed all the continuous variables via the Kolmogorov-Smirnov test and histogram. We used the Wilcoxon-Rank test to compare the variables. Importantly, we statistically analyzed the data obtained in the study by using SPSS for Windows version 22.0.

Results

This study included 134 adult patients with clinical varicocele. The mean age of the patients was 26.2 years (range: 20-38 years). No patient had any systemic disease or a history of testicular surgery. The preoperative physical examination revealed grade 1, grade 2, and grade 3 varicocele diagnosed in 14 (10.4%), 18 (13.4%), and 102 (76.1%) patients, respectively. Unilateral varicocele was determined in 110 (82%) patients, whereas bilateral varicocele was determined in 24 (18%) patients (Table 1). All the patients underwent microscopic subinguinal varicocelectomy operation under general anesthesia. The mean surgery time was 26.14 mins (range: 21-40 mins). None of the patients had perioperative or postoperative complications related to general anesthesia. Hydrocele not requiring surgical intervention was determined in 12 patients, epididymitis-orchitis was resolved with antibiotic therapy in 6 patients, and an allergic reaction to the skin suture was determined in one patient, which was corrected by removing the suture (Table 2). Semen volume, number, fast forward motion (A), and slow forward motion (B) values were compared, preoperatively, and at three and six months postoperatively. A statistically significant increase was observed in all the sperm parameters in the postoperative third and sixth months as compared to the preoperative period ($p<0.001$). The number of sperm and sperm movements A and B were statistically higher in the sixth month as compared to the postoperative third month ($p<0.001$). There was no statistically significant difference between the semen volume and morphology ($p>0.05$) (Table 3). Spontaneous pregnancy was observed in 4 couples (2.9%) in the first 3 months and in 32 couples (23.8%) between the 3rd and 6th months. Thus, spontaneous pregnancy was observed in 36 couples at the rate of 26.8% in the first 6 months.

Table 1. Varicocele data of study population

Varicocele		**patients (n=134)**	**%**
Varicocele grade	Grade 1	14	10.4
	Grade 2	18	13.4
	Grade 3	102	76.1
Varicocele side	Unilateral	110	82
	Bilateral	24	18

Table 2. Complications

Complications	**Patients (n)**
Hydrocele	12
Epididymitis-orchitis	6
Allergenic reaction	1

Discussion

The aim of this study is to determine the spontaneous pregnancy rate and difference in the sperm parameters in the third and sixth months after surgery in patients with varicocele and primary infertility, who wanted to have children. Varicocele, which is the most common cause of correctable male infertility, is detected in high rates among infertile couples. Patients believe that the results of treatment will be long-lasting and they may also want assisted reproductive techniques. Varicocelectomy is highly cost-effective, but it would be better for the patients to wait for six months before applying for assisted reproductive techniques. The results of this study showed that surgery was effective both in the third and sixth months postoperatively in increasing both the sperm parameters and the spontaneous pregnancy rate in patients with primary infertility and varicocele.

Few studies have shown the time when spermatogenesis improves after varicocelectomy. Al Bakri et al. (2) published a study showing recovery at up to three months in men with oligospermia. However, there was no increase in the sperm parameters in the follow-up after six months (2). Another study by Enatsu et al. (5) showed a positive increase in the sperm count and motility in patients with varicocele and oligospermia with a mean follow-up of 8.2 months. Thomas et al. (3) evaluated patients with severe oligospermia between the third and sixth months after surgery and after six months. They found that the sperm count increased in both the groups (different periods) as compared to the preoperative period, but there was no difference in the sperm quality between three and six months and after six months (3). Postoperative improvements in the sperm parameters have been observed in 95% of cases (6); however, most studies have shown varicocele to have negative effects on spermiogram (7-9).

Our study observed a significant positive difference in the sperm count, motility, and morphology in the postoperative third and sixth months as compared to the preoperative period.

Reports on varicocele and infertility issued by the Practice Committee of the American Society for Reproductive Medicine and the American Urological Association's Male Infertility Best Practice Policy Committee suggest that for couples dealing with infertility in which if there is no proof (or potential cause) of infertility in a woman, the correction of abnormal sperm parameters in the males with varicocele may be considered (10,11). However, the guidelines of the European Association of Urology on male infertility found varicocele treatment for pregnancy to be controversial (12). The National Institute for Health and Clinical Excellence clinical guideline on fertility does not recommend varicocele surgery for men in the treatment of infertility because it does not increase the pregnancy rates (13).

Table 3. The comparison of pre and postoperative results of sperm analysis

	Preoperative	Postoperative third month	Postoperative sixth month	p^1	p^2	p^3
Semen volume (mL)	2.32±0.5	2.35±0.4	2.39±0.45	0.6	0.25	0.48
Sperm number (million/mL)	13±6.4	17.7±8.4	27.8±7.8	<0.001	<0.001	<0.001
A fast forward	0.9±1	3±1.4	9.9±3.1	<0.001	<0.001	<0.001
B slow forward	10.5±7.2	20.4±4.9	23.1±3.5	<0.001	<0.001	<0.001
Sperm morphology	1.1±0.9	4.5±1.1	4.6±1.2	<0.001	<0.001	0.16

p^1: Preoperative vs postoperative third month, p^2: Preoperative vs postoperative sixth month, p^3: Postoperative third month vs postoperative sixth month

Early studies showed that sperm parameters and pregnancy rates increased after varicocelectomy. Schlesinger et al. (14) reported that the semen quality increased in 70%, especially sperm density, and spontaneous pregnancy rates increased from 30% to 60%. In a study conducted by Marmar and Kim (15), 186 male patients who underwent varicocele surgery had a one-year spontaneous pregnancy rate of 36%, whereas the pregnancy rates of 19 patients with varicocele receiving medical treatment was 16%. In another study conducted by Madgar et al. (16), 25 patients who underwent varicocelectomy had a one-year pregnancy rate of 60%, whereas 20 male patients treated conservatively had a pregnancy rate of 10%. Marmar et al. (17) reviewed five studies with two randomized controlled trials and three observational studies, and selected infertile men with palpable varicoceles and abnormal sperm parameters. The odds of spontaneous pregnancy after varicocelectomy as opposed to conservative management were 2.6-2.9. That study suggested that varicocelectomy had beneficial effects on fertility in the selected patients (17). None of those studies investigated the third- and sixth-month pregnancy rates. This study found an increase in all the sperm parameters and pregnancy rates in the third and sixth months. The spontaneous conception rate was 2.9% (four patients) in the first third months, and 23.8% (32 patients) between the third and sixth months. The total pregnancy rate in the first six months was 26.8% (36 patients).

Spontaneous pregnancy rates increased in the third and sixth months due to the increase in the sperm parameters. Although there was a difference in the sperm count and sperm slow motion between the two periods, the difference between the fast-forward sperm movement increased significantly in the 6th month (Figure 1).

Varicocelectomy has been shown to be a more advantageous procedure than assisted reproductive techniques in terms of cost-effectiveness. Penson et al. (18) reported that intrauterine insemination (IUI) costs $50,000 more than varicocelectomy per additional live birth. Considering the positive changes observed in the sperm parameters after varicocele surgery, its contribution to the national economy should not be ignored. Our study observed high rates of spontaneous pregnancy even in the first 6 months in couples who wanted to have children.

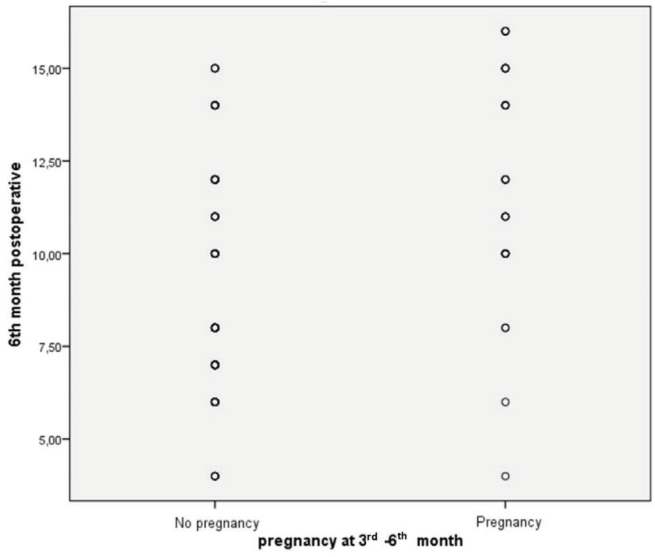

Figure 1. Determination of spontaneous pregnancy rates with fast-forward sperm motions between third month and third-sixth months

Therefore, the surgical correction of varicocele before assisted reproductive techniques would be economically beneficial.

Many patients with varicocele may still require assisted reproductive techniques for pregnancy. As the sperm parameters will improve after varicocele surgery, the ejaculate sample to be used in IUI will be of better quality and the results will be better. If IUI fails, then intrastoplasmic injection as an alternative treatment will increase the chances of success and avoid the invasive procedures [such as micro-testicular sperm extraction (TESE)]. Some studies have shown that the use of ejaculated sperm is technically easier and provides better results than the sperm harvested from TESE (15,19). Additionally, it avoids the risk of ICSI cycle cancellation by an unsuccessful TESE or the use of donor backup (20).

Study Limitations

The primary limitations of this study are the small sample size and retrospective design. In addition, it was not possible to obtain full information about the lifestyle of patients (medical treatment for infertility, smoking, sports, etc) either pre- or postoperatively. Therefore, there was no evaluation of any positive or negative effects of lifestyle changes on

sperm parameters. More studies should also be conducted for evaluating the effects of varicocelectomy to pregnancy after a long period. Furthermore, the age and fertility history of the female partner was not considered.

Conclusions

The observations of this study suggest an increase in the sperm count, morphology, and motility after microscopic subinguinal varicocelectomy in patients with clinical varicocele. These changes were observed in the spermiogram performed in the third month after surgery, but more positive results can be obtained in the spermiogram in the sixth month. For these patients to obtain a spontaneous pregnancy, waiting for at least six months for assisted reproductive techniques would be more effective.

Ethics

Ethics Committee Approval: It was received for this study from the ethics committee of Trabzon Karadeniz Medicalpark Hospital (no: 229/2020).

Informed Consent: Written informed consent was obtained from the all patients before the surgery.

Peer-review: Externally and internally peer-reviewed.

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Does Masturbation Frequency Effect Sperm Parameters?

Mastürbasyon Sıklığı Sperm Parametrelerini Etkiler mi?

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What's known on the subject? and What does the study add?

To date, no extensive research has been conducted on the relationship between masturbation and infertility directly in studies. We found that the frequency of masturbation during the teenage years may be related to infertility.

Abstract

Objective: To evaluate the relationship between male infertility and masturbation habits of patients who cannot provide a sperm sample.
Materials and Methods: A total of 48 male patients aged 22-44 years who presented with complaints of primary infertility were included in the study. Patients who met the study criteria were requested to provide a spermiogram sample after a 3-7-days abstention from sexual relations. Sperm samples were surgically taken from patients who could not provide a sperm sample and pathology results of the samples from the testes were assessed. Patients with a surgically obtained sperm sample were named Group 1 and patients with no live cells found group 2. According to the parametric conditions of the data, the Independent Samples t-test or the Mann-Whitney U test were applied ($p<0.05$).
Results: The rate of obtaining a sperm sample was statistically significantly higher in the group with a higher monthly frequency of masturbation. No significant difference was seen between the groups with respect to age ($p=0.81$). There was a statistical significant difference between the groups with respect to the number of masturbations per month (group 1: mean 4.0 ± 1.3, group 2: mean 1.9 ± 0.9) ($p<0.001$).
Conclusion: The results of this study showed that there could be a relationship between the frequency of post-adolescent masturbation and azoospermia, although this relationship is not scientifically explained.
Keywords: Azoospermia, Infertility, Masturbation

Öz

Amaç: Sperm örneği veremeyen hastaların mastürbasyon alışkanlığının erkek enfertilitesi ile olan ilişkisini değerlendirmektir.
Gereç ve Yöntem: Çalışmaya primer enfertilite şikayetiyle başvuran 22-44 yaş arası toplam 48 erkek hasta dahil edildi. Uygun koşullar sağlanıp hastalardan 3-7 günlük cinsel perhiz sonrası spermiyogram örneği istendi. Sperm örneği veremeyen hastalardan cerrahi yollarla örnek elde edildi ve testisten patolojik örnek yollanarak sonuçları değerlendirildi. Cerrahi işlem sonrası sperm örneği bulunan hastalar grup 1, canlı hücre bulunamayan hastalar grup 2 olarak sınıflandırıldı. Verilerin parametrik durumuna göre independent samples t-test veya Mann-Whitney U test uygulandı ($p<0,05$).
Bulgular: Her iki grup karşılaştırıldığında aylık mastürbasyon sayısı yüksek olan gruptaki hastalardan sperm elde etme oranı daha yüksek bulunmuş olup istatiksel olarak anlamlı fark tespit edilmiştir. Gruplar arasında yaş açısından anlamlı fark gözlemlenmedi ($p=0,81$), ancak gruplar arasında aylık mastürbasyon sayısı (grup 1: ort. $4,0\pm1,3$, grup 2: ort $1,9\pm0,9$) açısından anlamlı fark gözlemlendi ($p<0,001$).
Sonuç: Bilimsel olarak açıklanmış olmasa da yapılan çalışmada ergenlik sonrası yapılan mastürbasyon sıklığı ile azospermi arasında ilişki olabileceği görülmüştür.
Anahtar Kelimeler: Azospermi, İnfertilite, Mastürbasyon

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Introduction

Infertility is defined as no pregnancy after at least 12 months of regular sexual relations according to the World Health Organization. It is seen in 10%-15% of married couples and in 30%-50% of these, the pathology is usually associated with the male (1,2). Azoospermia is a condition in which there is no sperm in seminal fluid, this is seen in 1% of the male population, and has been reported to be at the rate of 15% in infertile males (3,4). Semen analysis is required after abstention from sexual relations for 2-3 days when assessing male infertility (5). After putting in place all favorable conditions, if the patient is unable to provide an ejaculated sperm sample, the micro testicular sperm extraction (TESE) or testicular sperm aspiration (TESA) operation can be carried out. The micro TESE operation is a surgical operation first described by Schlegel in 1998 for patients with non-obstructive azoospermia (6,7).

Masturbation is the stimulation of the erogenous zones of the sexual organs generally to the point of orgasm (8). Masturbation has been reported to have extensive effects on the mental status of women, with many authors claiming that frequent masturbation increases depressive symptoms independent of a decreased frequency of penile-vaginal coitus (9,10). However, to the best of our knowledge, there is no study in literature of male masturbation. While a healthy sexual penile-vaginal relationship may be achieved in a physical and physiological aspect, frequent masturbation has a negative effect on a healthy sex life (11).

From a comprehensive screening of literature, no study was found to have studied the frequency of masturbation as a factor which could cause azoospermia. In addition, there is insufficient information related to the effect of masturbation habits on patients who cannot provide a spermiogram sample.

The aim of this study was to evaluate the masturbation habits of patients with primary infertility and patients who could not provide a spermiogram sample. The null hypothesis of the study was that there would be an association between patients who cannot provide a spermiogram sample and the masturbation habits of those patients.

Materials and Method

The study was approved by Ethical Committee (approval no: 122/2020). A total of 48 patients, aged 22-44 years, who presented at the urology polyclinic between 2014 and 2019 with the complaint of primary infertility and could not provide a sperm sample despite the provision of appropriate conditions in the hospital were included in the study. The patients were classified according to their level of education. A retrospective evaluation of the anamneses, procedures applied, and results of the patients included in the study was made. A spermiogram sample was requested from the patients after a period of 3-7 days abstinence from sexual relations. Laboratory values of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and testosterone was recorded. Patients were excluded from the study if they were using any drugs that could cause azoospermia, if they had any disease (hormonal or systemic) or were engaged in any occupation that could affect the sperm parameters, had atrophic testes or unilateral testis, were smokers, had any disease that could cause erectile dysfunction or ejaculation problems, or had never masturbated.

To motivate the patients who were unable to provide a sample on the first visit, they were called a second time and a sample requested. Those who could not provide a sample for unknown reasons underwent a micro TESA operation or percutaneous TESA. The sperm freezing procedure was explained to the patients and the type of operation was decided by the patient. MicroTESE was performed on 34 patients and TESA on 14 patients. Informed consent was gotten from all the patients. Both procedures were performed under general anesthesia and samples sent to the laboratory for evaluation at the same time, the procedure continued bilaterally with the results. In patients where no sperm was found, pathological sampling was applied.

Following the surgical procedures, patients with a sperm sample were classified as group 1, and patients with no live cells determined were classified as group 2. The anamnesis taken from each patient was reviewed again and patients with insufficient information were called by phone and were asked the question, "how many times do you masturbate a month?." Responses were evaluated and monthly masturbation frequency was compared between the two groups. The patients applied with micro TESE or TESA were azoospermic and the specimens obtained were evaluated pathologically.

Statistical Analysis

Variables were shown as mean ± standard deviation, median, and range values. Conformity of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test and histogram. Then, according to the parametric conditions, the Independent Samples t-test or the Mann-Whitney U test were applied. All statistical analyses were made using SPSS version 20.0 software (Chicago, IL, USA). A value of $p<0.05$ was accepted as statistically significant.

Results

Group 1 comprised of 21 patients with a mean age of 30.3±5.3 years (range: 23-42 years), and reported mean frequency of masturbation as 4.0±1.3 times per month (range: 2-6). Group 2 comprised of 27 patients with a mean age of 29.9±5.9 years

(range: 21-44 years), and reported masturbation frequency of mean 1.9±0.9 times per month (range: 0-4) (Table 1). The marriage periods of the two groups were 17.8 and 18.1 months respectively. When the two groups were classified according to the level of education, no significant difference was observed between the groups.

Before the procedure, scrotal ultrasonography was done to all patients. No difference was observed between the groups in respect of testis size and blood hormone levels (FSH, LH, prolactin, testosterone). No significant difference was observed between the groups with respect of age (p=0.81). A statistically significant difference was determined between the groups with respect to the mean number of masturbations per month (p<0.001).

The specimens taken from the azoospermic patient who underwent the microTESE or TESA were sent for pathological examination. The results were evaluated as Sertoli cell only in 44 testis units, testis tissue showing hypospermatogenic activity in 30 units, and atrophic testis tissue with germ cells present but no spermatogenic activity in 22 units (Table 2).

Discussion

The results of the study confirmed the null hypothesis that there is an association between patients who cannot provide a spermiogram sample and the masturbation habits of those patients. Although there was no significant difference between groups 1 and 2 with respect to age, a statistically significant difference was seen with respect to the frequency of masturbation before marriage. The incidence of azoospermia differs according to genetic differences, geographic region, and type of employment, lifestyle, and dietary habits (12). Genetic causes resulting in infertility include Klinefelter syndrome, Y chromosome anomalies, and single gene anomalies. There may also be hormonal causes such as hypogonadotropic hypogonadism, anatomic reasons or orchitis, trauma or tumor surgery, cancer, radiotherapy or chemotherapy (13,14). When the patients included in the current study were re-evaluated, these types of factors were not seen in any of the patient.

In a study by Ramadan et al. (15), 412 patients who presented with the complaint of infertility were separated into 2 groups. Group 1 comprised of patients who were not able to provide a sperm sample at the hospital for various reasons, but could give a sample at home during sexual relations or with the aid of vibrator stimulus, and group 2 included patients who had no difficulty in providing a sperm sample. The sperm concentration, sperm motility and normal sperm functions of group 1 patients were lower than those of group 2, but not to a statistically significant level. The duration of infertility was determined to be longer in group 1 than in group 2, and the partners of the patients in group 1 stated that the patients experienced extreme anxiety when providing the sample (15).

In a study by Saleh et al. (16), it found that sperm concentration and motility was reduced in sperm samples provided under stress and anxiety in the hospital. It was observed in our clinic that patients who could not provide a sperm sample in the hospital environment were generally anxious and lacking in self-confidence. The majority of these patients did not attend the clinic with their spouse, but came with their mother, father or sibling and were not able to speak about their problems themselves. The vast majority of patients who were not azoospermatic but could not provide a sample for various reasons (anxiety, hygiene, excitement, etc) attended the clinic alone or with their spouse. When sexual activity was questioned in the anamnesis, conflicting responses were obtained from patients who attended without their partner and an objective result could not be obtained. In some studies, male infertility has been determined to cause severe sexual dysfunction between couples, and it has been reported that there may be an association between male sexual dysfunction and reduced sperm motility (17). Pathologies accompanying ejaculation disorders such as premature ejaculation, non-ejaculation, retrograde ejaculation and erectile dysfunction may cause male infertility. Furthermore, infertility may be caused by some systemic diseases and the drugs used to treat those diseases (18).

Table 2. Evaluation of the pathological results of the patients

Pathological result	microTESE	TESA
Sertoli cell only syndrome	28 units	16 units
Hypospermatogenetic activity	24 units	6 units
Atrophic testis	16 units	6 units

TESA: Testicular sperm aspiration

Table 1. Data of the patients included in the study

	Group 1 (n=21)			Group 2 (n=27)			p
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
Age (year)	30.3±5.3	30	23-42	29.9±5.9	29	21-44	0.81
Number of masturbations in a month	4.0±1.3	4	2–6	1.9±0.9	2	1-4	<0.001

SD: Standard deviation

Study Limitations

There were some limitations of this study. The number of patients included in the study was relatively low. When the anamneses were evaluated, most patients had not given sufficient information about sexual life, erectile functions and masturbation habits because of embarrassment or unwillingness to answer, so objective results could not be obtained. As some information was received some patients over the telephone, the responses may not have been clear. There was no information about the frequency of sexual intercourse before and after marriage. When the study results were evaluated, it was clearly seen that the patients who could not provide a spermiogram sample had masturbated very infrequently. There is a need for further more extensive studies with more patients to evaluate different parameters.

Conclusion

According to the observations made during this study, it was seen that the majority of patients who could not give a sperm sample and who did not have sperm after surgery, also had communication problems. Even though the effect of frequent or infrequent masturbation on azoospermia has not yet been proven, it was concluded from the results of this study that patients with a low frequency of masturbation were azoospermic.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethical Committee of Trabzon Medicalpark Karadeniz Hospital (approval no: 122/2020).

Informed Consent: Informed consent was gotten from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Role of Resveratrol on the Effect of Resistin in Rabbit Corpus Cavernosum

Resistinin Tavşan Korpus Kavernosumundaki Etkisi Üzerine Resveratrolün Rolü

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What's known on the subject? and What does the study add?

Resistin has been shown to disrupt endothelium-dependent relaxation responses in *in vitro* experimental studies in vessels via increasing reactive oxygen species, decreasing nitric oxide activity and increasing synthesis of endothelin 1. Resveratrol has been shown to prevent and restore vascular and penile endothelial dysfunction. Resveratrol has also been reported to reduce elevated resistin levels in the white adipocytes. Four hours incubation period of resistin did not impair penile endothelial functions but tend to increase nicotinamide adenine dinucleotide phosphate oxidase activity. Resveratrol administration caused a significant decrease in nicotinamide adenine dinucleotide phosphate oxidase activity in the penile tissue.

Abstract

Objective: Resistin is an important factor in the pathogenesis of obesity-induced insulin resistance and endothelial dysfunction-mediated cardiovascular system diseases. Endothelial dysfunction is one of the most important causes of erectile dysfunction. Polyphenol resveratrol has several pharmacological functions, such as preventing endothelial dysfunction and inducing endothelium-dependent vascular relaxation via redox regulation and nitric oxide production. The present study tested the hypothesis that resveratrol restores endothelium-mediated responses that are disrupted by resistin.

Materials and Methods: After a 24 h incubation period of tissues with resistin, endothelium-dependent and independent relaxation responses and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase level were evaluated in the presence and absence of resveratrol in rabbit corpus cavernosum (CC).

Results: Resistin caused no impairment in the endothelium-dependent and -independent relaxation responses. In the presence of resistin, NADPH oxidase levels increased by 28% in the CC tissues. However, the difference was not statistically significant. Resveratrol administration caused a significant decrease in NADPH oxidase activity in the resistin-treated group compared with the resistin-alone group.

Conclusion: Resistin caused no changes in the functional responses of CC and NADPH oxidase activity, but resveratrol incubation significantly reduced NADPH oxidase activity in penile tissue. Based on the results of the study, resveratrol may be a treatment target under conditions in which NADPH oxidase activity is increased in penile tissue. In line with the results of this study, the effect of resistin on CC must be investigated at different concentrations and incubation times.

Keywords: Resveratrol, Resistin, Erectile dysfunction, Corpus cavernosum, Rabbit

Öz

Amaç: Resistin, obezite ile indüklenen insülin direnci ve endotelyal disfonksiyon aracılı kardiyovasküler sistem hastalıklarının patogenezinde önemli bir faktör olarak bilinmektedir. Endotel disfonksiyonu, erektil disfonksiyonun en önemli nedenlerinden biridir. Polifenol resveratrol, endotel disfonksiyonu önlemek, redoks regülasyonu ve nitrik oksit üretimini sağlayarak endotel bağımlı vasküler gevşemeyi indüklemek gibi çeşitli farmakolojik fonksiyonlara sahiptir. Bu çalışma ile, resistin ile bozulan endotel aracılı yanıtları resveratrol düzeltir, hipotezi test edilmiştir.

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Gereç ve Yöntem: Dokuların resistin ile 24 saatlik inkübasyon periyodunun ardından, tavşan korpus kavernosumunda (KK), resveratrol varlığında ve yokluğunda, endotel bağımlı ve bağımsız gevşeme yanıtları, nikotin amid adenin dinükleotid fosfat (NADPH) oksidaz seviyesi değerlendirildi.
Bulgular: Resistin, endotel-bağımlı ve bağımsız gevşeme yanıtlarını bozmadı. Resistin varlığında, NADPH oksidaz seviyeleri CC dokularında %28 arttı, ancak fark istatistiksel olarak anlamlı değildi. Resveratrol varlığında resistin uygulanan gruptaki NADPH oksidaz aktivitesinde, tek başına resistin grubuna oranla, anlamlı derecede azalma oldu.
Sonuç: Resistin, KK'de fonksiyonel yanıtlar ve NADPH oksidaz aktivitesinde herhangi bir değişikliğe neden olmadı, ancak resveratrol inkübasyonu penil dokudaki NADPH oksidaz aktivitesini anlamlı olarak azalttı. Çalışmanın sonuçlarına dayanarak, resveratrolün, penil dokuda NADPH oksidaz aktivitesinin arttığı koşullarda bir tedavi hedefi olabileceği düşünülmektedir. Bu çalışmanın sonuçları doğrultusunda, resistinin KK üzerindeki etkisinin farklı konsantrasyonlarda ve farklı inkübasyon sürelerinde araştırılması gereklidir.
Anahtar Kelimeler: Resveratrol, Resistin, Erektil disfonksiyon, Korpus kavernosum, Tavşan

Introduction

Resistin, a hormone released from adipose tissue, is associated with increased endothelial dysfunction in types 1 and 2 diabetes, coronary artery disease, and atherogenic dyslipidemia (1). In clinical and experimental studies, increased resistin level was also associated with obesity (2). *In vitro* experimental studies, in which resistin concentration was equivalent to high resistin concentration in humans, showed disrupted endothelium-dependent relaxation responses in vessels, resulting in endothelial dysfunction (3,4). Resistin causes endothelial dysfunction by increasing the reactive oxygen species and decreasing nitric oxide (NO) activities (4), promoting the synthesis of endothelin-1 (ET-1) a vasoconstrictor substance (5). Risk factors, such as hyperlipidemia, obesity, smoking, and high blood pressure, cause endothelial dysfunction-mediated erectile dysfunction (ED) (6). The relationship of resistin and ED has not been demonstrated. One clinical study reported an increase in blood resistin levels in patients with ED accompanying type 2 diabetes (7).

Resveratrol as an antioxidant flavonoid has highly targeted molecular effects on the endothelium. Resveratrol increases endothelial NO production through upregulation of endothelial nitric oxide synthase (eNOS) expression, enhancement of eNOS activity, and prevention of eNOS uncoupling (8). Resveratrol prevents vascular and penile endothelial functions in hypercholesterolemic rabbits (9). In addition to its effect on the endothelium, resveratrol reduces elevated resistin levels due to obesity (10). The present study was designed to answer the following questions:

1. Does resistin impair *in vitro* functional responses in rabbit corpus cavernosum (CC) tissue?

2. If so, does resveratrol restore this effect?

Material and Methods

Animals, Tissue Preparation, and Study Protocols

This study was approved by the Animal Care and Investigational Committee (22/2016) in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the United States NIH. Adult New Zealand male rabbits weighing 2-3 kg were housed individual in identical cages in an air-conditioned room under a 12 h light–dark cycle. The animals were sacrificed with 60 mg/kg thiopental. The penis was rapidly removed and placed in a cold (+4°C) Krebs solution composed of the following (mM): 136.9 NaCl, 2.7 KCl, 0.5 KH_2PO_4, 1.8 $CaCl_2$, 0.6 $MgSO_4$, 11.9 $NaHCO_3$, and 11.5 glucose; pH: 7.4. After removal of the tunica albuginea and corpus spongiosum tissue, the CC was divided into two pieces longitudinally. Two or three cavernosal strips of approximately equal size (3×3×4 mm^3) were obtained from each part of the cavernosum. The incubation protocol included three different conditions: a) incubation of CC tissues in Krebs solution with for 24 h at 4°C as the control group, b) incubation of CC tissues in Krebs solution containing 40 ng/mL resistin for 24 h at 4°C as the resistin group, and c) incubation in Krebs solution containing 40 ng/mL resistin for 24 h and added with 30 µM resveratrol in the last 2 h of incubation period at 4°C as resistin + resveratrol group. The *in vitro* treatment conditions for resistin and resveratrol were based on previously published doses (4,11).

In Vitro Organ Bath Studies

After 24 h of incubation period, the CC strips were suspended between two stainless steel hooks in organ baths containing 10 mL Krebs solution. The solution was kept at 37°C and gassed continuously with a 95% O_2 and 5% CO_2 gas mixture at pH 7.35. The CC was mounted under 1 g tension. The tissues were washed with Krebs solution every 15 min for 90 min. After an equilibrium period at resting tension, we conducted a viability protocol as follows. CC tissues were contracted with 120 mM potassium chloride (KCl) at the beginning and end of the study protocol. The tissues whose end KCl contraction response decreased by more than 10% compared with the initial KCl contraction response were excluded. KCl-induced contraction responses obtained after 24 h of incubation period were also compared with obtained from tissues immediately contracted with KCl after sacrifice to evaluate the effect of incubation condition on the tissue viability.

Following the viability protocol, CC tissues were contracted to ~80% of their maximal contractions via the addition of 30 mM phenylephrine (Phe). Then, relaxation dose-response curves were constructed by the addition of cumulative concentrations of acetylcholine (Ach) (10^{-8}-10^{-5} M) and sodium nitroprusside (SNP) (10^{-9}-10^{-6} M) to evaluate the endothelium-dependent and -independent relaxation. Dose-response curves were obtained with cumulative doses of ET-1 (10^{-11}-10^{-7} M) to evaluate the endothelium-dependent contraction responses. Isometric tensions were recorded with an amplifier system (MP30 BIOPAC Systems, Santa Barbara, CA, USA) on a computer by using the BIOPAC computer program.

Measurement of NADP+ / NADPH Concentration

Following the incubation period, the tissues were frozen in liquid nitrogen and were used in the working day. NADP+ / NADPH Assay Kit (Abnova, KA1663) was used to determine NADP+ / NADPH concentration in cavernosal samples. Briefly, the concentration of NADP+ / NADPH was determined following the manufacturer's protocol.

Chemicals

The chemicals used in this study were as follows: resveratrol (Biovision), dimethyl sulfoxide (DMSO; Merck), ET-1; diphenyliodonium chloride; Ach; SNP; Phe (Sigma-Aldrich); recombinant human resistin (ab73252) (Abcam), Phe, Ach, ET-1, and SNP stock solutions prepared in distilled water. Resveratrol stock solution was prepared with 0.01% DMSO. The drugs were prepared as stock solutions and diluted on the working day.

Statistical Analysis

Relaxation responses to Ach and SNP were calculated based on the percentage of Phe contraction. Contraction responses to ET-1 were calculated based on the percentage of KCl contraction. The sensitivity to agonists was assessed by potency (pD2)=-logEC50 (M). Data were expressed as mean ± standard error of the mean. Statistical analysis was performed by one-way analysis of variance, post-hoc Tukey's test in the case of three groups, and Student's t-test in the case of two groups (GraphPad, San Diego, CA, USA). P-values <0.05 were considered statistically significant.

Results

Evaluation of Functional Responses of CC Tissue in *İn Vitro* Organ Bath

To evaluate the effect of 24 h incubation period on tissue viability, we applied 120 mM KCl to CC tissues which were suspended in organ bath on the same day (n=8) and 24 h after sacrifice (n=8). When we compared the KCl-induced contractions of both groups, no statistically significant difference was observed between them (0 h, 1354 mg; 24 h, 2180.5 mg) (p>0.05).

To evaluate tissue viability on the study day, we applied 120 mM KCl to CC tissues at the beginning and end of the organ bath experimental protocol. The mean of KCl-induced contractile responses of three groups obtained at the beginning of the study protocol (1572.25 mg) were not statistically different from those obtained at the end of the study protocol (1727.46 mg) (p>0.05).

Evaluation of Ach-mediated Relaxation Responses

The dose-response curves of Ach were obtained using CC tissue to evaluate the effect of resistin on endothelium-dependent relaxation in the absence and presence of resveratrol. In the control group, Ach (10^{-8}-10^{-5} M) elicited a concentration-dependent relaxation with a maximal relaxation (Emax) value of 79.03%±8.18% and a pD_2 value of 6.24±0.23. In the resistin group, Ach caused relaxation with an Emax value of 82.83%±10.91% and a pD2 value of 6.39±0.32. Ach caused relaxation with an Emax value of 68.71%±11.81% and a pD2 value of 6.17±0.49 in the resistin and resveratrol group. No

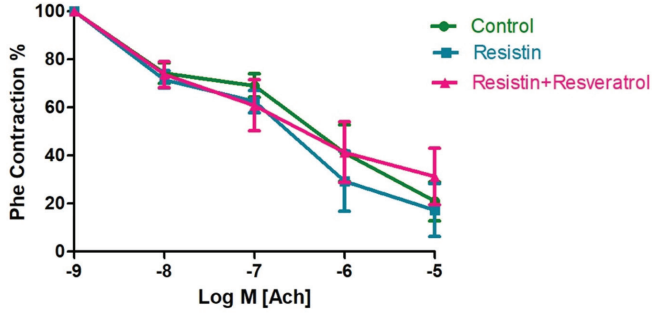

Figure 1. Ach-mediated relaxation responses: control, resistin, and resistin + resveratrol group (each group included n=8 strips). One-Way ANOVA and post-hoc Tukey's test were used. p<0.05 was considered significant

Table 1. Emax and contraction responses and pD2 of the agonists in rabbit corpus cavernosum tissues

	Acetylcholine		Endothelin-1		Sodium nitroprusside	
	Emax %	pD_2	Emax %	pD_2	Emax %	pD_2
Control grup	79.03±8.2	6.24±0.2	99.54±15.7	8.01±0.4	161.3±13.2	8.37±0.4
Resistin group	82.83±10.9	6.17±0.5	77.8±5.5	7.48±0.1	146.2±16.9	8.63±0.4
Resistin + resveratrol group	68.71±11.8	6.17±0.5	77.58±11.3	7.41±0.2	150.8±13.2	8.58±0.5

Control, resistin and resistin + resveratrol groups (each group included n=7 strips), One-Way ANOVA post-hoc Tukey test was used, p<0.05 was considered significant

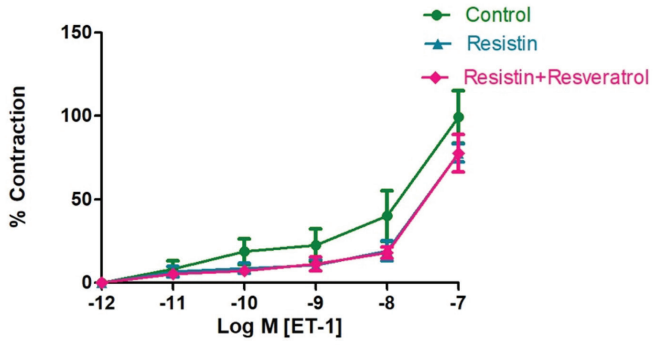

Figure 2. Endothelin-1-mediated contractile responses: control, resistin, and resistin + resveratrol group (each group included n=8 strips). One-Way ANOVA and post-hoc Tukey's test were used. p<0.05 was considered significant

significant difference was observed between the groups. Resistin alone and the presence of resveratrol did not augment the efficacy and pD2 of Ach (p>0.05) (Figure 1).

Evaluation of ET-1-mediated Contraction Responses

In the control, resistin, and resistin + resveratrol groups, ET-1 caused dose-dependent contraction responses. Maximum contraction responses obtained with ET-1 were 99.54%±15.67%; 77.8%±5.53%; 77.58%±11.26%. No significant difference was noted in the Emax values of the groups (p>0.05) (Figure 2). When pD2 values were compared, no significant difference was observed between three groups (8.01±0.35, 7.48±0.12, and 7.41±0.16) (p>0.05).

Evaluation of SNP-mediated Relaxation Responses

Cumulative doses of SNP (10^{-9}-10^{-6} M) were administrated to the organ bath to evaluate endothelium-independent relaxation. SNP elicited a concentration-dependent relaxation with Emax values of 161.3%±13.17% in the control group, 146.2%±16.85% in the resistin group and 150.8%±13.15 % in the resistin + resveratrol group (Figure 3). pD_2 values were 8.37±0.42, 8.63±0.37, and 8.58±0.45 in control, resistin, and resistin + resveratrol groups, respectively. No significant difference was observed between the groups for both Emax and pD_2 values (p>0.05).

Evaluation of NADP+ / NADPH Measurement in CC Tissues

The NADP+ / NADPH ratio increased by 28% in the resistin group, although no statistical difference was observed. However, resveratrol incubation caused a significant decrease in NADP+ / NADPH ratio compared with the resistin group (p<0.05) (Figure 4).

Discussion

In the present study, resistin did not impair endothelium-dependent and -independent relaxation responses. In the

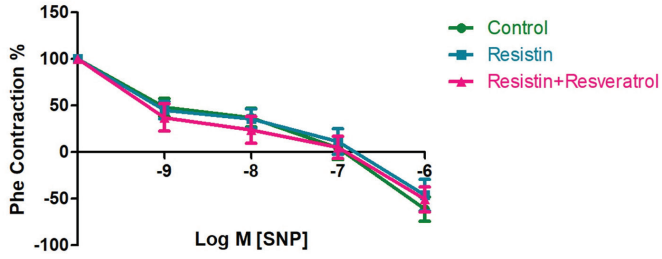

Figure 3. Sodium nitroprusside-mediated relaxation responses: control, resistin, and resistin + resveratrol group (each group included n=8 strips). One-Way ANOVA and post-hoc Tukey's test were used. p<0.05 was considered significant

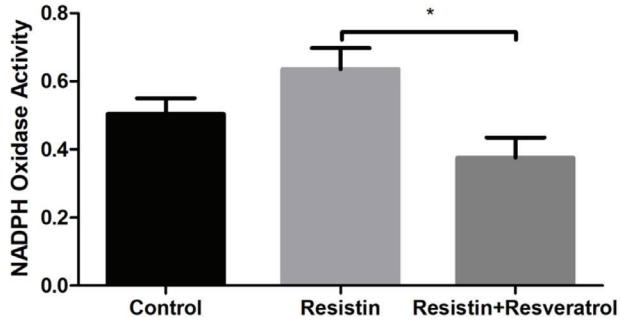

Figure 4. NADP+ / NADPH measurement: control, resistin, and resistin + resveratrol groups (each group included n=7 strips). One-Way ANOVA and post-hoc Tukey's test were used. p<0.05 was considered significant

NADP: Nicotinamide adenine dinucleotide phosphate

presence of resistin, NADPH oxidase levels increased in the CC tissue. However, the difference was not statistically significant. Resveratrol administration caused a significant decrease in NADPH oxidase activity in the resistin-treated group compared with the resistin-alone group.

The integrity of endothelium in cavernous tissue is important for erection physiology. Endothelium-released NO has a major role among many mediators in the erection. NO activates a cyclic guanosine monophosphate (cGMP)-dependent cellular mechanism in the smooth muscle cell and causes relaxation of smooth muscles. eNOS, which is involved in the synthesis of endothelium-derived NO in penile tissue, is activated in two ways. The initial phase of erection occurs via binding of Ach to the muscarinic receptor, which leads to Ca/calmodulin-induced activation of the eNOS and NO synthesis. NO-dependent relaxation in cavernous smooth muscle induces blood flow shear forces that cause eNOS phosphorylation and activity of the enzyme at resting Ca level. Endothelial dysfunction is one of the leading causes of ED. Chronic diseases causing endothelial dysfunction, such as atherosclerosis, diabetes, and metabolic syndrome, are accompanied by a high rate of ED. Impaired NO bioactivity has also been supported by various animal models of hypertension, diabetes, and hypercholesterolemia-induced ED (12).

Resistin is an adipokine that plays a role in the development of insulin resistance and obesity (13). High circulating resistin levels (>40 ng/mL) are related to types 1 and 2 diabetes (14). Resistin has also been found in atherosclerotic tissues (15). Studies linking resistin with vascular dysfunction have investigated the effect of resistin on endothelium-released relaxing factors, such as insulin, bradykinin, and Ach (3,4,16,17). To our knowledge, no study has investigated the *in vitro* effect of resistin on penile tissue. Thus, in the present study, we aimed to investigate the cellular effects of resistin and its derivatives on functional responses of CC. After 24 h of incubation with 40 ng/mL resistin, endothelium-dependent relaxation and contraction responses were assessed by Ach and ET-1 dose-response curves, respectively. Relaxation dose-response curves of SNP were obtained to evaluate the endothelium-independent relaxation. We also investigated the effect of resistin on endothelium-dependent and independent responses of CC in the presence of resveratrol.

In the present study, 24 h of incubation of penile tissues with resistin caused no change in Emax response and pD_2 of Ach. Several studies evaluated the effects of resistin on coronary arteries of different species. One research reported that 10 min incubation with low- and high-dose resistin (10 or 40 ng/mL) did not alter Ach-induced relaxation responses but decreased bradykinin responses without disrupting NO or prostacyclin signaling in dog coronary artery (16). Another study on porcine coronary artery reported a decrease in bradykinin-mediated relaxation responses and an increase in superoxide (O_2^-) anions with 24 h resistin incubation (40 ng/mL) (4). According to the results of these studies, resistin impairs bradykinin-mediated relaxation responses but not Ach in the coronary artery, which is independent of incubation period and dose. However, the *in vitro* effect of resistin on Ach-mediated relaxation was observed in the mouse aorta. Seto et al. demonstrated decreased Ach-mediated relaxation responses in healthy and diabetic mouse aorta after 30 min incubation with 40 ng/mL resistin (3). On the other hand, Lou and colleagues showed that 1 h incubation with 100 ng/mL resistin did not alter Ach-mediated NO responses in mouse aorta but changed insulin-dependent NO responses and reduced eNOS phosphorylation via increasing NADPH oxidase activity and free oxygen radicals (18). In the present study, we observed an increase in NADPH oxidase activity after a 24 h incubation at 40 ng/ml dose, but the difference did not reach statistical significance. According to the literature, resistin responses on endothelium can vary depending on the species of animal, vessel, incubation period, and dose. As the major limitation of our study, regardless of the absence of any effect, the ineffectiveness of resistin cannot be proven given that we have not tested its effect on a different substance that produces endothelial-mediated relaxation at various times and doses.

Resistin's interaction with ET-1, a vasoconstrictor substance, contributes to its effect on vascular tone. In a clinical study, resistin and ET-1 levels correlated with each other in blood samples collected from 76 metabolic syndrome patients (19). In an in vivo study, infusion of 30 mg/h/kg resistin potentiated ET-1-induced enhancement in blood pressure in rats (20). *In vitro* cell culture studies have reported that after a 24 h incubation period, resistin increased ET-1 secretion in endothelial cells (5) but caused no effect on its expression (21). In the present study, based on the finding that resistin exposure to endothelial cells for 24 h leads to an enhancement in ET-1 release, we investigated whether resistin causes alteration in the functional responses of ET-1 in CC. Although in vivo studies have shown that resistin potentiates the vasoconstriction response of ET-1, to our knowledge, no study investigated the effect of resistin on functional responses of ET-1 in vitro. In the present study, ET-1, which was cumulatively tested in CC, produced negligible contraction response in the first doses, whereas the contraction response was observed at 10^{-7} M. Similar dose-response curves were obtained in the presence of resistin without observing changes in the Emax response.

SNP, a NO donor, causes endothelium-independent relaxation response via the cGMP pathway in smooth muscles (22). Several clinical studies stated that a correlation exists between circulating resistin levels and endothelium-independent relaxation responses-induced by SNP (23), although others reported otherwise (24). Kougias et al. (4) reported that resistin caused a significant reduction (11%) in the relaxation response of porcine coronary artery-induced by a single dose of SNP (10^{-6} M). In the present study, the Emax response obtained with the cumulative (10^{-9}-10^{-6} M) addition of SNP was 161% and reduced to 146% in resistin-treated penile tissues. Resistin caused a 12.4% reduction in the SNP Emax response. Although the dose and incubation periods were the same as those in the work of Kougias et al. (4), the difference between Emax responses was not statistically significant. This result may be due to tissue difference.

Resveratrol, which is commonly consumed as a plant in the Mediterranean diet, is associated with a reduced risk of cardiovascular disease (25). Vascular dysfunction is the first step in the emergence of many disease states in the cardiovascular system, and oxidative stress is a key mechanism in the pathogenesis of vascular dysfunction (26). Oxidative stress results from the generation of reactive oxygen species, which is considered as a critical factor in the development of NO bioavailability and ED (26). NADPH oxidase is a key source of O_2^- in the penile tissue (27). In a recent study of our laboratory, the protective effect of resveratrol on ED was shown in hypercholesterolemic rabbit CC (9). Following this study, resveratrol was shown to improve vascular dysfunction in

addition to its protective effect. These effects reduced NADPH oxidase activity and increased the phosphorylation of the domain responsible for the activation of eNOS (28).

Study Limitations

In the present study, resveratrol significantly reduced NADPH oxidase activity in the penile tissues incubated with resistin. However, our findings reveal that although an increase in NADPH oxidase activity was recorded in the resistin-treated group, the finding was not statistically significant. Therefore, we could not confirm that resveratrol reduces the resistin-mediated increase in NADPH oxidase activity. The reduction caused by resveratrol may be due to the NADPH oxidase binding capability. Given the lack of a group incubated with resveratrol only, its direct efficacy on NADPH oxidase activity could not be evaluated, thus limiting our study.

Conclusion

Our findings suggest that the effect of resistin on endothelium-dependent responses and NADPH oxidase activity at different doses and incubation should be confirmed in the penile tissue. The effects of resistin differ depending on the species, and further studies are needed to investigate the relationship between erectile pathophysiology and resistin in human penile tissue. Given the results of this study and those of previous studies conducted in our laboratory, resveratrol may be an alternative treatment target for ED and may serve as guide for future studies.

Ethics

Ethics Committee Approval: This study was approved by the Animal Care and Investigational Committee (22/2016) in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the United States NIH.

Informed Consent: Patient consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.G., S.A., N.D., Design: T.G., S.A., N.D., Data Collection or Processing: T.G., S.A., N.D., Analysis or Interpretation: O.B., Literature Search: T.G., Writing: T.G., N.D.

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

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ORIGINAL RESEARCH
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Which One Is More Effective for Lower Urinary Tract Dysfunctions in Children? Pelvic Floor Contraction or Pelvic Floor Relaxation in Biofeedback Therapy

Alt Üriner Sistem Disfonksiyonlu Çocuklarda Hangisi Daha Etkili Bir Tedavi Yöntemidir? Biofeedback Tedavisinde Pelvik Taban Kasılması veya Pelvik Taban Gevşemesi

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What's known on the subject? and What does the study add?

Biofeedback treatment in children with lower urinary tract dysfunction will be a more effective treatment modality as it determines the biofeedback nature in accordance with the presence of electromyography activity.

Abstract

Objective: The objective of this study is to investigate the results of contraction- and relaxation-based biofeedback (BF) in children with lower urinary tract dysfunction (LUTD).

Materials and Methods: Between 2007 and 2017, we randomly directed children with the diagnosis of LUTD and refractory to standard urotherapy modifications via BF by using two different animations: animation A with relaxation nature BF (RBF) and animation B with contraction nature BF (CBF). The categories of non-response, partial response, and full response were defined as a 0-49% decrease, 50-99% decrease, and 100% decrease in the LUTD Symptom score, respectively. Results of biofeedback using RBF or CBF were compared.

Results: There were 100 and 70 children in the RBF and CBF groups, respectively. Patients with an abnormal voiding pattern (abnormalVP) and a positive electromyography (EMG) activity (positive EMG) had a better resolution with RBF (p=0.001), whereas patients with abnormalVP and a negative EMG activity (negative EMG) had a better resolution with CBF (p=0.039). Despite being statistically insignificant, patients with a normal voiding pattern (normalVP) and positive EMG had a better resolution with CBF (p=0.452), whereas patients with normalVP and negative EMG had a better resolution with RBF (p=0.083).

Conclusion: The EMG activity identifies the BF nature in children with LUTD and abnormalVP. Importantly, positive EMG had better results with RBF, whereas negative EMG had better results with CBF.

Keywords: LUTD, Biofeedback, EMG activity, Voiding pattern, Contraction, Relaxation

Öz

Amaç: Alt üriner sistem disfonksiyonu (AÜSS) olan çocuklarda kasılma ve gevşeme bazlı biofeedback (BF) sonuçlarının araştırılması amaçlandı.

Gereç ve Yöntem: 2007-2017 yılları arasında AÜSS tanısı alan ve standart üroterapi tedavisine dirençli olan çocuklar iki farklı animasyon kullanılarak rastgele BF'ye yönlendirildi: Animasyon A gevşeme niteliğinde BF (RBF) ve animasyon B kontraksiyon niteliğinde BF (CBF) idi. Cevap vermeme, kısmi cevap ve tam cevap, AÜSS'de sırasıyla %0 ila %49 düşüş, %50 ila %99 düşüş ve %100 düşüş olarak tanımlandı. RBF veya CBF kullanan biofeedback sonuçları karşılaştırıldı.

Bulgular: RBF ve CBF grubunda sırasıyla 100 ve 70 çocuk vardı. Hastalarda anormal işeme akımı (abnormalVP) ve pozitif EMG aktivitesi (positive EMG) olan hastalarda RBF ile daha anlamlı iyileşme (p=0,001); anormalVP ve negatif EMG aktivitesi (negative EMG) olan hastalar CBF ile daha anlamlı iyileşmeye sahip olduğu tespit edildi (p=0,039); İstatistiksel olarak önemsiz olmasına rağmen, normal işeme akımı (normalVP) ve positive

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EMG olan hastalar CBF ile daha iyi çözünürlüğe sahip iken (p=0,452); normalVP ve negative EMG hastalarında RBF ile daha anlamlı iyileşme gözlendi (p=0,083).
Sonuç: LUTD ve Anormal VP'li çocuklarda, EMG aktivitesi biofeedback tedavisinin tipini belirlemektedir: positive EMG, RBF ile daha iyi sonuçlara sahip iken, negative EMG, CBF ile daha iyi sonuçlara sahiptir.
Anahtar Kelimeler: LUTD, Biofeedback, EMG aktivitesi, İşeme akımı, Kasılma, Gevşeme

Introduction

Biofeedback (BF) is a non-invasive and non-pharmacologic treatment option for lower urinary tract dysfunction (LUTD) in children. In 1970s, the first data of BF results were presented in the urology literature (1,2). The above-described BF method was urodynamic bladder BF therapy that was performed during bladder filling in urodynamic testing. The animated voiding BF therapy in pediatric voiding dysfunction was first reported in 1990 (3). It was easier than urodynamic bladder BF therapy because of the lack of the usage of any invasive catheterization. Since then, there has been a wide clinical usage of animated voiding BF therapy for LUTD in children. In animated voiding BF, video computerized systems obtain the data from the body and let the children see, learn, and control their pelvic muscles (PM).

BF encompasses more than just teaching the pelvic floor relaxing techniques (PFRT) and standard urotherapy (SU) modifications, which are defined by conveying simpler explanations to children and parents about urinary tract functions, abnormal voiding, voiding posture, adapted standardized fluid intake, timed voiding, and proper diet. Some different studies have inferred the superiority of BF to PFRT and SU. For example, McKenna et al. (3) reported recovery rates of 89% and 90% in the symptoms of incontinence and enuresis, respectively. However, Vesna et al. (4) reported resolution rates of 83% and 66% in the SU + PFRT group, as well as resolution rates of 11% and 33% in only the SU group, respectively (3,4). Additionally, Kibar et al. (5) documented better post-void residual (PVR) urine resolution in the BF group than in the SU group. However, there is still a need for more randomized controlled studies that aim to compare SU, PFRT, and BF (6).

There is no standardized BF method in the literature. Some centers only use curves as an animation and they have a relaxation-based nature (7); however, others use a wolf and a bird providing 3 seconds of submaximal contraction followed by 30 seconds of prolonged relaxation with a relaxation-based nature (8). Some others use dolphin that should pass over hoops with a contraction-based nature (9,10). We believe that there may be differences among techniques, especially according to the relaxation or contraction nature.

In this study, we hypothesized that contraction-based and relaxation-based animated voiding BF techniques reveal different results in children with LUTD, and we have investigated the uroflowmetry (UF) results and electromyography (EMG) data.

Materials and Methods

The local ethics committee (Gülhane Training and Research Hospital Ethical Committee, protocol no: 26.11.2014/2014-07) approved this study's design, conduct, and procedures. We followed the Institution's Review Board of Human Subject Guidelines while performing this study. Informed consent was obtained from the participants' parents before conducting this study.

This study had been planned in a randomized nature, but we could not completely manage the randomization protocol due to children's claims regarding animations. Children mostly liked one animation more than the other. However, we managed to understand the prospective nature of study.

This is a retrospective study that includes the children with the diagnosis of LUTD and refractory to SU modifications without any history of urinary infection. These children were followed up at our institute between 2007 and 2017 (4,11). The data from all the children who applied to the urology clinic and underwent BF with the assistance of a urology nurse by using two different animations reported no differences: relaxation nature biofeedback (RBF) with 5 seconds of contraction followed by prolonged 20 seconds of relaxation by using the animation of a mushroom and a bird; and contraction nature biofeedback (CBF) with 15 seconds of contraction followed by 10 seconds of relaxation by using the animation of a submarine and a starfish.

We used the data of the children aged between 5 and 15 years without any medical treatment for LUTD in this study. Importantly, we obtained the medical data including the diet, the voiding habit, the defecation habit, the psychosocial problems, and the constitutional urologic abnormalities from all the children (12-14). In our clinic as a routine clinical practice, all the patients underwent a complete physical examination including a neurourologic examination focusing on the anal tone and voluntary control of the anal sphincter, the bulbocavernosus reflex, lower limb reflexes, and perineal sensitivity. We also recorded urinalysis, urine culture, serum urea and creatinine, the lumbosacral spine radiography, and the urinary ultrasonography of the patients. Additionally, we documented the answers of the

normal defecation habits, physical examination, laboratory and radiological tests, and any psychosocial problems, which have been enquired from the parents. We also recorded the data of the three-day bladder diary for cataloging the voiding habit at their home under regular conditions. Among the answers, more than seven voids were defined as frequency (15). We used the LUTD Symptom score (LUTDSS) to compare the LUTD symptoms according to the different animations (16).

In our clinic, UF combined with perineal EMG that documents the pelvic floor contractions were performed for the determination of voiding phase deficit by our trained nurse with the urodynamic device (MMS 5000, by Colosseum, Netherlands) at our urodynamic laboratory. The individuals were instructed to come to the visit with an empty bladder. Before UF-EMG, they were informed to drink water to acquire the sufficient volume by bladder ultrasonography. The UF-EMG was performed at least two times; it was reviewed and determined under the decision of two different urologists. The UF-EMG curves were classified as normal, staccato-, tower-, and plateau-shaped (15). PVR was measured ultrasonographically by BladderScan BVI 6100 (diagnostic ultrasound, Bothell, WA) immediately after voiding. PVR of less than 21% of estimated bladder capacity was defined as increased PVR (15).

The RBF and CBF were discussed with each parent, and there was no reported difference between these animations. The same trained nurse who performed UF-EMG also performed the BF therapies with the same MMS 5000 (Colosseum, the Netherlands) device. Two electrodes to show the external sphincter activity were placed at 3 and 9 o'clock positions in the perineal area. Another electrode was placed over the left thigh or rectus abdominis to identify the proper relaxation of these muscles. Children were asked to sit on the BF closet, which was specially designed for children with their feet on a basement, thus providing a relaxed position. The total treatment period was 6 months for each child. The children had a BF session at weekly intervals in the first month. Each session consisted of 20 minutes with RBF or CBF. After each BF session, children were told to continue to exercise their external sphincters with daily 30 contraction and relaxation cycles at their home by imagining the animation in their minds together with SU instructions. The children were controlled at the third month, and UF-EMG tests and control BF sessions were performed. Then, the children were told to continue to exercise their external sphincters. The final UF-EMG tests and BF sessions were then performed, and LUTDSS were analyzed at the sixth month. The categories of nonresponse, partial response, and full response were defined as a 0-49% decrease, 50-99% decrease, and 100% decrease in LUTDSS, respectively (12). Thereafter, we compared the results of BF by using both RBF and CBF.

Statistical Analysis

We performed statistical analysis by using Statistical Package for Social Sciences 20.0 software (SPSS 20.0 for MAC). We noted descriptive statistics with median (min-max), frequency, and percentiles. We used the Shapiro-Wilk, kurtosis, and skewness tests to assess the normalization of variables. Additionally, we used McNemar test to compare the nominal samples of LUTD symptoms before and after the BF therapies. We employed the related samples Wilcoxon Test to compare the scale samples of LUTD symptoms before and after the BF therapies. We used the chi-square test to compare the success rates of RBF and CBF groups. We also compared non-response and other types of responses. Probability of $p<0.05$ was accepted as statistically significant for this study.

Results

There were 120 and 92 children in the RBF and CBF groups, respectively. The data of the 20 patients in the RBF group and 22 patients in the CBF group were excluded from the study because we were unable to obtain the follow-up records. The RBF group comprised 100 children with 75 (75%) girls and 25 (25%) boys, and the CBF group comprised 70 children with 56 (80%) girls and 14 boys (20%) (p=0.78). The median ages in the RBF and CBF groups were 8.54 (min-max, 6-15) and 8.55 (min-max, 5-15) years, respectively (p=0.721). Figure 1 depicts the symptoms of RBF and CBF groups (p=0.819). The median LUTDSS was 16.46 (min-max: 9-33) and 13.27 (min-max: 9-35) in the RBF and CBF groups, respectively.

In the RBF group, 49 patients had a staccato voiding pattern (StaccatoVP) with positive EMG activity (positive EMG), 20 had StaccatoVP with a negative EMG activity (negative EMG), 17 had a normal voiding pattern (normalVP) with positive EMG, 5 had normalVP with negative EMG, 6 had a tower voiding pattern (TowerVP) with positive EMG, and 3 had a plateau-shaped voiding pattern (plateauVP) with positive EMG. With BF therapy, the complaints of daytime incontinence (p=0.001; success=0.43), enuresis (p=0.001; success=0.51), dysuria (p=0.027; success=0.52), incomplete emptying (p=0.035; success=0.68), urgency (p=0.001; success=0.47), making holding maneuvers (p=0.001; success=0.49), urgency incontinence (p=0.001; success=0.56), and frequency (p=0.045; success=0.53) demonstrated a statistically significant change as compared to baseline. However, strain (p=0.263; success=0.31) and intermittency (p=0.54; success=0.38) showed no statistically significant changes. The median LUTDSS decreased from 16.46 (min-max: 9-33) to 7.38 (min-max: 1-22) (p=0.001). In total, 35 (35%) patients had increased PVR, and the median PVR of these patients was 92 (min-max: 22-197) mL. After BF, 19 patients with increased PVR showed resolution (PVR of less than 21%

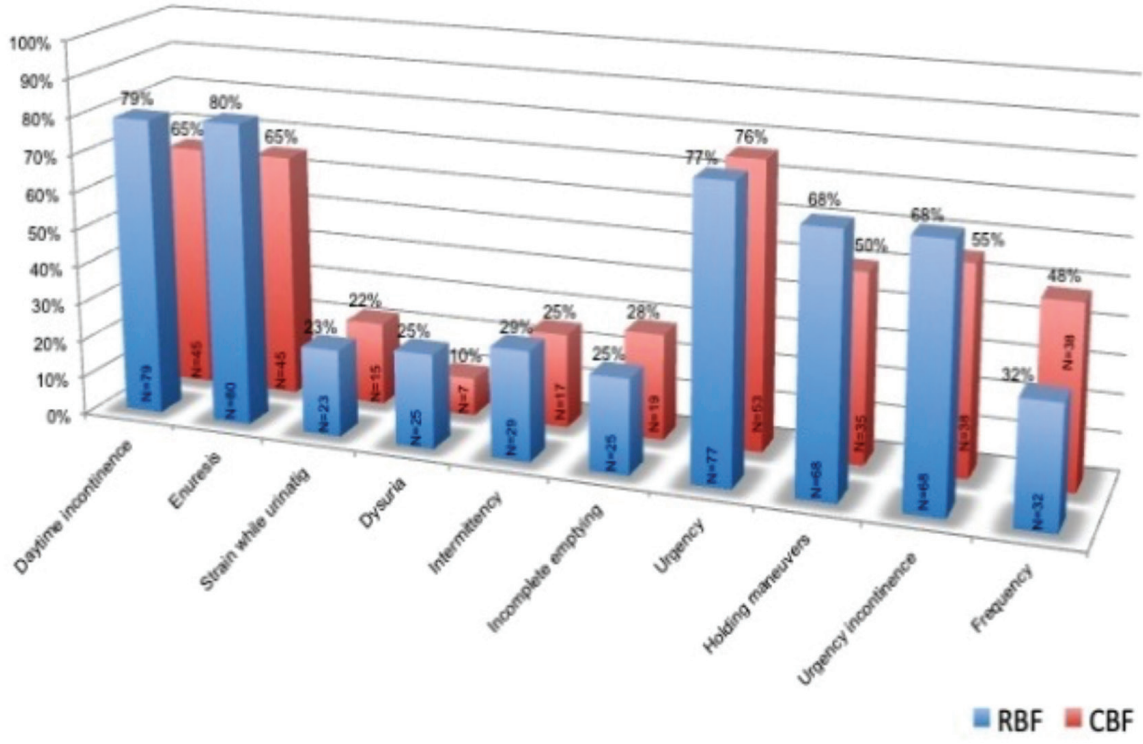

Figure 1. Symptoms of patients according to animations

of estimated bladder capacity). PVR decreased to 51 (min-max: 23-92) in rest of the 16 patients (p=0.451).

In the CBF group, 16 patients had StaccatoVP with positive EMG, 16 had StaccatoVP with negative EMG, 19 had normalVP with positive EMG, 10 had normalVP with negative EMG, 4 had TowerVP with positive EMG, 1 had TowerVP with negative EMG, and 4 had plateauVP with positive EMG. After BF therapy, the complaints of daytime incontinence (p=0.004; success=0.54), enuresis (p=0.009; success=0.52), urgency (p=0.001; success=0.49), making holding maneuvers (p=0.02; success=0.51), urgency incontinence (p=0.004; success=0.55), and frequency (p=0.041; success=0.57) had a statistically significant change. However, strain (p=0.542; success=0.1), dysuria (p=1; success=0), intermittency (p=0.109; success=0.38), and incomplete emptying (p=0.345; success=0.35) did not show any significant changes. The median LUTDSS decreased to 9.13 (min-max: 1-27) (p=0.001). In total, 28 (40%) patients had increased PVR, and the mean PVR of these patients was 67.43 (min-max: 25-142) mL. After BF, 18 patients with increased PVR showed resolution (PVR of less than 21% of estimated bladder capacity). PVR decreased to 42 (min-max: 21-82) in rest of the 10 patients (p=0.362).

Table 1 shows the success of BF in accordance with the UF-EMG patterns and symptoms. The statistically significant points in this table are as follows: patients with abnormal VP (abnormalVP) and positive EMG had a better resolution with RBF (p=0.001), whereas patients with AbnormalVP and negative EMG had a better resolution with CBF (p=0.039). Despite being statistically insignificant, patients with normalVP and positive EMG had a better resolution with CBF (p=0.452), and patients with NormalVP and negative EMG had a better resolution with RBF (p=0.083).

Discussion

Abnormally learned behaviors of voiding cause a spectrum of symptoms such as daytime incontinence, enuresis, urgency, urgency incontinence; this condition is termed as LUTD (15) There are two main subgroups of LUTD: overactive bladder (OAB) and dysfunctional voiding (DV) (12). BF is used as a non-invasive and non-pharmacological treatment option for both the subgroups of LUTD. Glazier et al. (17) reported symptom improvement at the rate of 85.7% in 89 patients by OAB. Yamanishi et al. (18) also reported a cure rate of 65.7% and improvement rate of 11.4% in 35 patients. Meijer et al. (19) documented success and improvement rates of 42.9% and 31.4%, respectively, in refractory cases. Success rates of daytime incontinence, nocturnal enuresis, constipation, and encopresis were defined at 89%, 90%, and 100%, respectively, for DV (3). Prona et al. reported that the success rates of BF on enuresis, as a component of DV, were 87.1% and 80% in the second and fourth years, respectively (20). Hence, BF is used for all the subgroups of LUTD when PFRT and SU were failed, and also before initiating the medical therapy.

Table 1. Success of biofeedback by using relaxation biofeedback (animation A) and contraction biofeedback (animation B) according to the electromyography activity in the uroflowmetry pattern.

			Animation A		Animation B		p
Voiding pattern	**Electromyography activity Response**		**Frequency**	**Percent (%)**	**Frequency**	**Percent (%)**	
Normal	Negative	None	3	60.0	8	80.0	**0.083**
		Partial	2	40.0	2	20.0	
	Positive	None	9	52.9	8	42.1	**0.452**
		Partial	8	47.1	4	21.1	
		Full	-	-	7	36.8	
Tower	Negative	-	-	-	1	100.0	**-**
	Positive	None	2	33.3	2	50.0	**0.037**
		Partial	4	66.6	2	50.0	
Staccato	Negative	None	12	60.0	4	25.0	**0.04**
		Partial	-	-	4	25.0	
		Full	8	40.0	8	50.0	
	Positive	None	20	40.8	11	68.8	**0.001**
		Partial	18	36.7	3	18.8	
		Full	11	22.4	2	12.5	
Plateau	Positive	None	-	-	2	50.0	**0.034**
Full		Partial	-	-	2	50.0	
		3	100.0	-	-		

LUTD is related to two organs: bladder and PM. In a UF-EMG chart, EMG reflects the PM function, and flow pattern along with EMG activity that reflects the combination of both activities of bladder and PM. NormalVP in UF has a bell-shaped regular pattern, StaccatoVP has sharp peaks and troughs in the flow curve, TowerVP has a high amplitude curve with short duration, and PlateauVP pattern has a low amplitude with a longer duration. EMG activity might be accompanied with these flow patterns (15). StaccatoVP and NormalVP with positive EMG were the most detected UF-EMG patterns in our study, thus expressing deficits in both bladder and PM.

Urodynamic bladder BF therapy has been believed as an alternative method for the treatment of LUTD by illustrating both bladder and PM movements since 1970s. The technique resembles urodynamic testing: PM contraction was continued during bladder filling, till to the willingness to voiding. At the end of the filling, when the child felt the voiding sensation, voiding was accomplished with suitable PM relaxation. This was repeated several times when the catheters were inside the body. In 1978, Cardozo et al. (1) reported six patients with LUTD and demonstrated significant success. In 1979, Maizels et al. (2) reported the cases of three patients undergoing urodynamic bladder BF and showed success in two patients. In 1982, Sugar and Firlit (21) reported ten patients undergoing urodynamic bladder BF with success in eight of them. However, the main limitation of the urodynamic bladder BF was invasiveness.

McKenna et al. (3) has reported the first animated voiding BF results in 1999. The technique has gained popularity as a non-invasive method with good resolution rates in the symptoms of LUTD. Since then, several reports have been published regarding the animated voiding BF data in children with LUTD. However, each technique has different standardization procedure with the focus on different aspects of PM. In Glazier et al.'s (17) report, children were instructed to perform five quick contractions during a 5-second period, which was followed by a 5-second relaxation period. The children performed these exercises for 10 minutes or until the exercises were mastered. After each BF session, the children were asked to do the exercise at least three times per day at home. At the fourth month, they reported 86% resolution in frequency (17). This technique was predominantly focused on PM relaxation. We have previously reported that the children underwent BF by using an animation of a wolf and a bird providing 3 seconds of submaximal contraction followed by 30 seconds of prolonged relaxation (22) with the success rates of 64%, 59%, 50%, and 66% in enuresis, daytime incontinence, urgency, and urgency incontinence, respectively. We mainly focused on the relaxation in our method. In another study, children underwent BF by using different animations (dolphin, bird, monkey, etc.), and they had to tighten their PM according to the instructions provided by computer games. The total BF time was 6 months, and they have reported success rates of 75-84% and 68% in the symptoms of frequency and urgency, respectively (10). The key part of this method was contraction. In Kaye and Palmer (9) reports, BF was conducted by using a

dolphin and a water band. The children had to contract PM to maintain the swimming of dolphin in the water band. There were success rates of 84%, 92%, 89%, and 90% in enuresis, daytime incontinence, urgency, and frequency symptoms, respectively (9). This technique was mainly focused on contraction.

McKenna (6) provided the following conclusion for our previous study: "our future investigations should be directed toward understanding how the pelvic floor causes changes in bladder function, and we need to standardize and simplify BF treatment methods" (8). This conclusion led us to consider the possibility of improvement in the success of animated voiding BF in LUTD, and we assumed that the contraction or relaxation nature of the animated voiding BF might play a role in the success of BF, which was the aim of this study. Here both techniques have good resolution effects in the symptoms. However, patients with AbnormalVP and positive EMG had better resolution rates with RBF, whereas patients with AbnormalVP and negative EMG had better resolution rates with CBF. We concluded that the main pathology in patients with abnormalVP and positive EMG is the inappropriate contraction of PM during voiding; therefore, performing RBF yields better results by making the children learn how to relax the PM. For patients with abnormalVP and negative EMG, the main pathology is likely to appear at the bladder, and performing CBF reveals better results by compensating the abnormal movements of bladder.

Study Limitations

Our study has limitations. First, we had a small sample size. Second, we were unable to conduct analysis according to the symptoms. We could not completely manage the randomization protocol due to children's claims about animations. Children mostly liked one animation more than the other. There is an urgent need of future studies that are designed with respect to the comparisons of symptoms with UF-EMG patterns along with the aspects of contraction- and relaxation-based animated voiding BF.

Conclusion

The patients with LUTD and abnormalVP EMG activity identify the BF type. Positive EMG had better results with RBF, whereas negative EMG had better results with CBF. There is an urgent need of future studies that are designed with respect to the comparisons of symptoms with UF-EMG patterns with the aspects of contraction- and relaxation-based animated voiding BF.

Ethics

Ethics Committee Approval: The local ethics committee (Gülhane Training and Research Hospital Ethical Committee) approved the design, protocol and procedures of the study (protocol no: 26.11.2014/2014-07).

Informed Consent: Informed consent form was filled out by all the parents of the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept and Design: B.K., T.E., Data Collection and/or Processing: B.K., G.E. Analysis and/or Interpretation: T.E., Literature Research: E.K., Writing: B.K., T.E., Y.K.

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Evaluation of Short-term Postoperative Complications According to the Clavien-Dindo Classification System in Thermocautery-assisted Circumcision Cases

Termokoter Yardımlı Sünnet Olgularında Kısa Süreli Postoperatif Komplikasyonların Clavien-Dindo Sınıflandırma Sistemine Göre Değerlendirilmesi

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What's known on the subject? and What does the study add?

Our retrospective study demonstrated that thermocautery-assisted circumcision has a short operative time. In addition, adapted short-term complications to Clavien-Dindo classification system indicate that is tolerable and easily overcome following this surgical technique. Therefore, thermocautery-assisted circumcision may become a practical and fast method for circumcision in areas where circumcision is a common procedure.

Abstract

Objective: Circumcision is one of the most performed surgical procedures in the world. This study is a retrospective study on the short-term postoperative complications after a thermocautery-assisted circumcision on a series of patients according to the Clavien-Dindo classification system (CDCS).

Materials and Methods: A total of 2.356 male thermocautery-assisted circumcision cases, performed by two urologists in a hospital, were examined retrospectively. The mean age, type of anesthesia, peri- and postoperative complications, durations of the procedures, mean number of sutures, cohesive bandage requirements, and mean recovery times were evaluated.

Results: The age of the patients ranged from 1 to 32 years with the mean age being 8.33 years. While 1.943 patients (82.47%) were only locally anesthetized, the remaining 413 (17.53%) were sedated in addition to local anesthesia. The mean values of the operative time, suture count, total requirement of cohesive bandages, and recovery time were 5.19±1.38 min (range of 4-20), 5.71 (range of 4-12), 69 (2.92%), and 6 days (range of 4-25), respectively. The short-term postoperative complications of 1.573 patients who returned to the hospital for a physical examination after being discharged were edema (mild, moderate, and severe), bleeding (simple and hematoma-causing), and infection (mild, moderate, and serious). The postoperative complications were adapted to the CDCS as grade 1 (638 patients, 40.55%), grade 2 (12 patients, 0.76%), grade 3 (6 patients, 0.38%), grade 4 (0 patients, 0%), and grade 5 (0 patients, 0%). There was no statistically significant difference between the patients in terms of complications adapted to the CDCS who received local anesthesia and those who received sedation + local anesthesia ($p>0.05$). Additionally, there was no significant difference in the development of penile edema between the patients who were sutured with Vicryl Rapide and normal Vicryl ($p>0.05$).

Conclusion: Our retrospective results indicate that thermocautery-assisted circumcision has a short operative time and is tolerable despite its short-term complications. Thermocautery-assisted circumcision may be a useful method in regions where circumcision is common.

Keywords: Circumcision, Clavien-Dindo classification system, Complications, Edema, Thermocautery

Öz

Amaç: Sünnet, dünyada en çok yapılan cerrahi işlemlerden biridir. Bu çalışma, Clavien-Dindo sınıflandırma sistemine (CDSS) göre bir hasta serisinde termokoter yardımlı sünnet sonrası kısa dönem postoperatif komplikasyonlar üzerine yapılan retrospektif bir çalışmadır.

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Gereç ve Yöntem: Bir hastanede iki ürolog tarafından gerçekleştirilen toplamda 2,356 erkek termokoter yardımlı sünnet olguları retrospektif olarak incelendi. Ortalama yaş, anestezi tipi, peri ve postoperatif komplikasyonlar, işlem süreleri, ortalama sütur sayısı, yapışkanlı bandaj gereksinimi ve ortalama iyileşme süreleri değerlendirildi.
Bulgular: Hastaların yaşı 1 ile 32 yıl arasında olup, ortalama yaş 8,33 yıl idi. 1,943 hastaya (%82,47) sadece lokal anestezi uygulanırken, kalan 413 (%17,53) hasta lokal anesteziye ek olarak sedatize de edildi. Ameliyat süresi, sütur sayısı, yapışkanlı bandajların toplam gereksinimi ve iyileşme süresinin ortalama değerleri sırasıyla; 5,19±1,38 dk (4-20 dk.), 5,71 (4-12.), 69 (%2,92) ve 6 gün (4-25 gün). Taburcu edildikten sonra fizik muayene için hastaneye başvuran 1,573 hastanın kısa dönem postoperatif komplikasyonları; ödem (hafif, orta ve şiddetli), kanama (basit ve hematom nedenli) ve enfeksiyon (hafif, orta ve ciddi) idi. Postoperatif komplikasyonlar CDSS'ye göre; derece 1 (638 hasta,%40,55), derece 2 (12 hasta,%0,76), derece 3 (6 hasta, %0,38), derece 4 (0 hasta, %0) ve derece 5 (0 hasta, %0) olarak görüldü. Lokal anestezi alan hastalar ile sedasyon + lokal anestezi alan hastalar arasında CDSS'ye göre komplikasyonlar açısından istatistiksel olarak anlamlı fark yoktu (p>0,05). Ek olarak rapid vikril ile normal vikril ile sütürüze edilen hastalar arasında penil ödem gelişimi açısından anlamlı bir fark yoktu (p>0,05).
Sonuç: Retrospektif sonuçlarımız, termokoter yardımlı sünnetin kısa bir ameliyat süresine sahip olduğunu ve kısa dönem komplikasyonlarına rağmen tolere edilebilir olduğunu göstermektedir. Termokoter yardımlı sünnet, sünnetin yaygın gerçekleştirildiği bölgelerde kullanışlı bir yöntem olabilir.
Anahtar Kelimeler: Sünnet, Clavien-Dindo sınıflama sistemi, Komplikasyonlar, Ödem, Termokoter

Introduction

Circumcision is a surgical procedure mostly performed for religious and medical reasons. It involves the excision of the foreskin that covers the distal end of the male penis (1) and is one of the most frequent surgical interventions in the world (2). Although circumcision is not accepted by many people worldwide, there are several health benefits of it, such as reduction in the risk of acquiring HIV, urinary tract infections, herpes simplex, balanitis, phimosis, and penile cancer and a reduction in the risk of causing bacterial vaginosis in female partners and transmitting human papilloma virus and syphilis (3,4).

However, with all the aforementioned benefits circumcision can have, it is still a surgical procedure and bears a few potential complications. Therefore, this procedure must be done under sterile and safe conditions as with any surgical acts. Many different techniques (such as Gomco clamp, PlastiBell, Mogen clamp, and dorsal slit) are used for performing circumcision (5,6), however, thermocautery-assisted circumcision is a technique that has become popular in recent years (6-8), especially in Turkey, where a circumcision center has been using the thermocautery-assisted shield technique for over 30 years. Over 80,000 circumcisions have been performed without any complication related to the thermocautery device (8).

Further, the standardization of complications allows the comparison of surgical experiences with other studies. Hence, the modified Clavien-Dindo classification system (CDCS) is one of the most popular categorization systems for complications (9,10).

In this study, we aimed to evaluate the short-term complication rates of thermocautery-assisted circumcision cases in a single institution of the eastern region of Turkiye. Then, we standardized the postoperative complications according to the CDCS.

Materials and Methods

Male thermocautery-assisted circumcision cases that were carried out by two urologists (MTÖ and KT) were examined between 1 June 2016 and 15 November 2017 at the Agri State Hospital, Clinic of Urology, Ağrı, Turkiye. A total of 2.679 patients were circumcised during the period. Those who had previous penile surgery or trauma, bleeding disorders, allergic reactions to the anesthetics, systemic diseases, or paraphimosis and patients who were noncompliant were excluded from the study. Patients with phimosis were included in this cohort. The mean age, anesthetic type, number of sutures, operation time, cohesive bandage requirements, recovery time, and complication rates of these cases are indicated in Table 1. The study was performed retrospectively with the approval of the Erzurum Atatürk University Faculty of Medicine, Clinical Research Ethics Committee (approval number: B.30.2.ATA.0.01.00/127). All patients gave informed consent prior to being admitted to the study.

Surgical Preparation

Dorsal penile nerve blockade was performed with lidocaine HCl 20 mg/mL ampoule (Jetokain Simplex, Adeka, Turkiye) 2-4 mL for patients who received only local anesthesia. Ketamine HCl vial (Ketalar, Pfizer, USA) in 4.5 mg/kg or midazolam ampoule 0.1-0.5 mg/kg (Dormicum, Roche, Switzerland) were applied intravenously, then local anesthesia was performed on sedo-analgesia-receiving patients. Sedo-analgesia doses were increased or decreased during sedation by an anesthesiologist.

Surgical Technique (Figures 1. a,b,c,d,e,f)

The prepicium was removed from the glans penis with the help of a clamp and a sponge, and the remaining smegmas were cleaned again with povidone iodine 10% solution (Poviiodeks, Kimpa, Turkiye). In a manner similar to the one in the guillotine method, the prepicium was clamped with a flat clamp, described

Table 1. The complication rates of patients who underwent thermocautery-assisted circumcision before and after discharge from the hospital	
Before discharge	
Total circulation cases (n)	2.356
Mean age ± SD (years), (range)	8.33±3.46, (1-32)
Type of anesthesia Local (%) Sedation + Local (%)	 1.943 (82.47%) 413 (17.53%)
Bleeding (%) Perioperative (%) Postoperative (%) -Hematoma (%)	68 (2.88%) 43 (1.82%) 25 (1.06%) -4 (0.16%)
Mean duration of procedure (minute), (range)	5.19±1.38, (4-20)
Mean number of sutures (range)	5.71±1.68, (4-12)
Total usage of cohesive bandage (%)	69 (2.92%)
After discharge	
The patients who were controlled after discharge (n) The patients who did not visit the hospital for examination after discharge (n)	1.573 (66.76%) 783 (33.23%)
Edema (%) Mild edema (%) Moderate edema (%) Severe edema (%)	592 (37.63%) 439 (27.90%) 124 (7.88%) 29 (1.84%)
Infection (%) Mild infection (%) Moderate infection (%) Serious infection (%)	39 (2.47%) 25 (1.58%) 9 (0.57%) 5 (0.31%)
Bleeding	None
Mean recovery time ± SD (day), (range)	6.00±1.50, (4-25)
SD: Standard deviation	

as "shield technique" earlier (11). A thermocautery tool (Warme Medizinische, Beschneidung Gerat, QX - 2100, Germany) was used to cut the prepuce. The device had seven levels for cutting. Appropriate heat levels were used according to the patient's age and the foreskin thickness. We also had multiple cautery probes. The sterilization of probes was strictly performed using high-level disinfectants. Bleeding dorsal vein and mucosal vessels were thermocauterized after cutting the prepuce. Thereafter, the remaining excessive tissue of mucosa was excised using a thermocautery tool. Synthetic, absorbable suture materials (3/0-4/0, Polyglactin 910, Vicryl Rapide®, Ethicon, USA or 3/0-4/0, Polyglactin 910, Vicryl, Ethicon, USA) were used for skin closure of the surgical wound by interrupted sutures. Vicryl Rapide was used in patients aged <10 years, while other type of Vicryl was used in patients aged ≥10 years. After circumcision, a dressing containing nitrofurazone 2% cream (Furacin, Zentiva, Turkiye) was applied. Cohesive bandages were used for hemostatic dressing in patients with bleeding. The time from the start of cutting the prepuce to the last suture was recorded as the procedure time (in min).

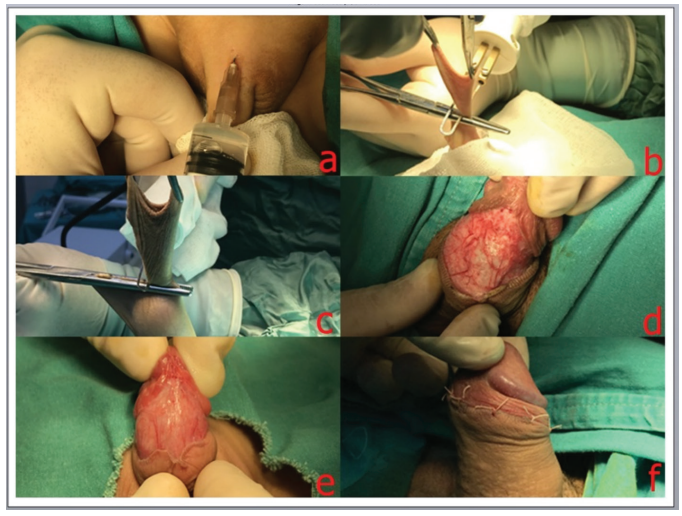

Figure 1. Thermocautery-assisted circumcision steps: (a) Dorsal penile blockage. (b,c) Excision of prepicium with thermocautery device from different patients. (d,e) Imaging of the frenulum from different patients after excision. (f) Imaging of the penis after suturing

Follow-up and Discharge

The sedo-analgesia-receiving patients were monitored for a minimum of 12 hr, and the local-anesthesia-receiving patients were monitored for a minimum of 3 hr in the hospital. Patients with no postoperative problems (bleeding, allergic reactions, etc) in their follow-ups were discharged. As a standard procedure, for patients aged <15 years, ibuprofen 20-30 mg/kg oral suspension (Dolven, Sanofi, France) and for patients aged >15 years, diclofenac sodium tablet 50 mg (Dolorex, Abdi Ibrahim, Turkey) 2x1 by oral route were prescribed, respectively, as an anti-inflammatory. As a standard procedure, it was recommended that the dressings should be removed at the 24-48-hr mark by patients or their families after soaking them in warm water for 10 min. Patients were recommended to apply bacitracin 15.000 UI + Neomycin Sulphate 150 mg skin pomade (Thiocilline, Abdi İbrahim, Turkiye) 4x1, limiting motion, bed rest, wearing a skirt or underpants suitable for circumcision, and refraining from bathing for three days post circumcision. They were also advised to return to the hospital without any delay if bleeding, color change to the glans penis, pain that was nonresponsive to analgesic, edema, leakage from the wound, itching, or rush occurred anywhere in the body. In the absence of any complications, the patients were advised to return to the hospital on the fourth day post circumcision. Furthermore, patients' phone numbers were recorded so that the hospital staff could reach them later when required. The observation of skin integrity between the sutures was defined as the healing wound. The recovery period was determined based on the complete wound healing.

The complications that occurred during and after circumcision (peri- and postoperative) were recorded. The postoperative

complications were also categorized according to the modified CDCS (9,10) and are presented in Table 2.

Statistical Analysis

The mean and range values were calculated using the Statistical Package for the Social Sciences version 22.0. The chi-square test was used for comparing the categorical variables among groups such as anesthesia and the development of edema due to suture type. Spearman's rank test was used to evaluate the correlation between the age and the complications according to the CDCS.

Results

The patients who had a previous penile surgery or trauma (n=18), bleeding disorders (n=4), allergic reactions to the anesthetics (n=9), systemic diseases (n=11), or paraphimosis (n=5), and patients who were noncompliant (n=87) were excluded from the study. In addition, the data from 189 cases were not noted properly. Thus, a total of 323 cases were excluded from the study. After all exclusions (n=323), a total of 2.356 out of the 2,679 cases were found to be appropriate for this study. The mean age of the 2,356 patients was 8.33±3.46 (range of 1-32) years. A total of 1,943 (82.47%) patients were given only local anesthesia and 413 (17.53%) were given both sedation and local anesthesia. The mean number of sutures, operative time, and the total usage of cohesive bandages are summarized in Table 1. A total of 1.573 (66.76%) patients returned to the hospital for a physical examination on the fourth postoperative day and the remaining 783 patients (33.23%) who failed to visit the hospital were contacted via telephone calls. It was found that the patients who did not return to the hospital did so because they had no complaints. Additionally, of the 1,573 patients who returned (59.88%), 942 did not present with any postoperative complications in the physical examination (Table 1).

The most common complication registered in this study was postoperative edema. Patients signaled that postoperative edema started two-four days after the patients were discharged.

Table 2. Classification of short-term postoperative circumcision-related complications according to the Clavien-Dindo Classification system

Grade	Definition (9,10)	Our study	Management
Grade 1 (n=638, 40.55%)	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological interventions. Allowed therapeutic regimens include drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.	Edema (n=592, 37.63%)	Maintenance ibuprofen, daily dressing
		Mild infection (n=25, 1.59%)	Oral sultamicillin, daily dressing
		Simple bleeding (n=21, 1.33%)	Daily dressing with cohesive bandage
Grade 2 (n=12, 0.76%)	Requirement for pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	Moderate infection (n=9, 0.57%)	Hospitalization, IV sultamicillin treatment, daily dressing
		Bleeding causes of hematoma (n=3, 0.19%)	Hospitalization, daily dressing with cohesive bandage
Grade 3 (n=6, 0.38%)	Requirement for surgical, endoscopic or radiological intervention		
3a (n=5, 0.32%)	Not under general anesthesia	Serious infection (n=4, 0.26%)	Penile debridement under local anesthesia, IV sultamicillin treatment daily dressing
	Not under general anesthesia	Bleeding causes of serious hematoma (n=1, 0.06%)	Hematoma drainage under local anesthesia, daily dressing with cohesive bandage
3b (n=1, 0.06%)	Under general anesthesia	Serious infection with serious penil skin necrosis (n=1, 0.06%)	Debridement of necrotic tissue and reconstruction with scrotal flap under general anesthesia, IV piperacillin + tazobactam
Grade 4 (n=0)	Life-threating complications (including central nervous system) requiring intensive care unit		
4a	Single organ dysfunction (including dialysis)	None	–
4b	Multiorgan dysfunction	None	–
Grade 5 (n=0)	Death	None	–
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. Follow-up is recommended.		

A total of 592 of the 1.573 patients who returned to the hospital presented with edema (37.63%, CDCS grade 1). The degree of mild, moderate, and severe on the edema scale was determined when the edema was completely resolved. The resolution of edema was observed at 4-7 days, 7-10 days, and 10 or more days in mild (439 patients, 27.90%), moderate (124 patients, 7.88%), and severe (29 patients, 1.84%) edema cases, respectively. The mild or moderate edema cases were easy to overcome and no further complaints were heard from the patients and/or their parents. Maintenance ibuprofen and daily dressing were recommended to patients in these cases, and the edema fully disappeared. However, in the cases of severe edema, it was observed that the patients and/or patients' relatives quite often became agitated. There were no clinical findings other than the appearance of severe edema in such patients. Maintenance ibuprofen and daily dressing with topical hydrocortisone cream (HIPOKORT 0.5% 30 g, ORVA, İzmir, Turkiye) were recommended. The edema in such patients healed completely (Figure 2). Vicryl Rapide was used in 1.536 patients aged <10 years and Vicryl in 820 patients aged ≥10 years. Of those who came to follow-up, Vicryl Rapide was used in 1.024 cases and Vicryl in 549 cases. No significant difference was observed in the development of penile edema between the patients who were sutured with Vicryl Rapide and those sutured with normal Vicryl (381 vs 211, respectively, p=0.632).

The second most common complication was bleeding, which occurred in 68 (2.88%) patients before discharge. No bleeding was signaled after the discharge. There were 43 (1.82%) and 25 cases (1.06%) of peri- and postoperative bleeding, respectively. While in the perioperative bleeding cases, the bleeding was stopped via thermocautery and the dressings were then supported by cohesive bandages, in postoperative bleeding cases, the dressings of the patients were changed and supported by cohesive bandages, and the patients were followed-up for 12 hr. A total of 21 patients presented with postoperative simple bleeding and were treated with daily cohesive bandage dressings; they were discharged after 12 hr (0.89%, CDCS grade 1). Furthermore, hematomas developed in four patients (0.16%) with postoperative bleeding. Such patients were observed for 48 hr in the hospital and treated with daily cohesive bandages. While the hematomas in three cases regressed and recovered (0.12%, CDCS grade 2), due to the amount of hematoma in a 10-year-old patient who had continuous leakage from the wound area that did not decrease, the suture of the frenulum was opened (Figure 3. a,b). The bleeding vessels were found and thermocauterized via device, and the wound area was sutured again under local anesthesia (0.04%, CDCS grade 3a, Figure 3c). Cohesive bandages were used to support the dressing again. The patient was discharged on the third postoperative day without any complications.

The total infection ratio was 39 (2.47%) in the patients who followed-up at the hospital after circumcision. We categorized the cases as mild (a minimal rush and color change to the wound area), moderate [an occasional leakage in the wound area or minimal necrosis (<1 cm^2) on the suture line], and serious infections [a continuous leakage or serious necrosis (>1 cm^2) on the suture line or anywhere on the penile skin]. Twenty-five cases of mild infection were treated with oral sultamicillin and daily dressing (1.58%, CDCS grade 1, Figures 2. a,b,c). Nine patients with moderate infections were treated with daily IV sultamicillin 500 mg (Sulcid, İbrahim Ethem, Ulagay, Turkiye) 4x1 and bacitracin 15,000 UI + neomycin sulfate 150 mg skin pomade (Thiocilline, Abdi İbrahim, Turkiye) 8x1 daily dressing (0.57%, CDCS grade 2). Five cases (0.31%) had serious infections, four of which were given IV sultamicillin in the hospital. In addition, necrotic tissue debridement and daily dressing were

Figure 2. Imaging of short-term complications after circumcision. (a) Moderate edema of subcorona. (b) Serious infection of dorsal part of glans. (c) Serious infection of the frenulum

Figure 3. Imaging of hematoma after circumcision. (a) Imaging of ventral penis. (b) Imaging of dorsal penis. (c) Imaging of the penis at the first day after drainage of hematoma

performed under local anesthesia for these four patients (0.25%, CDCS grade 3a). All patients with mild and moderate infections recovered. Four patients with serious infections recovered as a result of the treatment. One 19-year-old patient did not respond to the treatment. An approximately 6 cm^2 area with necrosis was debrided from the right mid-lateral to the penis root, and it was surrounded with scrotal flap by a plastic surgeon (0.06%, CDCS grade 3b, Figure 4. a,b,c,d). The patient was treated with IV piperacillin + tazobactam 4.5 g (Tazocin, Pfizer, USA) 4x1 and 2x1 cohesive bandage dressing for 10 days before discharge. On the 10th day of the patient's follow-up, the scrotal flap was determined to be successful (Figure 4d). All these complications and data are summarized in Table 1.

As shown in Table 2, all postoperative complications were also adapted according to the CDCS; grade 1 (638 patients, 40.55%), grade 2 (12 patients, 0.76%), grade 3 (6 patients, 0.38%), grade 4 (0 patients, 0%), and grade 5 (0 patients, 0%) (9,10). No statistically significant difference was observed between the patients who received local anesthesia and those that received sedation + local anesthesia (p>0.05, Table 3). There was no correlation between the age and complications according to the CDCS (p=0.858, r=0.005). Additionally, the mean recovery period for patients was six (range of 4-25) days (Table 1).

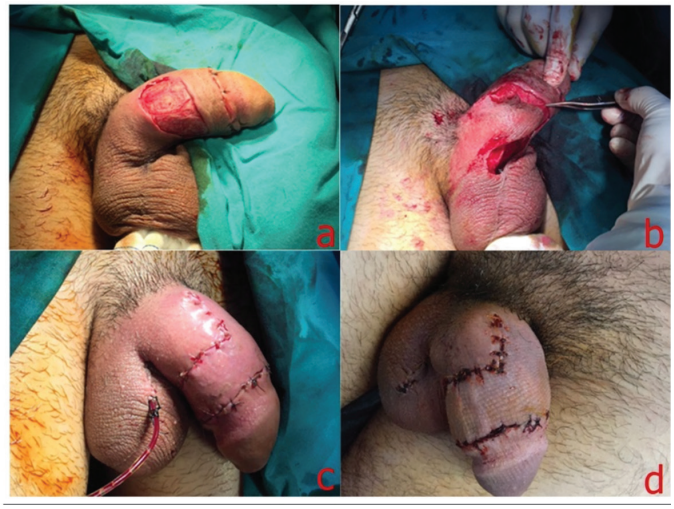

Figure 4. Imaging of debridement and reconstruction of a patient with serious infection accompanied with penile skin necrosis. (a) Imaging of the right part of the penis after debridement. (b) Transfer of scrotal flap to the defective area. (c) Imaging of the penis at the first day after reconstructive surgery. (d) Imaging of the penis at the 10th day after the reconstructive surgery

Discussion

The thermocautery-assisted shield technique has been proven to be an inexpensive, fast, and practical circumcision method and has therefore become more popular. However, there is a lack of proven results for this method in the literature (11,12).

Table 3. The comparison of standardized complications between groups with different anesthetized approach

	Local (n=1224)	Local + sedation (n=349)	p-value
Grade 1 (n=638)	509*	129*	0.680
Grade 2 (n=12)	10*	2*	0.482
Grade 3 (n=6) 3a (n=5) 3b (n=1)	 4* 1*	 1* 0*	 0.692 0.778
Grade 4 (n=0)	0*	0*	-
Grade 5 (n=0)	0*	0*	-

*Chi-squared test was used for nonparametric tests. There were no statistically significant differences between groups. P<0.05 was considered as statistically significant

This article provides several statistical results and comparisons within a huge set of patients (a total of 2,356-1,573 examined physically, 783 reached by telephone after discharge) that underwent thermocautery-assisted circumcisions. The short-term complications were examined within four postoperative days, and the thermocautery-assisted circumcision technique was discussed in light of the current literature.

There are various techniques for circumcision. Other than the sleeve, slit, and guillotine techniques, which are performed with standard surgical equipment, there are Gomco, Mogen, PlastiBell, Tara, and Shang Ring techniques, which use special clamps (13,14). Furthermore, modified techniques have been identified recently (15).

As with every surgical procedure, circumcision comes with some potential complications. Bleeding, wound infection, secondary phimosis, urethral or glandular injuries, and urinary retention can be observed soon after the operation. Long-term complications of the circumcision are excess or inadequate excision of the foreskin, concealed penis, adhesions between penile skin and the glans penis, penile deformations, secondary hypospadias skin bridges, poor wound healing, granu¬loma, and psychological disorders, besides frequent, long-term meatal stenosis (16-19).

The most common complications in circumcision using conventional methods are bleeding and infection (20). A Turkish study reported the rates of these complications as 3.1% and 0.52%, respectively (21). Contrary to the conventional methods, the complications and distribution of complications are somewhat different in the thermocautery-assisted circumcision. For instance, Makhlouf and Kootb (22) pointed out that the most common complications in their series of 518 patients who underwent circumcision with a thermocautery device were reversible edema on the suture line (2.5%), infection (1%), and bleeding (0%) (22). Another paper in Egypt similarly reported that there was no bleeding in thermocautery-assisted

circumcisions in 2,000 children (23). Furthermore, Arslan et al. (24) performed 5,871 thermocautery-assisted circumcisions and applied suture-less bandages in 3,420 patients in Sudan, while 2,451 patients were given sutures and bandages. While bleeding developed in only three patients (0.05%) and a scrotal abscess (0.01%) was noted, no further complications were determined in that study. As a result of Arslan et al.'s (24) study, it has been determined that thermocautery-assisted circumcision can be performed safely with appropriate equipment and personnel in regions where circumcisions cannot be performed in hospitals for socioeconomic reasons. According to these studies, the decrease in bleeding and infection rates is remarkable when compared with conventional methods. However, we found that the rates of complications were 2.88% for perioperative bleeding (after discharge none) and 2.47% for infection in our study.

Saracoglu et al. (14) in their study compared the conventional and thermocautery techniques. The study consisted of a total of 110 patients, and no bleeding was reported in the thermocautery group. Moreover, Karaman et al. (11,12) have reported that the thermocautery technique is suitable and cost-effective method for patients with bleeding disorders because it reduces the factor replacement. Although, in our study, bleeding and infection rates were slightly higher than the aforementioned studies, these-short term complications were tolerable and easily treated.

In Aykac et al.'s (6) study, the most common complication of thermocautery-assisted circumcision is edema. While this ratio was 29.6% in total for transient and prolonged edema, bleeding and infection were not observed in their study (6). In our cohort, the most common complication was mild-degree edema (27.90%) on the suture line that disappeared in about four–seven days (37.63% for all patients). The increased local hypervascular permeability due to heat-induced trauma on the circumcision line may be the possible reason for edema. There is no information about the standardized or optimal heat adjustment to perform thermocautery-assisted circumcision in the literature. Non-standardized and/or non-optimal thermocauterization may possibly lead the edema on the suture line. Further studies are needed to investigate the cause of edema and find the optimal head adjustment to perform thermocautery-assisted circumcision.

Thermocautery device for circumcision is different from electro cautery systems. Tuncer et al. (25) compared the effects of thermocautery, bipolar cautery, monopolar cautery, and the scalpel in rat circumcision model. They reported that (1) thermocautery caused higher collagen proliferation compared with the monopolar device and that (2) thermocautery group had a superior epithelization and injury depth when compared with the bipolar cautery group. Despite these histopathological alterations, the use of thermocautery for circumcision has found to be safe and resulted in better wound healing in rats without any complications (25).

In the current literature, tissue necrosis or ischemia could be observed in some cases of penile blockage with lidocaine plus epinephrine (26), hence we did not use lidocaine plus epinephrine for penile blockage. The necrosis seen in our study was thought to be related to infection.

Recently, a modified CDCS has been used to classify surgical complications. The CDCS has also been accepted for use in post-operative complications (27). Surgery-related complications have been standardized and published according to the CDCS (28-30). Tuncer and Deger (31) in their study reported the CDCS-adapted version of circumcision complications and compared their data with a few other published studies. In this research, the perioperative, early- and late-postoperative complications of 1,780 patients who underwent thermocautery-assisted circumcision were presented under the guidelines of the CDCS. For instance, bleeding (four patients), glans-skin bridge (one patient), and secondary phimosis/trapped penis (three patients) in peri- and postoperative patients were determined as grades 3a, 3a, and 3b complications, respectively (31). On the other hand, according to the CDCS, complications that would require additional surgery, such as grade 3 complications, were seen in six patients (0.035%) in our study, and grades 4 and 5 complications (0%) were not seen at all. Consequently, this CDCS-adapted complication assessment provides convenience and a comparison with the data of other studies.

In pediatric cases, suture-less tissue adhesive techniques have been reported to be safe (32). However, it is known that sutures are much more cost-effective than tissue adhesives. When the number of suture in our study was compared with that of Saracoglu et al.'s (14), they were found to be similar (5.71 vs 6.7, respectively). In conventional methods, cohesive bandages are used in most circumcisions because of the pressure effect to control bleeding. In our study, the bandage requirements were very low, as in Saracoglu et al.'s (14) (2.92% vs 3.6%, respectively). While the duration of the conventional circumcision varies from 13.8 to 23.7 min (33-35), the mean operation time for each of the three studies conducted on thermocautery-assisted circumcision [our study, Saracoglu et al. (14), and Aykac et al. (6)] was approximately 6 min. These results show that thermocautery-assisted circumcision is more advantageous than conventional techniques in terms of procedure time. With conventional techniques, recovery time ranges between 7 and 10 days, while in our study, the mean recovery time was 6 days. In Aykac et al.'s (6) study, this decreased to 4.3 days (6), indicating that thermocautery is successful in terms of the recovery process.

Study Limitations

The limitations of this study could be the retrospective design for short-term postoperative complications after circumcision on a series of patients (children and adults) and a lack of long-term analysis in the study.

Conclusion

Our retrospective study demonstrated that thermocautery-assisted circumcision has a short operative time. Additionally, the adapted short-term complications to CDCS indicate that it is tolerable and can be easily overcome following this surgical technique. Therefore, thermocautery-assisted circumcision may become a practical and fast method for circumcision in regions where circumcision is a common procedure. Furthermore, well-designed, prospective trials are needed to indicate the short- and long-term complications of this technique in the future.

Ethics

Ethics Committee Approval: The study was performed retrospectively with the approval of the Erzurum Ataturk University School of Medicine Clinical Research Ethics Committee (approval number: B.30.2.ATA.0.01.00/127).

Informed Consent: All patients gave informed consent prior to being admitted to the study.

Peer-review: Externally peer-review.

Authorship Contributions

Concept: M.T.O and K.T., Design: M.T.O. and K.T., Data Collection or Processing: M.T.O., Analysis or Interpretation: M.T.O. and K.T., Literature Search: M.T.O. and K.T., Writing: M.T.O. and K.T.

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Epidemiologic Analysis of Urological Cases Admitted to an Emergency Department of a Tertiary Care Center

Üçüncü Basamak Sağlık Merkezinin Acil Servisine Başvuran Ürolojik Olguların Epidemiyolojik Analizi

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What's known on the subject? and What does the study add?

Emergency physicians should be familiar with simple urological interventions that are vital for patients. Such epidemiological studies can help us determine with which subjects we should be more sensitive during medical intervention.

Abstract

Objective: We evaluated emergency urology patients admitted to the emergency department of our hospital in terms of demographic and epidemiological characteristics, in order to contribute to the relevant data of our country.

Materials and Methods: Of 362,139 patients, the demographic characteristics, established diagnoses, treatments, and results of 1409 emergency urology patients, who were admitted to Zonguldak Bülent Ecevit University Faculty of Medicine, Hospital's Emergency Department between January 2012 and December 2018, were analyzed retrospectively.

Results: Of the 362,139 patients admitted to the emergency department, 1409 (0.39%) were emergency urology patients. 69.9% of the patients were male (mean age: 57), and 30.1% of them were female (mean age: 54). The most frequent illness was renal colic constituting 25.5% of the cases followed by massive macroscopic hematuria (20.7%). Among the emergency urology patients, 381 (15.5%) underwent surgical procedures. The most performed procedure was for treating urethral stricture, which required urological expertise.

Conclusion: While some of the emergencies can be diagnosed using simple methods and most urological emergencies can be managed with simple interventions, urologists' intervention may be needed quickly if necessary. All emergency physicians should be aware of these simple approaches that otherwise may have severe consequences for patients.

Keywords: Emergency, Epidemiology, Urological cases

Öz

Amaç: Hastanemiz acil servisine başvuran ürolojik acil olguların demografik ve epidemiyolojik özellikleri açısından değerlendirerek, ülkemiz güncel verilerini gözden geçirmektir.

Gereç ve Yöntem: Zonguldak Bülent Ecevit Üniversitesi Hastanesi Acil Servisine Ocak 2012 - Aralık 2018 tarihleri arasında başvuran 362.139 hasta içinden 1409 ürolojik olgunun demografik özellikleri, teşhis, tedavi ve sonuçları retrospektif olarak incelendi.

Bulgular: 362.139 acil olgudan 1409'u (%0,39) ürolojik acil durumludur. Olguların %69,9'u erkekti (yaş ortalaması: 57) ve %30,1'i kadındı (yaş ortalaması: 54). En sık görülen olgu masif makroskopik hematüri (%20,7) ve ikinci en sık olgu %25,5 ile renal kolikti. Ürolojik acil olgular için 381 (%15,5) cerrahi müdahale gerçekleştirildi. En sık uygulanan işlem ürolojik uzmanlık gerektiren üretral darlık içindi.

Sonuç: Çoğu ürolojik acil durum basit müdahalelerle düzeltilebilir ve öte yandan, bazı acil durumların ise basit yöntemlerle tanısı konabilir; ancak gerektiğinde hızlı bir şekilde üroloji uzmanı müdahalesine ihtiyaç duyulabilir. Tüm acil servis doktorları, uygulanmadığında hastalar için ciddi sonuçlar doğurabilecek bu basit yaklaşımların farkında olmalıdır.

Anahtar Kelimeler: Acil, Epidemiyoloji, Ürolojik olgu

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Introduction

Emergency departments are the most important unit of the hospitals which are available 24 hours a day, 7 days a week, and where patients are evaluated quickly after determining the appropriate triage level (1). Urological emergencies can be overlooked by emergency services' specialists as they constitute only a small proportion of patients presenting to the emergency department (1). A significant proportion of urological emergency cases admitted to the hospitals are considered acute cases and require rapid intervention (2). When the patients are evaluated in the emergency department, it may be necessary to seek a urologist's opinion. However, in the absence of urologists, emergency physicians should be able to handle these conditions. Urological emergencies may occur due to accidents, as well as iatrogenic causes, stones, infections, or tumoral events (3). Urological emergencies, which can easily be overlooked in all emergency cases, should be carefully and systematically evaluated. Urological emergencies seen in the emergency departments can be listed as acute renal colic, massive hematuria, acute urinary retention, acute scrotal diseases, priapism, urinary tract infections (UTIs), and genitourinary traumas (4). In our country, several epidemiological studies have been conducted to cover urological emergencies (1,5). In order to contribute to the relevant data of our country, we evaluated patients with urological emergencies admitted to the emergency department of our hospital in terms of demographic and epidemiological characteristics.

Material and Methods

Ethical approval was obtained from the local ethic committee (protocol number: 2019-203-18/2). Of 362,139 patients, the data of 1409 emergency urology patients, who were admitted to Zonguldak Bulent Ecevit University Hospital's Emergency Department between January 2012 and December 2018, were analyzed retrospectively. A written informed consent was obtained from the patients. The medical files of the so-called urological emergencies were retrieved from the hospital's database, and the demographic characteristics, established diagnoses, treatments and results of the urological emergency cases were analyzed. 12.8% of the emergency cases were elective cases that actually did not require emergency evaluation.

The patients admitted to the emergency department were first evaluated by the emergency department assistant and specialist and then, if deemed necessary, were evaluated by the urology assistant and specialist. Cases with suspected genitourinary infections were evaluated by complete blood count and urinalysis and urine culture when necessary. In patients with renal colic complaints, complete urine analysis, kidney-urethra-bladder radiograms, and urinary ultrasound were performed. Noncontrast spiral computed tomography of the whole abdomen was requested in patients with urinary stone disease or a history of stones. Color Doppler ultrasonografi of the scrotum was requested in patients with penoscrotal traumas and acute scrotal pathologies. Direct radiographs (cystography, urethrography, etc) with contrast were requested for all patients with suspected urethral and bladder traumas. In patients where the upper urinary tract may be affected, contrast-enhanced abdominal tomography was requested. Patients with visible hemorrhage in the urine were diagnosed as having macroscopic hematuria, and patients with impaired micturition and hemodynamic stability were diagnosed as having massive hematuria.

Statistical Analysis

Statistical analysis were performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as frequency and percent. Continuous variables were expressed as median (minimum-maximum).

Results

A total of 1409 patients with urological emergencies were evaluated in the emergency department. 69.9% (n=985) of the patients were male and 30.1% (n=424) were female. The mean age of male patients was 57 (2-298) years and 54 (1-96) years for female patients, respectively. 7.2% (n=101) of the patients were younger than 16 years and 46.2% (n=651) were older than 65 years. The distribution of the clinical diagnoses of urological cases admitted to the emergency department is given in Table 1. Subclass diagnoses of trauma and acute scrotum cases were shown in Tables 2 and 3. Genitourinary infection was found in 5.8% (n=89) of the patients, 56.2% (n=50) of which were female and 43.8% (n=39) were male. 21.3% (n=19) of the

Table 1. Distribution of clinical diagnoses of urological emergencies

Diagnosis	Patients, n	%
Acute renal colic	359	25.5
Massive macroscopic hematuria	292	20.7
Genitourinary system traumas	165	11.7
Acute urinary retention	150	10.6
Acute scrotum	115	8.2
Genitourinary system infections	89	6.3
Priapism	23	1.6
Scrotal abscess	13	0.9
Fournier's gangrene	13	0.9
Penile fracture	9	0.6
Elective cases	181	12.8
Total	**1409**	**100**

Table 2. Distribution of trauma cases		
Diagnosis	**Patients, n**	**%**
Minor renal trauma	50	30.3
Penile and scrotal injuries	49	29.7
Major renal injury	25	15.2
Urethral injuries	15	9.1
Ureteral injury	15	9.1
Bladder injury	11	6.7
Total	**165**	**100**

Table 3. Distribution of acute scrotum cases		
Diagnosis	**Patients, n**	**%**
Epididymo-orchitis	42	35
Penoscrotal edema	42	35
Testicular torsion	20	16.7
Torsion of the appendix testis	10	8.3
Testicular mass	6	5
Total	**120**	**100**

patients were hospitalized for treatment. Acute renal colic was diagnosed in 23.6% (n=359) of the patients. 44% (n=158) of the patients were male, 56% (n=201) were female, and 65 (18.1%) were hospitalized for treatment. Of the 150 (9.9%) patients diagnosed with acute urinary retention, 133 were male patients (88.7%) while female patients were 17 (11.3%). Twenty-eight patients (18.7%) were hospitalized and treated. Percutaneous cystostomy catheter was inserted in 4.7% (n=7) of the patients admitted to the emergency department due to urinary retention. Of the 292 (19.2%) patients with macroscopic hematuria, 30.8% (n=90) were hospitalized and treated. 20.6% (n=37) of the patients who were evaluated due to genitourinary system trauma were multitrauma cases. 26.1% (n=43) of the patients had renal trauma, all of which were hospitalized. Four of the major renal trauma cases were explored, and three patients underwent nephrectomy. Suprapubic cystostomy catheters were inserted in 3 of 15 patients with urethral trauma diagnosed by urethrography. Urethral catheters were placed in seven patients by a urologist, and the other patients were catheterized via the urethral route by the emergency specialists. Testicular torsion was diagnosed in 20 of the patients who had a preliminary diagnosis of acute scrotum. Seventeen patients underwent surgical detorsion, and one patient underwent manual detorsion. Two patients required orchectomy.

A total of 1028 (72.6%) patients were treated using simple interventions without the need for hospitalization. Detailed information about the type of the surgical treatment needed for patients is given in Table 4. During this period, none of the patients needed referral to another center.

Table 4. Distribution of the patients who had undergone surgical interventions		
Diagnosis	**Patients, n**	**%**
Opening of urethral stricture/using guide/ requiring expertise	95	24.9
Clot evacuation, and bladder irrigation	78	20.5
Double-J catheter insertion	67	17.6
Testicular detorsion and/or fixation	20	5.2
Renal exploration	20	5.2
Percutaneous cystostomy	19	4.9
Debridement of Fournier's gangrene	13	3.4
Drainage of the scrotal abscess	13	3.4
Priapism (distal shunts)	13	3.4
Orchiectomy	10	2.6
Repair of penile fracture	9	2.4
Repair of scrotal cuts	7	1.8
Repair of bladder rupture	5	1.3
Urethral stone extraction	2	0.5
Total	**381**	**100**

Discussion

The emergency department is the unit where rapid interventions are performed and multidisciplinary approaches are applied from time to time. In general, urological cases requiring emergency intervention are less common than other cases. Acute renal colic, genitourinary infections, urinary retention, genitourinary trauma, acute scrotal and penile pathologies, and gross hematuria are the main urological emergencies (6). In our country, the statistical data related to urological emergency cases presenting to the emergency services vary greatly.

UTIs are the most encountered in urological practice. Almost 50% of the population experience UTIs at least once in their lifetime (7). Although various risk factors increase the probability of developing UTIs, it is especially more common in females (8). Uncomplicated infections respond to medical treatment, whereas complicated cases require inpatient treatment. In our study, 5.8% of the patients admitted to the emergency department had genitourinary system infections, where 56.2% of the patients were females and 21.3% were hospitalized for treatment. The rates in our study were lower than those in the literature (1,5,9). We believe that this may be due to low patient rates.

Renal colic is a condition that 1%-10% of the people may experience in their lifetime (10). Renal colic pain is an important complaint that urges patients with a history of renal stones to go to the emergency department (10). On searching the literature, it was found that renal colic attacks, seen especially among men, make up only 1% of emergency admissions (2,11).

In Europe, 8% of the first-aid emergency ambulance service calls are because of acute renal colics (12). Topaktas et al. (1) reported that renal colic is the second most common case. In another study, Akıncı (5) reported a similar rate of renal colic as the second most common case. In our study, however, renal colic cases were the leading cause for emergency admissions. Again, unlike the literature, the dominant gender among these patients was female. This high rate reflects the incidence of urinary stone disease in our region in particular.

The risk of acute urinary retention, an important cause of emergency admissions, increases with age (5). Acute urinary retention is treated using catheterization (5). The first choice and less invasive option is urethral catheter insertion. This procedure can be done by emergency doctors. However, in cases such as benign prostatic hyperplasia, urethral trauma, urethral strictures, and foreign body in urethra which may cause difficulties in catheterization, interventions requiring urological expertise or percutaneous cystostomy may be warranted (2). In a study by Fall et al. (13), the incidence of suprapubic cystostomy insertion was 59.8%, compared to 22.3% in the study by Topaktas et al. (1). In our study, urethral catheter insertion rate requiring urology expertise was found to be 24.9%, while this rate was 4.89% for percutaneous cystostomy.

The incidence of hematuria has been reported in the literature between 4% and 20% (14). Macroscopic hematuria is defined as the presence of a noticeable amount of blood in the urine, which has a major cause (15). Massive hematuria is a more severe form of macroscopic hematuria and may cause acute urinary retention due to clot development in the patients (16). Although macroscopic hematuria occur for many reasons, it is important to evaluate the patient's vital signs and clot retention in the emergency department. If retention developed due to clot in emergency conditions, it should be evacuated manually with the help of a urethral catheter or using endoscopic methods. In our study, irrigation was applied to 78 of the patients who presented to the emergency department with massive hematuria. Of these, 10 patients required endoscopic intervention.

Acute scrotum is characterized by scrotal pain, tenderness, and swelling. Different pathologies may cause acute scrotum. While infective causes are in the foreground, testicular torsion, which should be diagnosed, and managed in a short time, constitutes the most urgent pathology. 30% of patients with acute scrotum experience testicular torsion, and in this study, it was 17.4%. Orchectomy was performed in four (20%) patients.

10%-15% of traumas include the genitourinary system (1,5). These are mostly blunt traumas (17). The kidneys are the most affected organ (9). Although ureteral injury is rare, it is mostly iatrogenic (18). Pelvic fractures may also be involved in bladder and urethral injuries (1). Penis and scrotal injuries are relatively less common (1). In our study, the most common genitourinary trauma was kidney injuries (48%). Less than 10% of renal traumas require surgical intervention (19). Renal exploration was needed in 26.6% of our patients, and nephrectomy was required only in one (1.3%) patient.

Priapism is a condition that needs to be evaluated and managed rapidly in order to maintain the erectile function. Ten of 23 patients with priapism responded to penile aspiration and irrigation treatment. The remaining 13 patients underwent distal shunt technique. However, the technique was not sufficient in three patients.

Scrotal abscess and Fournier's gangrene are very rare conditions that can have serious consequences when emergency interventions are not performed (20). In this study, 13 patients had scrotal abscesses. They were treated successfully with drainage. In seven of 13 patients with Fournier's gangrene, the departments of anesthesia, general surgery, and plastic reconstructive surgery were involved. In four of the seven patients, the departments of anesthesia and plastic surgery were involved and in two patients only the anesthesia department was involved.

Study Limitations

This study has several limitations. First, the fact that it is based on electronic hospital data constitutes the biggest limitation. Second, the decision of the physicians who performed the first triage of the patients affected the treatment method.

Conclusions

Emergency departments are an important part of hospitals. Some of the patients admitted to the emergency department experience urological emergencies. In this study, the emergency department doctors evaluate the patients, make the appropriate triage, and invite the urology doctor if necessary. Although the rate of urological cases in the emergency department was reported to be 15.6% in the literature, in our study, this rate was 0.39%. Some of the urological emergencies can be diagnosed using simple tests, so a quick triage can be performed, and some of the cases can be relieved with simple interventions. The familiarity of the emergency department with these cases and the ability to perform some interventions can be life-saving and prevent the patient from developing unwanted future outcomes.

Ethics

Ethics Committee Approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later

amendments or comparable ethical standards. Zonguldak Bülent Ecevit University Local Ethic Committee (protocol number: 2019-203-18/2) approval is present.

Informed Consent: Informed written consent was obtained before oparation from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authors Contributions

Concept: R.G., Design: R.G., Data Collection or Processing: K.E., Analysis or Interpretation: K.E., Literature Search: R.G., K.E., Writing: R.G.

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

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Biomarkers and Cellular Infiltration of the Bladder in Interstitial Cystitis/Bladder Pain Syndrome

İnterstisyel Sistit/Mesane Ağrısı Sendromunda Mesane Biyobelirteçleri ve Hücresel İnfiltrasyonu

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What's known on the subject? and What does the study add?

The search for a biomarker for interstitial cystitis/painful bladder syndrome (IC/BPS) is of great interest. Assume the participation of nerve growth factor (NGF), cytokines, activated mast cells in the pathogenesis of IC/BPS. An analysis of the current literature showed a lack of consensus on the potential biomarkers of this disease. We have identified elevated levels of NGF and interleukin-8 in the urine, as well as lymphocytes and mast cells in the biopsy specimens of the bladder. However, no strong relationship between these indicators was observed.

Abstract

Objective: To study the content of nerve growth factor (NGF), interleukin (IL)-8 in the urine, mast cells, and white blood cells in a biopsy of the bladder and the relationship between them in women with interstitial cystitis/bladder syndrome (IC/BPS).

Materials and Methods: Forty-one women with IC/BPS (mean age: 46.6±14.0 years) and 20 women without IC/BPS (mean age: 35.3±9.7 years) were examined in this study. Cystoscopy with hydrodistension was performed. NGF and IL-8 were determined in the urine by enzyme-linked immunosorbent assay. The number of mast cells and leukocytes was determined in biopsy specimens of the bladder wall. Statistical calculations were performed in Excel 2016 (SPSS 15.0). Results were processed using the Pearson's correlation coefficient to describe the relationships between variables.

Results: Diffuse submucosal hemorrhages (43.9%) were more common. The level of NGF was 142.26±134.906 ng/mL, IL-8 was 51.3±9.36 pg/mL, and lymphocytes (238.0±166.42) and mast cells (82.27±38.76) predominated in the biopsy specimens. A correlation of the mast cells with the plasma cells (r=-0.228), neutrophils (r=-0.227), and lymphocytes (r=-0.156) was observed. NGF and IL-8 correlated with mast cells, neutrophils, and plasma cells with weak multidirectional bonds.

Conclusion: With IC/BPS, the concentration of NGF and IL-8 in the urine is increased. In biopsy specimens, mainly lymphocytes and mast cells, the correlation of NGF and IL-8 with mast cells, neutrophils, and plasma cells is weak. These indicators can be included in a complex of diagnostic studies.

Keywords: İnterstitial cystitis/bladder pain syndrome, Urine, Women, Nerve growth factor, Interleukin, Must Cells

Öz

Amaç: Bu araştırmanın amacı, idrar kesesi duvarı biyopsi örneklerinde idrardaki sinir büyüme faktörü (NGF), interlökin (IL) -8 seviyesini, mast hücrelerini ve beyaz kan hücrelerini araştırmak ve interstisyel sistit/mesane ağrısı sendromu (İS/MAS) kadınlarda bu parametreler arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: İS/MAS'li 41 kadın (ortalama yaş: 46,6±14,0 yıl) ve bu hastalığı olmayan 20 kadın (ortalama yaş 35,3±9,7 yıl) incelendi. İS/MAS tanısı hidrodistrasyon sonrası sistoskopik verilere dayanılarak konuldu. Mesane duvarının biyopsi örneklerinde mast hücresi ve lökosit sayısı belirlendi. İstatistiksel hesaplamalar Excel 2016'da yapıldı (SPSS 15.0). Sonuçlar, değişkenler arasındaki ilişkileri tanımlamak için Pearson'un korelasyon katsayısı kullanılarak işlenmiştir.

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Bulgular: Hastalığın süresi 6,0±2,8 yıl idi. Visual analog skala ve ICSI skalalarının ortalama skoru sırasıyla 5,47±0,91 ve 14,7±2,2 puan idi. Çoğu zaman (%43,9) mesane duvarında submukozal kanamalar meydana geldi. İdrardaki ortalama NGF seviyesi 142,26±134,906 ng/mL ve IL-8 - 51,3±9,36 pg/mL idi. Biyopsi örneklerinde lenfositler (238,0±166,42) ve mast hücreleri (82,27±38,76) baskındır. Mast hücrelerinin sayısı, plazma hücrelerinin (r=-0,228), nötrofillerin (r=-0,227) ve lenfositlerin (r=-0,156) zayıf geri bildirimi ile korele idi. NGF ve IL-8 seviyeleri, zayıf çok yönlü ilişkileri olan mast hücreleri, nötrofiller ve plazma hücreleri ile korelasyon gösterdi.
Sonuç: İS/MAS'li hastalarda idrardaki NGF ve IL-8 konsantrasyonu artar. Mesane biyopsi örnekleri ağırlıklı olarak lenfositler ve mast hücreleri tarafından enfiltre edilir. NGF ve IL-8 seviyeleri, zayıf ilişkileri olan mast hücrelerinin, nötrofillerin ve plazma hücrelerinin sayısı ile ilişkilidir. Elde edilen sonuçlar İS/MAS etiyolojisinin daha iyi anlaşılmasını sağlar ve teşhis prosedürleri kompleksine dahil edilebilir.
Anahtar Kelimeler: İnterstisyel sistit/mesane ağrısı sendromu, İdrar, Kadınlar, Sinir büyüme faktörü, İnterlökin, Zorunlu hücreler

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is one of the urological impairments that has a huge impact on one's quality of life (1,2). According to the literature, 300 of every 100,000 women suffer from this disease worldwide (3).

The diagnostic criteria for this disease are complex and ambiguous. The diversity of symptoms and differences in patients' susceptibility to treatment indicate that IC/BPS has a polyetiological nature (4).

Moreover, the nature of IC/BPS is yet not fully understood. At present, there are different theories of this disease. The etiological factors of the disease include autoimmune, allergic, infectious, neurological, and vascular diseases, as well as infiltration of the bladder wall by increased number of mast cells, injury of the protective layer of the mucous membrane, and the impact on the bladder wall of toxic substances contained in urine. One of the existing theories of the disease is the activation of mast cells and neurogenic inflammation theory (5,6). The lack of standard diagnostic procedure and poor correlation of the patient's clinical features with cystoscopic data or a hydrodistension procedure are some of the reasons why biomarkers are more promising for clinical diagnosis as well as for understanding the pathophysiology of IC/BPS (7). Nerve growth factor (NGF) as a potential biomarker is particularly of great interest for the diagnosis of patients with IC/PBS. Studies have shown a direct relationship between the painful inflammatory processes in the lower urinary tract and increased NGF level in bladder tissues and urine (8-10). Data from several studies have indicated the central role of activated mast cells in the IC/BPS pathogenesis and pathophysiology. When activated, mast cells secrete biologically active mediators that can cause symptoms of this disease (11). Recently in the medical scientific literature, much attention has been paid to the study of cytokines in IC/BPS. According to these studies, the interaction of cytokines and receptors can activate signaling pathways that cause transcription and release of other proinflammatory/nociceptive mediators, including NGF and other cytokines and chemokines from peripheral neurons or glial cells. The expression of cytokines alone or in combination with other cytokines, growth factors, or other mediators can form a bidirectional communication network between the nervous system and the immune system (12).

Thus, the diagnosis and management of patients is often difficult due to the incomplete clear pathogenesis of IC/BPS and its unknown etiology. IC/BPS mandates an in-depth study, basic and clinical research, especially regarding the diagnostics and biomarkers. Therefore, the etiology, pathogenesis, and clinical features of IC/BPS require in-depth fundamental and clinical investigations, especially with regard to the diagnosis of the disease and determination of the diagnostic value of biomarkers.

The aim of this research was to investigate the levels of NGF and interleukin (IL)-8 in urine, mast cells, and white blood cells in urinary bladder wall biopsy specimens and to assess the relationship between these parameters in women with IC/BPS.

Materials and Methods

This study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki: Recommendations guiding physicians in biomedical research involving human subjects (13). In addition, informed consent was obtained for each patient and the examined control group.

In this study, 41 women with IC/BPS (main group) and 20 women without IC/BPS (control group) were included. IC/BPS was diagnosed according to the cystoscopic data after hydrodistension.

The inclusion criteria of the study were:

- Women aged 17 years and over who have had an onset of IC/BPS signs during at least the last six months;

- Non-ulcer type of IC/BPS; and

- An absence of diabetes, arthritis, systemic lupus erythematosus.

The exclusion criteria, on the other hand, were:

- The presence of acute or exacerbation of a chronic urinary tract infection, as well as asymptomatic bacteriuria during the last three months before inclusion into the study;

- The presence of diseases or conditions that could be the cause of pelvic pain and urinary discomfort, including neurological

diseases, bladder and ureteral stones, severe prolapse of the pelvic organs, infravesical obstruction;

- Tumors of the pelvic organs at the time of the investigation period or in anamnesis;

- Therapeutic treatment of IC/BPS for three months prior to the start of study;

- Bladder hydrodistension and/or intravesical injections of botulinum toxin in anamnesis; and

- A negative lidocaine test.

In addition, in the control group, none of the examined women had a history of IC/BPS and any diseases of the lower urinary tract.

The bladder pain in patients with IC/BPS was measured using a visual analog scale. According to this scale, each centimeter on the line corresponds to 1 point. So, the minimum value 0 represented a complete absence of pain syndrome; up to 2 points was classified as weak; 2-4 as moderate; 4-6 as strong; 6-8 as the strongest; and the maximum value, that is, 10 corresponded to an intolerable pain.

Further, the O'Leary-Sant Interstitial Cystitis Symptoms index (ICSI) was used to evaluate the treatment of patients with IC/BPS (14). The scale consists of four questions, each of which is rated between 0 and 5 points, the maximum number of points being 20. The questions reflect the severity of the major IC/BPS symptoms over the last month prior to the survey. How often have you felt the strong need to urinate with little or no warning? Have you had to urinate again less than 2 hours after you finished urinating? How often do you most typically get up at night to urinate? Have you experienced pain or burning in your bladder?

All patients underwent a comprehensive examination, including cystoscopy and hydrodistension of the bladder, which was performed in an endoscopic operating room under general anesthesia using Olympus endoscopes (Japan) with 30- and 70-degrees optics. For the analysis of cystoscopic changes, a grading system was used that included five classes: 0 - no changes in the mucosa, I- rare glomerulations at least in two quadrants, II- diffuse submucosal hemorrhages, III- diffuse mucosal bleeding, and IV- Hunner's lesions.

To determine the NGF and IL-8 in urine, 10 ml urine was collected in a sterile test tube and the obtained biosamples were placed on ice and delivered to the laboratory within 15-20 minutes. The samples were centrifuged for 10 min at 3000 rpm and a temperature of 4°C. For storage, supernatants were poured into 1 mL Eppendorf tubes and stored until analysis at a temperature of -80°C. While the NGF was determined by the enzyme-linked immunosorbent assay using a set of NGF Emax® Medispec 6000 M apparatus (Israel), the concentration of IL-8 was determined by the method of solid-phase immunoenzymatic analysis using the reagent sets of Vector-Best company (Russia). Additionally, the number of mast cells and leukocytes was determined in biopsy specimens of the bladder wall taken during cystoscopy. Finally, a deep biopsy from the bladder wall till the muscle layer was performed under short-term intravenous anesthesia. The biopsy site was re-examined after which the cystoscope was removed, and 30-60 minutes later the patients urinated on their own. Moreover, after a biopsy of the bladder wall, the patients were monitored for 5-6 hours. No cases of bleeding or other complications were noted. Samples of biopsies were fixed in 10% buffer of a neutral solution of formalin. Next, the specimens were prepared in alcohol solutions at the concentrations of 75%, 85%, 95%, and 99.9%. Subsequently, the samples were contained in a xylene solution and enclosed in paraffin blocks from which serial sections 3-5 microns were prepared and stained by the May-Grünwald-Giemsa method to detect mast cells. Each cross-section was divided into 10 areas. Cell infiltration was evaluated in each of these areas using the following scale: 0- no cells; 1- <20 cells; 2- 20-45 cells; 3- >45 cells. The points of all 10 sections were added and then divided by 30 (maximum possible score) and multiplied by 100. Therefore, the cell scores were the average of the three studied sections. Microscopy was performed at ×200 magnification (15).

Statistical Analysis

Data were analyzed using Excel 2016 (SPSS 15.0). Statistical indicators were expressed as mean ± standard deviation as well as in numbers and percentages. The Pearson's correlation coefficient was calculated to describe the relationships between variables, and $p<0.05$ was considered as statistically significant.

Results

The patients in this study were aged between 21 and 76 years, with a mean age of 46.6±14.0 years. Out of the 41 women with IC/BPS, 12 patients (29.3%) were of reproductive age and 29 (70.7%) of premenopausal and menopausal age. In the control group, the age of the examined women ranged between 17 and 53 years and the average age was 35.3±9.7 years.

In the main group, based on the obstetric-gynecologic history, 2 (4.9%) women had no pregnancies and the 39 (95.1%) had one-four pregnancies; 4 (10.3%) women belonged to the unborn and 35 (89.7%) had 1-3 genera; and 4 (10.3%) women were nulliparous and 35 (89.7%) had 1-3 births. Overall, gynecological diseases were registered in 12 (29.3%) women, and there were 9 (22.0%) cases of pelvic organ prolapse and 3 (7.3%) cases of uterine myoma. While more than half of the observed patients

(58.5%) could not associate the onset of IC/BPS symptoms with any history event, 11 (26.8%) associated them with previous urinary tract infections and 6 (14.6%) indicated emotional stress as a possible reason for the development of IC/BPS. Table 1 presents the clinical characteristics of the examined main group.

Of note, in the control group, there were equal number of women at reproductive age and those at premenopausal and menopausal age, that is, 10 (50%) in each age group.

When comparing the main and control groups, a statistically smaller number of women with IC/BPS of reproductive age (41.4%, $p<0.05$) and a larger number of premenopausal and menopausal women (29.28%, $p<0.05$) were revealed. During the cystoscopy in women in the control group, no changes in the mucous membrane of the bladder were detected.

According to the results of the ICSI scale, the largest number of patients, that is, 23 (56.1%) had 14 points, 2 (4.9%) had a minimum score of 10, and 6 (14.6%) had a maximum score of 20. In 24 (58.5%) patients, urination more than 8 times a day was noted.

While the level of NGF in urine in the main group ranged from 35.7 to 848.8 ng/mL, which averaged 142.26±134.906 ng/mL, in the control group, the NGF level ranged from 0 to 746.19 ng/mL, which averaged 130.69±124.985 ng/mL. The measurement of the concentration of IL-8 in urine showed its increase in the patients in the main group. The average level in the main group was 51.3±9.36 pg/mL (30.4-67.6 pg/mL) and in the control group was 24.1±5.37 pg/mL (11.2-31.0 pg/mL). When evaluating the biopsy samples, inflammatory cell infiltration was revealed (Table 2).

Mast cells correlated with weak feedback with plasma cells (r=-0.228), neutrophils (r=-0.227), and lymphocytes (r=-0.156).

While the correlation analysis did not reveal any relationship between NGF and IL-8, there was a weak relationship between the level of NGF and IL-8 with the cells of the bladder biopsy (Table 3).

Table 1. Clinical characteristics of patients with interstitial cystitis/bladder pain syndrome

Indicators	Main group (n=41)	Control group (n=20)
Age 21-44 years, n/%	12/29.3	10/50.0
Age 45-76 years, n/%	29/70.7	10/50.0
Duration of the disease, years	6.0±2.8	-
The average score of the VAS	5.47±0.91	-
2-4 points (mild pain), n/%	8/19.5	-
5-6 points (moderate pain), n/%	23/56.1	-
7-8 points (severe pain), n/%	10/24.4	-
O'Leary-sant interstitial cystitis symptoms index	14.7±2.2 (10-20)	-
Frequent urination, n/%	24/58.5	-
Imperative urination, n/%	11/26.8	-
Urgent incontinence, n/%	6/14.6	-
Bladder capacity, Mπ	276.0±61.8* [108; 360]	405.4±37.2 [322, 486]
Urethral polyps, n/%	5/12.2	
Cystoscopy of the bladder mucosa		
Without changes, n/%	4/9.7*	20/100
Diffuse submucosal hemorrhages, n/%	18/43.9	
Glomerulations, n/%	8/19.5	
Diffuse bleeding, n/%	6/14.6	
Hunner lesions, n/%	5/12.2	

VAS: Visual analogue scale, *: Statistical significance of differences between groups ($p<0.05$-0.001)

Table 2. Cellular spectrum of bladder biopsies in women with interstitial cystitis/bladder pain syndrome

Indicators	Main group (n=41)
Mast cells	82.27±38.76 (0-237)
Eosinophils	1.61±1.44 (0-22)
Lymphocytes	238.0±166.42 (12-589)
Neutrophils	26.06±17.67 (0-312)
Plasma cells	60.12±53.26 (0-221)

Table 3. Correlation coefficient of cells with nerve growth factor and IL-8

Cells	NGF	IL-8
Mast cells	+0.120	+0.062
Eosinophils	+0.053	+0.165
Lymphocytes	+0.017	-0.117
Neutrophils	-0.129	-0,158
Plasma cells	+0.187	-0.131

NGF: Nerve growth factor

Discussion

In this study, we reviewed the anamnesis, clinical picture of patients with IC/BPS. The predominant symptom of IC/BPS is pain (16). In women with IC/BPS, severe pain was observed in 24.4%, moderate in 56.1%, and mild pain in 19.5% of cases. Bladder volume ranged from 108 mL to 360 mL. A capacity of <200 mL was reported in 7.3% of patients, which is consistent with other researchers who note that only about 8% of the patients have a small volume of bladder (200 mL) (17).

IC/BPS diagnosis often includes the exclusion of disorders such as malignancy, infectious processes, bladder hyperactivity, and other sources of bladder pain and urinary symptoms that can mimic IC/BPS symptoms. There is no consistent cystoscopic

diagnostic results for IC/BPS because cystoscopy can be completely normal in many patients (18). According to our data, 9.7% of patients had no changes in cystoscopy. However, Hunner's lesions and inflammatory phenomena are often the only cystoscopic findings that contribute to the diagnosis of IC/BPS (19). In addition, petechial hemorrhages, also known as glomerulations, were identified as diagnostic signs, but they can also be found in asymptomatic patients. In our investigation, out of the 41 patients in the main group, only 8 (19.5%) had glomerations that covered >60% of the bladder surface.

Our results showed a slight increase (8.13%) of NGF in urine in patients with IC/BPS compared to the control value and a statistically significant increase in IL-8-53.0 ($p<0.05$). Our data on elevated NGF in urine at IC/BPS are comparable to the results of Tonyali et al. (8) and Kim et al. (20). However, in our studies, the difference was not statically significant, whereas according to these authors, the increase was statistically significant. Currently, many researchers propose to introduce urinary NGF as a biomarker (21). It regulates the development and maintenance of sensory and sympathetic neurons and plays a role in painful somatic and visceral inflammation (22).

It is believed that the urinary NGF plays a key role in the correlation between inflammation and pain impulse, as it is produced by urothelial cells, smooth, and mast cells activating their degranulation and proliferation (22).

Chronic inflammation leads to increased secretion of NGF in the urine which leads to morphological changes in the system of sensitive and motoneurons of the bladder. Nevertheless, despite the availability of numerous studies aimed at the search for new IC/BPS biomarkers, the contribution of NGF to the bladder function is not entirely clear.

Although the results showed an increase in the NGF and IL-8 levels, they did not correlate with each other. However, in the etiology of IC/BPS, these indicators as factors of inflammation play an important role, as inflammation has a direct effect on the function of the bladder (23). Chronic inflammation of the bladder is accompanied by infiltration of the bladder wall by lymphocytes, mast, and plasma cells leading to irreversible changes in tissues. Moreover, the analysis of the obtained data showed that the morphological picture was represented by different degrees of expression by cellular infiltration, mainly lymphoplasmatic with mast cells. Our study found the correlation of mast cells with neutrophils and plasma cells. In addition, the cystoscopic picture (the presence of glomerulation, Hunner's lesions, the severity of hematuria, and bladder volume) did not directly correlate with the morphological changes in the biopsy specimens. Approximately similar data were obtained by Syed et al. (24).

Modern electron microscopy and modern immunohistochemistry data as well as staining methods confirm the central role of mast cells in the pathogenesis and pathophysiology of IC/BPS. However, researchers recommend continuing research aimed at finding IC/BPS biomarkers.

Study Limitations

The main limitation of the present study is the small group of surveyed patients. However, identifying urinary biomarkers with IC/BPS will improve the diagnostic strategies and reduce patient invasiveness, while also improving the exclusion criteria and reducing the diagnostic time.

Conclusion

In patients with IC/BPS, an increase of urinary NGF and IL-8 levels was observed. Inflammatory cell infiltration of biopsy samples of the bladder mainly by lymphocytes and mast cells was detected. A weak correlation was found between the NGF and mast cells, neutrophils, and plasma cells. IL-8 was correlated with a weak direct relationship with eosinophils and reverse with neutrophils and plasma cells. The obtained results contribute to a better understanding of the etiology of IC/BPS and can be included in the complex of diagnostic studies.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Republican Centre of Diagnosis and Treatment (number: 2018/136).

Informed Consent: Informed consent was obtained for each patient and the examined control group.

Peer-review: Externally peer-reviewed.

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Comparison of the Abdominal and Transvaginal Techniques in the Surgical Treatment of Vesicovaginal Fistula and Analyzing the Factors Affecting Its Recurrence

Vezikovajinal Fistülün Cerrahi Tedavisinde Abdominal ve Transvajinal Tekniklerin Karşılaştırılması ve Nükse Etki Eden Faktörlerin Analizi

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What's known on the subject? and What does the study add?

Vesicovaginal fistulas are disorders with different etiologies and have significant psychological and social consequences. The incidence of fistula due to gynecologic trauma can reach up to 10%. Surgical treatment of complex fistulas can be performed by vaginal or abdominal techniques. However, there is limited data in the literature on comparisons of these techniques. In this study comparing the results of these two techniques, we found that abdominal technique provides more successful results and we concluded that the risk of recurrence increases in patients with a history of radiotherapy.

Abstract

Objective: To compare the abdominal and transvaginal techniques in the surgical treatment of vesicovaginal fistula (VVF) and analyze the factors affecting its recurrence rate.

Materials and Methods: Patients were divided into two groups according to the operation technique used (abdominal-transvaginal) and the recurrence status (recurrent and non-recurrent). The primary endpoint of the study was the comparison of the factors related to fistula and surgical techniques.

Results: The number of cases with radiotherapy history was found to be higher in the recurrent group (68.2% vs 11.5%, p<0.001). Although fistulas were more subtrigonally located in the transvaginal repair group, the supratrigonal localization was more frequent in those operated with abdominal technique (p=0.019). While the rates of first and second recurrences were more in the cases managed by the transvaginal technique (p=0.041), the length of hospitalization and the mean operation time were longer in women managed by abdominal technique (p=0.025 and p=0.019, respectively).

Conclusion: The abdominal technique provides more favorable outcomes by allowing extensive tissue exposure and omental tissue flep in the surgical treatment of VVF. Patients with a history of radiotherapy are more likely to have a recurrence after the surgery and repetitive treatment may be needed.

Keywords: Vesicovaginal fistula, Vesicovaginal fistula repair, Gynecological trauma, Transvaginal technique, Abdominal technique

Öz

Amaç: Vezikovajinal fistül (VVF) onarımında abdominal ve transvajinal tekniklerin karşılaştırılması ve nükse etki eden faktörlerin analizini yapmaktır.

Gereç ve Yöntem: Hastalar operasyon tekniğine göre (abdominal-transvajinal) ve nüks durumuna göre (nüks edenler-nüks etmeyenler) gruplara ayrıldı. Fistül ve cerrahi yöntemlerle ilişkili faktörlerin karşılaştırılması, çalışmanın birincil sonlanım noktasıydı.

Bulgular: Radyoterapi öyküsü olan olgu sayısı rekürren grupta daha fazlaydı (%68,2 vs %11,5, p<0,001). Transvajinal onarım yapılan grupta fistüller sıklıkla subtrigonal yerleşimli iken, abdominal teknikle ameliyat edilenlerde supratrigonal yerleşim daha sık görüldü (p=0,019). Transvajinal teknikle tedavi edilen olgularda hem birinci hem de ikinci rekürrens oranı daha fazlaydı (p=0,041). Hem hastanede kalış süresi hem de ortalama operasyon süresi abdominal teknikle ameliyat edilenlerde daha uzundu (sırasıyla, p=0,025 ve p=0,019).

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Sonuç: Abdominal teknik, VVF'nin cerrahi tedavisinde geniş doku ekspojuruna ve omental doku flepine olanak sağlayarak daha olumlu sonuçlar sağlar. Radyoterapi öyküsü olan hastalarda ameliyat sonrası nüks riski daha yüksektir ve tekrarlayan tedaviler gerekebilir.
Anahtar Kelimeler: Vezikovajinal fistül, Vezikovajinal fistül onarımı, Jinekolojik travma, Transvajinal teknik, Abdominal teknik

Introduction

Vesicovaginal fistula (VVF) is an abnormal pathological connection between the bladder and the vagina that allows a continuous and involuntary discharge of urine into the vaginal vault. VVF, besides having variable etiology, is a cause of physiological and social problems in both developing and developed countries (1). The most common reason for this in the developed countries is the overlooked trauma of the genitourinary tract during gynecological operations such as hysterectomy, endometrioma, and prolapse surgery. Other rare reasons include radiation therapy and locally advanced pelvic organ cancers. It is estimated that the incidence in developed countries is between 0.3% and 2% (2). The incidence of VVF is reported to be about 0.5% after simple hysterectomy and 10% after radical hysterectomy (3,4). The most common reason with respect to underdeveloped countries is the labor, which is responsible for >90% of the cases. In Africa, the low socioeconomic status and early marriages are some of the important factors (5). Small, non-irradiated, and single fistulas are classified as simple fistulas; whereas, large, irradiated, recurrent, and multiple fistulas are classified as complex fistulas. Simple fistulas are usually managed by vaginal technique and complex fistulas by vaginal or abdominal techniques using a myocutaneous flep (4). The Latzko and layered closure techniques are the two commonly used methods in transvaginal technique (6). The abdominal technique, on the other hand, can be performed with both transvesical (excision of the fistula) or extravesical (bivalve technique) approaches. In both approaches, the bladder is opened and mobilized before the incision in the bivalve technique (7), while the fistula is made apparent through the bladder dome in the transvesical approach (8).

The success rates of the transvaginal and transabdominal techniques are reported to be about 50-100% and 80-100%, respectively (9-12). However, it is impossible to make an exact suggestion as to which technique is more appropriate for which patient, because the techniques differ among the patient groups and their follow-up periods are not standardized. There are a limited number of studies comparing the two techniques head-to-head in the literature (13). Therefore, the aim of this study was to compare the outcomes of these two techniques used in the surgical treatment of VVF.

Materials and Methods

Formation of Patient Groups and Data Collection

This study was conducted in a university hospital between January 2016 and January 2019. A total of 124 patients diagnosed with VVF had been treated at the hospital, out of which, 28 patients whose data were inconsistent were excluded and the remaining 96 patients were included in the study.

Thirty patients underwent VVF repair by transabdominal technique and 66 through transvaginal technique. Data on comorbidities, diabetes, history of hysterectomy, cesarean and non-gynecological surgery, history of radiotherapy, oral medication use from diagnosis to operation, time from prior operation to VVF repair, time from gynecologic operation to fistula formation, double-J stent insertion, method and duration of postoperative catheterization, postoperative complication, length of hospital stay, first and second recurrences, mean recurrence time, and post-recurrence operation technique were obtained from the hospital registration system.

The authors declare that the research was conducted adhering to the principles of the World Medical Association Declaration of Helsinki: "Ethical Principles for Medical Research Involving Human Subjects," (as amended in October 2013). All patients gave a written informed consent before the surgery for the use of the collected data at any given time.

Diagnosis of VVF

The diagnosis of VVF was made after a detailed anamnesis and speculum examination with a full bladder. Stress test with cough maneuver was made to exclude a possible leakage from urethral meatus. Diagnosis was confirmed by the presence of suspicious site of fistula in the cystoscopy, visualization of the tract through the speculum, and the fluid coming from the vagina. In suspected cases, first, the bladder was filled with methylene blue, and the patients with blue vaginal tampon were diagnosed with VVF. Patients with continuous urine leakage after the first operation were evaluated for recurrence, and a re-operation was planned for them. Patients with urinary tract infection were treated with appropriate antibiotic medications according to culture-antibiogram results.

Evaluation Criteria and Classification of Fistula

A procedure was considered as successful when the patients had no urine leakage after the removal of the catheter in the postoperative period. Any urine leakage after a period of dryness was considered as recurrence. Fistula location was categorized into three groups according to the intertrigonal line as follows: fistulas located in the distal of the trigone was named as subtrigonal; those located in the trigonal line as trigonal; and those located in the proximal of the trigone as supratrigonal.

Operation Techniques

Transvaginal Technique

The Latzko procedure was used in patients treated with the transvaginal technique (6). The location and size of the fistula were evaluated through an endoscope in the lithotomy position under general anesthesia. Transvaginal inspection was performed with a speculum. A small right angle clamp was inserted through the fistula tract and it was confirmed by endoscopy that the tip of the clamp was in the bladder. A 12 Fr Foley catheter was inserted through the transvaginal fistula tract with a right angle clamp and the balloon was inflated with 5 mL saline. Vaginal exposure was made after the bladder was emptied with the Foley catheter. The fistula tract was cut annular completely with the traction of Foley catheter. The bladder and vaginal mucosa were separated from each other by sharp dissections without excision of the fistula tract. The bladder mucosa and the vaginal mucosa were sutured in a water-tight manner with 3/0 polyglactin sutures separately. We did not use any fleps in transvaginal technique. An 18 Fr Foley catheter was inserted to the bladder at the end of the procedure. The catheter was removed after 21 days of bladder drainage.

Abdominal Technique

For the patients treated with abdominal technique, the bivalve technique was used (7). In this technique, the bladder was exposed with a median incision in the supine position, then opened through the dome. Bladder was incised from the dome to the fistula tract. The fistula tract was excised after annular incision. The bladder around the excised fistula tract was also closed perpendicular to the vagina after the closure of the vagina. An omental tissue flep was inserted between the vagina and the bladder. The bladder was completely closed and the procedure was terminated with an 18 Fr Foley catheter insertion. The catheter was removed after 21 days of bladder drainage.

Some patients used oral anticholinergic treatment preoperatively. For patients diagnosed at an external center, a homogenization could not be provided for the initiation of medication in the preoperative period. Postoperatively, all patients received anticholinergic treatment and topical estrogen treatment for six months. The anticholinergic treatment was started from the time of diagnosis of fistula to the postoperative sixth month, and no specific agent was recommended. The topical estrogen treatment was started in the postoperative period and 1×1 daily in the first week and then twice a week for a total of six months was recommended. Our preferred agent for topical estrogen treatment was intravaginal 10 mcg estradiol.

Outcome Measures

The patients were divided into two groups (group I; VVF repair by transvaginal technique, group II; VVF repair by abdominal technique). The primary endpoint was the comparison of the factors specific to the disease and surgical techniques between the two groups. Then, the patients were again divided into two groups but according to recurrence (group A; recurrent, group B; non-recurrent). The secondary endpoint was the analysis of the factors affecting the recurrence rate.

Statistical Analysis

Fisher's exact and Pearson's chi-square tests were used for analyzing the frequency of categorical variables. The normality analysis for continuous variables was made through the Kolmogorov-Smirnov test. While, Student's t-test was used for normally distributed variables, Mann-Whitney U test was used for non-normally distributed variables. Normally distributed data were presented as mean ± standard deviation, whereas non-normally distributed data were presented as median (minimum-maximum). $P<0.05$ was considered as statistically significant. All statistical analysis was performed using the IBM SPSS Statistics version 24.0.

Results

In this study, the data of 96 patients who underwent a VVF surgery between January 2016 and December 2018 were analyzed. Thirty patients (31.2%) were included in the abdominal group and 66 (68.8%) in the transvaginal group. Patients' data on the mean age, comorbidity, and diabetes history were similar between the two groups ($p>0.05$). The rate of radiotherapy history was also similar in patients operated via the two techniques ($p=0.584$). The length of hospital stay and the mean operation time were longer in the abdominal group than the transvaginal group ($p=0.025$ and $p=0.019$, respectively). No significant pre- and postoperative complications were observed in both groups. There was no significant difference between the two groups in terms of estimated blood loss. While the fistulas were more subtrigonally located in the transvaginal group, supratrigonal localization was more frequent in those operated with abdominal technique ($p=0.019$). There was no significant difference between the groups in terms of fistula size according to the operation technique and the recurrence status ($p=0.904$ and $p=0.519$, respectively). We did not encounter any donor-site complications in any of the patients with fleps.

The number of both first and second recurrent cases was higher in the transvaginal group than the abdominal group ($p=0.004$ and $p=0.041$, respectively). The comparison of categorical and continuous variables according to the operation techniques is summarized in Table 1.

Forty-four patients experienced a recurrence (45.8%). The length of hospital stay and the mean operation time were shorter in the recurrent group than the non-recurrent group ($p=0.011$

and p=0.034, respectively). While the rate of anticholinergic use from the diagnosis of fistula to the operation was lower in the recurrent group (9.1% vs 34.6%, p=0.014), the subtrigonal location was higher in this group (p=0.033). The rate of radiotherapy history was higher in recurrent patients (68.2% vs 11.5%, p<0.001). Table 2 shows the comparison of categorical and continuous variables according to the recurrence.

Table 3 summarizes the recurrence rates according to the operation techniques in patients with a radiotherapy history

Table 1. Comparison of categorical and continuous variables according to the operation technique

Variables	Group I (n=66)	Group II (n=30)	p
Comorbidity	16 (24.2)	4 (13.3)	0.388*
Diabetes Mellitus	6 (9.1)	0 (0)	0.542*
Operation history	66 (100)	30 (100)	–
Hysterectomy	62 (93.9)	26 (86.7)	0.579*
Cesarean section	6 (9.1)	4 (13.3)	0.642*
Radiotherapy history	22 (33.3)	14 (46.7)	0.584*
Anticholinergic use from diagnosis of fistula to operation	14 (21.2)	8 (26.7)	0.418*
Double-J stent implementation	4 (6.1)	6 (20.0)	0.307*
Postoperative catheterization Foley catheter Cystostomy catheter	66 (100) 66 (100) 32 (48.5)	30 (100) 30 (100) 20 (66.7)	– – 0.241**
Postoperative complication Hemorrhage Infection	0 (0) 0 (0) 0 (0)	2 (6.7) 0 (0) 2 (6.7)	0.313* –
Fistula location			
Supratrigonal Trigonal Subtrigonal	12 (18.2) 21 (31.8) 33 (50.0)	18 (60.0) 6 (20.0) 6 (20.0)	**0.019****
Fistula size (mm)	12.6±2.8	10.4±1.9	0.904***
Recurrence	40 (60.6)	4 (13.3)	**0.004***
Second recurrence	18 (27.3)	0 (0)	**0.041***
Age	51.3±6.46	50.0±4.89	0.297***
Duration from the operation to the fistula repair (month)	2.24 (1-10)	2.4 (3-12)	0.641****
Cystostomy catheterization time (day)	18 (14-25)	21.82 (12-24)	0.227****
Foley catheterization time (day)	19 (13-28)	21 (14-26)	0.323****
Hospitalization time (day)	4.00±3.31	7.07±3.34	**0.025*****
Operation time (min)	28.10±9.64	42.88±24.13	**0.019*****
Estimated blood loss (mL)	45.11±9.72	66.71±12.90	0.611***
Recurrence time (month)	1.25 (1-3)	3.48 (1-7)	**0.001*****

Data were presented as mean ± SD or median (minimum-maximum), Group I, transvaginal technique; Group II, transabdominal technique, *Fisher's Exact test; **Pearson's chi-square; ***Student t-test, ****Mann-Whitney U test, SD: Standard deviation

Table 3. Recurrence rates according to the operation techniques in patients with radiotherapy history

	Group I (n=66)		Group II (n=30)		p*
	RT+	RT–	RT+	RT–	
Number	22 (33.3)	44 (66.7)	14(46.7)	16 (53.3)	0.584
Recurrence	20 (90.9)	20 (45.4)	4 (28.6)	–	**<0.001**

Group I: Transvaginal method, Group II: Transabdominal method, RT: Radiotherapy, Data are presented as number (%), *Fisher's Exact test

Table 2. Comparison of the categorical and continuous variables according to the recurrence status

Variables	Group A (n=44)	Group B (n=52)	p
Comorbidity	8 (18.2)	12 (23.1)	0.677**
Diabetes Mellitus	6 (13.6)	0 (0)	0.052**
Operation history	40 (90.9)	48 (92.3)	1.000*
Hysterectomy	26 (86.7)	62 (93.9)	0.579*
Cesarean section	6 (13.6)	4 (7.7)	0.649*
Radiotherapy history	30 (68.2)	6 (11.5)	**<0.001***
Anticholinergic use from diagnosis of fistula to operation	4 (9.1)	18 (34.6)	**0.014***
Double-J stent implementation	6 (13.6)	4 (7.7)	0.649*
Postoperative catheterization Foley catheter Cystostomy catheter	44 (100) 44 (100) 20 (45.5)	52 (100) 52 (100) 32 (61.5)	– – 0.265**
Postoperative complication Hemorrhage Infection	(0) 0 (0) 0 (0) 0	2 (3.8) 0 (0) 2 (3.8)	1.000* – 1.000*
Fistula location			
Supratrigonal Trigonal Subtrigonal	9 (20.5) 6 (13.6) 29 (65.9)	32 (61.5) 13 (25.0) 7 (13.5)	**0.033****
Fistula size (mm)	13.8±2.1	11.9±1.7	0.519***
Second recurrence	18 (40.9)	0 (0)	**<0.001***
Operation technique			
Transabdominal Transvaginal	4 (9.1) 40 (90.9)	26 (50) 26 (50)	**0.004***
Age	50.13±6.50	51.61±5.57	0.235***
Duration from the operation to the fistula repair (month)	3.2 (3-5)	3.6 (2-6)	0.304****
Cystostomy catheterization time (day)	21.00 (21-28)	19.16 (14-25)	0.313****
Foley catheterization time (day)	19.62 (14-29)	17.13 (13-28)	0.358****
Hospitalization time (day)	4.14±3.72	7.08±3.17	**0.011*****
Operation time (min)	26.22±10.09	39.13±13.45	**0.034*****
Estimated blood loss (mL)	71.42±16.82	52.23±14.83	0.482

Data are presented as number (%), mean ± SD, or median (minimum-maximum), Group A: Recurrent, Group B: Non-recurrent, *Fisher's Exact test, **Pearson's chi-square, ***Student t-test, ****Mann-Whitney U test, SD: Standard deviation

Table 4. Recurrence rates of the surgical techniques according to fistula location							
	Group I (n=66)			Group II (n=30)			p*
	Fistula location			Fistula location			
	Supratrigonal	Trigonal	Subtrigonal	Supratrigonal	Trigonal	Subtrigonal	
Number	12 (18.2)	21 (31.8)	33 (50.0)	18 (60.0)	6 (20.0)	6 (20.0)	**0.019**
Recurrence	10 (83.3)	16 (76.2)	14 (42.4)	1 (5.6)	1 (16.7)	2 (33.3)	**<0.001**
Group I: Transvaginal technique, Group II: Transabdominal technique, data are presented as number (%), *Fisher's Exact test							

and shows that the recurrence rates in such patients were significantly higher in both groups (p<0.001).

Recurrences were most frequently seen in supratrigonal location for the transvaginal group and in subtrigonal location for the transabdominal group (p<0.001). Table 4 shows the comparison of the recurrence rates in both groups according to the location of the fistula.

Discussion

VVF is a disease that generally develops due to obstetric and gynecological etiology and causes extreme discomfort that often leads to social isolation in women. In this study, we analyzed the outcomes of patients who underwent a VVF repair. It was found that the history of radiotherapy and the use of anticholinergic medication were important factors for the recurrence of the disease, and that the abdominal technique can yield a higher success rate than the transvaginal technique. Although, the estimated blood loss was similar in both methods, the length of hospital stay and the mean operation time were shorter in the transvaginal technique.

While there is no clear consensus on the "gold-standard" surgical treatment of VVF, a recent meta-analysis showed that the transvaginal (39%), combined transabdominal/transvaginal (36%), and laparoscopic/robotic (15%) approaches were the most commonly preferred methods for VVF repair (14). Abdominal transvesical approach – as described by O'Conor and Sokol in the early 1950s - is considered as the gold-standard for the supratrigonal VVF treatment (15,16). The most important advantage of the abdominal approach is the availability of a peritoneal or omental flep. It is recommended that the abdominal approach should be performed after a failed transvaginal VVF repair, in ureteral involvement, and if vaginal access to the fistula is not possible. Transvaginal approach has been shown to provide shorter operation and hospitalization duration and less blood loss. In addition, peritoneal flep, Martius fat flep, and gracilis muscle flep can be used in this method. While the success rates of the vaginal and abdominal approaches were similar (3), the main disadvantages of the former are as follows: there may be a dead space in the Latzko technique and shortening of vaginal length (17); the basic surgical principles of VVF repair are good exposure, adequate mobilization of tissues, suturing without tension, good hemostasis, and water-tight bladder closure (18,19); there was a shorter operation and hospitalization duration similar to the literature in the cases that were operated with the transvaginal technique, but the success of this technique was significantly lower than the abdominal technique, contrary to the literature. We believe that the repair with transvaginal technique without the excision of the fistula as described in the Latzko technique and the use of omental fleps in the abdominal method are responsible for this difference. However, the success rates in both techniques were lower than those reported in the literature. In this study, a significant proportion (approximately half) of the patients had a history of radiotherapy, which was found to be an important factor for the recurrence in both groups. This effect, in particular, was more pronounced in patients who were treated by transvaginal technique. The use of fleps in the repair of these fistulas is very critical due to the poor vascularization of the fistula field after radiotherapy. Radiotherapy is also known for being an important factor for complex fistula development (3).

Many surgeons place a tissue interposition graft between the bladder and the vagina in VVF repair. These tissues serve as a barrier between the suture lines. The presence of another tissue that is well-vascularized between the two organs is believed to be a factor that reduces the likelihood of recurrence. Although omental fleps are predicted to accelerate healing by reducing the risk of infection and fluid collection by providing lymphatic drainage during the healing process (16), a body of evidence indicates that there is no difference in the healing process of VVF repairs with and without grafts (20). Non-tissue grafts such as fibrin glue may also be used, but the routine use of it is not recommended as the data is based on small case series (21). In our study, we used omental fleps in the abdominal technique and the success rate turned out to be higher than the other group. Our results support the view that fleps increase the success of surgery.

Conservative treatment can be recommended for treating simple fistulas diagnosed shortly after surgery. There are many studies showing that approximately 10% of cases with fistula are closed with bladder drainage and anticholinergic treatment for 2-8 weeks after the diagnosis (22,23). However, in a recent meta-analysis, only 8% of 239 patients managed conservatively by catheter drainage for 2-12 weeks spontaneously regressed

and the remaining 92% underwent surgical repair (14). The data on anticholinergic use prior to VVF repair is inadequate in the literature. Approximately one-fourth of our patients used preoperative anticholinergics and the recurrence rate was significantly lower in such patients. This may be due to the accelerated tissue healing by reduction in bladder contractions due to the use of anticholinergics.

The timing of fistula repair is another debate. The vitality of the surrounding tissue and the repair performed in the presence of this tissue are important factors for a successful closure. It is believed that 6-12 weeks of waiting period will be sufficient to disperse granulation and exudate tissue, and increase the success rate. However, some recent studies have reported that surgery after 1-2 weeks will provide similar success rates (24,25). On the other hand, the presence of a healthy tissue is important for early planned operations. Delaying surgery for 2-3 months decreases inflammation, infection, edema, and necrosis and increases the success rate. In our study, the mean operative time was 8 weeks and the operation time was not an important factor for the recurrence rate. The timing of the VVF repair must be considered individually.

For a long time, the excision of the fistula tract was a definite recommendation for successful repair. However, this approach has recently been disputed. While some authors suggest that the remaining healthy tissue edges can increase success after the excision of the tract (26), others argue that if a wide excision is made, a large defect will increase the tension in the sutured tissue and the risk of recurrence (27).

The choice of fistula repair methods described in the literature is mainly based on the location, size, and severity of the fistula, in particular the experience and preference of the surgeon (28). Numerous data on transabdominal, transvaginal, laparoscopic, and robotic VVF repair are available in the literature, but none of them are currently considered as the "gold standard" (29,30). The most important criteria we have considered while deciding the surgical method were fistula location, size, and experience of the surgeon. We prefer mostly transvaginal technique for fistulas <2 cm and close to the bladder neck. In our study, we found that the transvaginal method was the most commonly performed method for subtrigonal fistulas and the transabdominal method was the most common for supratrigonal fistulas. However, recurrence locations were, on the contrary, most commonly supratrigonal for the transvaginal method and subtrigonal for the transabdominal method. The distal location of the subtrigonal fistulas and its close proximity to the vagina are more challenging for the transabdominal approach than for the proximal fistulas. On the other hand, it is easier to access and repair the fistulas located distally by the transvaginal method, while repairing the proximal fistulas may be more challenging with transvaginal exposure. In a recent study, 10-yeear results of 58 patients who underwent transvaginal VVF repair were reported. The authors concluded that transvaginal repair of vaginally accessible fistulas provides similar outcomes with lower morbidity rates than the abdominal method. However, unlike ours, fistulas secondary to radiotherapy were excluded and the majority of fistulas (60%) were subtrigonal. In addition, flep interposition was performed in the majority of patients, although there was no significant effect on the outcome (31). Fistula size has been discussed as another factor affecting repair success. Thus, 0.5 cm and 2.5 cm thresholds are used to differentiate between simple and complex fistulas (3). In the study of Kumar et al. (31), fistula size was not an important factor affecting the outcome in patients who underwent transvaginal repair, whereas Kati et al. (32) emphasized that the surgical success was higher in patients with fistula <20 mm in size and those without a history of urinary infection. In our study, fistula size was not an important factor affecting the outcome, similar to Kumar et al. (31) study.

Study Limitations

The retrospective nature and the relatively small number of cases were the major limitations of our study. Although the most common method used was transvaginal for subtrigonal fistulas and transabdominal for supratrigonal fistulas, and that the transabdominal method had more outstanding outcomes, selection bias, which is a result of the method of operation based on the fistula location, may be another limitation of the study.

Conclusion

In this study, we have achieved significant outcomes in the treatment of VVF; the abdominal method provides more successful results by providing extensive tissue exposure and omental tissue flep. Patients with a history of radiotherapy are more likely to have recurrence and such patients should be informed that repetitive treatment may be needed. Anticholinergic drug use from diagnosis until surgery should be recommended as a factor that can reduce the recurrence rate. A waiting period of approximately two months after the onset of the fistula formation is sufficient for repair. Shorter mean operation time and length of hospital stay can be achieved through transvaginal method. It should also be noted that recurrent interventions may be required in patients undergoing VVF repair.

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Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: All patients provided written informed consent.

Peer-review: Externally peer-review.

Authorship Contributions

Concept: F.K., A.Ş., Design: F.K., A.Ş., Data Collection or Processing: F.K., T.Ö., B.A., S.K., Analysis or Interpretation: F.K., A.Ş., C.Ö., Literature Search: F.K., Writing: F.K.

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CASE REPORT
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Stent Encrustation due to Forgotten Double-J Stents: A Series of Five Cases

Unutulmuş Double-J Stentlere Bağlı Stent Enkrustasyonunun Görüldüğü Beş Serilik Olgu Sunumu

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Abstract

Although Double-J stents have become very common in the urological practice and are effectively used for various reasons, several complications related to it, such as hematuria, infection, irritative symptoms, pain, perforation, encrustation, and migration, have been observed. The present study reports five case reports of stent encrustation due to forgotten stents.
Keywords: Double-J, Kidney stone, Urolithiasis, Percutaneous nephrolithotomy, Lithotripsy

Öz

Üroloji pratiğinde, Double-J stentler çeşitli nedenlerle etkili bir şekilde kullanılır. Hematüri, enfeksiyon, irritatif semptomlar, ağrı, perforasyon, taşlaşma, migrasyon gibi komplikasyonlar görülebilir.Unutulmuş Double-J stentlere bağlı gelişen stent enkrustasyonu ile ilgili beş olgu sunumu sunuyoruz.
Anahtar Kelimeler: Double-J, Böbrek Taşı, Ürolitiazis, Perkütan nefrolitotomi, Taşlaşma

Introduction

While Double-J (DJ) stent has become an essential tool in the modern urological practice, there has been a significant increase in the number of complications and side effects such as urinary tract infection, hematuria, irritative voiding symptoms, and encrustation related to ureteral stents with the increasing use of it in urology clinics. One of the most prominent of these complications is stent encrustations due to forgotten ureteral stents. Urinary obstruction due to stent encrustations can typically lead to problems such as hydronephrosis, loss of renal function, and urosepsis (1,2). Numerous methods including some minimally invasive procedures such as ureterorenoscopic lithotripsy, percutaneous nephrolithotomy, and open surgical methods have been used in the literature for the treatment of stent encrustations due to forgotten DJ stents (3,4). This study presents five cases with stent encrustation due to forgotten DJ stents and the removal of these stents with holmium laser and percutaneous intervention.

Case Presentation

Case 1

A 28-year-old male patient with dysuria was admitted to our clinic in November 2019. The anamnesis of the patient revealed that he was operated in 2014 due to an external left ureteric stone. A DJ stent was implanted, and the patient did not come to postoperative controls. A kidney, ureter, and bladder (KUB) radiograph showed a DJ stent with encrustation at both ends, one end extending from the kidney to the iliac cross level and the other end in the bladder (Figure 1). The patient underwent one session of cystolithotripsy and one session of percutaneous nephrolithotomy one month later.

Case 2

A 49-year-old male patient with hematuria was admitted to our clinic in May 2019. The anamnesis revealed that the patient was operated in 2016 due to right kidney stone in an external center

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and did not come to the controls. A KUB radiograph showed an encrusted DJ stent fragment extending from the kidney to proximal ureter with its distal part in the bladder. Of note, the cystolithotripsy and ureterorenoscopy were both performed in the same session.

Case 3

A 53-year-old male patient with no active complaints was referred to our clinic after a visit to another outpatient clinic due to mental retardation in February 2018, during which a forgotten right DJ stent was found in the patient. The anamnesis of the patient revealed that he had undergone ureterolithotomy due to proximal ureteral stone in 2016 and did not come to controls. An abdominopelvic CT showed a DJ stent extending from the kidney to the bladder with an encrusted proximal end. The proximal part was cleared of encrustations by ureterorenoscopic holmium laser lithotripsy.

Case 4

A 47-year-old male patient was admitted to our clinic with the complaint of a foreign body coming out from urethra during urination in September 2019. The medical history of the patient revealed an operation performed in an external center due to left ureteral stone in 2012. A KUB radiograph revealed a spontaneous severed DJ stent extending from the left kidney to the distal part of the ureter with its distal part in the bladder (Figure 2). A two-stage operation was planned, and the patient underwent one session of cystolithotripsy followed by a session of left percutaneous nephrolithotomy one month later.

Case 5

A 54-year-old male patient with hematuria was admitted to our clinic in August 2017. The anamnesis of the patient revealed that he was operated due to right kidney stone in 2013 and did not come to the controls. A KUB radiograph showed a spontaneous ruptured DJ stent with proximal part in the right kidney and distal part in the bladder. The patient underwent one session of cystolithotripsy and one session of right percutaneous nephrolithotomy one month later. Informed consent was obtained from all the patients before the operations.

Discussion

DJ stents are widely used in urology to provide urine flow between the kidney and bladder in various operations such as renal stone surgery, retroperitoneal fibrosis, genitourinary system injuries, renal transplantation, and reconstructive surgical procedures (5,6).

Stents are generally made using polyurethane, polyethylene, and silicone materials. While stents made of silicone can be kept in the body for longer periods, stents made of polyurethane or polyethylene should be replaced every eight weeks (7). Moreover, DJ stenting has late complications such as hydronephrosis, stent migration, encrustation, and fragmentation (8,9), and one of the most important in terms of its results is stent encrustation that may develop due to ureteral stents forgotten in the body for long periods of time. In addition, life-threatening complications such as loss of renal function and urosepsis may also develop as a result of urinary obstruction due to stent encrustations (2). Encrustations developing in DJ stents after being forgotten or long-term applications may cause problems during stent removal. Treatment modalities such as percutaneous nephrolithotomy, ureterorenoscopic pneumatic lithotripsy, and laser lithotripsy can be used for this purpose (9).

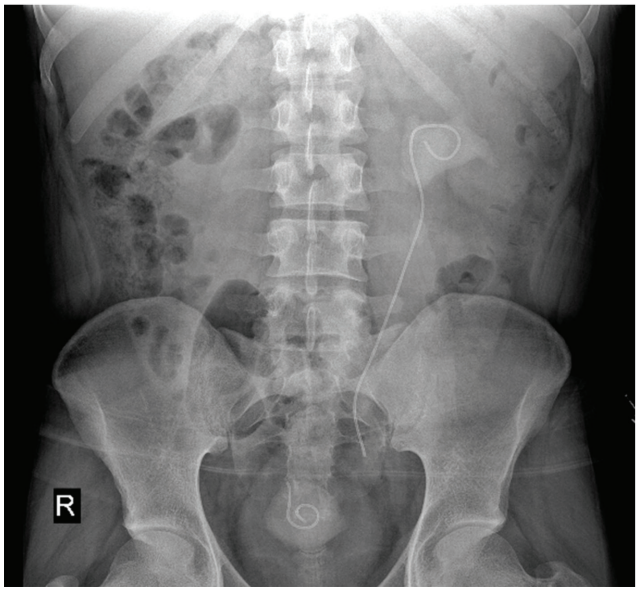

Figure 1. Kidney, ureter, and bladder radiograph

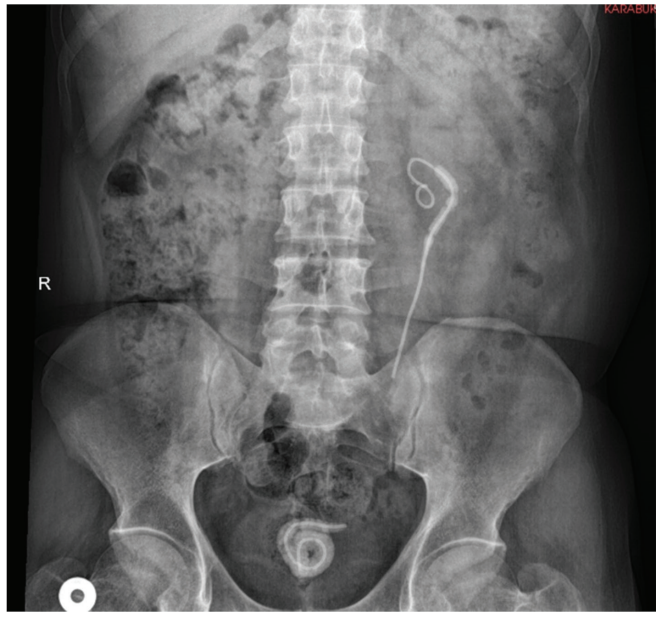

Figure 2. Kidney, ureter, and bladder radiograph

To conclude, we suggest that while selecting the appropriate treatment modality, the encrustation load around the stent, its location, and surgical equipment should be considered and possible options should be discussed with the patient. Patients treated with ureteral stents should be informed in detail about the stent, and the ureteral stent should be removed as soon as possible.

Ethics

Informed Consent: Informed consent was obtained from all the patients before the operations.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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CASE REPORT
Pediatric Urology

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Parameatal Urethral Cyst: A Case Report

Parameatal Üretral Kist: Olgu Raporu

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Abstract

A parameatal urethral cyst is a rare benign congenital anomaly. Approximately 50 patients with parameatal urethral cysts have been reported in the literature. These cysts are usually asymptomatic. They are recognized and diagnosed in the neonatal and early childhood periods. They are usually less than 1 cm in diameter and occur on the ventral or lateral edge of the meatus. These cysts are treated by complete excision. In this report, we present a nine-month-old boy with an asymptomatic parameatal urethral cyst who underwent surgical excision and simultaneous circumcision.
Keywords: Parameatal, Urethral, Cyst, Pediatric

Öz

Parameatal uretral kist nadir görülen benign konjenital anomalidir ve literatürde 50 civarında olgu bildirilmiştir. Bu kistler genelde asemptomatiktir. Yenidoğan ve erken çocukluk dönemlerinde kendini gösterir. Genellikle 1 cm'den küçük olur ve üretral meatusun ventral veya lateral kenarında oluşur.Tedavisinde cerrahi eksizyon uygulanır. Biz bu raporda semptomatik olmayan, parameatal üretral kisti olan ve tarafımızca cerrahi eksizyon ve eşseanslı sirkümsizyon uygulanan 9 aylık bir erkek çocuk rapor ediyoruz.
Anahtar Kelimeler: Parameatal, Uretral, Kist, Çocuk

Introduction

Parameatal urethral cysts are rare benign congenital lesions. Approximately 50 patients with parameatal urethral cysts have been reported in the literature. They were first described by Lantin and Thompson and in 1956. They are usually less than 1 cm in diameter and occur on the ventral or lateral edge of the meatus (1,2,3). They are usually asymptomatic, but sometimes changes in urine flow, urinary obstruction, dysuria, and complaints of poor cosmetic appearance may occur (4,5). Surgical excision is the recommended treatment option (6). In this report, we present a nine-month-old boy with an asymptomatic parameatal urethral cyst.

Case Presantation

A nine-month-old baby boy was admitted to the clinic after his parents had noticed a cyst. He did not have any complaints. His urine output was normal. His feeding and growing patterns were normal. Physical examination revealed a yellow 5-6 mm cyst on the left side of the urethral meatus (Figure 1). No signs of systemic and local inflammation were observed. On ultrasound examination, no urinary tract pathology was observed. The surgical excision of the cyst, under general anesthesia, and circumcision were performed in the same session. After cyst excision, wound lips were repaired with 6/0 Vicryl Rapide suture (Figure 2). No perioperative and postoperative complications were observed. The pathology study reported a benign cystic lesion. On follow-up, in the second postoperative month, no urethral stenosis was observed (Figure 3). No recurrence occurred.

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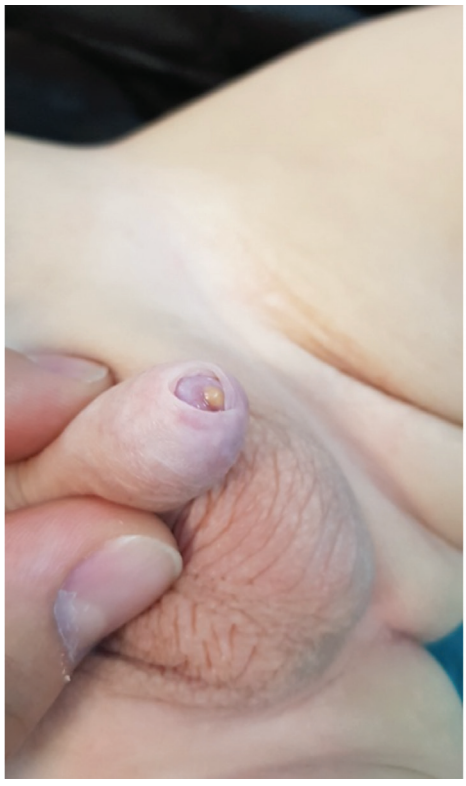

Figure 1. Preoperative (a yellow 5-6 mm cyst on the left side of the urethral meatus)

Figure 2. Perioperative

Figure 3. Postoperative (two months after surgery)

Discussion

Parameatal urethral cysts were first described by Lantin and Thompson (1) in 1956. Although they are more common in males, they can also be seen in females (7,8). These cysts usually occur on the ventral and lateral edge of the meatus and are asymptomatic. However, changes in urine flow, urinary obstruction, dysuria, painful sexual intercourse, and complaints of poor cosmetic appearance may occur (4,5). The etiology is unclear. Thompson and Latin argue that they are caused by a pathology resulting from the separation of the foreskin and glans penis. Shiraki cited paraurethral canal obstruction as a cause (9). Hill and Ashken (7) suggest the possibility of infection-induced obstruction of the paraurethral canal. The cyst wall may consist of columnar, squamous, cuboidal, and transitional epithelium (4,10). The cysts are treated by complete excision with the patient under anesthesia, with care taken not to cause meatal stenosis (6). Aspiration is not a preferred treatment option due to recurrence, while marsupialization is not preferred as it can result in poor cosmetic appearance.

Parameatal urethral cysts are very rare, benign, asymptomatic lesions. They can be easily diagnosed by physical examination. Complete surgical excision is the preferred treatment option because of good cosmetic results and no recurrence.

Ethics

Informed Consent: The consent of the patient and his parents was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Ç., Design: M.S., Data Collection or Processing: S.Ç., Analysis or Interpretation: E.C.B., Literature Search: M.Y.K., Writing: S.A.

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