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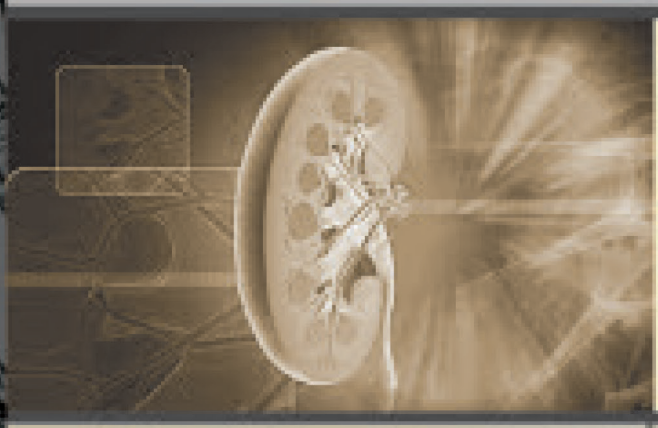
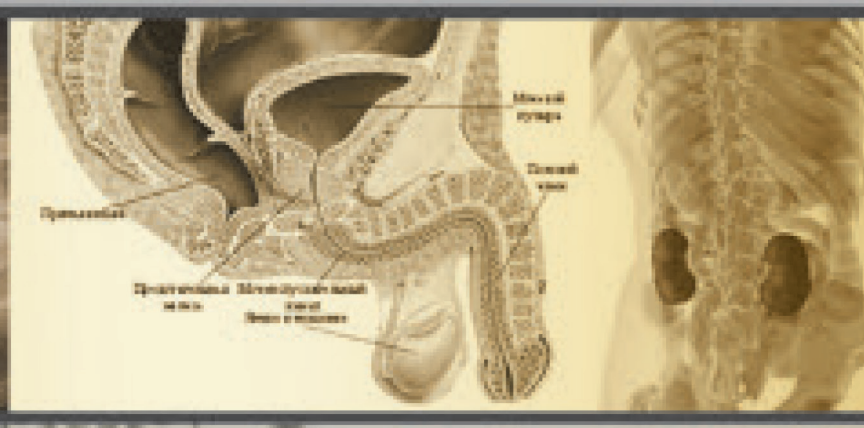
Society of Urological Surgery in Turkiye

E-ISSN 2148- 9580

JOURNAL OF UROLOGICAL SURGERY

Volume 10 / Issue 1 / March 2023 www.jurolsurgery.org





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Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: March 2023
E-ISSN: 2148- 9580
International scientific journal published quarterly.

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Technical and other assistance should be provided on the title page.

Title Page

Title: The title should provide important information regarding the manuscript's content.

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Materials and Methods: Important methods should be written respectively.

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Results: Important findings and results should be provided here.

Conclusion: The study's new and important findings should be highlighted and interpreted.

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Abstract length: Not to exceed 250 words. "What is known on the subject and what dos the study add" not exceed 100 words.

Article length: Not to exceed 3000 words.

Original researches should have the following sections:

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Statistics: Describe the statistical methods used in enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. Statistically important data should be given in the text, tables and figures. Provide details about randomization, describe treatment complications, provide the number of observations, and specify all computer programs used.

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Conclusion: The conclusion of the study should be highlighted.

References

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1. List All Authors

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, 201, 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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How I do?

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Acknowledgments

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Doi: 10.4274/jus.galenos.2022.2022.0027
J Urol Surg, 2023;10(1):1-8

Duloxetine in the Treatment of Women with Urinary Incontinence: A Systematic Review and Meta-analysis of Efficacy Data from Randomized Controlled Clinical Trials

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Abstract

Duloxetine is the only available agent for the medical treatment of stress urinary incontinence (SUI). In this systematic review, we analyzed the efficacy and safety of duloxetine treatment in women with SUI and stress-predominant mixed urinary incontinence (SPMUI). We searched the literature using OVID MEDLINE, Embase and ULAKBIM (Turkish database) databases for placebo-controlled studies on the use of duloxetine in women with SUI or SPMUI. Data on change in incontinence episode frequency (IEF), decrease in the number of continence pads used, increase in voiding interval (minute) and discontinuation rates due to adverse effects and lack of efficacy (%) were extracted. A total of 12 randomized controlled trials were included. Duloxetine treatment results in an 18% decrease in IEF and 16% decrease in the number of incontinence pads used compared to pre-treatment status. It also increases the time interval between the voids by 18 min. Duloxetine treatment was associated with higher treatment discontinuation rates compared with placebo. The reason for discontinuation was related to the side effects of the treatment rather than lack of efficacy. Duloxetine can be an effective treatment option in women with UI based on high-level evidence supporting its efficacy. Further studies with larger patient populations and longer durations of follow-up are required to assess its safety profile.

Keywords: Urinary incontinence, stress, urinary incontinence, mixed, duloxetine hydrochloride, systematic review

Introduction

Stress urinary incontinence (SUI) is the involuntary leakage of urine on effort or exertion, or on sneezing or coughing (1). The prevalence of SUI increases with age, affecting 1 in 5 women in the population (2,3), necessitating a surgical intervention in most of these patients. Recently, the surgical treatment of SUI in women has come under serious public scrutiny after the recent issues related to the use of vaginal mesh products (4,5). The mid-urethral sling surgeries using a vaginally inserted polypropylene mesh, has been the first line surgical treatment for women with SUI in the last 10-20 years with success rates up to 93% in 5 years of follow-up (4). Despite high success rates, life changing complications have been reported in some patients (6). Currently the vaginal mesh issue is pronounced as the second biggest health scandal after the thalidomide disaster and many countries are now suspending the use of vaginal mesh products for the treatment of women with SUI. This creates an unmet clinical need in this area and urologists are now revisiting other available treatment options for the treatment of SUI such as duloxetine and laser therapies (7).

Duloxetine is the only available agent that can be used in medical therapy of SUI. It is a potent inhibitor of serotonin (5-

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Received: 20.03.2022 **Accepted:** 16.05.2022

Cite this article as: Mangır N, Uçar M, Gülpınar Ö, Özkürkçügil C, Demirkesen O, Tarcan T. Duloxetine in the Treatment of Women with Urinary Incontinence: A Systematic Review and Meta-analysis of Efficacy Data from Randomized Controlled Clinical Trials. J Urol Surg, 2023;10(1):1-8.

hydroxytriptamine = 5-HT) and norepinephrine (NE) reuptake at the neuromuscular junction. Increased concentrations of serotonin and NE are thought to increase the stimulation of the pudendal nerve efferent neurons leading to an increased resting tone and contraction strength of the external urethral sphincter (8). Currently, the use of duloxetine for this indication is approved by the European Medicines Agency but not the US Food and Drug Administration.

Data from clinical trials support the use of duloxetine in the treatment of SUI in women (9). A meta-analysis of randomized controlled clinical trials showed the effectiveness of duloxetine in reducing the frequency of incontinence episodes and improving quality of life. Additionally, some clinical trials demonstrated a decrease in the number of incontinence pads used in women with SUI and stress-predominant mixed urinary incontinence (SPMUI) (10). However, this comes at the cost of side effects on various organ systems including the central nervous system and gastrointestinal tract, most frequent ones being nausea, constipation, dizziness, fatigue, headache and insomnia (11).

The main concern for a practicing urologist when prescribing duloxetine is probably more related to its side effects rather than its efficacy. Particularly, side effects related to mental health and suicidality would be the most concerning for the treating physicians, due to the relatively controversial reports on the association between suicidal behavior and antidepressant medications (12). This issue pertains mainly to a specific group of patients with mental disorders and more to children and adolescents with mental health problems, however it has also been suggested that some anti-depressant medications can double the risk of events that may lead to suicide and violence in healthy individuals (13). In the context of urinary incontinence, a recent meta-analysis of clinical study reports (data submitted to regulatory bodies) did not find any reported cases of suicidality, violence, or akathisia with duloxetine use (14). Current urology guidelines support the use of duloxetine in adult women with SUI for whom surgical treatment is not indicated. Duloxetine has also been demonstrated to be effective in treating symptoms of MUI (15) and is recommended when a patient is unresponsive to conservative treatment options (16). Therefore, duloxetine is accepted as an effective treatment option for SUI but the adverse effects are still debatable.

The role of duloxetine in the treatment of women with SUI was been reviewed in a recent meta-analysis (9) which confirmed the efficacy and the higher discontinuation rates with duloxetine treatment. However, the reasons for discontinuation (lack of efficacy vs side effects) were not assessed in this meta-analysis. More importantly, the risk of bias in the clinical trials included in the systematic review was not reported in detail. Additionally, the efficacy parameters in this systematic review were expressed as categorical rather than continuous variables, which is not very useful when making a judgment on risk- benefit ratio. Altogether, this meta-analysis is limited in supporting the daily clinical decisions of urologists.

In this study, we wanted to systematically review all the evidence from randomized controlled trials assessing the efficacy of duloxetine in the treatment of women with SUI and SPMUI, to obtain quantitative figures of efficacy that can help practicing urologists when counseling women with SUI or MUI for duloxetine treatment. We also performed an assessment of discontinuation rates and the risk of bias that may influence the outcomes of the clinical trials reporting on the role of duloxetine in the treatment of women with SUI and SPMUI.

Methods

Literature Search

We conducted a systematic search of the literature using OVID MEDLINE, Embase and ULAKBIM (Turkish database) databases. The PRISMA guidelines were followed during the systematic review (Figure 1). The inclusion criteria were as follows: 1) the study was an randomized controlled trials (RCT); 2) the patient was diagnosed with SUI or SPMUI; 3) the treatment intervention was duloxetine vs. placebo; 4) objective and/or subject outcome measures were clearly defined. Studies were excluded if the following: 1) they were not RCTs; 2) patients were diagnosed

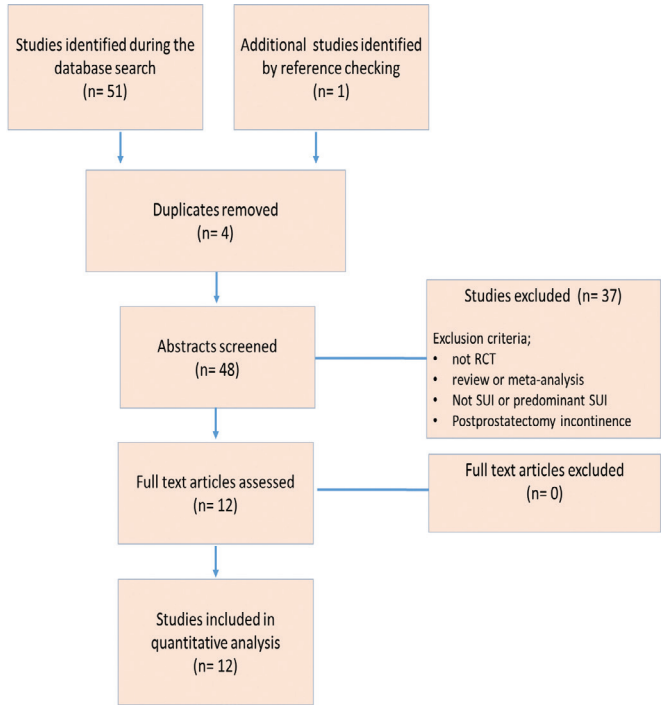

Figure 1. The preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram to demonstrate the search conducted

RCT: Randomized controlled trials

with urge or urge dominant urinary incontinence. The study protocol was registered beforehand and published online in PROSPERO (registration number: CRD42019149197).

Data Extraction

Two investigators evaluated all the potentially eligible studies independently and performed the data extraction separately. Any disagreements that could not be reconciled by discussion were considered by a third person.

The following data were extracted from each study independently by two authors; 1) study characteristics, 2) median change in IEF, 3) mean decrease in number of continence pads used, 4) mean increase in voiding interval (minutes), 5) discontinuation rates due to adverse effects and lack of efficacy (%).

During the meta-analysis, imputation of missing data was performed when necessary. The estimated mean and standard deviation (SD) values were calculated from the reported median value using the sample's reported median, range and number of measurements according to the method devised by Hozo et al. (17). For missing SD values, a study-level imputation of the missing data was performed assuming that the missing SD is similar to the SD of the same study baseline values (18). Missing data imputation was only performed where baseline values were presented. Review Manager 5.3 was used to conduct the meta-analysis.

Assessment of Risk of Bias

The risk of bias was assessed using the Cochrane risk of bias (RoB) assessment tool for randomized trials (19). Two researchers scored each study independently following the checklist provided. A total of five domains, each of which contains several items were assessed. An overall RoB judgment was reached following the Cochrane guidelines (20). An RCT was deemed at a high risk of bias in one particular domain when it had a high risk of bias in at least one item of that domain.

Results

Study Characteristics

A total of 12 randomized controlled trials were included in the systematic review (Table 1). In most the studies duloxetine treatment regimen of 40 mg BID was used. The duration of the studies was 8 weeks in most of them (n=6), followed by 12 weeks (n=4), 36 weeks (n=1) and 6 weeks (n=1).

Table 1. A summary of studies included in the systematic review

Trials	Total (n)	Duloxetine (n)	Placebo (n)	Treatment Regimen	Duration (w)	Outcome Measures
Norton 2002 (24)	278	140	138	40 mg BID	12	IEF, I-QoL, PGI-I, MTBV, SPT, CST, TEAE
Dmochowski 2003 (28)	683	344	339	40 mg BID	12	IEF, I-QoL, PGI-I, MTBV, continence pad use/week, TEAEs
Milliard 2004 (29)	458	227	231	40 mg BID	8	IEF, I-QoL, PGI-I, TEAEs
Van Kerrebroeck 2004 (11)	494	247	247	40 mg BID	8	IEF, I-QoL, PGI-I, TEAEs
Cardozo 2004 (27)	109	55	54	40 mg BID and 60 mg BID	8	IEF, I-QoL, PGI-I, TEAEs
Kinchen 2005 (30)	451	224	227	40 mg BID	36	I-QoL, PGI-I, TEAEs
Ghoniem 2005 (31)	97	52	47	40 mg BID	12	IEF, I-QoL, PGI-I, continence pad use
Mah 2006 (32)	121	61	60	40 mg BID	8	IEF, I-QoL, PGI-I, MTBV, continence pad use/week, TEAEs
Castro-Diaz 2007 (33)	256	136	120	40 mg BID	8	IEF, ICIQ-SF, I-QoL, PGI-I, TEAEs
Lin 2008 (34)	121	60	61	40 mg BID	8	IEF, I-QoL, PGI-I, MTBV, continence pad use/week, TEAEs
Schagen van Leeuwen 2008 (35)	265	134	131	20 mg BID and 40 mg BID	12	IEF, I-QoL, PGI-I, MTBV, continence pad use/week, BDIII, 3MS, TEAEs
Cardozo 2010 (10)	2758	1378	1380	40 mg BID	6	IEF, PGI-I, KHQ, SPT, TEAEs

IEF: Incontinence episode frequency, BID: Twice a day, I-QoL: Incontinence quality of life questionnaire, PGI-I: Patients' Global Impression of improvement, treatment emergent adverse effects, MTBV: Mean time between voids, CST: Cough stress test, KHQ: King's health questionnaire, SPT: Stress pad test, 3MS: Modified mini-mental state exam

Efficacy Outcomes

Decrease in the Frequency of Incontinence Episodes

Nine RCTs with 2.251 and 2.476 patients in duloxetine and placebo groups, respectively, were included in the meta-analysis. Duloxetine resulted in an 18.81 [95% confidence interval (CI) of 12.45-25.18, p<0.000] percentage decrease in incontinence episode frequency (IEF) (Figure 2).

The Decrease in the Number of Pads Used

Three RCTs reported a percentage decrease in the number of pads used per week. Duloxetine treatment resulted in a 15.6 (95% CI of 12.45- 25.18, p<0.000) percent decrease in the number of pads used per week compared to placebo (Figure 3).

Increase in Voiding Intervals

Five studies reported a mean increase in time between voids (based on voiding diary) after treatment. Duloxetine treatment resulted in 18.02 minutes (95% CI of 13.64- 22.4, p<0.000) increase in time between voids compared to placebo (Figure 4).

Adverse Effects

Treatment emergent adverse effects (TEAE) with the use of duloxetine have been reported in all studies. The most common side effect in the duloxetine group was nausea in 10 studies, in 1 study was dry mouth and in 1 study was constipation and dry mouth. The most common side effects were significantly higher in the duloxetine group than placebo in all studies. The most common side effects in the placebo group were headache in 5 studies, nausea in 4 studies, dizziness in 2 studies, fatigue in 2 studies.

Compliance with Duloxetine Treatment

An analysis of 2.845 and 2.931 patients randomized to duloxetine or placebo groups, respectively, treatment discontinuation due to adverse effects was significantly more common compared to placebo. The odds ratio (OR) was 5.52 (95% CI of 4.20-7.26, p<0.0001) (Figure 5).

There was no difference between the rates of discontinuation due to lack of efficacy between the treatment arms. The OR for treatment discontinuation due to lack of efficacy was 0.7 (95% CI of 0.33-1.45, p=0.33) (Figure 6).

Risk of Bias

All studies in the review had a low risk of biased allocation to interventions with a clear description of the randomization process and with adequate concealment of allocations before

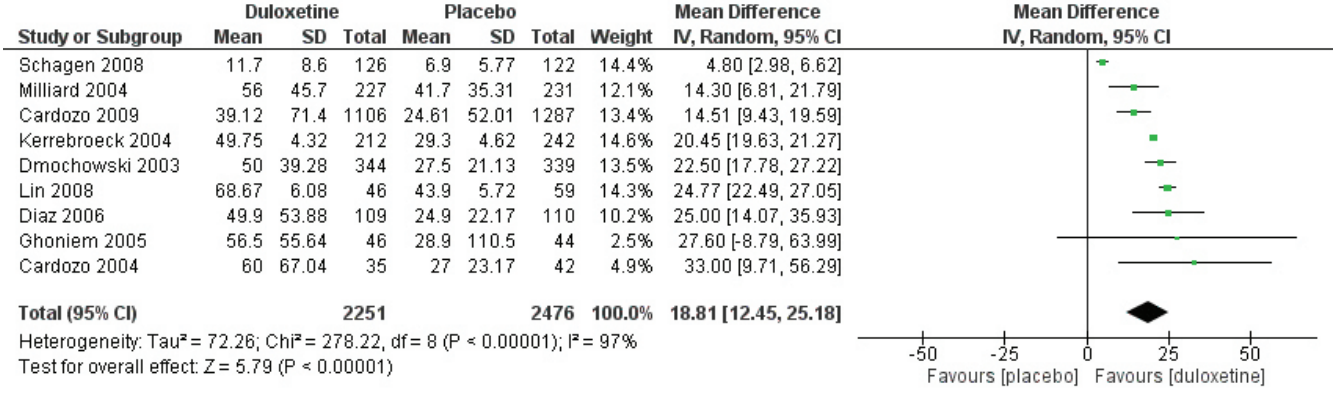

Figure 2. The percentage decrease in incontinence episode frequency (IEF) after treatment with duloxetine compared with placebo

SD: Standard deviation, CI: Confidence interval

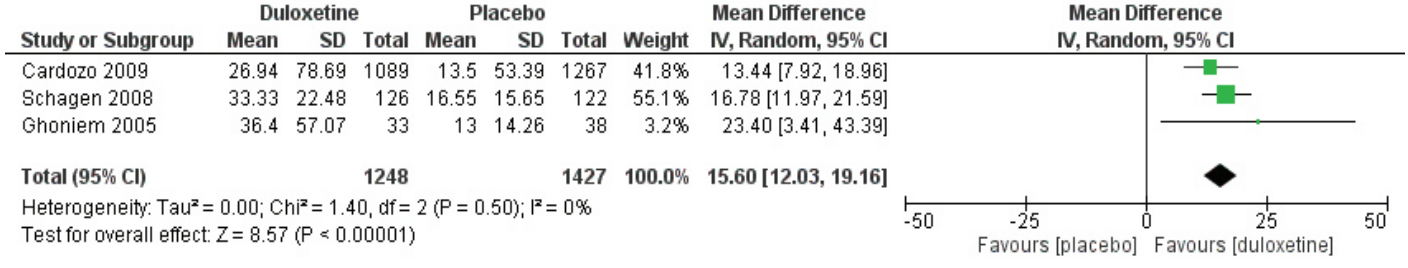

Figure 3. The percentage decrease in the number of incontinence pads after treatment with duloxetine compared with placebo

SD: Standard deviation, CI: Confidence interval

assignment. In all studies the medical staff and patients were blinded and outcomes were assessed with blinding thereby leading to a low risk of detection and performance biases (Figure 7).

However, most clinical trials included in this review had a high risk of bias in the outcome assessment domain. This was due to the disproportionately higher ratio of missing outcome data in the duloxetine group compared to the placebo group (28.4±6.4

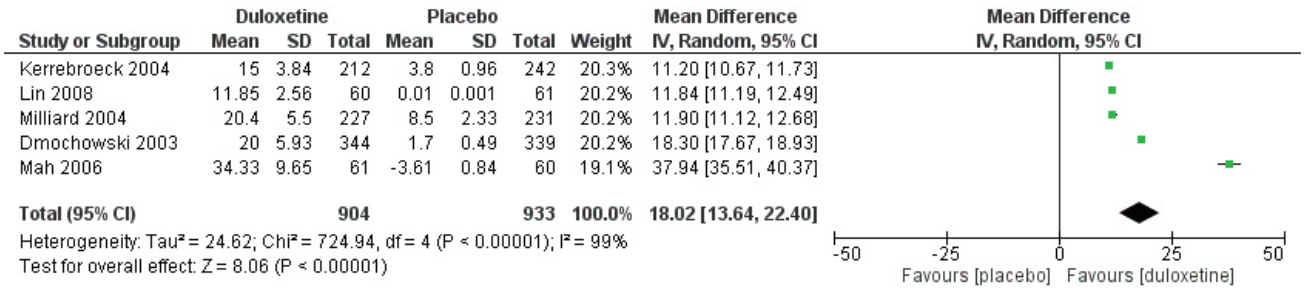

Figure 4. The mean increase in voiding intervals after treatment with duloxetine compared with placebo

SD: Standard deviation, CI: Confidence interval

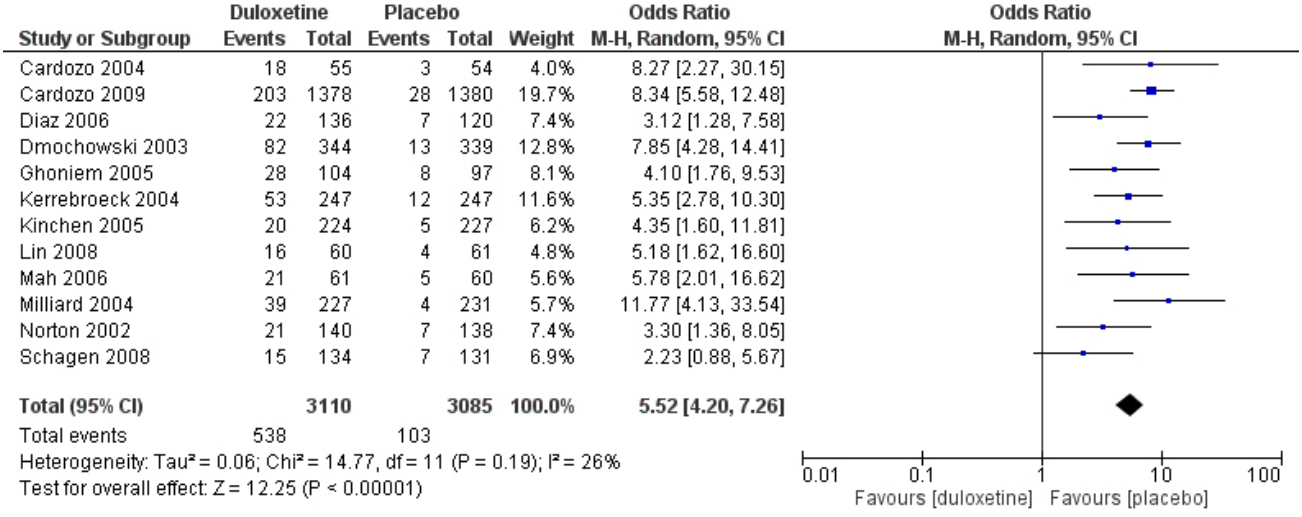

Figure 5. Number of patients discontinuing treatment due to adverse effects in the duloxetine group compared to placebo

CI: Confidence interval

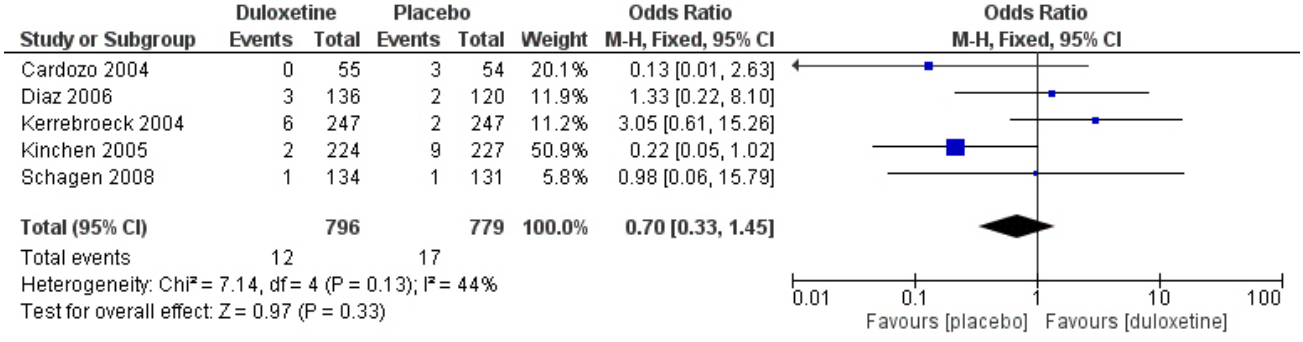

Figure 6. Number of patients discontinuing treatment due to lack of efficacy in the duloxetine group compared with placebo

CI: Confidence interval

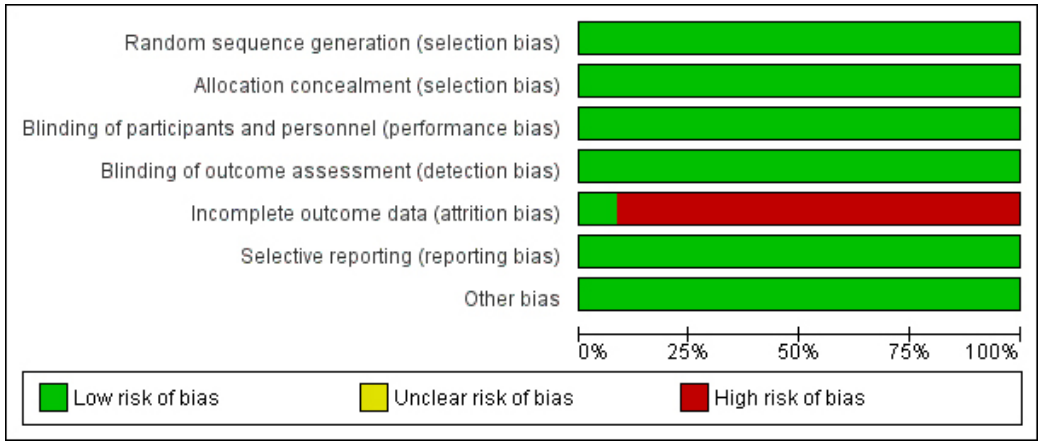

Figure 7. Summary of assessment of risk of bias among the randomized controlled trials included in the systematic review

versus 14.9±5.6, respectively). The most common reason for treatment discontinuation was related to treatment side effects rather than lack of efficacy or other reasons.

Discussion

This study provides the practicing urologists with useful quantitative figures on the clinical efficacy of duloxetine in women with SUI and SPMUI. Our meta-analysis shows that duloxetine treatment results in an 18% decrease in IEF and 16% decrease in the number of pads used compared to pre-treatment status. Also, the time interval between voids was increased by 18 minutes with duloxetine treatment compared to placebo. Such quantitative representation of the available clinical evidence can provide the clinicians with practical figures to guide their consultations with patients. This can be particularly useful when the decision on the risk- benefit ratio with duloxetine treatment is not straightforward.

The given data for the clinical efficacy of duloxetine are not biased, with a clear definition of appropriately used methods to prevent selection, detection, reporting and performance bias. With regard to the attrition bias arising from the missing data, all RCTs included have correctly used an intention to treat principle making the efficacy outcome data reliable. However, the evaluation of the safety of duloxetine will be biased by the missing outcome data. Generally, the extent of bias will increase as the amount of missing outcome data increase (21). If the percentage of missing outcome data is <5% it is generally deemed at a low risk of bias, whereas if it is more than 20% it is more likely to risk the biased outcomes (22). It is not only the proportion of the missing outcome data but whether or not the missingness of the outcome data relates to its true value (20). Within the context of this systematic review because the discontinuation rates were significantly higher in the duloxetine group compared to placebo and because the most common reason for discontinuation was reported as the side effects, it would be reasonable to think that the missingness of the outcome data is related to the true value of the outcome variable when assessing drug safety. Therefore, we made a judgment that most of the trials included in this review have a high risk of bias for the outcome variable safety/side effects.

Duloxetine is traditionally known to be effective for the treatment of SUI. Many RCTs evaluating duloxetine treatment in women with UI have included women with SUI and SPMUI, excluding women with predominant urgency. There is some evidence from animal studies that suggest duloxetine may decrease bladder over activity. However, this has not been thoroughly investigated. Clinically, one study showed that women with SPMUI, urgency predominant MUI and balanced MUI benefit from duloxetine treatment (15). Therefore, duloxetine can also be used for the treatment of MUI. The recent guidance recommends using duloxetine in the treatment of women with SUI when surgery is not indicated (level of recommendation strong). In women with MUI, duloxetine is recommended only for those who are unresponsive to other conservative treatments and who are not seeking a cure for their condition (23).

TEAE are frequently encountered with duloxetine treatment (24). Most TEAEs occur in the first 4 weeks of treatment and nausea is the most common TEAE in the duloxetine group (25,26). If patients can complete the first month of treatment, the side effects are less frequent in the later weeks (27). The current systematic review confirms that patients discontinue duloxetine treatment due of side effects rather than lack of efficacy.

This study provides the urologists with some useful figures on the magnitude of treatment efficacy obtained by systemic analysis of available clinical data from RCTs. However, there are some limitations. Firstly, we used statistical estimates to

impute missing data when necessary. This has been done by established methods, but the estimates may differ from the actual measurements. Secondly, we may have overlooked RCTs published in other languages or databases as we have only conducted the search in two different languages (English and Turkish) in the most frequently used databases. Thirdly, patient-reported outcomes were excluded from the meta-analysis.

In conclusion, duloxetine can is an effective treatment option in women with SUI and SPMUI. The efficacy of duloxetine is supported by a high level of clinical evidence from randomized controlled trials. Patients appear to discontinue treatment due to side effects rather than lack of efficacy. Further studies using more complicated analytical methods are needed to establish whether the benefits of treatment outweigh the risks or not.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.M., Ö.G., C.Ö., O.D., T.T., Design: N.M., O.D., T.T., Data Collection or Processing: N.M., M.U., T.T., Analysis or Interpretation: N.M., M.U., T.T., Literature Search: N.M., M.U., T.T., Writing: N.M., M.U., Ö.G., C.Ö., O.D., T.T.

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

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

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REVIEW
General Urology

Doi: 10.4274/jus.galenos.2022.2022.0030
J Urol Surg, 2023;10(1):9-16

Genital Pigmented Lesions

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Abstract

The genital region is the crossroad of the skin, reproductive and urinary system. In patients with genital skin lesions, the collaboration of urologists and dermatologists is frequent and this alleviates distress, anxiety and even hidden fears of patients, especially in genital pigmented lesions. differential diagnosis of genital pigmented lesions has a wide range spectrum like melanosis, melanocytic nevi, seborrheic keratosis, basal cell carcinoma, other diseases such as post-inflammatory hyperpigmentation, lichen planus, Bowen's disease, Bowenoid papulosis and most importantly melanoma. In approach to solitary or multiple pigmented lesions; dermoscopy is a non-invasive tool that captures clues which cannot be seen by naked-eye and provides guidance for unnecessary biopsies or surgery for dermatologists. This review intends to provide a dermatological approach and aspects for urologists in the differential diagnosis of pigmented lesions on the genital area in female and male patients.

Keywords: Genital pigmented lesions, melanoma, melanosis

Introduction

The genital region is the crossroad of three organ systems: Skin, reproductive and urinary system. Many patients are concerned and mostly fear that their genital skin lesion is either a sexually transmitting disease or a cancer. Urologists and gynecologists are at the forefront of the physicians consulted when genital lesions are concerned. The diagnosis of these lesions and managing patients with concerns about their genital region or genital disease takes skill and expertise but can be mastered with practice and with collaboration of different specialists (1).

The description of the genital region can be confusing dermatologically, histologically and anatomically. The lips, oral cavity, perianal region, penile and vulval genital areas are considered mucosal regions. In a comparison of mucosal regions and other skin areas; pigmented and non-pigmented lesions are rare in mucosal regions and due to that fact also published data and clinical knowledge are limited. The male genital region has less mucosal component compared with the female genital region. The anatomical and histological differences in male and female genital regions, such as the transition of mucosa and skin, glandular differences, follicular and non-follicular areas, make a regular recognizable lesions that are located on other parts of body sites, difficult to diagnose in the genital region, especially in women. Furthermore, mucosal or skin located pigmented genital lesions-with blue, brown, black appearance is less recognizable by the naked eye and for this reason they need additional diagnostic tools (2). In the differentiation of pigmented lesions from melanomas in the genital region, dermoscopy is a non-invasive tool that provides clues about skin structures in epidermis, dermo-epidermal junction and dermis.

Pigmented skin lesions in the genital area include melanosis, melanocytic nevi, seborrheic keratosis, basal cell carcinoma (BCC), other diseases such as post-inflammatory hyperpigmentation, lichen planus, Bowen disease, Bowenoid papulosis and most importantly melanoma. The population-based incidence of pigmented lesions is approximately 10-20% (3). According to the abovementioned facts, dermatology consultation of a patients with skin lesions in this specific region (including mucosal and non-mucosal areas) is frequent for suspected cases (4). Urologists should be able to perform patient and lesion-oriented evaluation together in the diagnosis and treatment of pigmented genital lesions. While patient-oriented data such as the patient's age, skin type, etc. gain importance when separating the preliminary diagnoses and making a biopsy or treatment

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Received: 23.03.2022 **Accepted:** 07.05.2022

Cite this article as: Erfan G, Bıyık Özkaya D. Genital Pigmented Lesions. J Urol Surg, 2023;10(1):9-16.

decision, consideration of the lesion's shape, structure, color symmetry and changes in the follow-up are important among the lesion-oriented data. This review intends to provide a dermatological aspect for urologists in the differential diagnosis of pigmented lesions on the genital area in female and male patients.

Genital Melanosis

Melanosis (lentiginosis) can occur in both in genital and oral mucosa and genital melanosis (genital lentiginosis, mucosal melanosis) is an infrequent and benign condition. Despite its benign behavior, genital melanosis can clinically mimic melanoma. It is discrete, hyperpigmented macules or patches on genitalia and histopathologically, the number of melanocytes is normal, but there is increased basal layer hyperpigmentation with lack of melanocytic hyperplasia (5). In other body parts most solar lentigines occur in fair-skinned individuals and are induced by exposure ultraviolet light exposure, but the etiology of genital melanosis is unknown. The estimated incidence is approximately 0.01% (5,6). In patients with syndromes like Laugier-Hunziker and Peutz-Jeghers mucosal melanosis can be diagnosed in high frequencies and in patients with inflammatory skin diseases like lichen planus genital melanosis have been reported (5,7-9). They occur in both sexes especially in darker skin-colored individuals and the onset occurs in the fourth decade in most of the patients. Genital melanosis lesions are asymptomatic, multiple or solitary brown or black macules (Figures 1,2). They frequently remain stable or enlarge slowly (5,10). In doubtful cases, the distinction from melanoma depends on the age of occurrence, clinical findings, clinical and dermoscopic follow-up. Dermoscopically; parallel, structureless, reticular, ring-like patterns and several subtype patterns are described (11,12). In clinically suspected lesions which are characterized by asymmetry, irregular borders, multifocality, variegated pigmentary patterns and large size, biopsy is usually necessary to exclude melanoma. In large lesions shave or incisional, in small lesions, punch or excisional biopsy can be adequate depending on the suspicion. No treatment is necessary in the diagnosis of genital melanosis. Even though they are not considered premalignant lesions, long-term clinical and dermoscopic follow-up of lesions is recommended (5,10). However, in another study, Haugh et al. (10) pointed out that in patients with a history of cutaneous melanoma genital melanosis was increased in number and they recommend in patients with genital melanosis total body skin examinations for the possibility of melanoma in any body site.

Melanocytic Nevi

Melanocytic nevi are congenital or acquired collection of melanocytes. In terms of location; melanocytic nevi such as compound, junctional and blue nevi, that are located in the genital region have a very low percentage of melanocytic nevi in the whole body (Figures 3-5). Melanocytic nevi in the genital region is frequently located on the labium major, minor, clitoris and glans penis (13-15). Melanocytic nevi are included in the differential diagnosis of melanosis and melanoma and

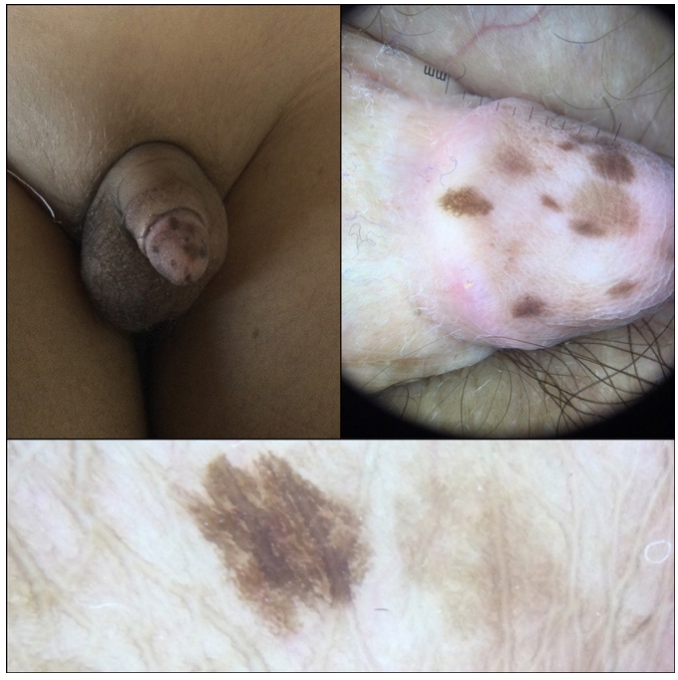

Figure 1. Sixteen-year-old male patient with genital melanosis-multiple, dark-brown, light-brown, different in size, regular shaped macules and patches located on glans penis. Dermoscopic image shows reticular and hyphal pattern

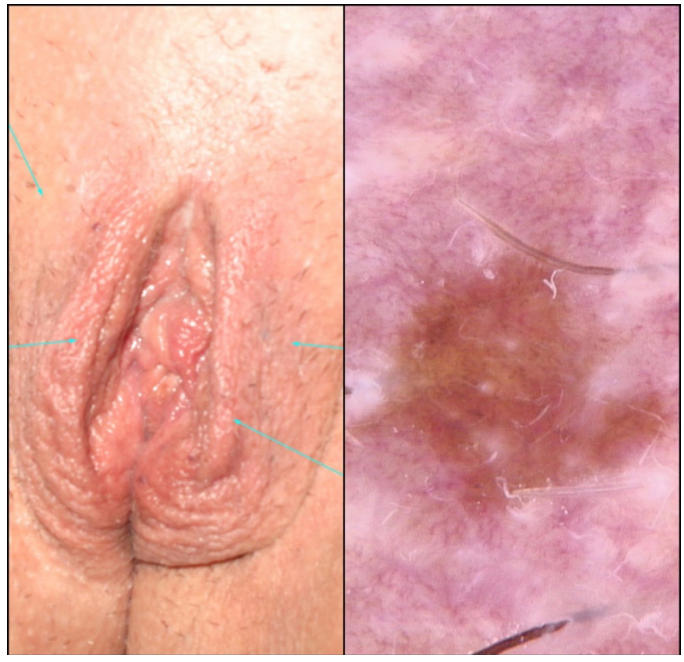

Figure 2. Forty-two-year-old female patient with one-month history of genital melanosis-a millimetric, regular bordered, hyperpigmented macule located on labium major. Dermoscopic image shows structureless and ring-like pattern

are often detected in younger patients. They are common in fairer-skinned individuals. In most cases, melanocytic nevi are detected solitary, often 0.5-1 cm in size. They can be flat macules, papules slightly raised from the skin, or nodular, and are asymmetrical lesions that may change in color from brown to gray (13-15). There is no evidence that melanocytic nevi of the genital skin have a greater risk of malignant transformation than those in other anatomical sites. In the last decade; it has become increasingly clear that benign melanocytic nevi on certain areas of the body, such as the scalp, flexural areas, genital area, needs special attention. Because to their nature exhibit unusual histopathological features, they can also clinically mimic dysplastic nevi and melanoma (16). This is a major concern for melanocytic nevi in young, premenopausal women, located in the vulvar region and there is an increased risk of over-diagnosing melanoma clinically and histopathologically (3,16). But because of lack of evidence, clinical and dermoscopic follow-up is recommended for genital melanocytic nevi. It has been reported that dermoscopically genital melanocytic nevi often exhibit a regular pigment network, but sometimes suspicious criteria such as atypical black network structure, irregular radial structure and irregular globules can be seen (14). However, eruptive multiple blue nevi, characterized by dermoscopically diffuse homogeneous gray-blue pigmentation in the penile region, were reported, but it was also emphasized that a possible melanoma metastasis could not be excluded without biopsy (17). Excisional biopsy is the preferred method for lesions that have melanoma in differential diagnosis, but in cases with glans penis localization, punch biopsy can be performed from the most dermoscopically suspected area of the lesion (18).

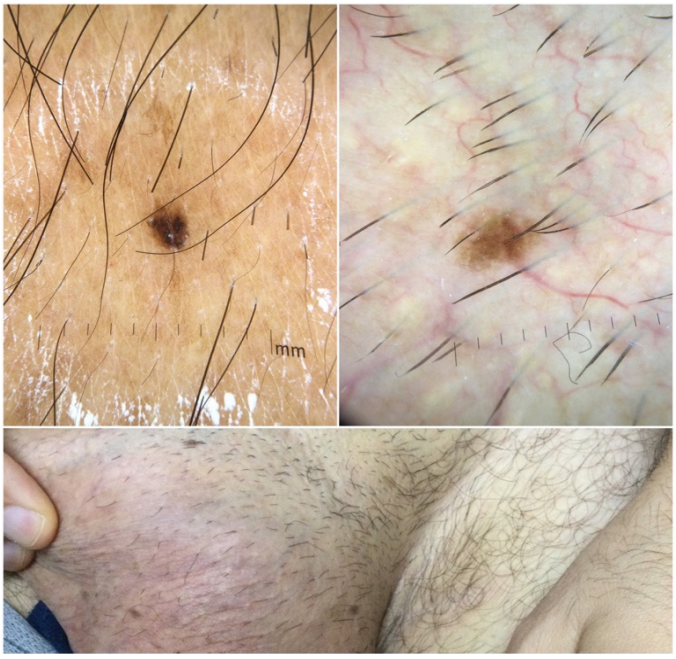

Figure 3. Thirty-five-year-old male patient with two melanocytic nevi-0.5 cm diameter, black and dark-brown, irregular shaped papules on scrotum. Dermoscopic images-(left) symmetrical globular pattern, (right) homogeneous structureless pattern

Seborrheic Keratosis

Seborrheic keratosis is one of a common benign keratocytic tumor, especially in fair skinned individuals. The main etiology

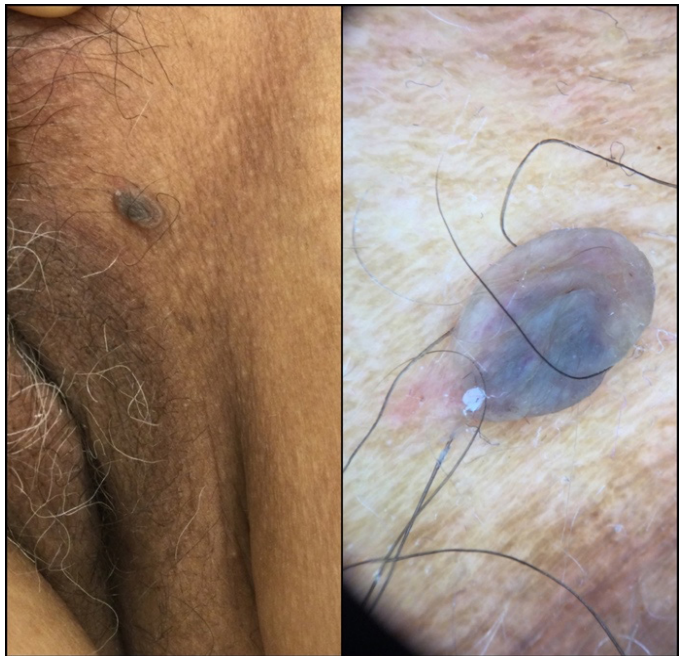

Figure 4. Forty-eight-year-old male patient with intradermal nevi-0.4 cm diameter, pedunculated, dark grey-brown papule. Dermoscopic images shows- comma vessels and homogenous bluish structureless areas

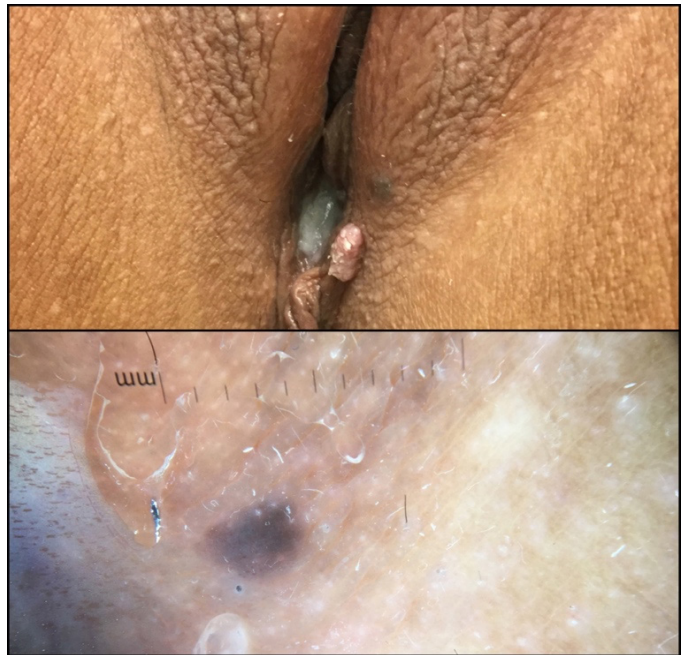

Figure 5. Twenty-eight-year-old female patient with blue nevi-0.5 mm, blue-black, regular bordered papule on labium major. Dermoscopic image shows homogenous pattern

is unknown, but genetic and environmental factors have been reported in some studies (19-23). The role of the human papilloma virus is controversial in etiology, sun exposure is a well-known factor, but it can also be diagnosed in sun-protected areas such as the genital region (19,24-26). It occurs on non-mucosal area of the genital region. The most frequent localization was the penile shaft. Seborrheic keratosis is frequent in middle age patients and increases in number by the age. Clinically; they vary in color-pink to black and they are asymptomatic, solitary, well-defined, waxy papules, plaques and nodules (Figure 6). They can mimic condyloma acuminata, pigmented BCC, bowenoid papulosis and melanoma and in some cases, clinical diagnosis is not easy (19-23). There are well-known dermoscopic features such as milia-like cysts, comedo-like openings, cerebriform appearance and mouth-eaten borders (27,28). In the lack of demonstrative dermoscopic appearance, shave or punch biopsy is necessary to distinguish other malignities that are mentioned above histopathologically (20-22). Treatment is usually unnecessary but due to patient-oriented cosmetic concerns and symptoms like pruritus, electrocauterization, cryosurgery and ablative treatments such as trichloroacetic aside, laser can be performed.

Basal Cell Carcinoma

BCC is the most common skin cancer all around the world (29). Ultraviolet exposure is considered a primary factor in pathogenesis, but 20% of lesions are located in non-sun exposed areas (30,31). In sun-protected areas such as genital region BCC is extremely rare and etiology of genital BCC is unknown. As with other body part localizations, genital BCC is diagnosed in elderly patients. The sex predominancy is unclear for genital BCC (32). The most frequent localization in women is labium majus whereas in men scrotum (33). All subtypes of BCC, such as nodular, morpheic, pigmented can be observed in the genital region. The most frequent subtype of BCC in the genital region is the nodular type same as non-genital BCCs (32). The usual clinical presentation is skin colored, plaque or nodules with elevated borders and telangiectasias. Pigmented BCC is a subtype with hyperpigmented plaque and nodules and resembles melanoma (Figure 7) (34). Dermoscopically, there are well-known criteria in diagnosis of BCC, such as arborising vessels, leaf-like brown, black areas, blue-grey ovoid nests with the absence of a pigment network. Most BCCs are local invasive and rarely metastasize (35). Because of lack of early diagnosis due to privacy of the genital region and misdiagnosis of initial lesions; genital BCC cases are frequently are large in diagnosis (32). Even it is rare metastasis of BCC in the genital area has been reported (36). In a cohort study; penile BCCs showed poorer prognosis than the scrotum (32). The treatment of choice is surgery, for relapsing cases, Mohs microsurgery is recommended. In cases of inoperability, radiotherapy, imiquimod, 5-flourouracil, photodynamic and target treatment for the hedgehog pathway can be other options for treatment (37). treatment, follow-up is recommended for 5 years (38).

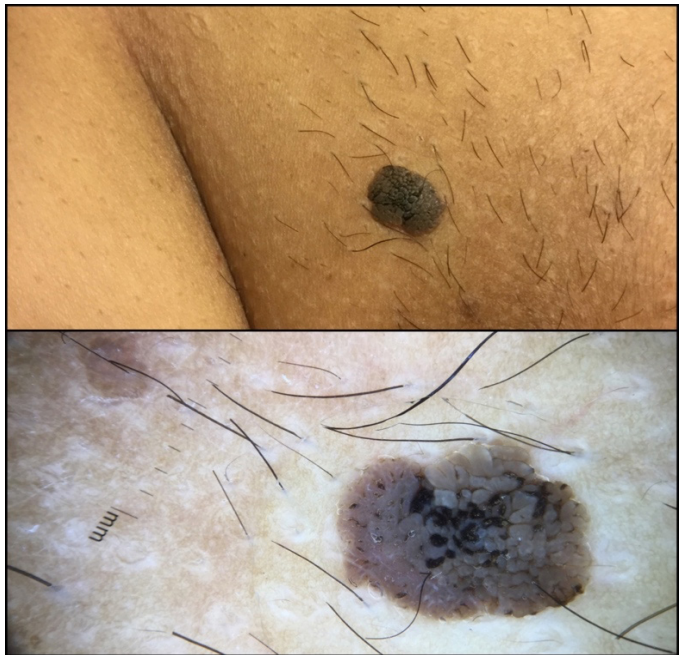

Figure 6. Forty-three-year-old male patient with seborrheic keratosis-1 cm diameter black vegetative plaque. Dermoscopic image shows cerebriform structures, comedo-like openings

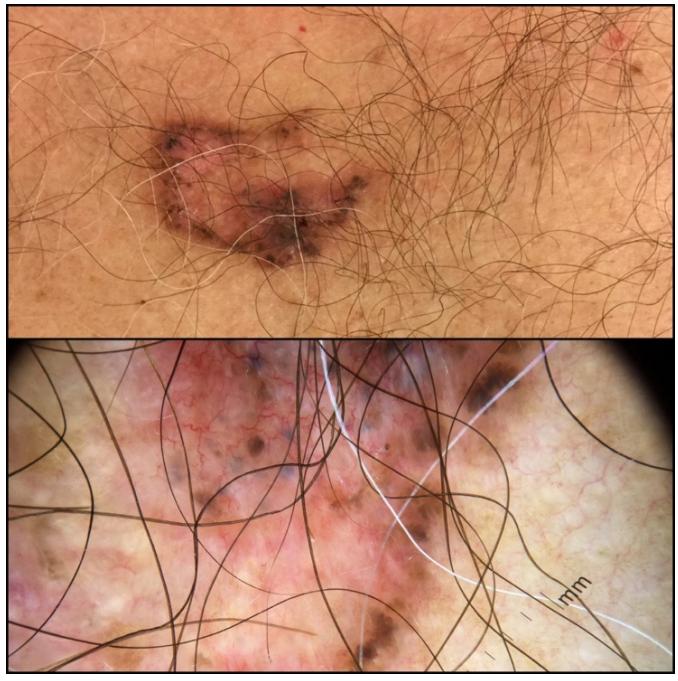

Figure 7. Fifty-two-year-old male patient with pigmented basal cell carcinoma on pubic region- 3 cm diameter, irregular shaped with elevated border, multicolored hyperpigmented plaque. Dermoscopic image shows arborizing vessels, maple-leaf structures

Other Diseases

Post-inflammatory hyperpigmentation in the genital region may occur after inflammation by previous diseases such as contact dermatitis (Figure 8), lichen planus (Figure 9), lichen sclerosus, trauma, burn, infections etc. (39-41). The color may vary from light tan to gray, blue, brown, or black. In diagnosis; history of patient is important rather than biopsy. Treatment depends on the primary inflammatory disease.

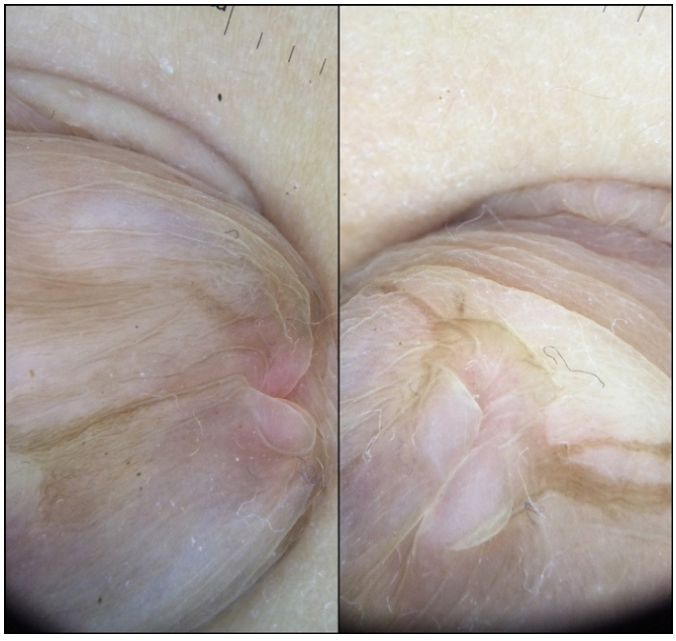

Figure 8. Nine-year-old male patient with post-inflammatory hyperpigmentation after irritant contact dermatitis with death nettle solution. Dermoscopic image shows linear brown blotches

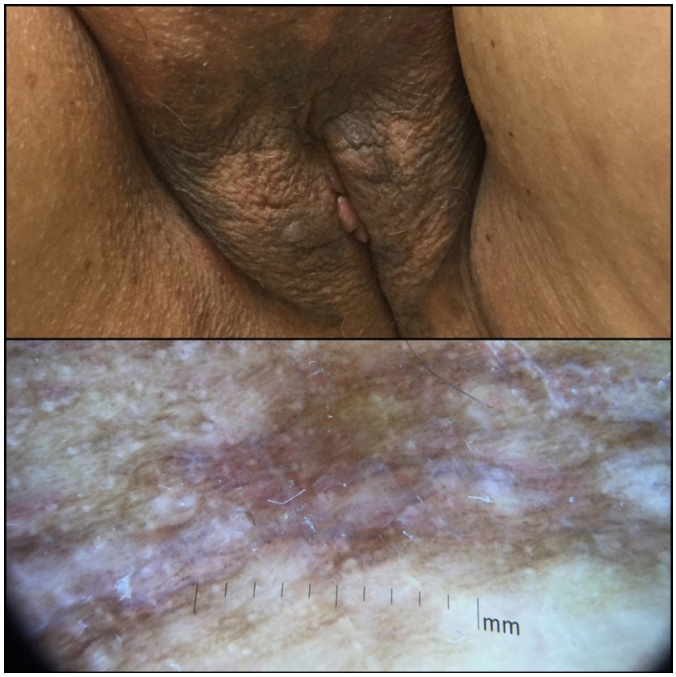

Figure 9. Fifty-two-year-old female patient with lichen planus-hyperpigmented plaque on genital area, including pubic region, labium major, minor and vagina. Dermoscopic image shows white lines and perifollicular hyperpigmentation

Bowen's disease is a frequent skin colored, erythematous, solitary plaque that increases in size and is histopathologically known as carcinoma *in situ* (41). Squamous cell carcinoma may arise in about 5% of Bowen's disease cases (42). Pigmented Bowen's disease is a rare subtype and clinically mimics pigmented BCC and melanoma (43,44). Treatment options are excision, CO_2 laser therapy, cryosurgery, topical imiquimod, 5-FU creams and there is no optimum treatment strategy (41).

Bowenoid papulosis is an intraepithelial neoplasia that etiologically related especially to oncogenic high-risk types of human papillomavirus. Multiple hyperpigmented papules and plaques on the anogenital region are a clinical presentation of Bowenoid papulosis (41,45). In the differential diagnosis of vascular lesions, melanosis, pigmented BCC, melanoma and Bowenoid papulosis, dermoscopy is a useful tool compared with naked-eye (46-48). Therapeutic options include local destructive methods such as cryosurgery, electrocauterization, laser therapy etc. (41,45).

Melanoma

Genital melanoma (Figure 10), is an extremely rare malignancy. Vulvar melanomas are 1% of all melanomas and approximately

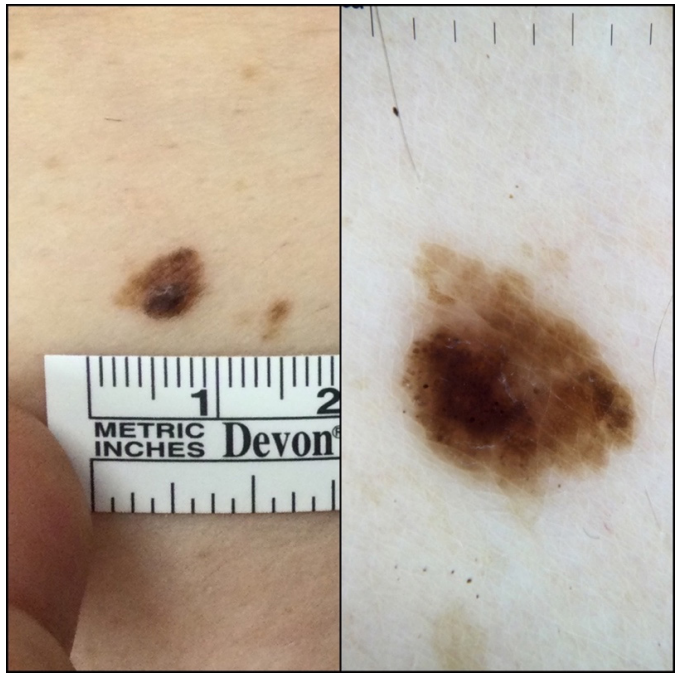

Figure 10. Sixty-three-year-old female patient with melanoma (Breslow: 0.83 mm) on pubic region-irregular shaped, multi-colored, 0.7 mm diameter maculopapular lesion. Dermoscopic image shows bilateral peripheral blotches, atypical globules, atypical vascularization

200 primary penile melanoma cases have been described in the literature that reflects less than 0.1% of primary melanomas (49-51). The common age-onset of both vulvar and penile melanoma is that they both affect elderly individuals from the sixth and seventh decades of life (51,52). It is a necessity to point out that; while distinguishing melanoma and other pigmented lesions in the genital region, the age-onset is one of the most important data from the history of patient. Ultraviolet light is a risk factor for cutaneous melanoma, but there is no sufficient data for genital melanoma. Recent studies indicate that while cutaneous melanomas frequently carry BRAF (serine/threonine kinase) mutations, mucosal melanomas carry mutations or extra copies of KIT (receptor tyrosine kinase) and rarely have BRAF mutations (53-55). Clinically; irregular bordered, single or multi-colored (more than 2: Light-brown, dark-brown, black, blue, gray, red, white), asymmetrical, ulcerated macule, papule, plaques or nodules can be seen. Dermoscopically well-known criteria for non-mucosal melanoma are atypical network, atypical globules, blue-white veil, pseudopods, radial streaming, atypical vascularization, focal sharply cut-off borders, and mucosal melanoma additionally color and structureless area (56,57). Multidisciplinary approach gives chance to early diagnosis. The histopathological features have greater value for staging and due to that fact, excisional biopsy is the ideal approach to suspicion of melanoma (49-52). Depending on the size and site of the lesion, punch, biopsy can be performed (49-52). Treatment for localized melanoma is surgical excision. In cutaneous melanoma, the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend surgical margins depending on tumor thickness (based on category I evidence): 0.5-1 cm for melanoma *in situ*, 1 cm for invasive melanoma with a Breslow's thickness ≤1 mm, 1-2 cm for Breslow 1.01-2 mm, and 2 cm for Breslow >2 mm. In accordance with the National Comprehensive Cancer Network guidelines, margins may be modified to accommodate individual anatomic or functional considerations. The prognosis of vulval, vaginal and penile melanoma is very poor (49,51,58). Because multiple primary melanoma cases in follow-up of melanoma patient there is expert work groups recommend at least annually dermatological follow-up, ranging from 3 to 12 months based on risks such as family history, atypical mole syndrome, a number of atypical nevi (59,60).

Conclusion

Genital pigmented lesions have a wide range spectrum of diseases. The diagnosis of genital pigmented lesions and managing these patients require multidisciplinary expertise but can be mastered with practice. Besides this; patient self-awareness should be increased, especially when follow-up is carried out in patients with known genital pigmented lesion. When pigmented genital lesions are encountered in the urological examination, the patient's advanced age, the existing or the new and rapidly growing lesions that show asymmetry in shape, color and structure may require biopsy indication. In cases that melanoma is among the preliminary diagnoses and excisional biopsy cannot be performed, it may help approach an accurate diagnosis that dermatologists and urologists determine the biopsy region together while biopsy is taken from a histopathologically appropriate part of the lesion. Generally, it is recommended that urologists should take excisional biopsies because it is a surgically challenging area. The management and approach of these lesions should be tailor-made and need to be organized in a multidisciplinary fashion because of the features that make the genital region special to other body parts.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Endourology

Doi: 10.4274/jus.galenos.2022.2022.0040
J Urol Surg, 2023;10(1):17-24

Ureteroenteric Anastomotic Strictures Following Robotic Radical Cystectomy: Extracorporeal Versus Intracorporeal Approaches in the Indocyanine Green Era

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

Benign ureteroenteric stricture formation after radical cystectomy is a common complication which is difficult to manage. This study shows the possible benefical effect of intraoperative indocyanine green utilization during robotic radical cystectomy in order to prevent benign ureteroenteric stricture formation.

Abstract

Objective: The aim of this study was to compare the early period iatrogenic benign ureteroenteric anastomotic stricture formation between robotic radical cystectomy with extracorporeal urinary diversion, robotic radical cystectomy with intracorporeal urinary diversion [without using indocyanine green (ICG)] and robotic radical cystectomy with intracorporeal urinary diversion (with using ICG).

Materials and Methods: A total of 30 patients (59 renal units) who underwent robotic radical cystectomy and urinary diversion intracorporeally or extracorporeally for muscle-invasive bladder cancer between 2014 and 2021 were included in this study. We retrospectively reviewed the demographic data and perioperative results. The primary endpoint of our study was the ureteroenteric stricture formation rate at the 6th week after the single-J ureteral catheter removal.

Results: From our study cohort; 13 of these patients (26 renal units) urinary diversions were performed using extracorporeal approach (group 1), 10 of these patients (20 renal units) urinary diversions were performed by intracorporeal approach without using ICG (group 2) and 7 of these patients (13 renal units) urinary diversions were performed by intracorporeal approach with using ICG (group 3). The overall incidence of early period ureteroenteric stricture formation (post-operative 6th week after the single J catheter removal) was 8.5% (5 renal units); 11.5% (3 renal units) after extracorporeal approach (group 1); 10% (2 renal units) after intracorporeal approach without using ICG (group 2). None of the patients with intracorporeal approach using ICG (group 3) had a demonstrable ureteroenteric stricture at post-operative 6th week after the single J catheter removal.

Conclusion: Robotic intracorporeal urinary diversion with using ICG is a promising approach in terms of preventing benign ureteroenteric strictures.

Keywords: Robotics, cystectomy, indocyanine green

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Received: 20.04.2022 **Accepted:** 09.09.2022

Cite this article as: Tuna MB, Doğanca T, Argun ÖB, Tüfek İ, Kara Esen B, Öbek C, Kural AR. Ureteroenteric Anastomotic Strictures Following Robotic Radical Cystectomy: Extracorporeal Versus Intracorporeal Approaches in the Indocyanine Green Era. J Urol Surg, 2023;10(1):17-24.

Introduction

The optimal treatment for muscle-invasive bladder carcinoma is radical cystectomy with urinary diversion and perioperative complication rates of this surgery may extend up to 70% (1,2). The incidence of benign ureteroenteric strictures after radical cystectomy is reported between 2.6% and 13% in the literature (3-9). The management of these strictures may be difficult and can cause obstruction, hydronephrosis, urinary stones and eventually kidney malfunction (10). Although it's thought that ischemia induced scar formation at the anastomosis may play a role in the development of the ureteroenteric anastomotic stricture; the exact mechanism is not well-known (5). Even though the best surgical principles are followed, including meticulous tissue handling and periureteric adventitial tissue preservation, vascularization of ureters can be jeopardized and eventually lead to ureteroenteric stricture development. Distal ureter vascularization may be assessed subjectively but is prone to error when inspected under white light and when using an open approach. Near-infrared fluorescence (NIRF) imaging after indocyanine green (ICG) injection has been proposed as a useful method for real-time imaging during the operation. ICG (Akorn, Lake Forest, IL) is a nontoxic and FDA approved near-infrared fluorescent dye, visualized by the assistance of an infrared camera, and cannot be identified under white light (11). The application of the Firefly technology (Novadaq Technologies, Mississauga, ON, Canada) integrated with the da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA, USA) has provided wide adoption of ICG usage in robotic surgeries. console surgeon can intraoperatively switch on the NIRF system when required, permitting shifting between white light and near-infrared light, leading real-time identification of the fluorescence of ICG (12). Unlike inspection under white light; ICG usage may aid better evaluation of tissue vascularization, thereby improving recognition and consequently excision of non-viable distal ureteric segments provided before ureteroenteric anastomosis.

In this study, we compared the incidence of the iatrogenic ureteroenteric strictures six weeks after three procedures: Robotic radical cystectomy with extracorporeal urinary diversion; robotic radical cystectomy with intracorporeal urinary diversion without ICG; and robotic radical cystectomy with intracorporeal urinary diversion using ICG.

Materials and Methods

The data of the patients who underwent robotic radical cystectomy with extracorporeal urinary diversion and robotic radical cystectomy with intracorporeal urinary diversion were retrospectively collected. The study was approved by Acibadem Mehmet Ali Aydinlar University Medical Research Ethics Committee (ATADEK) (decision number: 2021-09/51). In both groups, the radical cystectomy part of the operation was performed transperitoneally with six ports using Da Vinci SI or Da Vinci XI robotic systems (both from Intuitive Surgical, Sunnyvale, CA, USA). The operative approach (extracorporeal or intracorporeal urinary diversion) was at the discretion of the surgeon and was decided in consultation with the patient. All cystectomies and urinary diversions were performed by a single surgeon, Prof. Dr. Ali Riza Kural, who is very experienced in robotic surgery (≥2.500 cases) and with open surgery.

In the extracorporeal urinary diversion approach, a small midline infraumbilical incision was made at the end of the robotic cystectomy. After the removal of the cystectomy specimen, a tension-free Wallace anastomosis was performed. In conduits, the left ureter was transferred to the right side through a retro-mesenteric window. After the construction of the intestinal diversion, distal parts of the ureters were excised proximally to healthy tissue and only distal ureteric segments were handled at this point. Anastomosis over 6 F single J stents by 4/0 polyglactin absorbable sutures was performed after the spatulation of the ureters.

For the intracorporeal urinary diversion using ICG, the procedure was as follows. Firstly, left ureter was again transferred to the right side through a retro-mesenteric window. After this, 25 mg ICG was mixed with 10 mL-distilled water and 2 mL of this solution was injected intravenously just before the spatulation and construction of the uretero-enteric anastomosis, after isolation and construction of the neobladder or ileal loop. For the intracorporeal neobladder, the technique described by Wiklund and Poulakis (13) was used. The distal part of the ureters was assessed by the assistance of the NIRF system. After the fluorescence of small periureteric arteries within 30 secondsand ureteric wall fluorescence within 5 min due to the perfusion of ICG into the ureteric tissue. The vascularization of the neobladder or ileal conduit and bowel anastomosis were also inspected. The non-enhancing segments of the ureter (Figures 1,2) were excised and after the spatulation of the healthy vascularized distal part of the ureters, modified tension-free Wallace anastomosis was performed over 6F single J stents using Stratafix 4/0 sutures. Frozen sections of the distal ureteral segments during radical cystectomy were performed for each patient after clipping of the distal ureter. In both approaches, single J stents were left in place for 10 days.

Patient demographic records and histopathological data were reviewed. The length of the excised ureter segments was also assessed. However, excised ureteric segments suspected of malignancy on frozen section analysis were excluded from the study. Post-operative follow-up was performed by regular clinical visit with ultrasonographic examination, six weeks after the single-J catheter removal. Ureteroenteric stricture was defined as functional imaging proven obstruction that leads to

hydronephrosis. Patients with suspicious strictures (clinical or radiologic) were further evaluated with mercaptuocetyltriglycine (Mag3) renal scintigraphy.

Statistical Analysis

SPSS version 21 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Continuous variables are presented as median (interquartile range - IQR) while categorical variables are presented as frequency and percentage. Comparisons of the groups for continuous variables were made by Kruskal-Wallis test. Fisher's Exact test was used to analyze the categorical variables. Post hoc analyses were performed to test the significance of pairwise differences. All tests are two-sided and the significance level was set as $p<0.05$.

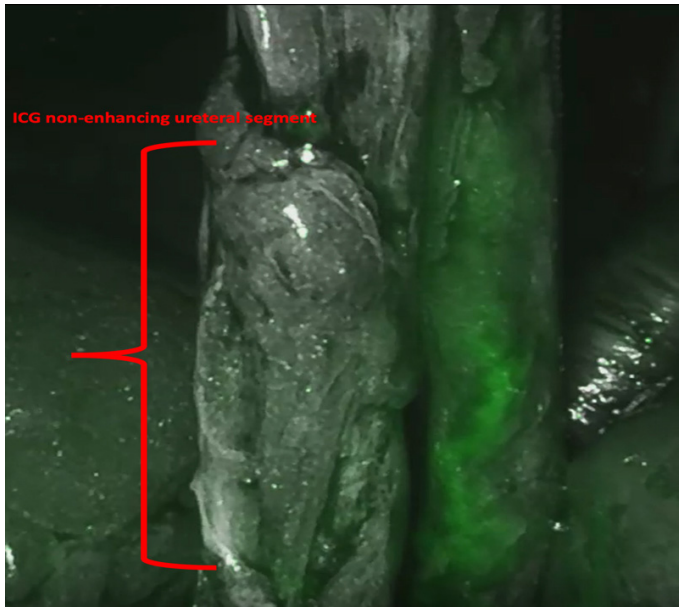

Figure 1. ICG non-enhancing ureteral segment

ICG: Indocyanine green

Results

Between April 2014 and December 2021, 30 (27 male, 3 female) robotic radical cystectomies for bladder cancer were identified and included. Baseline patient characteristics are summarized in Table 1. The median age for the extracorporeal urinary

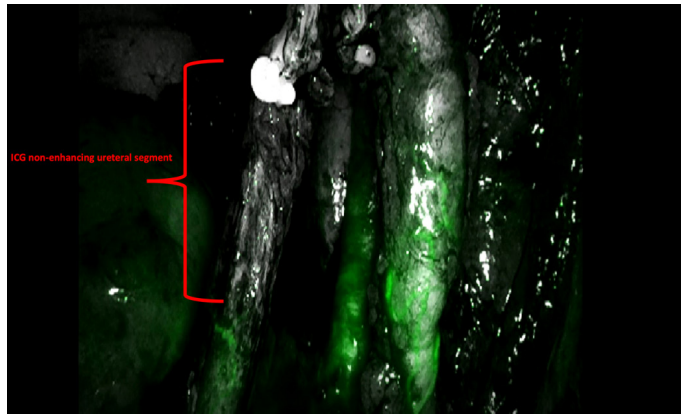

Figure 2. ICG non-enhancing ureteral segment

ICG: Indocyanine green

Table 1. Baseline characteristics of the operative approaches

Valuable	Robotic radical cystectomy with extracorporeal urinary diversion 13 patients 26 renal units (group 1)	Robotic radical cystectomy with intracorporeal urinary diversion (without using ICG) 10 patients 20 renal units (group 2)	Robotic radical cystectomy with intracorporeal urinary diversion (with using ICG) 7 patients 13 renal patients (group 3)	p-value
Sex, n (%)				
Male	12 (92)	9 (90)	6 (86)	1.000*
Female	1 (8)	1 (10)	1 (14)	
Age at RARC, years, median (Q1, Q3)	59 (58,62.5)[a]	70.5 (65.73)[b]	69 (67-78)[b]	**0.007****
Smoking history, n (%)	7 (54)	6 (60)	5 (71)	0.891*
Hypertension, n (%)	7 (54)	5 (50)	4 (57)	1.000*
Diabetes, n (%)	3 (23)	2 (20)	2 (28)	1.000*
Coronary artery disease, n (%)	2 (15)	1 (10)	2 (28)	0.687*
BMI (kg/m^2), median (Q1, Q3)	28 (26.5-30.5)	28.5 (27-31)	29 (28-30)	0.881**
Neoadjuvant chemotherapy, n (%)	5 (38)	3 (30)	2 (28.6)	0.1000*
Pre-op hydronephrosis, n (%)	1 (8)	1 (10)	1 (14)	1.000*
Intraoperative estimated blood loss, mL, median, (range)	400 (300-600)	425 (250-600)	425 (250-550)	0.793**

Each subscript letter denotes a subset of operation type categories whose column proportions do not differ significantly from each other at the 0.05 level, ICG: Indocyanine green, BMI: Body mass index, *: Fisher's Exact test, **: Kruskal-Wallis test

diversion group (group 1) was significantly lower than in both the intracorporeal urinary diversion without ICG (group 2) and the intracorporeal urinary diversion using ICG groups (group 3). No statistical differences were found in the other baseline characteristics. Five patients (38%) in the extracorporeal urinary diversion group (group 1), three (30%) in the intracorporeal urinary diversion group without ICG (group 2) and two (28.6%) in the intracorporeal urinary diversion group using ICG (group 3) received neoadjuvant chemotherapy. None of the patients in this study received pelvic radiotherapy post-operatively. Pre-operative hydronephrosis was detected in one (8%) patient in the extracorporeal urinary diversion group (group 1), in one (10%) in the intracorporeal urinary diversion group without ICG (group 2) and in one patient (14%) in the intracorporeal urinary diversion group using ICG (group 3). The type of diversion and baseline histopathological characteristic of the operative approaches are shown in Table 2. When using an extracorporeal approach, the type of urinary diversion was ileal neobladder in 12 patients and ileal loop in 1 patient. When using the intracorporeal approach, the type of urinary diversion was ileal neobladder in 7 patients (6 without ICG, 1 using ICG) and ileal loop in 10 patients (4 without ICG, 6 using ICG). Intraoperative ICG was used in 7 patients (ileal neobladder in 1, ileal loop in 6) patients with 13 renal units (in one patient concomitant robotic left nephroureterectomy was performed) in the intracorporeal urinary diversion group using ICG (group 3) for uretero-ileal anastomosis. In the intracorporeal urinary diversion group using ICG (group 3), 7 ureters on the right side required proximal resection due to poor perfusion with median length of resected ureter 23 (IQR 22.25-25.5) mm. On the left side 6 ureters (in one patient concomitant robotic left nephroureterectomy was performed) required proximal transection due to poor perfusion with a median length of the resected ureter of 28.5 (IQR 27-30) mm. The median (IQR) length of the resected distal ureter based on perfusion was 20.5 (IQR 20-22) mm for the extracorporeal urinary diversion group (group 1), 22 (20.5-25) mm for the intracorporeal urinary diversion group without ICG (group 2) and 26 (23-28.25) mm for the intracorporeal urinary diversion group using ICG (group 3). The median length of the resected distal ureter due to poor perfusion was significantly higher in the intracorporeal urinary diversion group using ICG (group 3) compared with the other two groups (p<0,.001). None of the resected ureteric segments based on perfusion revealed malignancy on final pathological examination. In the immediate post-operative 30-day period, Clavien-Dindo grade 2 complications were encountered in three patients in the extracorporeal urinary diversion group (group 1),

Table 2. Type of diversion and baseline pathologic characteristics of the operative approaches

	Robotic radical cystectomy with extracorporeal urinary diversion (group 1)	Robotic radical cystectomy with intracorporeal urinary diversion (without using ICG) (group 2)	Robotic radical cystectomy with intracorporeal urinary diversion (with using ICG) (group 3)
Type of diversion, n (%)			
Ileal loop	1 (8)	4 (40)	6 (86)
Ileal neobladder	12 (92)	6 (60)	1 (14)
Pathologic stage, n (%)			
NMIBC	9 (69)	6 (60)	2 (29)
MIBC	1 (8)	2 (20)	-
Non-OC (≥ T3)	3 (23)	2 (20)	5 (71)
Positive ureteral margins	-	-	-
Nodal disease, n (%)	3 (23)	2 (20)	0

ICG: Indocyanine green, NMIBC: Non-muscle invasive bladder cancer, MIBC: Muscle invasive bladder cancer, OC: Organ confined

Table 3. Characteristics of the uretero-enteric strictures according to the operative approach

	Robotic radical cystectomy with extracorporeal urinary diversion (group 1)	Robotic radical cystectomy with intracorporeal urinary diversion (without using ICG) (group 2)	Robotic radical cystectomy with intracorporeal urinary diversion (with using ICG) (group 3)
Stricture rate, n (%)	3 (26) 3/26=11.5%	2 (20) 2/20=10%	0 (13) 0/13=0
Laterality, n (%)			
Left	2 (66)	2 (100)	-
Right	1 (33)	-	
Intervention performed, n (%)	2 (66)	-	-

ICG: Indocyanine green

two patients in the intracorporeal urinary diversion without ICG (group 2) group and two patients in the intracorporeal urinary diversion using ICG group (group 3). During the same period, a single Clavien-Dindo grade 3a complication (spontaneous removal of Foley catheter on post-operative day 3 in an ileal neobladder patient) occurred in the intracorporeal urinary diversion without the ICG group (group 2). This complication was managed by re-insertion of the foley catheter under local anesthesia. Finally, a Clavien-Dindo Grade 3b complication (the tip of the drain was broken during removal) occurred in one patient in the intracorporeal urinary diversion using ICG group (group 3). For this patient, the tip of the drain was removed under general anesthesia from a small incision (2 cm) at the drain removal side.

Characteristics of the uretero-enteric strictures that occurred by the group are summarized in Table 3. None of the patients in the intracorporeal urinary diversion group using ICG (group 3) had demonstrable uretero-enteric strictures in the post-operative sixth week after the single J catheter removal. Benign uretero-enteric strictures were identified in five patients, three in the extracorporeal (group 1) and two in the intracorporeal urinary diversion group without ICG (group 2) (Figure 3). Four of these strictures were observed in ileal neobladder diversion and one in the ileal loop diversion. Furthermore, four were left sided and one was right sided. Two of these ureteral strictures were managed surgically, while three were not suitable for surgical management and persisted in follow-up. Of the two patients receiving surgical management of the stricture, one (extracorporeal urinary diversion group, ileal neobladder) had left-sided ureteral stricture diagnosed by ultrasonography and confirmed with Mag3 renal scintigraphy at six weeks after the single J catheter removal. Ureteral stent replacement failed, and percutaneous nephrostomy tube placement was performed in the fifth month post-operatively and ureteral stricture excision and ureteral reimplantation over 6-F JJ stent placement the open approach was performed three weeks after this procedure. The JJ stent was removed by cystoscopy four weeks after the procedure. The other patient (extracorporeal urinary diversion group, ileal neobladder) had right-sided ureteral stricture, again diagnosed by ultrasonography and confirmed with Mag3 renal scintigraphy six weeks after J catheter removal. At the post-operative nine month, ss an antegrade nephrostogram was performed and a right distal ureteral stricture was revealed on fluoroscopy. Subsequently, three-week ureteral JJ

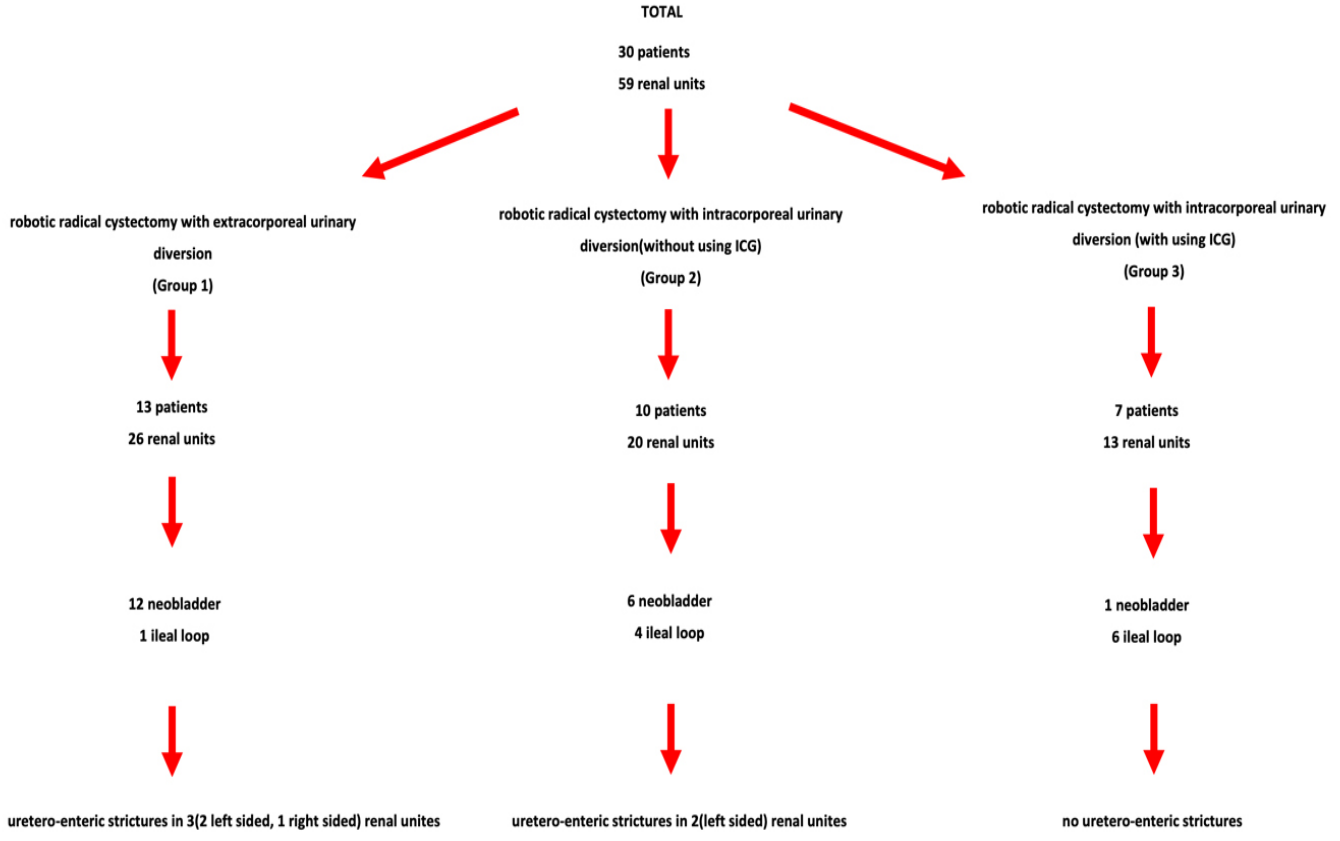

Figure 3. Ureteroenteric stricture distribution according to the groups

ICG: Indocyanine green

stent placement was performed. After JJ stent removal, the patient was informed about progress and agreed to definitive treatment at the post-operative 48th month. This right-sided ureteral stricture was excised via transperitoneally with a Da Vinci XI robotic system using ICG with NIRF and a ureteroileal reanastomosis over 4.8 F JJ stent was performed.

Discussion

The incidence of uretero-enteric stricture formation varies from 2.6% to 13% in the literature (3-9). The source of this difference in the published series is unclear, but it can be attributable to diagnostic criteria for uretero-enteric strictures, patient identification methods and patient population heterogeneity. Adequate vascularization of the distal ureteric segment is crucial for minimizing the uretero-enteric stricture formation. Devascularization can occur, even with minimal mobilization of the ureters, so careful handling, meticulous dissection for preserving periureteric tissue is crucial. Although the timing of uretero-enteric stricture formation after radical cystectomy is reported to vary, most are evident in the first year. Tal et al. (14) reported 75% of patients with stricture formation were diagnosed within 12 months with a median time to diagnosis of seven months. Anderson et al. (4) reported a median time of stricture diagnosis of 5.3 months; in their series of 478 patients with 60 uretero-enteric anastomotic strictures. Shah et al. (7) observed a median time to uretero-enteric stricture formation diagnosis of 10 months in their open radical cystectomy series. They identified 49 patients (2.6%) with benign uretero-enteric stricture in 1964 patients. Shen et al. (15) reported their time course of uretero-enteric stricture formation that required open revision in 33 patients after robotic radical cystectomy with extracorporeal urinary diversion. In their study cohort, they identified a total of 37 (29 unilateral, 4 bilateral) uretero-enteric strictures. Thirty-five of the 37 (94.6%) strictures were demonstrated on imaging (computerized tomography or ultrasound), performed no longer than two months after cystectomy. They recommended consideration of early imaging (by two months post-operatively) to identify uretero-enteric strictures to instigate early management to prevent renal insufficiency. To identify the uretero-enteric strictures in the early period, we also performed ultrasonographic examination six weeks after the single J catheter removal (15).

ICG fluorescence has been used in an expanding range of procedures in the robotic urological field (16). ICG is generally used during robotic partial nephrectomy operations for facilitating super-selective arterial clamping and predicting malignancy in kidney lesions (17-19). Moreover, ICG has been used for detecting sentinel lymph nodes during robotic radical prostatectomy (20). Additionally, in robotic ureteral reconstruction procedures, intraureteric ICG instillation may facilitate the identification and localization of ureteral strictures (21). Tuderdi et al. (22) reported their transnephrostomic ICG-guided robotic ureteral reimplantation experience for benign uretero-ileal strictures after robotic cystectomy and intracorporeal neobladder in 10 patients. They identified the ureteric segment by injecting ICG in an antegrade fashion through the nephrostomy tube. In this study, only one patient developed stricture recurrence and none of the patients developed worsening of the renal function at a median of 19 months of follow-up. Ahmadi et al. (23) assessed the impact of ICG for evaluating ureteric vascularity on the rate of uretero-enteric stricture formation in 179 patients (132 non ICG and 47 ICG group) undergoing robot assisted radical cystectomy and intracorporeal urinary diversion. After a median follow-up of 12 months, they found in the ICG group that none of the patients had uretero-enteric strictures. However, in their non-ICG group, after a median 14 months of follow-up, there was a per-patient stricture rate of 10.6% and a per ureter stricture rate of 6.6% (p=0.020 and p=0.013, respectively). They concluded that; the use of ICG to assess distal ureteric vascularity during robot assisted radical cystectomy and intracorporeal diversion appears to minimize the risk of uretero-enteric strictures (23). Ericson et al. (24) compared 279 open, 382 robotic extracorporeal and 307 robotic intracorporeal radical cystectomies in terms of incidence of uretero-enteric stricture formation. They reported a benign uretero-enteric stricture incidence of 9.3% after open, 11.3% after robotic extracorporeal and 13% after robotic intracorporeal radical cystectomy. They concluded that an intracorporeal approach following radical cystectomy had increased the risk of benign uretero-enteric stricture formation, especially with less experienced surgeons. Their evidence for this was that uretero-enteric stricture formation in intracorporeal urinary diversions declined as individual surgeon's case numbers of increased in their retrospective series. Furthermore, Ahmed et al. (6) retrospectively compared 269 intracorporeal urinary diversions and 138 extracorporeal urinary diversions in their single surgeon series. They reported uretero-enteric stricture formation of 16% for intracorporeal urinary diversion and 6% for extracorporeal urinary diversion. They reported that an intracorporeal urinary diversion following robotic radical cystectomy was an independent risk factor for ureteroenteric stricture development. Robotic radical cystectomy with extracorporeal urinary diversion has also been suggested to be a risk factor for uretero-enteric strictures. Although stricture formation was not the primary endpoint and comparative statistical analyses were not implemented, the Razor randomized trial reported uretero-enteric strictures at a rate of 9% for robotic radical cystectomy with extracorporeal urinary diversion and 7% for open radical cystectomy (3). Anderson et al. (4) retrospectively compared 103 robotic radical

cystectomies with extracorporeal urinary diversion and 375 open radical cystectomy cases. They reported uretero-enteric stricture in 12.6% for robotic extracorporeal urinary diversion and 8.5% for open radical cystectomy (4). More recently; Faraj et al. (25) compared uretero-enteric stricture rates between open radical cystectomy (8% stricture rate in 337 patients), robotic radical cystectomy with extracorporeal approach (9.6% stricture rate in 197 patients) and robotic radical cystectomy with intracorporeal urinary diversion (2.6% stricture rate in 39 patients). They showed that an intracorporeal urinary diversion was not associated with the uretero-enteric stricture formation. The proportion of urinary diversion type (ileal neobladder/ileal loop) in our study differed between each group. The low rate of ileal neobladder diversion (1/7) in the intracorporeal urinary diversion group using ICG (group 3) may be a factor for the low rate of uretero-enteric stricture. However, Presicce et al. (26) reported uretero-enteric stricture rates 12% for ileal loop and 15% for ileal neobladder in 210 patients with a mean follow-up of 30±22 months and the stricture rates between ileal loop and ileal neobladder did not differ statistically (p=0.658); it has been suggested that learning curve of the surgeon has some effects on the functional outcome in robot assisted radical cystectomy with intracorporeal urinary diversion (27). However, all procedures in our study were performed by a single surgeon who is experienced in both robotic (≥2.500 cases) and open surgery.

Study Limitations

Our study has several limitations. Firstly, it was a single center non-randomized study, and data were reviewed retrospectively with inherent selection bias. Secondly, the number of patients in our study is relatively low and larger prospective randomized studies are needed to strengthen our results. Additionally, long-term data are not available and unreported in our study. Nevertheless, this is the first study to report the possible advantages of ICG use in intracorporeal urinary diversion compared with extracorporeal urinary diversion and intracorporeal urinary diversion without ICG in the post-operative early period.

Conclusion

Robotic cystectomy with intracorporeal diversion using ICG is a promising approach in terms of preventing benign ureteroenteric stricture formation. Further prospective studies must confirm our outcomes.

Ethics

Ethics Committee Approval: The study was approved by Acibadem Mehmet Ali Aydinlar University Medical Research Ethics Committee (ATADEK) (decision number: 2021-09/51).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.B.T., Ö.B.A., A.R.K., Concept: M.B.T., T.D., Ö.B.A., A.R.K., Design: M.B.T., T.D., Ö.B.A., A.R.K., Data Collection or Processing: M.B.T., T.D., Ö.B.A., Analysis or Interpretation: M.B.T., T.D., İ.T., B.K.E., C.Ö., Literature Search: M.B.T., İ.T., C.Ö., Writing: M.B.T.

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

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2022.2022.0029
J Urol Surg, 2023;10(1):25-30

Effect of Ultrasound-guided Obturator Nerve Block on Complications in Transurethral Resection for Bladder Cancer

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

The higher incidence of bladder cancer in older ages increase sthe risk of complications that may develop due to anesthesia and surgery. Transurethral resection (TUR) of lateral bladder cancers with obturator reflex is an undesirable event for surgeons as the risk of complications may increase. It is thought that obturator nerve block application added to the anesthesia technique will provide safe surgery. In our study, we aimed to show the protective effect of obturator block on complications that may develop in TUR operation and to make a positive contribution to similar studies.

Abstract

Objective: This study explored the efficiency of obturator nerve block (ONB) along with spinal anesthesia on obturator reflex and related complications during transurethral resections (TUR-B) of bladder tumors on the lateral and inferolateral bladder walls.

Materials and Methods: We retrospectively reviewed the medical history of 248 patients having undergone TUR-B operations in our hospital between March 2017 and March 2019. Among them, we recruited the data of only 115 patients with bladder tumors on the lateral and inferolateral walls, according to the pre-operation ultrasound reports. Ultimately, 44 patients who received only spinal anesthesia (group A) and 37 patients who underwent spinal anesthesia combined with ONB (group B) were compared concerning postoperative bleeding, adductor muscle contraction, bladder perforation, reoperation, mortality - morbidity rates, length of hospital stay and conversion rates to general anesthesia.

Results: There was no significant difference between the groups in terms of age, gender, American Society of Anesthesiologists, length of hospital stay, postoperative bleeding and mortality ($p>0.05$). Yet, the incidence of obturator reflex in the group A was found to be significantly higher than in the group B ($p<0.001$), and major complications such as bladder perforation were not encountered in any of the patients.

Conclusion: ONB combined with spinal anesthesia in the operations for lateral and inferolateral bladder wall tumors is an effective method to prevent possible obturator reflex and related complications.

Keywords: Cystoscopic surgery complications, obturator nerve block, urinary bladder neoplasms

Introduction

Bladder cancers are highly prevalent diseases, and transurethral resection of a bladder tumor (TUR-B) still represents the most appropriate and effective treatment for carcinoma of the bladder and provides essential histopathologic information necessary for definitive diagnosis, staging and primary treatment (1). The obturator nerve, originating from the lumbar plexus, is responsible for the motor innervation of the thigh muscles and the sensory innervation of a small region. The anatomical course of the obturator nerve close to the lateral and inferolateral walls of the bladder is critical during TUR-B

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Received: 24.04.2022 **Accepted:** 23.10.2022

Cite this article as: Topçu H, Aydın C, Şentürk AB, Yağan Ö. Effect of Ultrasound-guided Obturator Nerve Block on Complications in Transurethral Resection for Bladder Cancer. J Urol Surg, 2023;10(1):25-30.

since the adductor muscle may contract due to involuntary stimulation of the obturator nerve. However, the electrical stimulation directly adjacent to the lateral wall of the bladder may induce the obturator nerve reflex and sudden adductor muscle contraction, which may cause incomplete tumor resection, bladder perforation, extravesical dissemination of the cancer cells and even injury to the obturator artery (2). An adductor muscle spasm is also called obturator reflex (1). Due to the involuntary obturator reflex; bladder perforation, regional hematoma, the spread of tumor cells outside the bladder, or inadequate resection of the tumor may cause adverse outcomes that elevate mortality and morbidity (1,3). It has been reported that the incidences of sudden thigh movement and bladder perforation during surgical procedures in the absence of ONB were 49% and 16% respectively (4). Accordingly, curarization is often recommended to relax muscles, which contributes to eliminating such undesirable effects.

Old age and many comorbidities of patients with bladder tumors and common postoperative pulmonary complications among such patients have often led to general anesthesia and curarization to be avoided, increasing the tendency to regional anesthesia. ONB was first introduced by Labat (5) in 1928, and Prentiss et al. (6) showed that it could be used to prevent the obturator muscle spasm in 1965. Now, frequent use of ultrasonography (US) in peripheral nerve block practices enables operators to see the obturator nerve between adductor muscles, which brings a higher rate of successful blocks with less drug use (3,6,7).

In this study, we retrospectively explored the effectiveness of US-guided ONB performed under spinal anesthesia in preventing undesirable surgical and anesthetic complications in TUR-B operations.

Materials and Methods

Study Design

Following the ethics committee approval from Hitit University School of Medicine, we retrospectively reviewed anesthesia

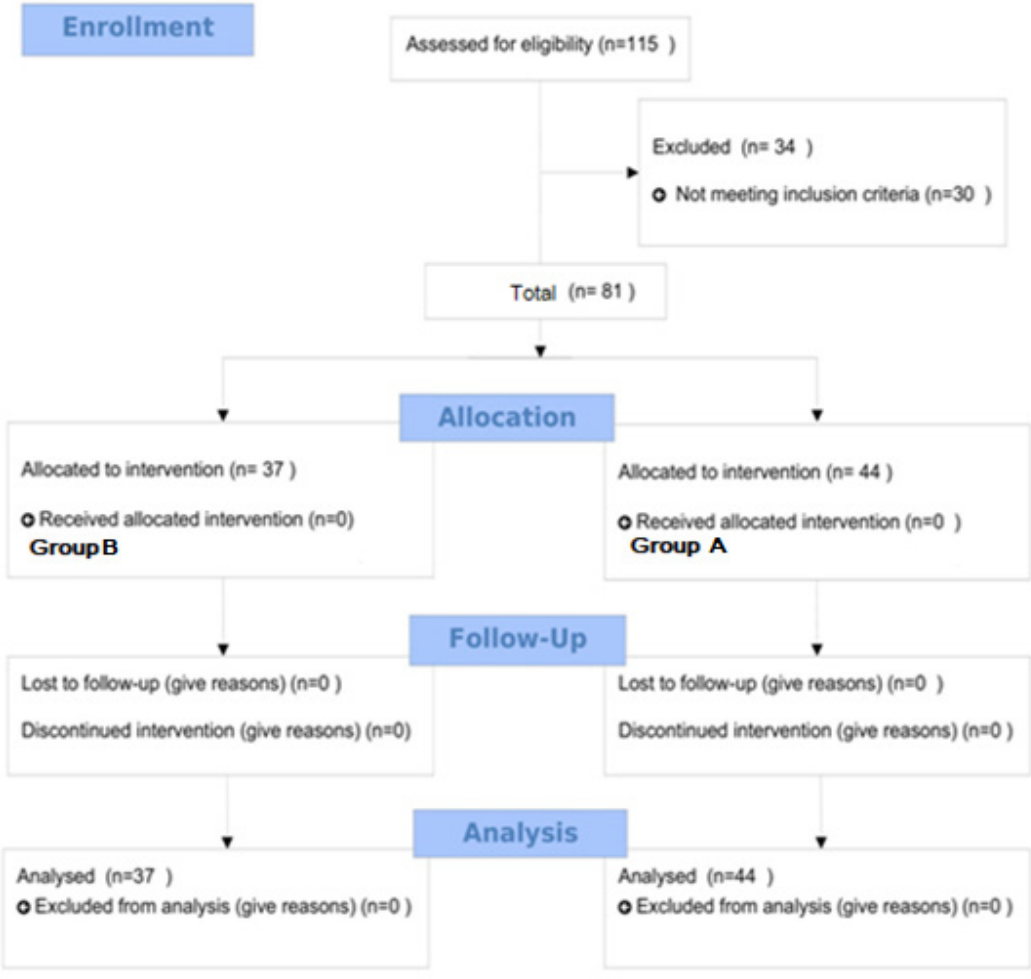

Figure 1. Consort follow chart

records of those having undergone TUR-B operations at Erol Olçok Training and Research Hospital between March 2017 and March 2019. The study was approved by the local ethics committee (Hitit University Faculty of Medicine Erol Olçok Training and Research Hospital Clinical Ethical Board No: 2019-158) and registered with clinicaltrials.gov (NCT04995445).

We determined that 115 patients underwent bipolar TUR-B operations because of lateral-inferolateral wall-located bladder tumors in a two-year period. While 30 patients were administered general anesthesia for various reasons, and the remaining ones received spinal anesthesia. We excluded 4 patients from the study since they had additional operations other than TUR-B and conducted the study with 81 patients (Figure 1). We divided 81 patients into two groups as those with and without obturator block. In the retrospective file review, it was determined that spinal anesthesia was applied to all patients. Patients who underwent obturator block after spinal anesthesia were grouped as group B, and patients who did not applied were grouped as group A. In our clinic, peripheral blocks have been routinely implemented under US guidance since 2017. The obturator block application in our clinic with ultrasound; the patients are in the supine position, the leg is slightly abducted, the pubic tubercle area is scanned with a superficial US probe and the obturator nerve is seen. The anterior branch of the obturator nerve, located between the adductor longus and the brevis, is reached by advancing a 21 gauge, 100 mm stimulating isolated needle from the lateral to the medial under US guidance. After negative aspiration, 5 mL of local anesthetic solution is injected. Then, the needle is withdrawn. A peripheral block needle is guided into the posterior branch of the obturator nerve, between the adductor brevis and the magnus, and an additional 5 mL of local anesthetic mixture is injected while the spread of the local anesthetic solution is monitored under real-time visualization (Figures 2, 3). In our clinic, 10 mL of local anesthetic mixture containing 40 mg 0.5% bupivacaine and 40 mg 2% lidocaine is used for obturator block.

While 44 patients were operated on after without ONB (group A), 37 were operated on after ONB (group B). We compared the demographic information of these patients, the presence of obturator reflex, obturator reflex-related complications, mortality (30 days) and morbidity rates during the hospital stay.

Statistical Analyses

Statistical analyses in this study were performed using the SPSS (version 22.0, SPSS Inc., Chicago, IL, USA) package program. Descriptive statistics were presented as mean ± standard deviation for normally distributed continuous data, as median (minimum-maximum) for non-normally distributed continuous and ordinal data, and as numbers and percentages (%) for categorical data. We checked whether the data showed a normal distribution using the Shapiro-Wilk test. The Mann-Whitney U test was used for non-normally distributed data in the mean comparisons of two independent samples. The chi-square test or Fisher's exact test was used for comparisons of nominal variables. We accepted $p<0.05$ as statistically significant in all statistical analyses.

Results

The files of 81 patients were reviewed retrospectively. We did not find any significant differences between the groups in terms of age, gender, American Society of Anesthesiologists (ASA), length of hospital stay, postoperative bleeding and mortality for 30 days ($p>0.05$) (Table 1). Although the mean age of the patients was 69.49 years (±11), there were 75 (92.6%) male patients. The tumor sizes of 32 (39.5%) patients were found to be smaller than 3 cm, whereas they were larger than 3 cm in 49 (60.5%) patients. Most patients (70.4%) had a smoking habit. Generally, 28.4% of the patients had lung diseases (COPD,

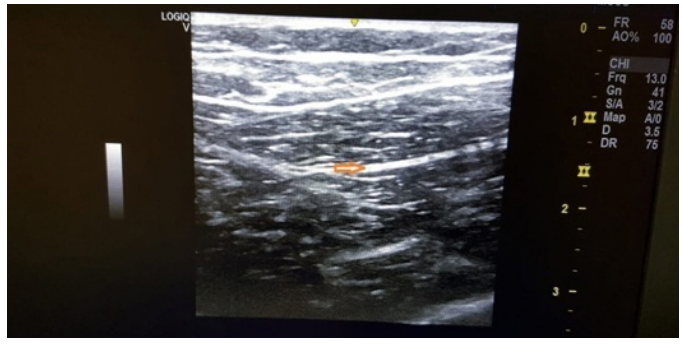

Figure 2. Obturator nerve with US

US: Ultrasonography

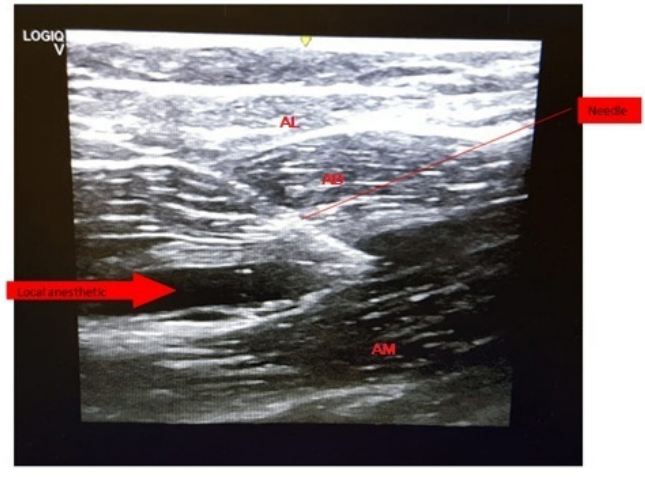

Figure 3. Obturator block with US

AL: Adductor longus muscle, AB: Adductor brevis muscle, AM: Adductor magnus muscle, US: Ultrasonography

asthma, etc.), 51.9% had cardiac diseases (CAD, HT, etc.), 21% had endocrinological diseases (DM, etc.), and 2% had central nervous system diseases (CVD, etc.). The mean age of in group B was 68.57, while it was 70.27 in the group A.

While there was no adductor contraction in the group B, we discovered that 13 (29.5%) patients in the group A experienced it. These 13 patients were switched to general anesthesia by administering neuromuscular blocking agents. Despite neuromuscular blockade in 2 patients, it was noted in the files of the patients that the operation was terminated due to the continuation of adductor muscle spasms.

Accordingly, adductor contraction rates were statistically significant (p<0.001) between the groups. Although the need for reoperation due to adductor contractions was not statistically significant, it was required for 2 patients in group A. Moreover, there was no significant difference between the groups in terms of age, gender, ASA, length of hospital stay, postoperative bleeding and mortality. No major surgical complications were observed in any patient (Table 2).

Discussion

TUR-B is a widespread urological operation to remove bladder tumors, predominantly diagnosed in the older adult population (1,3). In our study, the mean age was 69.49 years, which indicates that the participants were already in the risk group for bladder tumors. The frequent occurrence of comorbidities in this age group poses additional risks of severe complications arising from both anesthesia and operation. Accordingly, one of the critical surgical complications of TUR-B operations is the possibility of bladder perforation because of obturator reflex and adductor muscle contraction due to obturator nerve stimulation. The possibility of tumor cells spreading out of the bladder following perforation may lead surgeons to act hesitantly during resection, which may hinder adequate tumor

Table 1. Demographic information of the patients (mean ± standard deviation)

	Group A		Group B		
	Mean	Frequency	Mean	Frequency	p-value
Age	70.27 (±1.7)		68.57 (±1.9)		
Male		41		34	
Female		3		3	
Tumor size <3 cm		14		18	
Tumor size >3 cm		30		19	
ASA					
I		3		4	
II		19		13	
III		22		10	
Smoking					
(+)		16		8	
(-)		28		29	
Discharge (days)	3.86	4	3.22	3	0.833

Table 2. Complications ratios

	Group A		Group B		p-value
	YES	NO	YES	NO	
Obturator reflex	13 (29.5%)	31 (70.5%)	0	37 (100%)	**>0.001**
Postoperative bleeding	5 (11.4%)	39 (88.6%)	4 (10.8%)	33 (89.2%)	1.000
Reoperation	2 (4.5%)	42 (95.5%)	0	37 (100%)	0.498
General anesthesia ratio	13 (%29.5)	31 (70.5%)	0	37 (100%)	**>0.001**
Mortality (30 days)	1 (2.3%)	43 (97.7%)	4 (10.8%)	33 (89.2%)	0.173

chi-square test , p<0,005

resection (2). Although general anesthesia with neuromuscular blockade is recommended to prevent adductor muscle spasms, it was previously reported that the obturator reflex might be encountered even under general anesthesia in which muscle relaxants are used (8). In our study, obturator reflex persisted despite neuromuscular blockade in two patients. Among surgical measures, it is recommended to reduce the cautery flow, use bipolar cautery, and empty the bladder to reduce the possibility of obturator reflex. While under anesthesia, the other hand, it is recommended to use a neuromuscular blockade or ONB to be able to prevent the obturator reflex. So far, various methods, such as using laser resectors, using saline as an irrigation solution, reversing the polarity of electric current, and applying periprostatic infiltration, have also tried thanks to advances in medicine, which have brought success at varying rates (4,7,9-11).

Considering the advanced age and comorbid conditions, patients are likely to have an increased risk of mortality and morbidity, particularly in terms of postoperative pulmonary complications (1,3). Therefore, anesthesiologists tend to perform operations under regional anesthesia. ONB along with regional anesthesia is shown as a good option in those with advanced age comorbidity (9,12). ONB has been performed since 1965 to prevent the obturator reflex (7,13). The introduction of US to regional anesthesia practices for ONB has led to the emergence of relevant techniques in which ONB is performed under US (14,15). In our clinic, we apply the interadductor approach, defined by Wassef (16) used anatomical points in 1993, for the anterior and posterior branches of the obturator nerve under the guidance of US. While Manassero et al. (17) advocated the importance of blocking the posterior branch in practice, Marhofer et al. (7) considered blocking the anterior branch adequate. In their study, Han et al. (18) reported that blocking the anterior branch or posterior branch did not create a significant difference in terms of effectiveness and complications. Aksu et al. (19) concluded similar findings with the previous research when they blocked the anterior branch in their study. In our clinic, we performed the blockade of the anterior branch using the US-guided in-plane technique, and the results were similar to those in other studies. The relevant literature reports the success rates of ONB to be between 93%-97.2%, owing to the increase in the use of US (17,20). All the blocks administered in our clinic were successful, and we did not encounter any complications, which overlapped what was previously found in the literature. In most studies, ONB is presented as a safe method, as in our study.

Although the previous research reported different severities of obturator spasms, a study reported that the severity of spasms reached 100% in some patients and that bladder perforation developed in 8% of them (21). In our study, obturator reflex was observed in 29.5% of patients who underwent spinal anesthesia only, and reoperation was required in 4.5% of these patients. These high rates may indicate that US-guided ONB should be performed along with spinal anesthesia to prevent complications that may occur due to the obturator reflex formation.

Patel and Patel (21) reported that the complication most affecting the mortality and morbidity of patients was bladder perforation. In our study, the absence of a significant difference between the discharge day and mortality may be attributed to successful operations without bladder perforation. But, reoperation was required in 2 (4.5%) patients.

The most clear weakness of our study might be the small number of patients. Therefore, future studies should attempt to recruit a higher number of patients. Additionally, in our study, surgical teams especially favored obturator block in the operations because of obturator reflex findings in the previous operation history of the patients, which may explain the higher frequency of complications in the group A.

Regional anesthesia has been the recommended anesthesia method to protect both the patient and staff in pandemics affecting the respiratory system such as COVID-19. Due to the advanced age of the TUR-B patients in our study and the presence of pulmonary comorbidities, regional anesthesia supplemented with peripheral blocks is recommended be the first choice if there are no contraindications (22-25). In a meta-analysis study involving 448 patients, Krishan et al. (25) stated that the addition of an obturator block to spinal anesthesia is important and necessary for the safety of both patients and staff in TUR-B operations during the COVID-19 outbreak. Regional anesthesia methods are recommended to prevent pulmonary complications of general anesthesia and microbial contamination during intubation in respiratory system diseases such as pandemics (22-25).

Study Limitation

The limitation of this study is that it is single-centered and retrospective. It is recommended to increase the number of patients and to conduct randomized controlled studies.

Conclusion

Spinal anesthesia with ONB in TUR-B operations of lateral-inferolateral wall-located bladder tumors is an effective and safe method to prevent possible obturator reflex and related complications. Although there is no statistical self-mark in terms of discharge time and mortality, powerful data can be obtained by extending the follow-up periods and increasing the number of patients in line with numerical values.

Acknowledgments

We would like to thank our colleagues who contributed to the study and supported us.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (Hitit University Faculty of Medicine Erol Olçok Training and Research Hospital Clinical Ethical Board No: 2019-158) and registered with clinicaltrials.gov (NCT04995445).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.A., A.B.Ş., Concept: H.T., C.A., Design: H.T., Data Collection or Processing: H.T., Ö.Y., Analysis or Interpretation: H.T., Literature Search: H.T., Ö.Y., Writing: H.T.

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

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2022.2022.0033
J Urol Surg, 2023;10(1):31-35

Evaluation of Dynamic Thiol/Disulfide Homeostasis in Patients with Non-Muscle Invasive Bladder Tumor

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

Reactive oxygen species (ROS) can cause oncogenic transformation by damaging the normal functions of DNA and cellular structures. In transformed cells, intracellular ROS levels are maintained at a higher level than in normal cells due to abnormal metabolism. This may contribute to gene mutations involved in cancer initiation. Non-enzymatic antioxidants such as total thiol and non-protein thiol groups play a critical role in maintaining the intracellular structure and ensuring the function of normal cells. Sulfhydryl groups mediate the maintenance of redox homeostasis and elimination of free radicals. This study was determined that disruption in thiol/disulfide homeostasis may be effective in the development of superficial bladder tumors in cases where oxidant stress predominates over antioxidant mechanisms. The total thiol/disulfide balance plays a role in the etiology of bladder tumors and in many tumors and inflammations, and based on this, antioxidants may be beneficial in the prevention and treatment of bladder tumors. However, further more comprehensive studies should be conducted in order to obtain clearer and more definitive results on this subject.

Abstract

Objective: To evaluate the thiol-disulfide homeostasis in patients with a diagnosis of non-muscle invasive bladder tumor (NMIBC), which is a new oxidative stress marker, and to investigate the relationship between the development of NMIBC and native thiol, total thiol, and dynamic disulfide values.

Materials and Methods: Fifty-three patients who were operated for bladder tumor in Karabük University Karabük Training and Research Hospital, Clinic of Urology between February and November 2020 and diagnosed with NMIBC in the pathological examination and 60 healthy volunteers were included in the study. Plasma native thiol, total thiol and disulfide levels of these two groups were measured and compared.

Results: There was a statistically significant difference between the two groups in terms of native thiol, total thiol and disulfide values. In the subgroup analysis in those diagnosed with NMIBC, native thiol values were found to be 255,870 µmol/L in the low grade patient group and 169,420 µmol/L in the high grade patient group. This difference was statistically significant.

Conclusion: The thiol disulfide homeostasis shifted to the disulfide side in the NMIBC group. It was determined that an increase in serum disulfide level and a decrease in native thiol level may have diagnostic value in predicting NMIBC. In addition, in the group diagnosed with NMIBC, there was a significant decrease in native thiol values as the pathological grade increased. This was interpreted as a shift of the equilibrium towards the oxidant side as the tumor showed an aggressive course.

Keywords: Bladder cancer, thiol, disulfide

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Received: 03.04.2022 **Accepted:** 20.07.2022

Cite this article as: Bürlukkara S, Baran Ö, Aykaç A, Sunay MM. Evaluation of Dynamic Thiol/Disulfide Homeostasis in Patients with Non-Muscle Invasive Bladder Tumor. J Urol Surg, 2023;10(1):31-35.

Introduction

Bladder cancer, which is the second most common malignancy of the urinary system, is an important public health problem due to its aggressive course and poor prognosis (1,2). 70-80% of patients have a non-muscle invasive bladder tumor (NMIBC) at the time of diagnosis (3).

Oxidative stress plays an active role in the emergence and progression of various diseases, such as diabetes, hypertension and cancer (4). Reactive oxygen species (ROS) are physiologically released from aerobic cells and the release amount into the circulation increases in cases of cell damage (5).

ROS can cause oncogenic transformation by damaging the normal functions of DNA and cellular structures. In transformed cells, intracellular ROS levels are maintained at a higher level than in normal cells due to abnormal metabolism. This may contribute to gene mutations involved in cancer initiation (6). Chronic inflammation causes tissue damage by damaging nucleic acids, proteins and lipids because of ROS production. Tissue damage causes stem cell activation for tissue regeneration. Stem cells are damaged by ROS, and the resulting mutations can accumulate and lead to the development of carcinoma (7,8).

Non-enzymatic antioxidants such as total thiol and non-protein thiol groups play a critical role in maintaining the intracellular structure and ensuring the function of normal cells. Sulfhydryl (SH) groups mediate the maintenance of redox homeostasis and elimination of free radicals (9). In this study, we evaluated the relationship between the presence of oxidative stress and tumor formation and tumor characteristics by comparing the serum dynamic thiol/disulfide levels of patients with histologically diagnosed bladder tumors and healthy individuals. This is the first study on this subject in the English literature.

Materials and Methods

Study Groups

This study was planned as a prospective, non-randomized case-control study. Accordingly, patients who applied to Karabük University Training and Research Hospital, Clinic of Urology, between February 2020 and November 2020 were evaluated. Patients were divided into two groups as patients with NMIBC and healthy individuals. Fifty-three patients who underwent transurethral resection of bladder tumor (TUR-M) and were found to have NMIBC by histopathological analysis were included in the patient group. The control group was formed of 60 demographically matched volunteer participants among healthy individuals without any oncological diagnosis who applied to our clinic for general health screening.

In the control group, 2 patients with uncontrolled diabetes, 3 patients receiving anti-inflammatory therapy, 1 patient with hyperthyroidism, 2 patients with renal dysfunction, 1 patient with symptomatic heart failure, and 1 patient-receiving lymphoma treatment were excluded from the study. In the NMIBC group, 2 patients receiving anti-inflammatory therapy, 1 patient with uncontrolled diabetes, 1 patient with symptomatic heart failure, 4 patients with muscle-invasive bladder tumors in the pathology report, and 1 patient with colon carcinoma invasion into the bladder were excluded from the study.

Plasma native thiol, total thiol and disulfide levels, which indicate dynamic thiol/disulfide homeostasis (TDH), were measured in patients and healthy subjects who were planned to be included in the study after the initial evaluation (9). In the patient group, surgical and pathological data after TUR-B were examined and recorded.

Blood Sampling and Measurement of Dynamic Thiol/Disulfide Homeostasis

In patients diagnosed with NMIBC and healthy volunteers, blood samples were collected in empty and dry biochemistry tubes after 8 h of fasting to determine thiol/disulfite blood levels. After centrifuging at 1.500 rpm for 10 min, serum samples were stored at -80 °C. In this method, dynamic and reducible disulfide bonds in the samples were reduced to free functional thiol groups using sodium borohydride. $NaBH_4$ was removed with formaldehyde to prevent a reduction of unused reduced sodium borohydride to dithionite-2 nitrobenzoic compound (DTNB). Native thiol and total thiol levels were determined after reaction with DTNB and finally their levels were measured. Half of the difference between the amount of total thiol content and native thiol indicated the disulfide level.

At the end of the study, it was investigated whether there was a statistically significant difference between the two groups in terms of demographic data, native thiol, total thiol and disulfide levels. In the patient group diagnosed with NMIBC, a subgroup analysis was conducted to evaluate the relationship between tumor size and pathological data and native thiol, total thiol and disulfide levels.

Statistical Analysis

Statistical analysis was carried out using the SPSS 17.0 statistical package program. The compliance of numerical data with a normal distribution was checked with Kolmogorov-Smirnov test. Categorical variables are presented as frequency and percentage. Numerical variables were presented as mean and standard deviations or median and minimum-maximum values. Two independent means were compared with the Student's t-test and two independent medians were compared with the Mann-Whitney U test. The relationship between two independent categorical variables was examined with the chi-square (Fisher's Exact/Exact) test. All analyses were performed

at 95% confidence level (p<0.05 was accepted as statistically significant).

The G* Power (G* Power Ver. 3.0.10, Franz Faul, University Kiel, Germany, htpp://www.pyscho.uniduesseldorf.de/app/project/gpower) package program was used for determining sample size. The sample size was calculated as at least 31 individuals in each of the two groups with 62 individuals for a study with 95% power, Type I error (alpha) 0.05 and effect size 0.93.

This study was designed in accordance with the Declaration of Helsinki, with the approval of the local ethics committee (Karabük University Ethics Commitee) (2020/154). Informed signed consent was obtained from all participants.

Results

The data of 132 people (70 in the control group and 62 in the NMIBC group) were evaluated. After patients excluded based on exclusion criteria, a total of 113 patients, 101 males (89.4%) and 12 (10.6%) female, were included in the study. The mean age of the people included in the study was 69.9±10.26. Mean age was 72.19±10.24 in the patient group and 67.4±9.83 in the control group (p=0.13). The control group included 55 males (91.7%) and 5 females (8.3%), and the NMIBC group included 46 male (86.8%) and 7 female (13.2%) patients (p=0.401).

The control group and the patient group diagnosed with superficial bladder cancer were evaluated in terms of smoking and concomitant diseases. There were no significant differences between the two groups (Table 1).

When the pathology specimens of patients with NMIBC were evaluated in terms of tumor invasion, pTa tumors were detected in 35.8% (19 patients), pT1 high-grade tumors were detected in 50.9% (27 patients) and pT1 low-grade tumors were detected in 13.2% (7 patients) of the specimens. Additionally, when the patients were examined according to tumor size, tumor size was <3 cm in 41.5% (22 patients) and more than 3 cm in 58.6% (31 patients) of the patient group. In terms of tumor localization, it was observed that 67.9% were located on the right and left side wall, 24.5% on the bladder floor, and 28.3% were located on the bladder dome and posterior wall.

A single dose of intracavitary EpirubicinC 50 mg was given to 37.7% (20 patients) of the patients who did not develop complications in the early postoperative period. Patients with pathology results of T1 and high grade were resectioned approximately 4 weeks after the first operation. Intravesical Bacillus Calmette-Guérin treatment was administered to 34 patients (64.1%) according to the pathology results. Tumor recurrence was observed in 13 patients (24.5%) at a mean follow-up of 20 months.

When the control group and the NMIBC group were evaluated in terms of native thiol values, it was observed that the native thiol values were significantly higher in the NMIBC group (p<0.001) (Table 2).

Total thiol and disulfide values were found to be higher in the NMIBC group compared to the control group. Mean total thiol level was found to be 551.01±223.00 µmol/L in the NMIBC group and 412.21±132.15 µmol/L in the control group. Mean disulfide level was 162.49±105.31 µmol/L in the NMIBC group and 12.62±6.88 µmol/L in the control group (p<0.05).

When the NMIBC group was divided into two subgroups in terms of tumor invasion and grade, Ta and T1 low grade 26 (49.1%) patients and T1 high grade 27 (50.9%) patients were found to have statistically similar total thiol and disulfide levels. In the patient group with low-grade tumor, native thiol values were found to be higher than those in the patient group with high-grade tumors (p<0.05) (Table 3).

Table 1. Smoking and concomitant diseases in the control group and patients with bladder tumor

Variable n/(%)	Control Group	Bladder Tm Group	p-value
Smoking			
Yes	45/75	38/71.7	0.692
No	15/25	15/28.3	
Concomitant disease			
Yes	31/51.7	35/66	0.122
No	29/48.3	18/34	

Table 2. Native thiol disulfide and total thiol values in superficial bladder cancer and control group

	NMIBC	Control	p-value
Native thiol (SH) µmol/L	226.02±143.83	386.96±135.00	<0.001
Total thiol (TT) µmol/L	551.01±223.00	412.21±132.15	
Disulfide (SS) µmol/L	162.49±105.31	12.62±6.88	

NMIBC: Non-muscle invasive bladder tumor

Table 3. Comparison of total thiol, native thiol and disulfide levels between Ta/T1 low grade patient group and T1 high grade patient group

	Ta/T1 Low Grade	T1 High Grade	p-value
Native thiol	255.87	169.42	<0.05
Total thiol	506.55	486.60	>0.05
Disulfide	153.73	166.90	>0.05

When 22 (41.5%) patients with a tumor size of <3 cm and 31 (58.5%) patients with a tumor size of more than 3 cm were compared in terms of total thiol, native thiol and disulfide levels, no significant difference was observed between the two groups (p>0.05). Similarly, no significant difference was found between the total thiol, disulfide and native thiol levels of 13 (24.5%) patients with tumor recurrence in their follow-ups and 40 (75.5%) patients without tumor recurrence (p>0.05).

Discussion

In many epidemiological, experimental and clinical studies, oxidative stress markers have been shown to be associated with cancer development and progression. Higher lipid, protein and DNA oxidation markers detected in bladder cancer tissues confirm a potential role of oxidative stress in the molecular mechanism of the disease. Literature data support the overexpression of NO and a deficiency in antioxidant systems (SOD, CAT and GTPx) in bladder tissue, serum and plasma of patients diagnosed with bladder cancer. It is generally thought that the development of bladder cancer occurs because of a disruption in the antioxidant/pro-oxidant balance (10,11). In this regard, our study has the distinction of being the first study in the English literature.

There are studies investigating the changes in TDH in many diseases where oxidative stress is thought to play a role in the development of the disease (9). Hanikoglu et al. (12) examined patients with prostate cancer and found that native thiol, total thiol, and total oxidant status (TAS) levels in the sixth month follow-ups of patients after radical prostatechromia (RP) increased compared to the levels before RP. In the same study, when prostate specific antigen and thiol levels were compared, it was seen that there was a negative correlation between these two values. It was shown that decreased thiol and TAS levels weaken the antioxidant defense mechanism in patients with prostate cancer, and as a result, the balance shifts to the oxidative side. Similar results were obtained in this study, and it was found that there was a decrease in antioxidant levels in patients with bladder cancer compared to healthy individuals, and there was a shift in balance toward the oxidative side.

In this study, native thiol levelswere significantly higher in the healthy group compared to the NMIBC group. Disulfide levelswere found to be higher in the NMIBC group compared in the healthy group. In the subgroup analysis conducted in the NMIBC group, native thiol levels were found to be significantly higher in patients with low-grade tumors compared with patients with high-grade tumors. These results prove that there is a direct relationship between superficial bladder cancer and oxidative stress.

In another study, Senel et al. (13) reported that the mean plasma levels of native thiol and total thiol were lower in patients with prostate cancer compared in the healthy control group. In the same study, in the prostate cancer group, it was determined that patients with a Gleason score of ≥7 had lower plasma native thiol levels than patients with a Gleason score of <7, and there was no significant difference between the two groups in terms of total thiol and disulfide levels. These findings are similar to the results obtained in this study and are consistent with the data obtained in our subgroup analysis and support the decrease in native thiol levels with increasing tumor grade.

Sönmez et al. (14) performed a subgroup analysis in the prostate cancer group and the control group and found that the native and total thiol/disulfide levels in the prostate cancer group were lower than those in the control group. We concluded that oxidative stress, which is involved in the etiopathogenesis of cancer, also plays a role in the etiology of prostate cancer and that there is a decrease in the level of native thiol due to increased oxidative stress. In this study, native thiol levels were also found to be significantly lower in the cancer group.

In a study by Solak et al. (15) in 2018 between smokers and non-smokers, it was found that native, total and native/total thiol levels were lower in smokers. Furthermore, disulfide, disulfide/native thiol and disulfide/total thiol levels were found to be significantly higher in smokers than in non-smokers. As a result, it was determined that smoking increases oxidative stress and causes a shift in TDH to the disulfide side compared to the healthy group. In this study, no significant difference was observed between thecontrol and NMIBC groups smoking. Therefore, a separate subgroup analysis could not be performed for the relationship between smoking and thiol levels.

When we performed a subgroup analysis in the NMIBC group, no significant correlation was found between the dimensions of the bladder tumor and the native thiol, total thiol and disulfide levels. Similarly, in the NMIBC group, there was no significant difference in total thiol and disulfide levels between patients with pathological stages of and T1 low-grade tumors and patients with T1 high-grade tumors, while native thiol values were significantly higher in the low-grade tumor group. This result shows us that there may be a relationship between tumor aggressiveness and native thiol levels. Although the idea that there may be a relationship between the pathological stage of superficial bladder cancer and the TDH has emerged in this

study, it is necessary to conduct more comprehensive studies involving many patient groups to obtain clearer and more definitive results.

The literature data shows that because of the increase in oxidative stress, there is a decrease in the native thiol levels and the balance shifts to the oxidant side. Similarly, in this study, total thiol and disulfide levels were found to be higher in patients with superficial bladder tumors than in the healthy group. This finding is important as this is the first study in the literature to show dynamic TDH in superficial bladder cancer. The increase in the oxidant level seen because of the changes in TDH in patients with superficial bladder cancer also increases serum total thiol and disulfide levels, confirming the role of oxidative stress in the etiopathogenesis of bladder cancer. This supports the relationship between the formation of bladder cancer and oxidative stress. We believe that important complementary data regarding the etiopathogenesis of bladder cancer and data that help evaluate the severity of the disease can be obtained based on the results of this study. Early detection of the increase in serum total thiol and disulfide levels may be a guide for early cystoscopy or interventional procedures in patients with bladder cancer. Since there is no specific antigen or laboratory test in routine use in the follow-up of bladder cancer, we believe that it will guide patients and physicians in their follow-up since it is inexpensive and accessible if it is routinely used.

Study Limitations

The limited number of patients in our study and the exclusion of muscle-invasive bladder tumors caused the subgroup analyses were rather limited. Additionally, the possibility of disruptions in dynamic thiol-disulfide hemostasis in different diseases in which oxidative stress increases is among the limitations of our study.

Conclusion

In this study, it was determined that disruption in TDH may be effective in the development of superficial bladder tumors in cases where oxidant stress predominates over antioxidant mechanisms. Thus, we believe that the total thiol/disulfide balance plays a role in the etiology of bladder tumors and in many tumors and inflammations, and based on this, antioxidants may be beneficial in the prevention and treatment of bladder tumors. However, further more comprehensive studies should be conducted in order to obtain clearer and more definitive results on this subject.

Ethics

Ethics Committee Approval: This study was designed in accordance with the Declaration of Helsinki, with the approval of the local ethics committee (Karabük University Ethics Commitee) (approval number: 2020/154, date: 27.02.2020).

Informed Consent: Informed signed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2022.2022.0037
J Urol Surg, 2023;10(1):36-42

Efficacy and Safety of a 5-Alpha Reductase Inhibitor, Dutasteride, Added to Bacillus Calmette-Guérin Immunotherapy for Prevention of Recurrence and Progression of Intermediate- and High-Risk Non-Muscle Invasive Bladder Cancer: A Single-Arm, Phase 2 Clinical Trial

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

Androgens and receptor analyses, which constitute an important step in cell growth and differentiation, play a role in bladder cancer. Anti-androgen therapies have a positive effect on bladder tumors. Studies showed 30% decrease in the recurrence of bladder cancer among patients treated with 5α-R type-1/2 inhibitor. Dutasteride failed to show predicted efficacy in recurrence of bladder cancer. However the decrease in recurrences after the 6th month of dutasteride treatment and the fact that the lack of progression during the treatment is promising for future studies.

Abstract

Objective: To assess the efficacy and safety of 5α-R inhibitor dutasteride added to standard Bacillus Calmette-Guérin (BCG) immunotherapy for preventing recurrence and progression in intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: Patients received BCG immunotherapy in accordance with the European Association of Urology guidelines and dutasteride (0.5 mg) tablet were orally administered once a day. The participants were monitored for recurrence or progression for 24 months. Androgen receptor expression assay was performed on cystoscopic biopsy materials. According to the data from retrospective studies of patients with bladder cancer, the recurrence rate was 50% in patients with BCG immunotherapy without dutasteride, and 25% in those given dutasteride, with 23 patients included in the study.

Results: A total of 14 (60.9%) patients could finish the follow-up. Ten patients completed the 24 months follow-up without recurrence and 4 patients had recurrence. Nine (39.1%) patients failed to complete the follow-up. Of these patients, 28.5% had recurrence. No patient progressed to MIBC and no low-grade tumor progressed to high grade. There was no statistical significance between recurrence and non-recurrence groups for AR mRNA, ARV7 mRNA, AR protein and ARV7 protein expression. But all expressions were higher in the non-recurrence group.

Conclusion: Dutasteride failed to show predicted efficacy in recurrence in this prospective study, most likely due to the limited number of patients, however the decrease in recurrences after the 6th month of dutasteride treatment and the fact that the lack of progression during the treatment is promising for future studies.

Keywords: Bladder cancer, dutasteride, recurrence

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Received: 12.04.2022 **Accepted:** 30.05.2022

Cite this article as: Değer MD, Yıldız HA, İncir C, Özer S, Sarıkaya AE, Ergör G, Tunçok Y, Şen V, Bozkurt O, Esen AA. Efficacy and Safety of a 5-Alpha Reductase Inhibitor, Dutasteride, Added to Bacillus Calmette-Guérin Immunotherapy for Prevention of Recurrence and Progression of Intermediate- and High-Risk Non-Muscle Invasive Bladder Cancer: A Single-Arm, Phase 2 Clinical Trial. J Urol Surg, 2023;10(1):36-42.

Introduction

Bladder cancer is the ninth most common malignancy and the thirteenth most common cause of cancer death in the world (1). Intravesical instillation of Bacillus Calmette-Guérin (BCG) is recommended after transurethral resection for intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC) (2). Despite treatment, approximately 15-61% of NMIBC recur and 1-45% of NMIBC progress to muscle invasive bladder cancer (MIBC) (3). When MIBC develops, disease-related survival decreases and the treatment burden increases. Numerous clinical trials have focused on preventing NMIBC progression and recurrence.

Kourbanhoussen et al. (4) showed that anti-androgen therapies have a positive effect on bladder tumors in a systematic review. Moreover, in a prospective study, 5-alpha reductase (5α-R) type-2 inhibitor finasteride treatment was associated with decreased bladder cancer incidence (5). A retrospective study based on the findings of this prospective study suggested up to 30% decrease in the recurrence of bladder cancer among patients treated with 5α-R type-1/2 inhibitor, dutasteride (6). Dutasteride is a safe oral medication commonly used to treat benign prostatic hyperplasia (BPH). Many studies have revealed that androgen receptor (AR) expression in prostate cancer is associated with increased tumor progression (7). Also, some studies have found that AR expression was significantly associated with bladder cancer recurrence (8).

Although it was demonstrated in a retrospective study that dutasteride reduced the recurrence of intermediate- and high-risk NMIBC, to the best of our knowledge, there is no prospective clinical study focusing on dutasteride along with BCG immunotherapy. Furthermore, there is no evidence suggesting that the AR expression in recurrent and invasive bladder cancers is correlated with the therapeutic efficacy of dutasteride. Therefore, we designed a single-arm, single-center, phase 2 clinical trial to assess the efficacy and safety of 5α-R inhibitor, dutasteride, added to standard BCG immunotherapy for preventing recurrence and progression of intermediate- and high-risk NMIBC.

Materials and Methods

Overall Design

This single-arm, single center, open-label phase 2 clinical trial was designed to evaluate the efficacy and safety of dutasteride for preventing recurrence when added to BCG immunotherapy, which is used in the standard for intermediate- and high-risk NMIBC treatment. The patients received BCG immunotherapy in accordance with the European Association of Urology (EAU) guidelines and dutasteride (0.5 mg) tablet were orally administered once a day. Participants were regularly surveilled with cystoscopy every 3 months and thoracoabdominal computed tomography once a year in accordance with American Urology Association (AUA) and EAU guidelines. The participants were monitored for recurrence or progression for 24 months. The primary endpoint was the detection of recurrence because of cystoscopy. Secondary endpoints include observation of bladder tumor invasion into bladder muscle on cystoscopic biopsy material and determination of the relationship between AR expression and treatment efficacy. AR expression assay was performed on cystoscopic biopsy materials. This study was approved by the Local Ethics Committee (Dokuz Eylul University approval number: 2017/09-3, date: 18.05.2017).

Eligibility Criteria

Male patients older than 18 years old with primary intermediate- and high-risk NMIBC were eligible.

Exclusion criteria;

Patients with the Eastern Cooperative Oncology Group performance status 3 or more,

Patients with prior BCG or other intravesical treatment, radiotherapy to the pelvic area, or immunosuppressive disease,

Patients with prior malignancy within the previous 5 years, except for those with localized curable cancers such as basal or squamous cell skin cancer,

Patients ineligible to receive BCG or dutasteride,

Patients with serious medical conditions or psychiatric illnesses that may limit their ability to adhere to study protocol.

Quantitative Polymerase-Chain Reaction (qPCR) Analysis of AR-FL and AR-V7

Bladder cancer tissue samples were excised by transurethral resection, transferred immediately to Ribosave (Bio-Speedy, BS-NA-203-250), snap frozen in liquid nitrogen, and stored at -20 °C. Total RNA isolation from tissue samples was performed using a RNeasy Mini kit (Qiagen 74104) according to the manufacturer's instructions. RNA concentration and purity were checked by NanoDrop 1000 spectrophotometer following isolation (Thermo, US). An amount of 500 nanograms of RNA per sample was used for cDNA synthesis with the RevertAid First Strand cDNA Synthesis kit (Thermo, K1622) according to the manufacturer's instructions. cDNA synthesis was carried out in an Applied Biosystems, SimpliAmp Thermal Cycler. For AR-FL or AR-V7 primer evaluation, 10 or 20 ng of cDNA of each sample was applied per PCR, respectively. The Johns Hopkins Group adjusted the PCR reaction parameters for primers from the original Antonarakis et al. (9) publication. PCR primer pairs used for PCR targeted AR-FL fw-

CAGCCTATTGCGAGAGAGCTG, rev-GAAAGGATCTTGGGCACTTGC), AR-V7 (10) fw-CCATCTTGTCGTCTTCGGAAATGTTA, rev-TTTGAATGAGGCAAGTCAGCCTTTCT), and GAPDH (fw-GAAGGTGAAGGTCGGAGTC, rev-GAAGATGGTGATGGGATTTC). qPCR was performed using SYBR-Green fluorescent dye (Ampliqon, A323406) in an Applied Biosystems 7500 Fast Real-Time PCR Detection System. The samples were examined in quadruplicate. Relative gene expression of AR-FL and AR-V7 was normalized to GAPDH using the $2^{-deltaCT}$ method.

Western Blotting of AR-FL and AR-V7

Bladder cancer tissue samples were excised by transurethral resection, snap frozen in liquid nitrogen, and stored at -85 °C. Tissue samples were homogenized in an ice-cold modified RIPA buffer containing complete ultramini protease inhibitor cocktail (Roche 05892970001) and phosSTOP (Roche) using pestles (Tmomas Scientific, 1226C62) as described before (11). The homogenate was centrifuged at 15.000 x g for 20 min at +4 °C. Protein lysates were prepared and analyzed as described before (ref1) using 80 micrograms of protein. Blots were incubated with the following primary antibodies at indicated dilutions: Mouse anti AR-FL (sc-7305), 1:200, Mouse anti-AR-V7(Precision Antibody, AG10008) 1:500, rabbit calnexin (sc-11397), 1:5000. Proteins were detected using fluorescence-conjugated secondary anti-mouse (Licor 800CW: IRD 926-322-10) or anti-rabbit (Licor 680 RD: 926-68071) antibodies both at 1:15000 and Chemidoc MP Imaging System (Biorad). Equal loading and transfer were confirmed by repeat probing for Calnexin. Band intensities were quantified as pixels using ImageJ software (NIH).

Outcome Measures, Planned Sample Size and Statistical Analysis

According to the data from retrospective studies of patients with bladder cancer, the recurrence rate was 50% in patients with BCG immunotherapy without dutasteride, and 25% in those given dutasteride, with 80% power (Beta=0.20) and alpha=0.05, assuming 23 patients were included in the study (6,12,13). Less than 25% of this patient group were predicted to experience recurrence. The patients were divided into two groups as those with and without recurrence. The groups were compared in terms of general demographic data and tumor characteristics with Fisher's Exact test. The normality of AR-FL protein, AR-V7 protein, AR-FL mRNA and AR-V7 mRNA expression between the two groups was evaluated with histogram, the coefficient of variation, Skewness-Kurtosis, detrended normal Q-Q plot and Shapiro-Wilk test, and they all did not fit the normal distribution. The two groups were compared with the Mann-Whitney U test, using the statistical differences of two non-parametric-dependent samples. Data were analyzed using SPSS version 22.0 (SPSS, Chicago, IL, USA). The p-value was taken as $p<0.05$ for significance.

Results

A total of 23 patients were included in the study; 14 (60.9%) could finish the follow-up. Ten patients completed the 24 months follow-up without recurrence and 4 patients had recurrence. Nine (39.1%) patients failed to complete follow-up (2 patients were excluded by the investigator, 1 patient was unable to continue due to BCG side effects and 6 patients withdrew) (Figure 1). Recurrence was present in 28.5% of the patients. Dutasteride failed to show effectiveness for recurrence. No patient progressed to MIBC and no low-grade tumor progressed to high grade. The median age of the patients was 67 years and the median tumor size was 40 mm. The median EORTC recurrence risk score and CUETO recurrence risk score were 6 and 4, respectively. Baseline characteristics of the patients are shown in Table 1. There was no statistical significance between recurrence and non-recurrence groups for demographic and pre-treatment parameters (Table 2). There was no statistical significance between recurrence and non-recurrence groups for AR mRNA, ARV7 mRNA, AR protein and ARV7 protein expression. But all expressions were higher in the non-recurrence group (Table 3).

Discussion

The most effective treatment for preventing recurrence and progression in NMIBC is intravesical BCG immunotherapy. Despite treatment in intermediate- and high-risk bladder cancer, up to 50% recurrence and 10-15% progression are observed. In retrospective studies of patients taking 5α-R inhibitors, recurrence rates were found to be 50% less in those with concomitant NMIBC. In a study conducted in patients receiving finasteride, the recurrence of bladder cancer decreased by 36%, and this effect was seen in Whites and Hispanics, but not in Black races (13). This demonstrates the importance of prospective studies in specialized groups for the standardization of retrospective studies in large patient groups. The effects of genetics, drug interactions and environmental factors were more evident in small groups. Also, smoking, occupational exposure and herbal products affect the outcomes.

The time when the drug should be started to see the effect is an important question for 5α-R inhibitor treatment for bladder cancer. Mäkelä et al. (14) found that 5α-R inhibitors improved disease-specific survival in 10,720 Finnish men with bladder cancer. Moreover, these benefits were seen both with use before and after bladder cancer diagnosis. In this study, the drug was started after diagnosis. There is a need for studies with more samples about the optimal drug dose and duration. In our study, since 3 of the 4 patients with relapse occurred in the first 3 months, it can be considered that more than 3 months is required for the optimal effect. Additionally, 6 months of treatment is

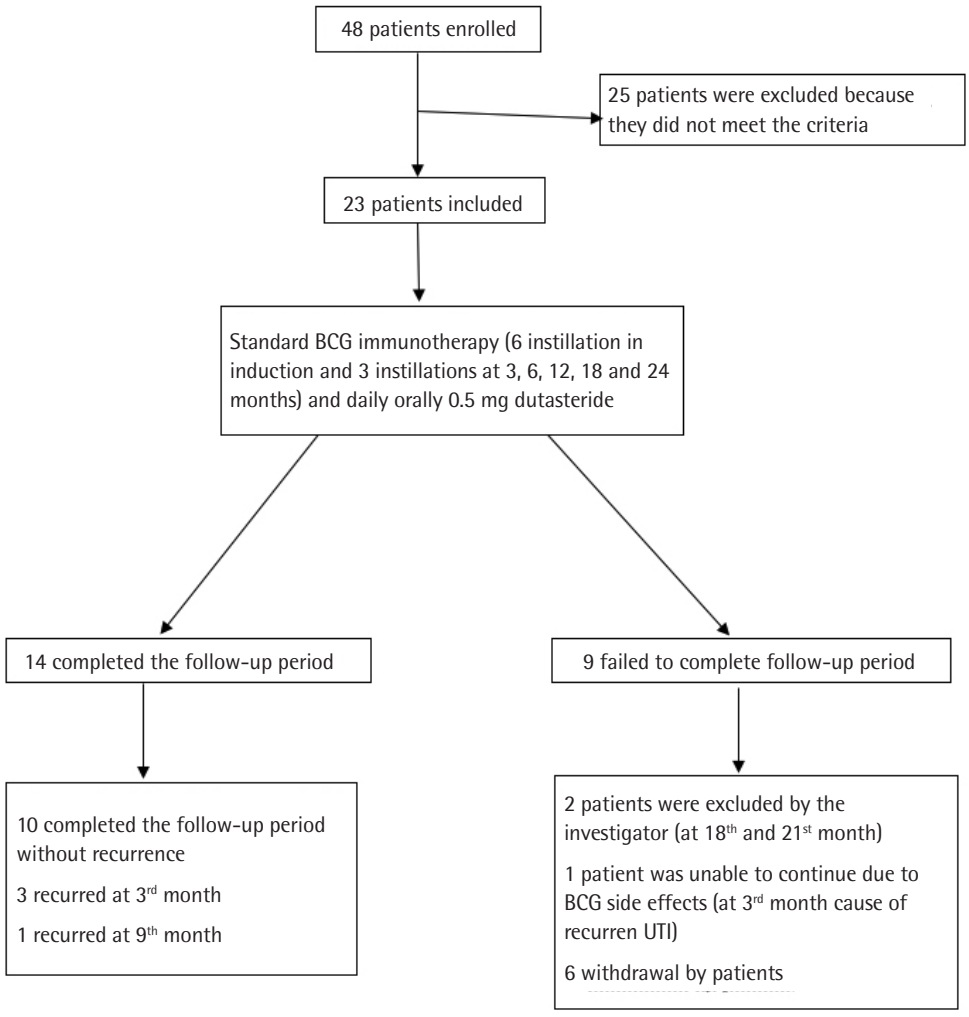

Figure 1. Patients overview

required for optimal effects for treating BPH (15). If we had created a protocol to evaluate the efficacy of dutasteride after the 6th month of treatment, our recurrence rate would have been 9% (per protocol) (4% according to intention to treat analysis). The recurrence of only 1 patient after 6 months makes it questionable that dutasteride may be an alternative treatment together with BCG, although statistical significance was not obtained.

Another expected outcome of intravesical BCG therapy is the prevention of progression. Despite BCG treatment, progression to 5-10% MIBC is observed in two-year follow-ups (16). At the 5-year follow-up, the progression reached 40% in some series. Tumor grade progression is expected to be 3% over 2 years (17). In this study, in addition to the absence of muscle invasion in any patient, the absence of stage and grade progression was interpreted as the effect of dutasteride.

McMartin et al. (18) found that the use of 5α-R inhibitors before cystectomy was associated with better overall survival, lower proportion of positive margins and lymphovascular invasion. Shiota et al. (6) found that androgen suppression therapy (androgen deprivation therapy for prostate cancer or dutasteride for BPH) lowered the risk of bladder cancer recurrence. Wang et al. (19) found that 5α-R inhibitors decreased the risk of bladder cancer-related death, but there was no significant difference in the recurrence rate. In this study, no effect on the 2-year mortality was observed. Additionally, how long and at which dosage the 5α-R inhibitor should be taken for reduced mortality could not be explained.

Many studies have been conducted on AR expression and its effects. While some studies have identified an association between AR positivity and tumor progression (20), some studies reported that high AR expression is associated with lower recurrence and better disease outcome (21). In this study, AR and AR-V7 mRNA and protein expressions were lower in the group with recurrence, but no statistically significant difference was detected. AR expression is affected by genetics, drug

use and many other factors (22). The lack of a standard for expression analysis and the fact that the factors mentioned are not homogenized cause different outcomes. In some studies, immunohistochemical methods were used and the required rate for positivity was between 1 and 30%. In the other group, RT-qPCR was used. In this respect, the standardization of positive tissues with different methods cannot be done at this stage. But tumors expressing AR are likely to respond better to 5α-R inhibitors and have a better prognosis.

Urinary tract infection and upper respiratory tract infection constituted most adverse events, while serious adverse events were reported as urethral stenosis, coronary artery disease and dyspnea. Adverse events are generally seen to be related to BCG. Sexual adverse effects are the most common side effects

Table 1. Baseline characteristics of the patients

Characteristic	n (%)
Number of patiens	23 (100)
Age	
>65	14 (60.9)
<65	9 (39.1)
Tumor stage	
pTa	15 (52.2)
pT1	7 (43.5)
pT1+	1 (4.3)
Tumor grade	
Low grade	13 (56.5)
High grade	10 (43.5)
Concurrent CIS	
Yes	2 (8.7)
No	21 (91.3)
Number of tumors	
Single	6 (26.1)
Multiple	17 (73.9)
Tumor size	
<3 cm	7 (30.4)
>3 cm	16 (69.6)
EAU risk group	
Low	0 (0)
Intermediate	13 (56.5)
High	10 (43.5)

CIS: Carcinoma *in situ*, EAU: European Associaton of Urology

Table 2. Recurrence status according to demographic and pre-treatment parameters of patients

Variables n (%)	Groups		p-value
	Non-Recurrence (10)	Recurrence (4)	
Age >65	7 (70%)	1 (25%)	0.175
BMI >25	9 (10%)	2 (50%)	0.176
Tumour >3 cm in diameter	8 (80%)	2 (50%)	0.311
Multiple tumour	6 (60%)	4 (100%)	0.210
Concomitant CIS	1 (10%)	0 (0%)	0.714
High grade tumour	3 (30%)	2 (50%)	0.455
T1 tumour	2 (20%)	2 (50%)	0.311
EORTC high risk	3 (30%)	2 (50%)	0.455

Fisher's Exact test was used for statistical analysis between groups. BMI: Body mass index, CIS: Carcinoma *in situ*, EORTC: European Organisation for Research and Treatment of Cancer

Table 3. AR-FL protein, AR-V7 protein, AR-FL mRNA, AR-V7 mRNA, AR-FL/AR-V7 protein, and AR-FL/AR-V7 mRNA expressions according to recurrence groups

Variables Median (min-max)	Groups		p-value
	Non-Recurrence (10)	Recurrence (4)	
AR-FL protein	0.53 (0.6-2.4)	0.31 (0.6-0.87)	0.374
AR-V7 protein	1.49 (0.2-4.32)	1.06 (0.87-14.23)	1.0
AR-FL mRNA	0.049 (0.0006-0.29)	0.015 (0.004-0.034)	0.188
AR-V7 mRNA	0.000089 (0.000007-0.00044)	0.000035 (0.000007-0.000079)	0.106
AR-FL/AR-V7 protein	0.39 (0.09-1.62)	0.28 (0.004-0.91)	0.539
AR-FL/AR-V7 mRNA	449 (52.6-1168.3)	343.42 (90.7-3377.6)	1.0

Mann-Whitney U test was used for statistical analysis between groups. AR-FL: Full-length androgen receptor, AR-V7: Androgen receptor splice variant 7

from 5α-R inhibitors (0.9-24.0%). Of these, the most common is erectile dysfunction, which is followed by ejaculatory dysfunction and decreased libido (23). Some studies have shown increased depression with 5α-R inhibitors, but there was no direct link found (24). Moreover, studies failed to demonstrate an increased risk of suicide (25). Adverse effects related to dutasteride were not reported by patients. Erectile dysfunction, one of the most important side effects of dutasteride, was not a complaint questioned and prioritized by the patients in this group.

Study Limitations

Dutasteride failed to show a predicted efficacy for recurrence in this prospective study. The difficulties experienced in the follow-up period during the COVID-19 pandemic, 6 patients withdrew from the study. The small number of patients who could complete the study may be the most important limitation.

Conclusion

Androgens and receptor analyses, which constitute an important step in cell growth and differentiation, play a role in bladder cancer. In our study dutasteride failed to show predicted efficacy in recurrence in this prospective study, most likely due to the limited number of patients. However, the decrease in recurrences after the 6th month of dutasteride treatment and the fact that the lack of progression during the treatment is promising for future studies.

Acknowledgments

This study was funded by TUBITAK (The Scientific and Technological Research Council of Turkey).

Ethics

Ethics Committee Approval: This study was approved by the Local Ethics Committee (Dokuz Eylul University approval number: 2017/09-3, date: 18.05.2017).

Informed Consent: Signed informed consent was collected from all subjects.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.D.D., C.İ., S.Ö., G.E., V.Ş., A.A.E., Concept: M.D.D., H.A.Y., A.E.S., G.E., V.Ş., A.A.E., Design: M.D.D., H.A.Y., C.İ., S.Ö., A.E.S., G.E., Y.T., V.Ş., O.B., A.A.E., Data Collection or Processing: M.D.D., H.A.Y., G.E., Y.T., V.Ş., A.A.E., Analysis or Interpretation: M.D.D., H.A.Y., S.Ö., G.E., Y.T., O.B., A.A.E., Literature Search: M.D.D., C.İ., S.Ö., A.E.S., G.E., Y.T., V.Ş., O.B., A.A.E., Writing: M.D.D., H.A.Y., C.İ., S.Ö., A.E.S., G.E., Y.T., V.Ş., A.A.E.

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

Financial Disclosure: Dutasteride provided by Koçak farma.

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ORIGINAL RESEARCH
Andrology

Doi: 10.4274/jus.galenos.2022.2022.0042
J Urol Surg, 2023;10(1):43-48

Does the Daily Dose of Tadalafil for the Treatment of Erectile Dysfunction Increase Penile Sensation?

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

This topic has not yet been studied in the literature yet. Our study demonstrates a quantative increase in penile sensation with the use of tadalafil.

Abstract

Objective: To investigate the effect of tadalafil, used for treating erectile dysfunction (ED) at a daily dose of 5 mg for 12 weeks, on penile sensation.

Materials and Methods: Our study included 30 male patients who applied to our andrology outpatient clinic with the complaint of ED and were prescribed tadalafil at a daily dose of 5 mg for 12 weeks. Before treatment, serum levels of testosterone and luteinizing hormone (LH) were measured. Demographic and clinical characteristics were recorded. Pre- and post-treatment electromyography (EMG) examinations for penile sensation and International Index of Erectile Function (IIEF-5) scoring were performed for each patient.

Results: The mean age was 53±9 years. The mean body mass index was 27±2. Before treatment, serum levels of testosterone and LH were within the normal range. There were 8 (29%) patients with diabetes mellitus and 7 (25%) patients with hypertension. The pre- and post-treatment IIEF-5 scores were 13±3 and 19±3, respectively. Nerve conduction velocities (NCV) increased from 35.5 m/sec to 38.05 m/sec. Latency values decreased from 2.32 ms to 2.14 ms. There was a statistically significant improvement in IIEF-5 scores and EMG results for penile sensation after treatment (IIEF-5, NCV and latency; $p<0.001$, $p<0.001$ and $p=0.001$, respectively).

Conclusion: In this study, we showed that tadalafil at a daily dose of 5 mg used for treating ED provides an increase in penile sensation.

Keywords: Erectile dysfunction, oral phosphodiesterase-5 inhibitors, penile sensation

Introduction

Erectile dysfunction (ED) is defined as the persistent or recurrent inability to achieve and/or maintain an adequate penile erection for sexual activity (1,2). It significantly affects the quality of life of many male individuals (3). It is also one of the most common sexual health problems, affecting an estimated 18 million men in the ultrasound alone (4). Epidemiological data have shown a high prevalence and incidence of ED worldwide (5).

Most men have multiple risk factors for ED, one or more of which may be more predominant, including psychological, neurological, hormonal, arterial, or cavernosal disorders, or a combination thereof (6).

Traditional electrodiagnostic studies for men with ED include pudendal somatosensory -evoked potentials and delays in bulbocavernosus reflexes. Neither of these two methods alone measures the functions of peripheral sensory nerves. The dorsal nerve of the penis (DPN) is the terminal sensory branch of the pudendal nerve, which carries sensory data from the glans and shaft of the penis (7,8). Sensory and tactile stimulation of the penis play an important role in erectile and sexual function. Interruption of sensory stimulation causes decreased libido, ejaculatory dysfunction, and loss of impotence (9,10).

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Received: 18.04.2022 **Accepted:** 20.07.2022

Cite this article as: Taş S, İslamoğlu E, Eren A, Savaş M. Does the Daily Dose of Tadalafil for the Treatment of Erectile Dysfunction Increase Penile Sensation? J Urol Surg, 2023;10(1):43-48.

Erection occurs through three different stimuli: Genital stimulation (contact and reflexogenic), central stimulation (non-contact or psychogenic), or stimulation to the central nervous system (night-time) (11). DPN carries sensory innervation from the penile shaft and glans. Therefore, tactile stimulation has an important role in erection (12). Sensory electromyography (EMG) to DPN showed the early occurrence of sensory disturbances in the distal penis (2).

Recently, inhibitors of the phosphodiesterase-5 (PDE-5) enzyme have been the most widely used treatment for ED. Tadalafil is an effective and well-tolerated treatment for ED (13). Tadalafil at a dose of 5 mg once daily significantly improves ejaculation and orgasm, sexual intercourse and overall satisfaction, and erectile function (14).

In this study, we showed the change in penile sensation in men after treatment with ED. Additionally, this topic has not yet been studied in the literature as far as we know. The inclusion of patients using daily therapy for ED regularly was aimed at a clear assessment of outcomes.

Materials and Methods

This research has a prospective and controlled study design. A signed consent form was obtained from all patients who volunteered to participate in the study. Ethics Committee approval for this study was obtained from the Ethics Committee of Health Sciences University, Antalya Training and Research Hospital (2020-352), and all steps were planned and conducted following the Declaration of Helsinki and its later amendments.

Patients who started treatment for ED in the andrology outpatient clinic were referred to the study by the secretariat. We included patients with a history of at least 6 months of ED who did not receive any treatment, patients with normal serum levels of testosterone and luteinizing hormones, and patients who were recommended to use tadalafil for 12 weeks. Patients with a history of hypogonadism, cryptorchidism, varicocele, peripheral neuropathy, uncontrolled diabetes mellitus (hemoglobin a1c >7%), and past and current illicit drug abuse were excluded from the study. The demographic and clinical characteristics of all patients were recorded.

All patients participating in the study completed the International Index of Erectile Function (IIEF-5) form and underwent penile EMG examination before and after treatment. Patients were divided into two groups as over 50 years old and under 50 years old. A comparative evaluation was made on the effect of age on the outcomes of treatment and penile sensorial EMG.

Electrophysiological studies were planned to be performed between 09:00 and 12:00, at a room temperature of 23 to 25 °C, in a quiet room with dim light, and with the relaxed and awake patient in the supine position. A two-channel electroneuromyography device (Nihon-Kohden-Neuropack, model MEB-2200) was used for recording.

Penile sensorial EMG was examined using Clawson's method. The penis was placed in the concavity of a specially designed Orthoplast penile traction device and stretched to reach its maximum length by pulling from the tip of the glans. A Cunningham incontinence clamp was placed on the glans, and the penis was maintained in tension by holding from the glans. An electroencephalography paste was used for the placement of active and reference steel electrodes. The active recording electrode was placed as proximal as possible to the root of the penis. The reference electrode was placed 4 cm above the active electrode. The proximal part of the dorsal penile shaft was stimulated orthodromically with an active electrode and the dorsal glans with a reference electrode (15).

Statistical Analysis

Categorical data were presented as number and percentages. Continuous data were evaluated by the Kolmogorov-Smirnov test to verify the normality of the distribution of variables. Normally distributed data were presented as mean + standard deviation, while non-normally distributed data were presented as median and IQR (25-75th). An independent simple t-test was used to compare two independent normally distributed data, while the Mann-Whitney U test was used for the comparison of non-normally distributed data. A paired sample t-test was used to compare two independent normally distributed data, while the Wilcoxon test was used for the comparison of non-normally distributed data. Spearman's Correlation analysis was used to analyze the parameters related to changes in IIEF scores. A p-value of <0.05 was considered statistically significant. Analysis of the dataset was carried out using the IBM Statistical Package for Social Sciences version 23.0 (IBM SPSS Corp.; Armonk, NY, USA).

Results

The study included 30 patients. One patient discontinued the treatment with the complaint of myalgia, and the study was continued with 28 patients since another patient did not come to the follow-up visit. The mean age of the patients was 53±9 years. The mean duration of ED was 6.8 months. There were 8 (29%) patients with diabetes and 7 (25%) patients with hypertension. The demographic characteristics and comorbidities of the patients are given in Table 1.

We showed statistically significant changes in pre-treatment and post-treatment IIEF-5 scores and penile sensorial EMG findings. Pre-treatment IIEF-5 scores of 13±3 were measured as 19±3 after treatment with tadalafil at a daily dose for 12

weeks (p<0.001). This improvement was consistent with the literature. The mean nerve conduction velocities (NCV) in EMG was 35.5 m/sec (33.3-41.2) before treatment, and 38.05 m/sec (34.5-43.6) after treatment (p<0.001). The increase in NCV is the most important finding of penile sensorial EMG showing an increase in penile sensation. Thus, the increase in NCV has been interpreted as an improvement in penile sensation. The changes in latency and amplitude values used in the calculation of NCV are given in Table 2.

Table 1. Demographic and clinical characteristics of the patients

Age, years	**53±9**
BMI, kg/m^2	27±2
Alcohol consumption, n (%)	2 (7)
Smoker, n (%)	10 (36)
Comorbidity, n (%)	
Diabetes mellitus	8 (28.6)
Hypertension	7 (25.0)
Coronary artery disease	1 (3.6)

BMI: Body mass index

The delta equation (Δ = the amount of change) was created for the IIEF-5 score and penile sensorial EMG findings as post-treatment value minus pre-treatment value. Factors that may be related to this change were evaluated. There was a significant correlation between age and IIEF-5 score and penile sensorial EMG findings. As age increases, the improvement in the IIEF-5 score (r=-0.614, p<0.001) and all penile sensorial EMG findings decrease (for Δ NCV, Δ Latency, Δ Amplitude, r=-0.746 p<0.001, r=0.637 p<0.001, r=-0.755 p<0.001, respectively). There was a significant correlation between the IIEF-5 score and NCV (r=0.663, p<0.001) and Amplitude (r=0.659, p<0.001). As improvement in IIEF-5 increases, so does improvement in NCV and Amplitude (Table 3).

The mean amplitude value in penile sensorial EMG was 4.47±1.32 before treatment, whereas it increased to 5.07±1.60 after treatment (p<0.015). Additionally, the mean latency value was 2.14±0.42 before treatment, whereas it increased to 2.32±0.38after treatment (p<0.001). The latency and amplitude parameters in the penile sensorial EMG are used to calculate NCV. The increase in these values after treatment was interpreted as an improvement in penile sensation. As a result, it has been shown that the improvement in IIEF-5 provides an improvement in penile sensation (Figure 1).

Table 2. Comparison of IIEF scores and EMG findings before and after PDE-5 inhibitor therapy

	Pre-treatment	Post-treatment	p-value
Overall			
IIEF-5	13±3	19±3	<0.001
NCV, m/s	35.5 (33.3-41.2)	38.05 (34.5-43.6)	<0.001
Latency, ms.	2.14±0.42	2.32±0.38	<0.001
Amplitude, uV	4.47±1.32	5.07±1.60	<0.015

IIEF-5: International Index of Erectile Function-5; NCV: Nerve conduction velocity, EMG: Electromyograph, PDE-5: Phosphodiesterase-5

Table 3. Possible factors related to improvement in IIEF scores and EMG findings

		Δ IIEF-5	Δ NCV	Δ Latency	Δ Amplitude
Diabetes mellitus	Correlation coefficient	-0.131	-0.029	-0.010	-0.338
	p-value	0.506	0.882	0.960	0.078
Hypertension	Correlation coefficient	-0.084	-0.312	0.148	-0.220
	p-value	0.670	0.107	0.451	0.261
Smoker	Correlation coefficient	0.014	0.138	-0.162	-0.176
	p-value	0.943	0.482	0.411	0.371
BMI	Correlation coefficient	-0.221	0.009	0.018	-0.187
	p-value	0.258	0.965	0.926	0.341
Age	Correlation coefficient	-0.614**	-0.746**	0.637**	-0.755**
	p-value	0.001	0.000	<0.001	0.000
Δ IIEF	Correlation coefficient	-	0.663**	-0.555	0.659**
	p-value	-	0.000	0.002**	0.000
	n	28	28	28	28

BMI: Body mass index, IIEF: International Index of Erectile Function, EMG: Electromyography, NCV: Nerve conduction velocity, Δ: Post-treatment values minus pre-treatment values, **Correlation is significant at the 0.01 level (2-tailed)

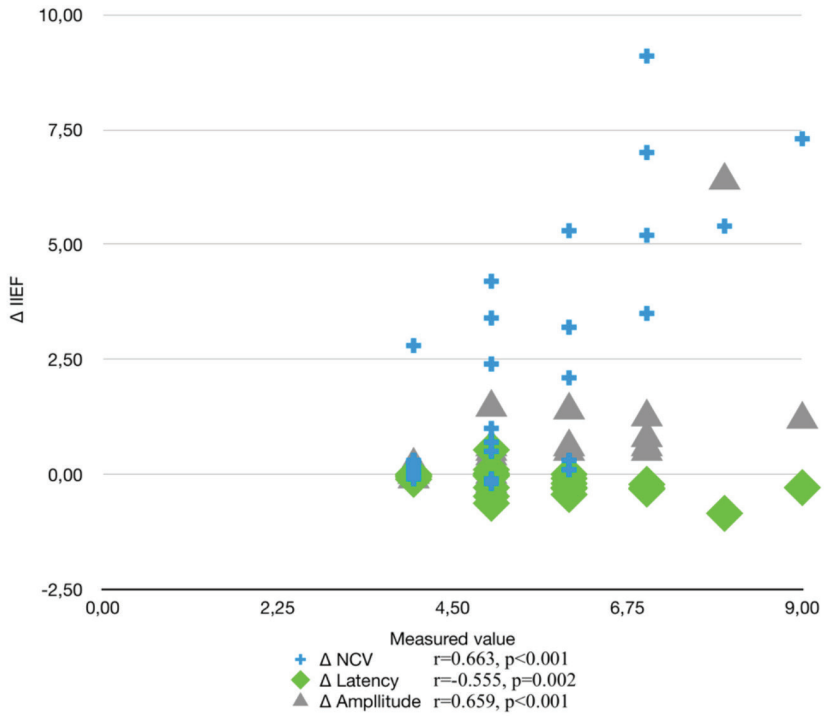

Figure 1. Graph showing the correlation between changes in IIEF-5 score and penile sensorial EMG findings

IIEF: International Index of Erectile Function, EMG: Electromyography, NCV: Nerve conduction velocity

Discussion

Currently, PDE-5 inhibitors are used as first-line therapy in patients presenting with ED. Our literature search did not find any studies reporting normal values of penile sensation during a normal erection. In our study, we performed sensorial measurements in patients with ED. Penile sensorial EMG can provide valuable additional information in the differential diagnosis of ED, particularly allowing the identification of different neurogenic lesion sites (16).

Başar et al. (17) injected intracavernosal papaverine in 15 patients with ED and compared the results of penile EMG and biopsy examinations. They demonstrated low -amplitude values in 5 patients with diabetes mellitus. Penile sensorial EMG is a less-invasive, valuable method for patients with ED, whereas penile biopsy examination did not reveal any specific results. Kayigil and Ergen (18) reported lower amplitude values in the EMG of the corpus cavernosum (CC-EMG) in 45%-65% of patients with ED.

In another study, Herbaut et al. (19) included 24 patients, 16 with normal findings on neurological examination, and 8 with diabetic neuropathy. They investigated the sensory conduction velocity in the dorsal penile nerve at rest and after injection of prostaglandin E1. They reported that the mean NCV values increased from 32.3+/-6.7 m/s to 47.4+/– 8.2 m/s after the injection of prostaglandin E1. They also reported an increase in NCV in patients with improvement in ED.

We also showed an increase in NCV after 12 weeks of daily treatment with tadalafil compared with pre-treatment values. The mean NCV in EMG was 35.5 m/s (33.3-41.2) before treatment, and 38.05 m/s (34.5-43.6) after treatment (p<0.001). The increase in NCV is the most important finding of penile sensorial EMG showing an increase in penile sensation. Thus, the increase in NCV has been interpreted as an improvement in penile sensation.

Itoga et al. (20) showed a reduction in proinflammatory cytokines in rats with a 12-week high-dose tadalafil therapy. Jamaluddin et al. (21) compared patients with vasculogenic ED and non-vasculogenic ED, both treated with tadalafil. They have demonstrated the therapeutic effects of tadalafil on non-vasculogenic ED. Chen et al. (22) showed that long-term tadalafil therapy in diabetic rats partially reduced penile oxidative stress lesions through a local antioxidative stress pathway. Accordingly, they reported that the initiation of long-term once-daily tadalafil therapy immediately after the diagnosis of DM may partially prevent the development of diabetic ED in rats.

In our study, we examined patients who received 12 weeks of tadalafil therapy regardless of the cause of ED and performed IIEF scoring and penile sensorial EMG examinations before and

after treatment. A significant correlation was observed between the IIEF score and penile sensorial EMG findings. A statistically significant improvement was observed in IIEF, NCV, and latency values in both age groups. ($p<0.001$, $p<0.001$, $p=0.010$ for ≤50 years of age; and $p<0.001$, $p=0.012$, $p=0.030$ for >50 years of age, respectively). There was a comparable improvement in the IIEF score in both age groups ($p=0.314$), whereas there was a statistically higher improvement in NCV and latency values in the group aged ≤50 years ($p<0.001$, $p=0.001$, respectively). A significant correlation was observed between the IIEF score and EMG findings. As age increases, the improvement in IIEF-5 ($r=-0.614$, $p<0.001$) and all penile sensorial EMG findings decrease (for Δ NCV, Δ Latency, Δ Amplitude, $r=-0.746$ $p<0.001$, $r=0.637$ $p<0.001$, $r=-0.755$ $p<0.001$, respectively). There was a significant correlation between IIEF and NCV ($r=0.663$, $p<0.001$) and Amplitude ($r=0.659$, $p<0.001$).

Study Limitations

Our study has some limitations, including the absence of data on normal values in penile sensorial EMG in individuals with normal erectile function. The literature search did not show any studies reporting normal values on penile sensorial EMG in a healthy male. Additionally, another limitation is the absence of any data on the effects of socioeconomic status on penile sensation in our study.

Conclusion

We demonstrated a direct correlation between improvements in IIEF-5 scores and NCV values with the use of daily tadalafil and showed that age is a factor affecting the improvement in penile sensorial EMG findings. We interpreted that tadalafil exerts its effects on erectile sensation by preventing the development of apoptosis in corporal sinusoids, preserving the proportion of smooth muscles and reducing pro-inflammatory cytokines.

Ethics

Ethics Committee Approval: Ethics Committee approval for this study was obtained from the Ethics Committee of Health Sciences University, Antalya Training and Research Hospital (2020-352).

Informed Consent: A signed consent form was obtained from all patients who volunteered to participate in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.T., E.İ., M.S., Concept: S.T., E.İ., M.S., Design: S.T., E.İ., M.S., Data Collection or Processing: S.T., E.İ., A.E., M.S., Analysis or Interpretation: S.T., E.İ., A.E., M.S., Literature Search: S.T., M.S., Writing: S.T., E.İ., A.E., M.S.

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

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Pediatric Urology

Doi: 10.4274/jus.galenos.2022.2022.0022
J Urol Surg, 2023;10(1):49-54

Torsion of the Testis or Appendix Testis? An Analysis of Presentation, Management and Outcome of Acute Scrotum in Children

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

Acute scrotum in children presents as a paediatric urological emergency. It is mainly caused by testicular torsion (TT), leaving a time window of only a few hours to irreversible damage, or in up to 50% by torsion of the appendix testis (ATT). TT requires immediate surgery, whereas ATT can be managed conservatively. Rate of surgical exploration revealing no TT is high when no clinical score criteria was applied. Aim of the study therefore was to establish clinical predictors to distinguish between TT an ATT, preventing unnecessary surgery. Our data promote that additional to an absent cremasteric reflex, testicular swelling and high-riding testis, age >10 years and symptom onset in the night support diagnosis of TT. The primary clinical approach should therefore remain and not be replaced by alternative indicators or color Doppler ultrasonography.

Abstract

Objective: To elaborate clinical predictors to safely distinguish between testicular torsion (TT) and the appendix testis torsion (ATT) and emphasize a diagnostic algorithm to reduce unnecessary exploration rates. TT requires prompt assessment and surgical intervention to achieve tissue function. Torsion of the ATT is the most common differential diagnosis, which can usually be treated conservatively. Colour-Doppler ultrasonography (CDUS) remains controversial for detection of TT.

Materials and Methods: Data were retrospectively collected from patients under the age of 20 years admitted to our hospital with acute scrotal pain from 2017 to 2020. The main outcome measures were the onset of symptoms, clinical criteria of absent cremasteric reflex, testicular swelling and high-riding testis, perfusion in CDUS and pathology found during scrotal exploration.

Results: Seventy-one patients met the inclusion criteria. Mean age was 10.6 years. 53.2% were diagnosed with TT, 41.6% with ATT, 1.3% with epididymitis and in 3.9%, no pathology was found. Patients with TT were significantly older compared to patients with ATT ($p<0.004$). TT showed a more frequent onset of symptoms during night-time ($p<0.006$). 87.8% of TT had two of the three defined clinical criteria, compared with 18.8% of ATT ($p<0.001$). The limitations of this study were the retrospective design and interobserver variability.

Conclusion: Our findings support the safety and importance of clinical criteria to distinguish between TT and ATT. CDUS should not supersede clinical evaluation. The decision to surgically explore should be made on clinical grounds as a standard approach for assessing acute scrotum.

Keywords: Acute scrotal pain, acute scrotum, testicular torsion, torsion of the appendage testis, scrotal elastography

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Received: 03.03.2022 **Accepted:** 23.05.2022

Cite this article as: Müller R, Lindner AK, Mayerhofer C, Laimer G, Aigner F, Radmayr C. Torsion of the Testis or Appendix Testis? An Analysis of Presentation, Management and Outcome of Acute Scrotum in Children. J Urol Surg, 2023;10(1):49-54.

Introduction

Testicular torsion (TT) is a pediatric urological emergency, leaving a time window of a few hours until irreversible damage occurs in the affected testis (1). In males younger than 18 years, the annual incidence of TT is 3.8% (2,3). The age distribution shows two peaks, one in the perinatal period and one in adolescence (4). In 5-25%, TT as the underlying cause of acute scrotum (5), requires quick surgical exploration within eight hours the maximum to avoid loss of testicular tissue (6). Clinical parameters indicative of TT include sudden onset of pain, high or horizontal position of the testicle, swelling, and missing cremasteric reflex (5,7). The absent cremasteric reflex has been described to be specific for TT (8). An appendix testis can be found in 83% of male individuals (9) and appendix testis torsion (ATT) grants for almost half of the boys presenting with acute scrotal pain (10), with an age peak of 7 to 12 years (11). ATT is a self-limiting condition treated primarily conservative including bed rest, scrotal elevation and non-steroidal anti-inflammatory drugs. Surgery should only be performed if the clinical differentiation from TT is uncertain. It has been shown that the rate of surgical exploration revealing no pathology was very high (86%) when neither systematic clinical criteria score, nor further diagnostics were applied (5). However, due to the intensity of pain as well as the young age, clinical examination might be difficult or inconclusive (12).

Colour-Doppler ultrasonography (CDUS) to distinguish TT from ATT is discussed controversially. Often a hyperperfusion of the upper pole is seen in case of ATT. Differential diagnostic an orchitis should be considered if the whole testicle shows an increased blood flow. Its availability and cost-efficiency in synopsis with a high rate of sensitivity (70-90%) and specificity (98-100%) leaves CDUS as the standard imaging method for acute scrotum (13). Limitations are still given, the examiner dependency with a high inter- and even intraoberserver variability (14), leading to waiving of surgical exploration, can result in inevitable testicular loss (15). Additionally, the persistence of arterial flow was found in 24% patients with TT and therefore not really a reliable parameter (16).

The aim of our retrospective single-centre study was to elaborate clinical predictors to distinguish between the presence of TT and ATT and to utilize a diagnostic algorithm to reduce unnecessary surgical interventions.

Materials and Methods

This is a retrospective observational study based on a retrospective analysis of the uro-paediatric database of our department. Research study was performed in accordance with the Helsinki declaration and institutional ethical standards. The project was approved by the local medical research ethics committee with the number 1393/2020.

Patients

All patients younger than 20 years who presented at the urological emergency department with acute scrotal pain between 2017 and 2020 were included. History was taken concerning the onset and duration of pain, local symptoms, history of trauma and other urological medical issues, such as inguinal surgery. All patients were thoroughly examined by a consultant. Three main clinical symptoms were evaluated at admission, including acute onset of scrotal pain, position of the testicle and presence of cremasteric reflex. CDUS was performed during day time department hours by a radiologist using a Hitachi Ascendus ultrasound machine with a 13-Mhz linear probe, otherwise ultrasound was carried out by a certified urologist with experience in pediatric scrotal sonography. Imaging defined normal-, hyper- or hypoperfusion, as well as elasticity, when applicable. Based on clinical criteria, additional CDUS findings - underpin the suspicion of TT - strengthened the indication for surgical exploration. When clinical criteria were suspicious of TT and CDUS was not, surgical exploration was mandatory. In all cases, concordant with the standard approach at our institution, it was of great importance that no time delay to surgery because of performing CDUS occurred. Final diagnosis was based on the results of the surgical exploration.

Surgical Management

Surgical scrotal exploration was performed by a urologist due to a standard local protocol. General anesthesia was used and the testis was exposed after a mid-scrotal incision. When the torsion of the spermatic cord was evident, detorsion was performed, followed by embedding the testis in warm saline soaked swabs. After reperfusion, the testicle was fixed with three standard self-absorbing sutures and prophylactic contralateral scrotal orchidopexy was performed subsequently. If exploration showed a twisted spermatic cord with a necrotic testis and without spontaneous reperfusion after detorsion, the testis was removed. In the case of an ATT, the appendix was removed. No antibiotic prophylaxis was administered.

Postoperative Management

All patients were discharged the following day with oral analgetic medication for two to three days. Follow-up examination was primarily performed by a pediatrician after 10 to 14 days. If the time between the first onset of pain and hospital admission was more than six hours or TT was shown to be greater than 360°, follow-up was performed at our outpatient department.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics (IBM, Version 22, Armonk, NY), with a p-value of $p<0.05$ being considered as statistically significant. Differences between the groups were calculated by t-test for independent samples for metric parameters, Mann-Whitney U test for ordinal parameters

and Pearson chi-square test for nominal parameters. Correlation analyzes were performed using the Cramer-V and Phi coefficient, influence was further evaluated in a logistic regression model. Graphs were created using GraphPad PRISM (GraphPad Software Inc., version 8, San Diego, CA).

Results

A total of 77 patients were admitted to our department because of acute scrotal pain. Seventy-one scrotal explorations were carried out during the study period. The mean age of our patient cohort was 10.6±4.8 years (range 0-20). Forty-one patients (53.2%) were diagnosed with TT, 32 (41.6%) with ATT, 1 (1.3%) with epididymitis and in 3 (3.9%) patients, no pathology was found intraoperatively. No clinical signs of orchitis were found intraoperatively. The mean duration from onset of symptoms to admission in all cases was 26.3 h, ranging from 1 h to 12 days, in which 49.4% of them were admitted to the hospital less than 6 h after onset. Our cohort included three (3.9%) neonatal cases. No preoperative manual detorsion attempts were performed and no major complications requiring a second surgical intervention or prolonged hospital stay were observed. Table 1 shows the patient characteristics and the clinical and physical findings in the TT and ATT groups.

There was a significant difference in patient age between the TT and ATT groups, as shown in Figure 1, with the mean age at presentation of 9.7±2.9 years and 11.9±5.5, respectively (p<0.004).

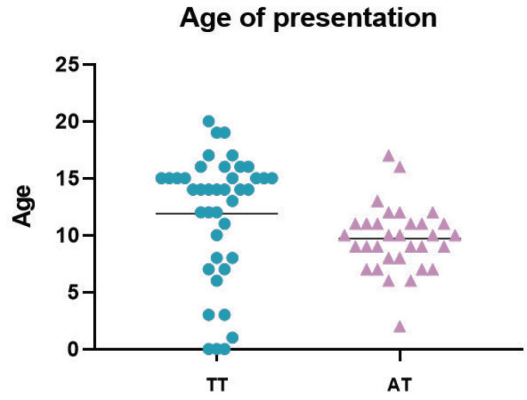

Figure 1. Age at presentation. There was a significant difference in the age of presentation between the group diagnosed with TT and ATT (p<0.004)

TT: Testicular torsion, ATT: Appendix testis torsion

Table 1. Patient characteristics

Variables	TT, n (%)	ATT, n (%)	p-value
Patients	41	32	
Underwent orchiectomy	5	0	0.041
Age (years)			
Mean ± SD	11.9±5.5	9.7±2.9	0.032
Median (range)	14 (0-20)	10 (2-17)	
Symptom onset (time)			
7 am - 7 pm	18 (43.9)	26 (81.3)	0.001
7 pm - 7 am	23 (56.1)	6 (18.7)	
Time from admission to surgery (hours)			
Mean ± SD	1.58±1.7	2.62±2.7	0.018
Median (range)	1 (1-8)	2 (1-14)	
Clinical criteria			
Abscent cremasteric reflex	38 (92.7)	4 (12.5)	<0.001
Testicular swelling	40 (97.6)	29 (90.6)	0.196
High-riding testis	31 (75.6)	3 (9.4)	<0.001
Clinical scoring			
0/3 criteria	1 (2.4)	2 (6.3)	0.416
1/3 criteria	4 (9.8)	24 (75)	<0.001
2/3 criteria	6 (14.6)	6 (18.8)	0.638
3/3 criteria	30 (73.2)	0 (0)	<0.001
CDUS			
Perfusion	8 (19.5)	32 (100)	<0.001
Absent perfusion	33 (80.5)	0 (0)	

SD: Standard deviation, CDUS: Colour-Doppler ultrasonography, TT: Testicular torsion, ATT: Appendix testis torsion

To evaluate the influence of age as a discriminating factor of TT, a receiver operating characteristic curve analysis was performed and showed an area under the curve of 0.71 (Figure 2).

When defining a cut-off age of 10 years, significance was shown for the presence of TT between the two groups older and younger than 10 years (p<0.001). For this cut-off age, sensitivity is 70.7% and specificity is 63.9% for diagnosis of TT, resulting in a positive predictive value of 69%, a negative predictive value of 65.7% and a likelihood ratio of 1.96, meaning that patients with scrotal pain and an age of more than 10 years are 1.96 times more likely to suffer from TT than from ATT.

The duration from admission to surgery was 1.56±0.18 h in the TT group and 2.62±0.53 h in the ATT group. In five patients with TT (12.2%), orchiectomy had to be performed because the testis already become necrotic, two of them being perinatal patients, of which or cohort had three. In cases of orchiectomy, mean time from symptom onset to admission was 51.8 (range 9-88) hours, which was significantly longer than in those patients, in whom the testis could be preserved, which had with a mean time of 6 (range 1-48) hours (p<0.032). Time between hospital admission and surgical exploration was not significantly different between the two groups, with 1.8±0.8 h in the ATT group and 2.15±2.14 h in the TT group (p=0.716).

Twenty-three (56.1%) patients with TT had an onset of symptoms during the night between 7 p.m. and 7 a.m. A significant correlation between symptom onset and diagnosis of TT and ATT could shown (p<0.001) resulting in a more frequent onset of symptoms of TT during night-time. Age (p<0.004) and time of onset of symptoms during the night (p<0.006) were significant factors for predicting TT. In a binary logistic regression model, age, as well as onset of symptoms, proved to be significant factors in predicting the presence of TT (R^2=22.3).

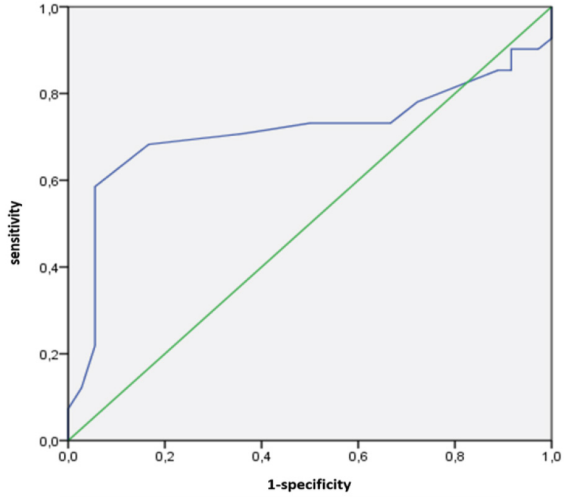

Figure 2. Receiver operating characteristic curve analysis showing an area under the curve of 0.71 for a cut-off age of older than 10 years

In 36 (87.8%) patients with TT, two out of the three defined clinical criteria were present. In contrast, only 6 (18.8%) of the boys with ATT showed the same number of clinical criteria at presentation (p<0.001). The overall distribution of the presence of clinical criteria is shown in Figure 3.

In patients who had at least two out of three clinical criteria, time from hospital admission to surgery was 1.82±0.18 h. There was a significant correlation between the absence of the cremasteric reflex and the presence of TT, as confirmed by the chi-square test (p<0.0001). The absence of the cremasteric reflex has shown to have a sensitivity of 92.7% and specificity of 80.6%. The absence of this reflex therefore had a positive predictive value of 84.4% for the presence of TT and a negative predictive value of 90.6%. The sensitivities of the presence of scrotal swelling were 97.6% and specificity 8.3%. In cases of high-riding testes, these values were 75.6% and 88.9%, respectively.

All our patients had CDUS before surgical exploration. Thirty-three (80.5%) patients with TT had no perfusion of the involved testis, whereas in the ATT group, perfusion was present in all cases. CDUS findings were significant and strongly correlated with the presence of TT, as shown by Fisher's exact test (p<0.0001). Follow-up data in our outpatient department were documented in nine patients in the TT group and eight in the ATT group. Clinical examination was normal with no signs of residual swelling or tenderness. On CDUS all testes showed a normal perfusion pattern. There were no cases of retorsion, atrophy after testicular fixation, or any other surgical long-term complications.

Discussion

TT is a pediatric urological emergency, accounting for 10% to 15% cases with acute scrotal pain (17). Moreover, TT is the third most common cause for malpractice lawsuits in adolescent males, emphasizing precaution in this sensitive topic (18). Surgical intervention within eight hours maximum is mandatory to prevent testicular loss or long-term impairment (6,19). The delayed presentation at admission cannot be influenced by

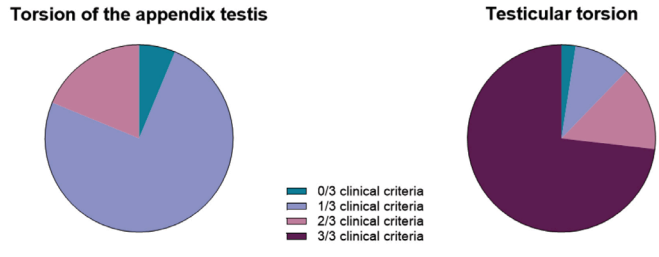

Figure 3. The overall distribution of the presence of clinical criteria in both groups

hospital management, so prompt diagnosis upon arrival is essential. In the past, most cases with acute scrotal pain were treated surgically, leading to unnecessarily high-exploration rates including the risks of general anesthesia. TT presented with a peak age of 11.9 years and ATT had a peak age of 9.7 (20,21). There was a significant difference in the age at presentation between both groups, indicating that age younger than 10 may be a useful predictor of ATT (22,23).

The correlation between the daytime onset of symptoms and the presence of TT was significant, showing a more frequent occurrence during night hours, as described by Fujita et al. (23). Late presentation to the hospital is described as the major cause leading to orchiectomy (24,25). This was likewise observed in our cohort, suggestive of low public awareness with respect to acute scrotal pain.

CDUS is commonly discussed as a specific method for differentiating TT from other causes of acute scrotal pain. It is widely used, but in clinical practice, this imaging method is highly dependent on the technique, expertise and routine of the examiner. False-negative results can be seen in TT, as is the case when systolic pressure is measurable, but diastolic pressure is absent due to twisting of the spermatic cord (26). Reactive hyperemia of the tunica vaginalis can accidentally be interpreted as arterial flow into the testis, it is therefore crucial to ensure that the blood flow that is visualized does indeed come from central vessel branches (27). Using CDUS, testicular arterial flow could be visualized in 19% of our patients, although the torsion of the spermatic cord was verified at surgery. It should be emphasized, that performing CDUS was shown to result in an up to 60-minute delay in treatment (28). CDUS should not question the findings of physical examination and therefore certainly not assign or detain patients from surgical intervention. This is in agreement with previous observations (16) and points out that TT cannot be efficiently diagnosed or ruled out using CDUS (14). Waiving of time-consuming imaging should shorten the time to surgery and help salvage testicular tissue since according to our results 50% presented six hours after onset of symptoms.

The clinical criteria triad, consisting of an absence of cremasteric reflex, swelling and high-riding testes, are widely used for symptoms indicative or strongly associated with TT (5). None of the criteria alone can prove the presence of TT, nevertheless, a combination of two or three of these criteria reliably predicted TT in 87% of our cases. The presence of the cremasteric reflex is observed in 61-100% boys between 24 months and 12 years of age (29). Absence of the cremasteric reflex alone therefore is a simple method with high sensitivity for TT (30) with verified sensitivity of 92.7% and specificity of 80.6% in our cohort.

Sheth et al. (28) developed a scoring system based on clinical criteria, assigning presenting patients to a low, intermediate, and high-risk group. The score allocates high-risk patients to immediate surgical intervention, avoiding possible time delay. Similar to our study, the authors found that no or only one clinical criterion was a powerful predictor to exclude the presence of TT. General agreement that the diagnosis of TT should primarily rely on physical examination, so that the scrotal exploration is not delayed by imaging procedures and treatment costs are kept low (5,7). The limitations were the study retrospective design, furthermore, evaluating clinical criteria depended on interobserver variability. Prospective studies on a larger number of patients are needed to confirm our findings.

Conclusion

TT is the most common diagnosis of acute scrotal pain after surgical exploration. Latter carries the risk of anesthesia and perioperative adverse events, therefore the ambition is to avoid surgical intervention if justified. Our proposed approach to distinguish between TT and ATT in cases of acute scrotal pain is consistent with using a clinical triad, which can be implemented quickly. Age older than 10 years and onset of symptoms during night hours support the diagnosis of TT. CDUS should not replace clinical evaluation. The traditional approach of physical examination to diagnose TT is safe and effective, hence it should remain the standard approach to assess patients with acute scrotal pain.

Ethics

Ethics Committee Approval: The project was approved by the local medical research ethics committee with the number 1393/2020.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.M., A.K.L., C.R., Concept: R.M., A.K.L., C.R., Design: R.M., A.K.L., C.R., Data Collection or Processing: R.M., A.K.L., C.M., G.L., F.A., C.R., Analysis or Interpretation: R.M., A.K.L., C.M., G.L., F.A., C.R., Literature Search: R.M., A.K.L., C.M., C.R., Writing: R.M., A.K.L.

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

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Basic Science

Doi: 10.4274/jus.galenos.2022.2022.0011
J Urol Surg, 2023;10(1):55-61

Protective Effects of Capsaicin on Experimental Testicular Torsion and Detorsion Injury

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

Recent investigations have demonstrated that there are many studies on the antioxidant mechanism of capsaicin (CAP), there is no study showing how CAP has an antioxidant effect in experimentally induced testicular torsion/detortion. In this study, we found that CAP will be an alternative treatment method for eliminating the pathological conditions resulting from ischemia.

Abstract

Objective: Testicular torsion is one of the most common genital diseases in males in adolescence and it should be treated as soon as possible without ipsilateral testicular dysfunction. We investigated the protective effect of Capsaicin, which is an active ingredient of red-hot pepper, an antioxidant substance, on tissue damage caused by ischemia/reperfusion (I/R).

Materials and Methods: Forty male, 250-300 g adult male rats were divided into 4 groups, 10 in each group. The torsion was created by rotating the spermatic cord of both testicles counterclockwise by 720°. In the experimental group where we applied capsaicin, detorsion was performed after 2 h of torsion. Malondialdehyde (MDA), superoxide dismutase (SOD), and catalase (CAT) were evaluated. Testicular tissue was stained with hematoxylin/eosin for histopathological evaluation.

Results: In the Capsaicin group showed reduced tubular damage and seminiferous tubules in a structure similar to ischemia and spermatogenic cell series in the tubular wall and decreased edema in the interstitial area. SOD, MDA and CAT levels evaluated for the determination of lipid peroxidation were observed to be close to the control group values in the Capsaicin administered group.

Conclusion: Capsaicin had a protective effect on I/R injury in the testicle.

Keywords: Capsaicin, ischemia/reperfusion, testis, torsion/detorsion

Introduction

Testicular torsion is a urological emergency characterized by the rotation of the spermatic cord and its anatomical structures. It is one of the most common genital diseases in men in adolescence and it should be treated as soon as possible without ipsilateral testicular dysfunction (1). Torsion occurs when the blood flow to the region decreases or is stopped completely. Increasing edema leads to arterial obstruction and subsequently results in ischemia and gonadal necrosis (2). Because of ischemia in the

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Received: 04.02.2022 **Accepted:** 01.04.2022

Cite this article as: Gören H, Öz S, Burukoğlu Dönmez D, Üstüner MC, Hız İ, Özden H, Kabay Ş. Protective Effects of Capsaicin on Experimental Testicular Torsion and Detorsion Injury. J Urol Surg, 2023;10(1):55-61.

tissue, it causes cell death, energy deficiency, deterioration in signal pathways and accumulation of reactive oxygen species (ROS) (3). While testicular torsion causes ischemic damage in the tissue, detorsion causes reperfusion damage, which is the main cause of tissue damage. Simultaneously, the duration of ischemia is critical for the damage to occur. Because of the long ischemia process, irreversible damage and necrosis occur in the cells (4,5). Studies have shown that the critical ischemia time should not be more than 4 h to avoid irreversible damage to the germinal and tubular epithelium in rat testicles (6,7). Studies have shown that ROS can have adverse effects by disrupting the structural elements of the tissue and it has been reported that these effects can be reduced with antioxidant therapy (8). Many antioxidant substances have been used to prevent tissue damage in the experimentally created testicular torsion and detorsion (T/D) models.

Capsaicin (CAP) (trans -8- methyl-N-vanillyl-6-nonenamide) belongs to the Capsicum plant family and is the active ingredient of red-hot pepper (Figure 1) (9). CAP has many pharmacological properties. In this study, we use its antioxidative properties but simultaneously, it is a very effective anticarcinogenic and antimutagenic agent (10). Protect cells against free radical-mediated damage caused by exogenous chemicals (10), inhibition of the generation of ROS (11) and induction of apoptosis (12,13). CAP protects against testicular damage through mTOR-dependent mechanism (14). The mammalian target of rapamycin (mTOR) is a kinase that humans are encoded by the mTOR gene (15). mTOR is a member of the phosphatidylinositol 3-kinase-related kinase family of protein kinases (16). The mTOR pathway plays an important role in cell growth, cell proliferation, protein synthesis. Phosphorylation of mTOR is increased in pathological conditions such as testicular torsion. Studies have shown that CAP reduces mTOR phosphorylation, thus proving that it is effective in the survival of cells in testicular tissue (14).

Evidence shows that CAP decreases the activities of superoxide dismutase (SOD), which is an important antioxidant enzyme involved in the scavenging of free radicals (10). Although there are many studies on the antioxidant mechanism of CAP, there is no study showing how CAP has an antioxidant effect in experimentally induced testicular T/D.

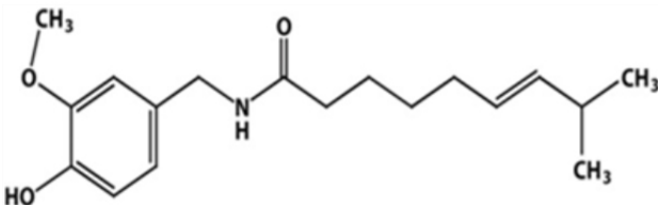

Figure 1. Chemical structure of capsaicin

In this study, we examined the effect of CAP on testicular T/D injury, by determining biochemical parameters and evaluating histopathological examinations.

Materials and Methods

Animals

The rats were obtained from the Medical and Experimental Research Center of Eskişehir Osmangazi University, Eskişehir, Turkey. For this study, 40 male Wistar-albino rats weighing 250-300 g were used and were housed in polycarbonate cages. The animal cages were maintained at 22±2 °C with a 12-hour light/12-hour dark cycle and the rats were fed with laboratory pellet shows and water was provided *ad libitum.* The treatment of the animals and experimental procedures were approved by the Experimental Animals Ethics Committee of Eskişehir Osmangazi University the decision no: 687/2018. After the surgical intervention, they were placed in individual polycarbonate cages to prevent intragroup injuries.

Groups

The rats were randomly separated into four equal groups and there were 10 rats in each group. Group I was the sham operated group. Only a scrotal skin incision was made in the rats in this group to evaluate the biochemical and histopathological basal values. Group II was the ischemia group in which we created testicular torsion. In this group, torsion was performed for 2 hours by 720-degree extravaginally testis. Group III was ischemia and reperfusion group. This group was designed to study the effect of detorsion after 2 h of torsion. Group IV was designed to determine the effect of CAP after ischemia. After surgical procedures as in group III, CAP (0.5 mg/kg, sc) (SİGMA Aldrich, Germany, M2028-250 MG) was administered before 30 min of detorsion. The CAP dose was injected subcutaneously as 0.5 mg/kg, which Zık et al. (17) determined as a safe and effective dose in rats.

Surgical Procedures

During all surgical procedures and euthanasia at the end of the experiment, the animals were placed under general anesthesia with xylazine/ketamine injection. Ketamine (Ketalar®) was injected intramuscularly (i.m.) at a dose of 50 mg/kg, and Xylazine (Rhompun®) was injected as 10 mg/kg i.m. After disinfecting the scrotal region, a midline vertical incision was made on the skin of the scrotal region and the testicular tissue was separated from the surrounding tissues (Figure 2A). To create testicular torsion, the double-sided testis was rotated 720 degrees counterclockwise along the longitudinal axis of the spermatic cord, and the testis was secured to the scrotum with a 4/0 non-traumatic suture passing through the tunica

albuginea and dartos (Figure 2B). After 2 h of ischemia (Figure 2C), the suture was removed and the testis was replaced in the scrotum for 2 h of reperfusion (Figure 2D). The rats were sacrificed by cervical dislocation under general anesthesia at the end of the experiment. Consequently, bilateral orchiectomies were performed for histopathological examination.

Histopathological Analyses

After the testicular tissues were removed, they were immersed in Bouin's fixative (7.5 mL of saturated picric acid, 2.65 mL of glacial acetic acid and 2.5 mL of 7% formaldehyde). The samples were processed through routine and standard paraffin embedding. After that they were sectioned into 5µ thickness and stained with hematoxylin and eosin (H&E) for histological analyses. Standard light microscopy (NIKON, Japan) was used for microscopic examination of rat testis tissue.

Biochemical Analysis

After the surgical intervention, blood was collected from the rats by the intracardiac route under general anesthesia. Biochemical analysis in blood; to determine lipid peroxidation (MDA), antioxidant enzyme levels such as SOD and CAT were evaluated. Erythrocyte hemolysate was prepared for the biochemical analysis to be made (18).

A. Measurement of Catalase Activity

Order to determine the catalase (CAT) activity, the procedures specified in the Cayman enzyme kit were applied for the preliminary preparation of the samples (CAYMAN, United States, Cat. no: 707002). At the last step of the procedure, a standard graph was drawn with the formaldehyde concentrations corresponding to the absorbance values read from the standard wells. The obtained values were calculated using the following formula. CAT activity (nmol/min/mL)=µM/20* sample dilution.

B. Measurement of Superoxide Dismutase Activity

SOD activity was studied with the water-soluble tetrazolium salt reaction-based Sigma SOD detection kit (SİGMA Aldrich, Germany, Cat. No:19160). The obtained values were calculated using the specified formula. (% inhibition rate) = {[(A blank 1-A blank3)- (A sample- A blank 2)]/(A blank 1- A blank 3)}.

C. Measurement of Malondialdehyde Levels

The measurement of the amount of malondialdehyde (MDA), which is effective in the determination of lipid peroxidation, is made using thiobarbituric acid (TBA). 0.1 mL homogenate, 3 mL of 1% phosphoric acid, 0.5 mL of distilled water and 1.0 mL of 0.6% 2-TBA were added. The mixture was boiled in the water bath for 45 min, followed by cooling in an ice. After the addition of 4 mL of n-butanol/pyridine, homogenate, and hemolysate MDA levels were measured spectrophotometrically at 532 nm and expressed as mmol MDA/mL (19).

Statistical Analysis

Statistical analyses were performed using the version of IBM SPSS 21 (Statistical Package for Social Sciences). Shapiro-Wilk Normality test and Kolmogorov-Smirnov test were used to determine whether the groups possessed normal distribution. The groups, which showed a normal distribution, were analyzed using One-Way analysis of variance (ANOVA) test. Variables that did not show normal distribution were analyzed with the Kruskal-Wallis test. All the data were expressed as mean ± standard deviation. The results were considered within 95% confidence bounds and a $p<0.05$ was considered to statistically significant.

Results

Because of the biochemical evaluations, SOD, MDA and CAT values, which are important parameters for the determination

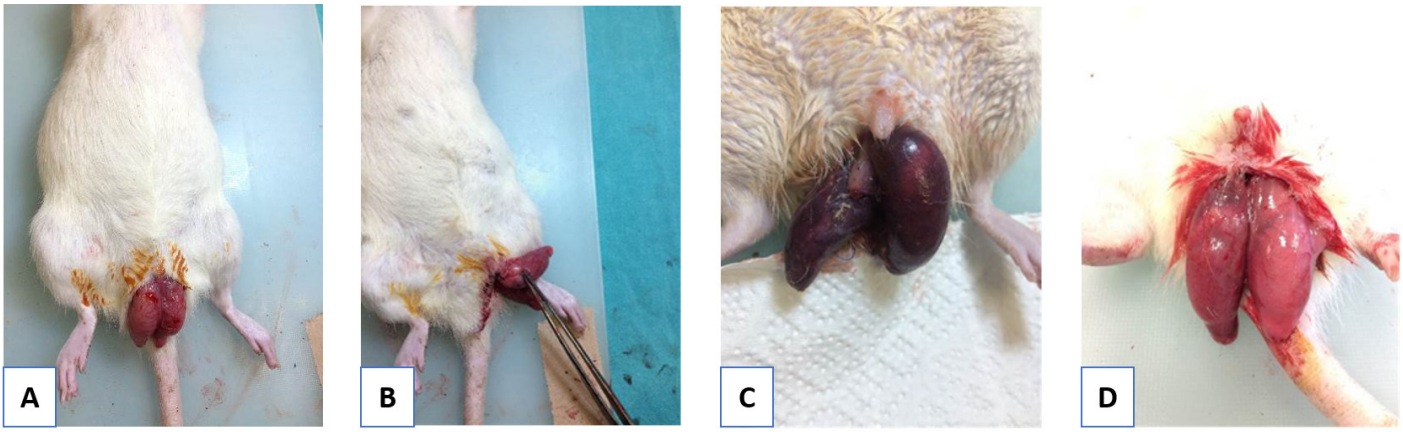

Figure 2. Rat testis image with experimental testicular torsion. (A) A midline vertical incision was made on the skin of the scrotal region and the testicular tissue was separated from the surrounding tissues. (B) The double-sided testis was rotated 720 degrees counterclockwise along the longitudinal axis of the spermatic cord for create testicular torsion. (C) Image of testis 2 hours after ischemia. (D) Image of testis 2 hours after reperfusion

of lipid peroxidation, are shown in Table 1 and Figure 3. MDA levels were significantly increased compared with groups II and group III in the group I and group IV. Additionally, MDA levels were significantly decreased in the CAP-treated group compared with the groups II and group III ($p<0.05$). But, there was no significant difference between the group II and group III ($p>0.05$). The SOD and CAT levels were significantly decreased in groups II and III when compared with groups I and IV, but after CAP administration, SOD and CAT levels increased and there weren't any difference between groups I and IV ($p>0.05$).

The histopathological examinations for each group are shown in Figure 4. The sham group showed a normal testicular structure. regular seminiferous tubular morphology and spermatogenic cells in the tubule wall, interstitial area and Leydig cells were seen in the normal structure in this group (Figure 4.A1-A3). In the ischemia group, it showed intense tubular damage, epithelial shedding, atrophic tubule structures, edema in the interstitial area and vascular congestion (Figure 4.B1-B3). In the ischemia/reperfusion (I/R) group, intense tubular damage, epithelial spills, edema in the interstitial area and vascular congestion were observed (Figure 4.C1-C3). CAP-treated group

Table 1. Antioxidant enzyme levels in testes tissue

Group	Group number	MDA (mmol/mL)	SOD (Inh%)	CAT (kU/L)
Group I (Sham)	GI	4.244±0.06	74.825±4.43	1.848±0.05
Group II (Ischemia)	GII	5.645±0.09	64.644±2.62	1.699±0.08
Group III (Ischemia+Reperfusion)	GIII	6.252±0.09	58.157±2.68	1.376±0.09
Group IV (Ischemia+Reperfusion+Capsaicin)	GIV	4.338±0.12	71.670±2.67	1.954±0.02
p values and multiple comparison of the groups	GI-GII	<0.001	<0.001	<0.001
	GI-GIII	<0.001	<0.001	<0.001
	GI-GIV	0.141	0.139	0.010
	GII-GIII	<0.001	<0.001	<0.001
	GII-GIV	<0.001	<0.001	<0.001
	GIII-GIV	<0.001	<0.001	<0.001

All of the data were expressed as means ± SD. Differences between groups were evaluated by One-Way analysis of variance (ANOVA) followed by Post-hoc comparison test. The significance was tested as n.s p>0.05, p<0.05, p<0.01 and p<0.001, SD: Standard deviation, MDA: Malondialdehyde, SOD: Superoxide dismutase, CAT: Catalase

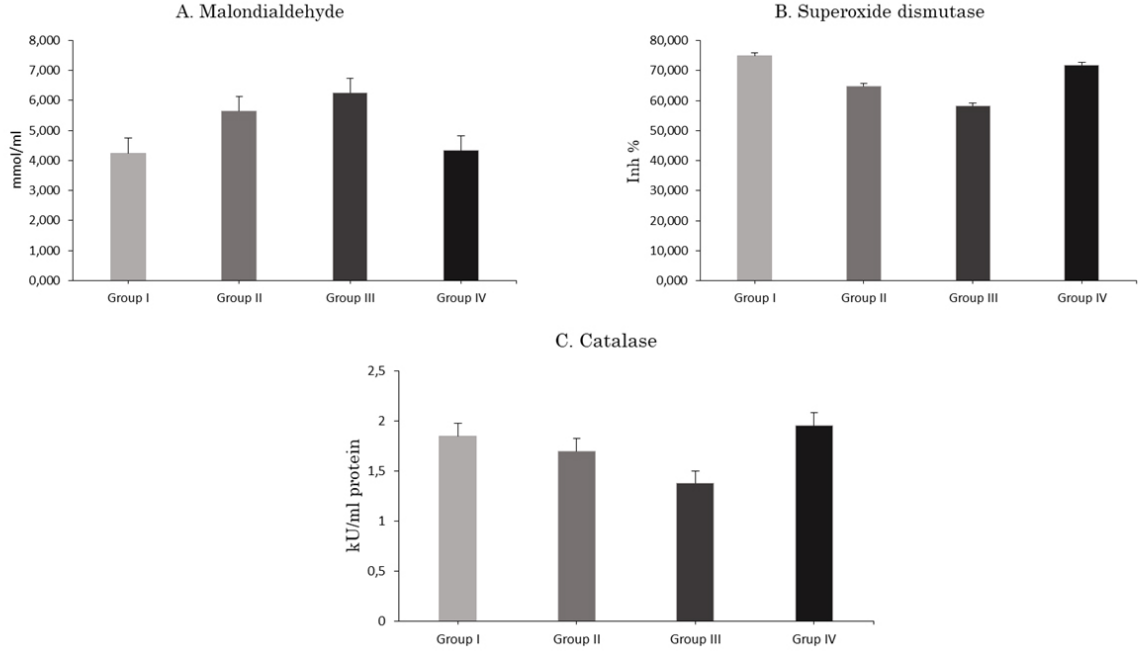

Figure 3. Mean MDA (A), SOD (B), CAT (C) activities of all groups. Data are presented as means ± SD. The significance was tested as n.s p>0.05, p<0.05, p<0.01 and p<0.001

showed decreased edema in the interstitial area and compared to the ischemia and IR group, decreased tubular damage and near-normal seminiferous tubules and spermatogenic cell lines in the tubule wall are seen (Figure 4.D1-D3).

Discussion

Testicular torsion is a urological emergency characterized by the rotation of the spermatic cord and the anatomical structures in it, which is frequently encountered especially during adolescence. Damage to testicular tissue varies depending on the degree and duration of torsion. While ischemic damage occurs during torsion, it has been observed that the main damage to the tissue occurs during detorsion. Many studies have shown that I/R damage can be improved with various antioxidant substances (ozone, diacerein, montelucast, curcumin, taurin etc.) (20,21). However, no study was found investigating the effect of CAP on I/R damage in testicular torsion. Therefore, the current study is first in the literature. The authors investigated the protective effect of CAP on testicles in I/R injury.

In the present study, CAP was given subcutaneously 30 min before reperfusion, showed effects on biochemical and histopathological levels in decreasing reperfusion injury in the testis. A previous study by Sarioglu-Buke et al. (22), demonstrated that CAP prevents apoptotic changes in the contralateral testis in ipsilateral testicular torsion. At another relevant study demonstrated that CAP has a strong neurotoxin effect on nerves and demonstrated this in her testicular ischemia study (23). However, Ilhan and Erdost (24), proved the beneficial effects of CAP on the reproductive system by showing that CAP increases the synthesis of ghrelin and thus triggers testicular cell proliferation and increases the testosterone level. Another recent study indicated that the protective properties of CAP by reducing the formation of free radicals, inhibiting the active caspase-3 and antioxidant defense mechanism (25).

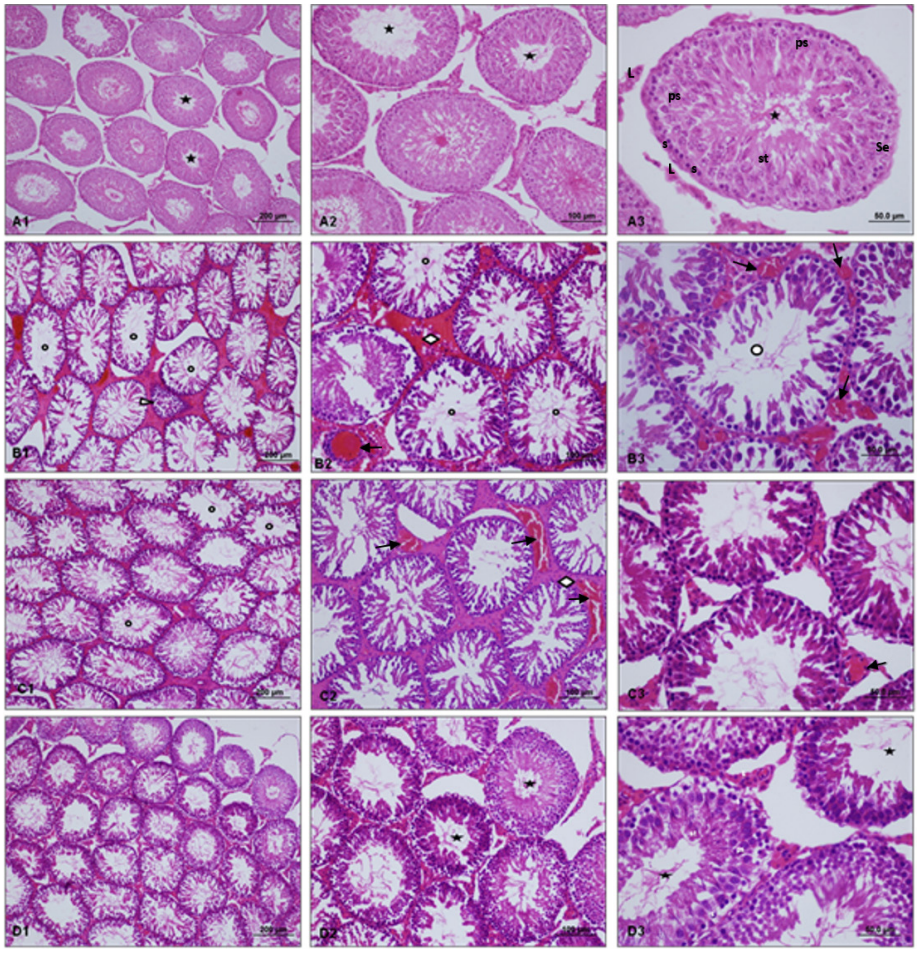

Figure 4. Light microscopic images of testes of rats in all groups at different magnifications. (HE, scale bar: 200 µm, 100 µm, 50 µm). (A1-A3) Sham group shows normal testicular structure. Regular seminiferous tubular morphology and spermatogenic cells in the tubule wall (*), interstitial area and Leydig cells (L) are seen in normal structure in this group. (B1-B3) In the ischemia group, it shows intense tubular damage (o), epithelial shedding, atrophic tubule structures (►), edema in the interstitial area ( ) and vascular congestion (→). (C1-C2) In I/R group, intense tubular damage (o), epithelial spills, edema in the interstitial area ( ) and vascular congestion (→) are observed. (D1-D3) CAP-treated group shows decreased edema in the interstitial area and compared to the ischemia and IR group, decreased tubular damage and near-normal seminiferous tubules (*) and spermatogenic cell lines in the tubule wall are seen

Studies have shown that one of the parameters that effective in the clinical importance of testicular torsion is the ischemia time, and the other is the degree of torsion. In this study, we complete ischemic damage at 720° counterclockwise and 2-hour ischemia period, which is sufficient time for the desired ischemic response to occur in the rat testis tissue. Both biochemical and histological evaluations showed that this time was sufficient to induce ischemia in the tissue. Turner and Brown (26) argued that even 1 h is sufficient for ischemic damage to the rat testis tissue. However, Gürdal et al. (27), showed that the testicular ischemia period, which was formed by 720° for 1 h, increased the level of lipid peroxidation with the increase in the malondialdehyde level in the tissue but they showed that the time for the formation of histopathological changes was insufficient. Another recent study emphasized that it is sufficient to torsion the testis tissue 360° and for 2 h for the formation of a moderate acute vascular response in the testis tissue (28). In another study, a counterclockwise 720° and 2-hour ischemia period was applied in the testicular torsion model and it was shown that the applied torsion period caused sufficient histopathological changes in the tissue and the desired ischemia table was formed because of MDA, SOD and CAT analyzes (3). The present results and studies have shown that the time we have planned in the experimental procedure is sufficient for the desired ischemic damage to the tissue.

The general idea in experimentally created ischemia models is that ischemia lasting longer than 4-6 hours will cause irreversible tissue damage. It has been shown that ischemia lasting longer than 4 h completely cuts off the blood flow in the testicular tissue and creates focal infarctions (29,2). Studies argue that the testicular tissue, which intervenes within 6 h, shows a recovery of 85-97% (28).

Biochemical and histopathological evaluations are the most reliable analysis to determine the degree of ischemic damage in ischemia and reperfusion studies. In the hypoxia caused by ischemia, the level of ROS in the tissue increases even more. Although the measurement of ROS for antioxidant activity is more reasonable, its short lifespan makes it impossible to measure ROS. For this reason, the measurement of MDA, a product of lipid peroxidation, gives more reliable results. MDA is the end product of lipid peroxidation and MDA levels in blood and tissue are an important indicator of oxidative damage in I/R studies. In our study, the level of MDA significantly increased in the T/D group compared with the sham group. Because of the increase in the I/R group, it shows that reperfusion has even more harmful effects on the tissues. Treatment with CAP significantly decreased MDA levels.

Endogenous antioxidant enzymes are used to eliminate free oxygen radicals formed during ischemia and reperfusion. We determined the levels of antioxidant enzymes such as SOD and CAT, which are frequently used in ischemia studies. It was observed that SOD and CAT values, which decreased in the ischemia and ischemia reperfusion group, compared with the control group, increased in the CAP group. It was stated that this increase in the CAP group approached the SOD and CAT values in the control group. In most of the experimental testicular torsion studies, SOD activity was decreased after reperfusion. Despite the decrease in SOD levels in I/R groups, there are also experimental studies in the literature studies to the contrary (20).

Histopathological examination in the I/R group revealed intense tubular damage, epithelial spills, edema in the interstitial area and vascular congestion in the rat testis. The present findings show that CAP-treated group had decreased tubular damage, near-normal seminiferous tubules and spermatogenic cell lines in the tubule wall.

Conclusion

The results of this study indicate that CAP treatment has a protective effect against I/R damage in testicular torsion with biochemical and histological examinations. Because of the meaningful data we have obtained, we suggest that CAP will be an alternative treatment method for eliminating the pathological conditions resulting from ischemia.

Ethics

Ethics Committee Approval: The treatment of the animals and experimental procedures were approved by the Experimental Animals Ethics Committee of Eskişehir Osmangazi University the decision no: 687/2018.

Informed Consent: Not necessary.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.G., S.Ö., İ.H., Concept: H.G., H.Ö., Ş.K., Design: H.G., H.Ö., Ş.K., Data Collection or Processing: H.G., S.Ö., D.B.D., M.C.Ü., Analysis or Interpretation: H.G., D.B.D., M.C.Ü., H.Ö., Literature Search: B.E., H.T., M.K., Writing: B.E.

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

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2022.2022.0005
J Urol Surg, 2023;10(1):62-66

The Effects of Listening to Music Embedded Binaural Beats on Anxiety Levels and Pain Scores in Male Patients Undergoing Prostate Biopsy: A Randomized Placebo-controlled Study

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

Listening to binaural beats is a different distraction method to reduce anxiety and pain scores of the patients who underwent in daily medical procedures. In this study, we found listening to music embedded binaural beats can be used to reduce anxiety and pain scores of the patients who underwent prostate biopsy.

Abstract

Objective: To investigate the effects of binaural beats (BB) embedded with music on pain and anxiety scores in patients who underwent transrectal ultrasound-guided prostate biopsy with the suspicion of prostate cancer under local anesthesia.

Materials and Methods: This was a prospective, randomized, placebo-controlled study. Patients were divided into three groups; binaural beat group (BBG), music group (MG), and control group (CG). Anxiety assessment was made with the State-Trait Anxiety Inventory (STAI) form. The initial anxiety scores of the patients were recorded as STAI initial (STAI-I) before the procedure. Post-procedure anxiety scores of the patients were recorded as STAI-T terminal (STAI-T). The difference between STAI-I and STAI-T was recorded as STAI delta (STAI-D). A visual analog scale (VAS) was used for post-procedural pain scores. Demographic data, STAI-I, STAI-T, STAI-D, and VAS scores were compared.

Results: A total of 270 patients who met the study criteria, 90 in each group, were included in the study. When STAI-T and STAI-D were evaluated, there was a significant decrease in BBG and MG compared with CG. When the VAS during the procedure was evaluated, there was a significant difference between the BBG, MG, and CG groups. When the BBG vs MG, BBG vs CG, and BBG and MG groups were compared separately in terms of VAS, $p<0.001$, $p<0.001$ and $p=0.04$, respectively.

Conclusion: As a result, music embedded BB may be an effective, safe, well-tolerated and inexpensive method in reducing anxiety and pain scores in male patients who will undergo prostate biopsy.

Keywords: Biopsy, prostate, anxiety, binaural beats, pain

Introduction

According to the latest studies, prostate cancer is the 2nd most common cancer and the 5th most common cause of death (1,2). Transrectal ultrasound-guided prostate biopsy (TRUS-PBX) is the standard method in the diagnosing of prostate cancer (3,4). Intrarectal and periprostatic nerve blockade are frequently used methods for reducing pain in TRUS-PBX (5,6). Between 19% and 30% of patients experience pain during TRUS-PBX (7,8). Various methods have been attempted to reduce pain and anxiety. Some of these have been shown in studies with medical methods and some with non-medical methods such as music (8,9).

Binaural beats (BB), first described in detail by Oster (10), are based on giving the same intensity but different frequencies to the ear (11). BB cause the brain to produce vibrations of the

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Received: 27.01.2022 **Accepted:** 20.07.2022

Cite this article as: Yılmaz K, Ölçücü MT. The Effects of Listening to Music Embedded Binaural Beats on Anxiety Levels and Pain Scores in Male Patients Undergoing Prostate Biopsy: A Randomized Placebo-controlled Study. J Urol Surg, 2023;10(1):62-66.

same amplitude and localization as perceived sounds. Studies reported BB reduces pain and anxiety as a distraction method (12-14).

In this study, we investigated the effects of music embedded BB on pain and anxiety scores in patients who underwent TRUS-PBX with the suspicion of prostate cancer. We hypothesized that BB embedded music would significantly reduce pain and anxiety scores in patients who underwent TRUS-PBX.

Materials and Methods

Participants Selection and Ethics Statements

The study was initiated after the approval of the ethics committee number 2019-096. Male patients with at least formal schooling (1-8 years of education), who underwent TRUS-PBX for the first time because of clinical suspicion of prostate cancer, were included in the study. Those patients with hearing and vision problems and/or mental retardation, neurological deficits, a history of chronic pelvic pain syndrome and anorectal diseases, analgesia use 24 hours before the procedure, use of transcylisers or antidepressants, declined to participate in the study, failed to complete questionnaires, failure to tolerate intervention were excluded from the study. The study and its aim were explained to all the patients. Informed consent was provided from all patients who wanted participated in the study. The age and body mass index (BMI) of the patients included in the study were recorded.

Randomization and Sample Size

The study was conducted in a prospective randomized, unblinded, and placebo-controlled manner. Patients were equally divided into three groups 1:1:1 by computer-generated block randomization; binaural beat group (BBG), music group (MG), and control group (CG). The block randomization method was used when the patients were allocated to the groups. A power analysis indicated minimum 267 patients were required for statistical comparison that has a power (1-β) of 0.80 at an alpha value of 0.05, with an effect size of 0.25 (G*Power 3.1, (Kiel, Germany) (15).

Preparation of Patients, Measurement of Anxiety Levels and Pain Scores

In this study, an Anxiety assessment was made with the State-Trait Anxiety Inventory (STAI) form. STAI is a form developed to determine the anxiety level of patients (16). The total score ranges from 20 to 80; higher scores indicate higher levels of anxiety. The Turkish version was translated by Öner and LeCompte (17). The initial anxiety scores of the patients were recorded as STAI initial (STAI-I) before the procedure.

Music embedded BB was listened to the BBG group of the patients. BB were produced with a software (artisan Spirit Inc. Binaural Beat version1.0.15) with an alpha wave frequency of 10 Hz (180 Hz for the right ear and 190 Hz for the left ear) and embedded in the music. During MG, patients were listened to the type of music they wanted. All audio types were listened with wireless stereo headphones (Sony WH-CH510; Sony Corporation, U.S.).

Local anesthesia was provided with periprostatic lidocaine injection after intrarectal injection of 2% lidocaine gel after cleaning the perianal region of the patients. Prostate biopsies were obtained by biplanar transrectal ultrasound (Mindray CB10-4, China) as 12 cores. Listening was continued during the procedure. The procedure time was recorded as the entry and exit of the TRUS probe from the anal region.

Post-procedure anxiety scores of the patients were recorded as STAI-T terminal (STAI-T). The difference between STAI-I and STAI-T was recorded as STAI delta (STAI-D).

The visual analog scale (VAS) is a common instrument in which patients score their pain levels between 0 and 10 (18). We used the VAS I to evaluate the patients' pain scores after the procedure.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY). The assumptions of normality were evaluated using the Shapiro-Wilk test. According to Shapiro-Wilk test the variables of the study have non-normally (non-parametric) distrubiton. Kruskal-Wallis test was used for non-parametric variables to determine differences between groups, Bonferroni-Dunn test was used as a Post-hoc test for significant cases. A p-value of <0.05 was considered statistically significant.

Results

A total of 382 male patients who underwent prostate biopsy between the December 2019 and February 2021 were admitted to our clinic. Patients who did not meet the study criteria were excluded. A total of 270 patients, 90 in each group, were included in the study. The flow diagram of the study is shown in the figure (Figure 1).

The mean ages of BG, MG, CG were 66 (47-75), 66.5 (45-77), 66 (47-77), respectively, and there was no significant difference between the groups ($p>0.05$). The mean BMI was 26.48 (19.03-43.09), 27.31 (17.51-37.92), 26.45 (18.87-37.34), respectively, and there was no significant difference between the groups in terms of BMI ($p>0.05$) (Table 1).

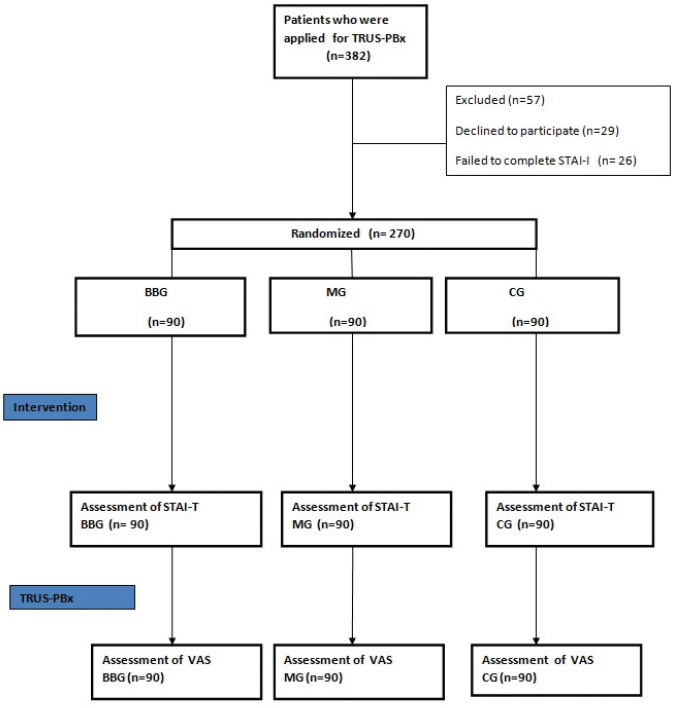

Figure 1. Flowchart diagram of participants who underwent transrectal ultrasound-guided prostate biopsy

TRUS-PBx: Transrectal ultrasound-guided prostate biopsy, BBG: Binaural beat group, MG: Music group, CG: control group, STAI-T: State-Trait Anxiety Inventory-terminal, VAS: Visual analog scale

There was no significant difference between the groups in terms of STAI-I (p>0.05). When STAI-T and STAI-D were evaluated, it was observed that there was a significant decrease in BBG and MG compared with the CG (p=0.003 and p<0.001, respectively). However, there was no significant difference between BBG and MG in terms of STAI-I and STAI-T (p=0.388 and p=0.571, respectively). There was no significant difference between the groups in terms of TRUS-PBX procedure time (p>0.05). When the VAS during the procedure was compared, it was observed that there was a significant difference between the BBG, MG, and CG groups (p<0.001) (Table 2). Separate comparisons of BBG vs MG, BBG vs CG, MG vs CG in terms of VAS were p<0.001, p<0.001 and p=0.04, respectively.

Discussion

In this study, we observed that music embedded BB significantly reduces anxiety and pain scores in men who underwent TRUS-PBx. Although there was no significant difference between were seen between BB and music in terms of anxiety score, it was seen that BB was significantly superior to music in terms of pain score.

Table 1. Patient demographics details

Variables	Binaural beat group (n=90)	Music group (n=90)	Control group (n=90)	p-value
Age (year, mean ± SD, range) (median, min-max)	63.86±7.15 66 (47-75)	63.76±7.85 66.5 (45-77)	64.61±6.58 66 (47-77)	0.838
BMI (mean ± SD, range) (median, min-max)	26.82±4.18 26.48 (19.03-43.09)	27.47±3.69 27.31 (17.51-37.92)	26.64±3.65 26.45 (18.87-37.34)	0.155
PSA (ng/mL), (median, min-max)	9.6 (5.7-15.8)	8.72 (2.7-18.5)	8.17 (3.1-16.7)	0.093
ASA score, n (%)				
1	29 (32.3)	25 (27.8)	27 (30)	0.376
2	53 (58.8)	56 (62.2)	53 (58.8)	
3	8 (8.9)	9 (10)	10 (11.2)	
PV (g, mean ± SD, range)	47.53 (33-92)	50.25 (29-85)	46.92 (35-85)	0.243

SD: Standard deviation, BMI: Body mass index, PSA: Prostate spesific antigen, ASA: American Society of Anesthesiologists, min: Minimum, max: Maximum

Table 2. Comparison of patients STAI-I, STAI-T, STAI-D, VAS scores and duration between the groups

Variables	Binaural beat group (n=90)	Music group (n=90)	Control group (n=90)	p-value
STAI-I (median, min-max)	39 (27-58)	42 (27-57)	40 (24-59)	0.817
STAI-T (median, min-max)	32 (23-58)[a]	37 (21-53)[a]	39.5 (24-59)[b]	**0.003***
STAI-D (median, min-max)	5 (0-16)[a]	5 (1-14)[a]	1 (-2-2)[b]	**<0.001***
Duration (minute, median, min-max)	4.5 (3.5-6)	4.5 (3.5-6.5)	4.5 (3.5-6)	0.89
VAS score (median, range)	1 (0-10)[a]	3 (0-10)[b]	4 (0-10)[c]	**<0.001***

STAI-D: State-Trait Anxiety Inventory-Delta, STAI-I: State-Trait Anxiety Inventory-Initial, STAI-T: State-Trait Anxiety Inventory-Terminal, VAS: Visual analog scale, [a, b, c]: Different lowercases denote statistically significant differences, *bolded values are significant p values between groups, min: Minimum, max: Maximum

Many studies have been conducted to reduce pre-procedural anxiety and pain during the procedure in male patients before prostate biopsy. Some of these include medical treatments, whereas others include distraction-based studies. The most common distraction methods used to reduce pain and anxiety in the prostate biopsy are visual and auditory. Auditory methods are used more frequently because they are easier to apply and are thought to be more effective.

It has been shown in studies and meta-analyses that listening to music before prostate biopsy significantly reduces pain and anxiety scores (9,19). In contrast, there are studies in the literature reporting that listening to music is not effective in reducing anxiety and pain (20). Music is effective in reducing anxiety and pain not only in prostate biopsy but also in other procedures that are frequently performed locally in urology practice (21-23).

There have been many studies showing that binaural music embedded in pure or music reduces anxiety and pain scores in surgical procedures. The mechanism of these effects of BB has not been fully elucidated. It has been suggested that this effect is due to the brain changing the dominant wave frequency toward the frequency of external stimuli to synchronize the neural activity with stimuli from binaural concerts (11). Alpha waves (8-13 Hz) in brain activity are associated with relaxation (14,24). It has been shown in various studies that BB are effective in this wave range, providing relaxation and reducing pain (12,14,24).

Isik et al. (12) conducted a randomized study that includes 60 patients who underwent dental intervention. They divided groups into two equal group. They used pure BBs in their study. As a result they reported that BB significantly reduces anxiety and pain scores in patients who underwent dental intervention. Padmanabhan et al. (24) reported that BB and music significantly reduced anxiety scores in patients who would undergo surgical intervention under general anesthesia. They found these results in a randomized study that included 108 patients. Similar results were obtained by Wiwatwongwana et al. (14). They observed patients while they were undergoing cataract surgery under local anesthesia. He also stated that BB significantly reduced pre-procedural HR and systolic blood pressure in patients compared with other groups (14). In both studies, it was reported that there was no significant difference between BB and music in terms of their effect on anxiety.

Studies have been conducted showing that BB reduce intraoperative pain and therefore reduce the need for analgesics (25-27). Debaouc reported that BB reduced the postoperative analgesic requirement and also shortens the length of hospital stay (25). According to Ölçücü et al. (13) showed that listening to pure BB significantly reduced pain and anxiety scores in patients who underwent cystoscopy and ureteral stent removal under local anesthesia. They stated that there was no difference between pure BB and music in terms of anxiety scores, they also reported that pure BB significantly reduced pain scores compared to music. They also stated that the tolerance rate of pure BB music was significantly lower compared to the MG and CG, and some patients stated that BB was meaningless and disturbing (13). However, in our study we music embedded BBs was used and there was no patient who could not tolerate it.

Study Limitations

This study has some limitations. The most important limitation is that the study was not blinded. The fact that it is single-centered can be considered a limitation. Another limitation is that different people perform prostate biopsy procedures. But since TRUS-PBX is a simple and easy procedure, we think that there can be no big differences between urologists. If blood pressure and pulse change were monitored in the study, it would have increased the power of the study.

Conclusion

As a result, music embedded BB may be an effective, safe, well-tolerated and inexpensive method in reducing anxiety and pain scores in male patients who will undergo prostate biopsy. To confirm our results, it would be more appropriate to conduct double-blind multicenter studies with a larger number of patients.

Ethics

Ethics Committee Approval: The study was initiated after the approval of the ethics committee number 2019-096, approval date: 16/05/2019.

Informed Consent: Informed consent was provided from all patients who wanted participated in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

Financial Disclosure: The authors declare that they have no relevant financial.

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ORIGINAL RESEARCH
General Urology

Doi: 10.4274/jus.galenos.2023.2022.0018
J Urol Surg, 2023;10(1):67-73

The Factors That Affecting Shockwave Lithotripsy Treatment Outcome of Kidney Stones

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

Shockwave lithotripsy (SWL) is still one of the essential treatment options in the treatment of kidney stones with lower complication rates compared to other treatment methods. In this study, factors and markers that determine SWL success and activity were evaluated.

Abstract

Objective: We analyzed the relation of shockwave lithotripsy (SWL) success and the combination of success predictors.

Materials and Methods: In this retrospective study, the outcomes of 1.880 patients with kidney stones treated with SWL were analyzed. A total of 124 adult patients with complete records with non-contrast computed tomography, stone analysis, laboratory data were involved in the study. Patients who were with urinary system anomalies, who were receiving alpha-blocker and/or calcium channel blockers and whom with impaired kidney function were excluded. The effect of stone density, skin-to-stone distance (SSD), perirenal tissue density (PTD), subcutaneous tissue density (STD), stone size, stone burden, stone localization, infundibulopelvic angle (IA), body mass index (BMI) and stone analysis results on the success of the treatment was evaluated.

Results: SSD, PTD, STD, stone localization, IA and BMI did not have any significant effect on SWL success. Stone size and stone burden had a significant association with treatment success (p=0.0001), and the cut-off values determined for stone size and stone burden were 12.95 mm (p=0.0006) and 121.38 mm^2 (p=0.004) respectively. Stone density also had a significant association with treatment success (p=0.0001), and the cut-off value determined for stone density was 739 Hounsfield Unit (p=0.001). Treatment success was significantly lower in cystine and calcium oxalate monohydrate stones compared to other stone types (p=0.019).

Conclusion: Significant markers that determine SWL effectiveness are stone size, stone burden, stone density and stone type.

Keywords: Shockwave lithotripsy, kidney stone, stone type

Introduction

Shock wave lithotripsy (SWL) is a very advantageous treatment option with a shorter hospital stay and recovery time compared to other surgical treatments (1). Endourological methods such as percutaneous nephrolithotomy (PNL) and retrograde intrarenal surgery, which have progressed with the latest technology, have made notable developments in stone treatment approaches. However, the popularity of SWL has not decreased because PNL and retrograde intrarenal surgery should be performed in the operating room conditions and anesthesia is required for these treatments (2). But prediction of SWL outcome is still challenging. Thus, some parameters have been established in predicting the success of the SWL process. Stone volume, stone density, the chemical composition of stone, the location of the stone in the kidney, skin-to-stone distance (SSD), and infundibulopelvic angle (IA) are essential factors that determine the outcome of treatment (3,4). However, one or more of these factors were separately analyzed but not all of them were analyzed for the patients treated with the same lithotripter.

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Received: 24.02.2022 **Accepted:** 15.01.2023

Cite this article as: Kayra MV, Gören MR, Özer C, Kılınç F. The Factors That Affecting Shockwave Lithotripsy Treatment Outcome of Kidney Stones. J Urol Surg, 2023;10(1):67-73.

In this study, it was aimed to estimate the predictability of the lithotripsy treatment success before the treatment with the data examined, and all the factors affecting the lithotripsy success were studied to be more beneficial in clinical practice.

Materials and Methods

Patients

In the retrospective study, 1.880 patients who underwent SWL treatment according to the current European Association of Urology guidelines at the time of treatment in our clinic between January 2011 and December 2015 were analyzed (5). A total of 124 adult patients (≥18 years old) who had uncontrasted computed tomography (NCCT), stone analysis, laboratory data, complete patient records and had a radiopaque single kidney stone was included in the study. Patients who were with urinary system anomaly, who were receiving alpha-blocker and/or calcium channel blockers that may affect the stone-free rate and who had kidney dysfunction were excluded from the study. This study was approved by Baskent University Institutional Review Board (project no: KA16/227) and supported by Baskent University Research Fund.

Age, gender, body mass index (BMI) and stone analysis results were obtained from the patient records. From the NCCT images, stone localization, stone density, SSD, perirenal tissue density (PTD), subcutaneous tissue density (STD), stone size, stone burden and IA were determined.

On NCCT images, the longest diameter of stone that could be measured on the axial and coronal plane was accepted as stone size (Figure 1). The stone burden was calculated by the combination of maximal axial and coronal diameters on NCCT. SSD was defined as the distance between the center of the stone at 45° and 90° angles to the skin in axial sections on NCCT images. Stone density was obtained by calculating the mean density of the largest elliptical area drawn in the stone on the basis of the Hounsfield Unit (HU) at the level where the stone had the largest diameter in axial sections (Figure 2). The PTD was defined as the mean density of the area between kidney and abdominal wall in HU. STD was determined as the mean density of adipose tissue between the skin and the abdominal wall in HU. IA was calculated by obtaining the angle of the renal lower pole calyx to the ureteropelvic junction on NCCT coronal section or intravenous pyelography (IVP) images.

SWL Procedure

The procedure was performed to all patients under sedoanalgesia. For sedoanalgesia, midazolam (0.03-0.07 mg/kg) and fentanyl (0.5-1 mcg/kg) or ketamine (0.5-1 mg/kg) were administered

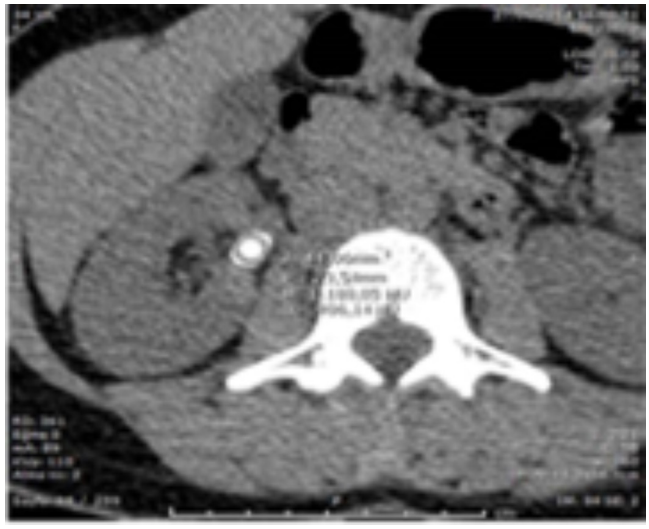

Figure 2. Measurement of stone density on NCCT

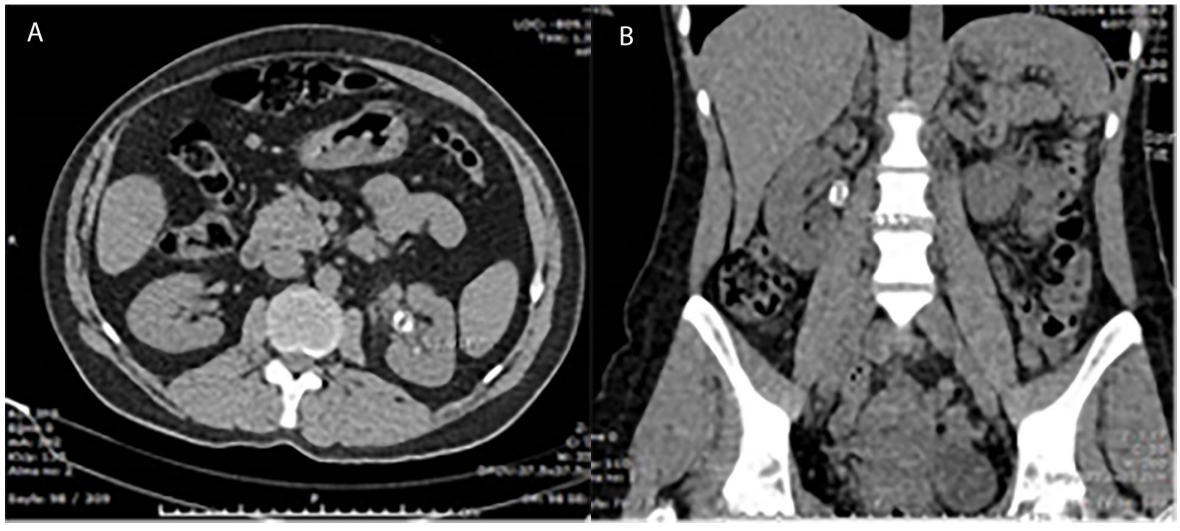

Figure 1. Measurement of the widest diameter of the stone in two planes on NCCT

intravenously (IV) under the control of an anesthesiologist. Lithostar Modularis Uro-plus (Siemens Medical Systems©, Erlangen, Germany) was used for SWL. During the SWL session, the opaque stones were treated with fluoroscopy guidance. The process began with a 0.1 power setting (9.506 kV) and the voltage was increased sequentially in the first 1.000 shocks and reached a maximum of 3.5-4 power settings (47.65-52.03 kV). Between 3.500 and 5.000 shock waves were applied in total by giving 60 shock waves per minute. All procedures were done by the same SWL technician.

Follow-up

In all patients, stone fragmentation was checked by a kidney-ureter-bladder X-ray (KUB), NCCT or ultrasonography (USG) after 24-48 hours of the SWL session. If the stone was not fragmented, the second session SWL was planned. The interval between additional SWL sessions was at least three days. No more than three sessions of SWL treatment was applied. The patients were followed up with NCCT, USG, or IVP after three months of the last SWL session. The treatment success was defined as stone-free status or clinically insignificant residual fragments (≤3 mm) after 3 months of the last SWL session. To collect stone specimens, patients were asked to urinate into a clean container to collect stone fragments after SWL sessions. Stone analysis was done with Fourier Transform Infrared Spectroscopy.

The records of the patients were reviewed for post-SWL treatments such as PNL, ureteroscopy which were used to calculate efficacy coefficient (EQ). The EQ is the percent of the patients who are stone free X 100 ÷ (100% + percent re-treatment rate + percent having auxiliary procedures).

Statistical Analysis

For the comparison of the continuous measurements between successful and unsuccessful groups, the distributions were checked. Since the parametric distribution prerequisite was not satisfactory, non-parametric Kruskal-Wallis test and Mann-Whitney U tests were applied, and chi-square tests were employed to evaluate the success rates. In the study, a cut-off value was determined for the values that were statistically significant between the groups and the area under the receiver operating characteristic curve (ROC) was evaluated by ROC Analysis, by calculating the sensitivity and specificity values. The statistical significance level was determined as $p<0.05$ in all tests.

Results

The overall success rate was 90/124 (72.5%). There was no statistically significant difference between age, gender, BMI and treatment success. (respectively p=0.079, p=0.632, p=0.557). It was determined that the side and localization of the kidney stone did not affect the success of the treatment (respectively p=0.119, p=0.225). Lower calyx stones were compared with all stones in other localizations, and there was no significant difference (p=0.089). It was also found that SSD, PTD, STD and IA did not affect the success of treatment (respectively p=0.778, p=0.985, p=0.488, p=0.549). Patient variables, stone features, SWL characteristics and success rates of the two groups are summarized in Table 1.

There was a statistically significant association between the size of the stone and the success of treatment (p=0.0001). The cut-off value for the stone size was 12.95 mm (p=0.0006, sensitivity=70.6%, specificity=72.2%) It was determined that the success of treatment was higher for the stone sizes below this value. The association between stone burden and treatment success was also statistically significant (p=0.0001). The cut-off value of the stone burden for treatment success was 121.38 mm^2 (p=0.004, sensitivity=70.6%, specificity=72.2%). It was determined that the treatment success rate was higher below this value. There was statistical significance between stone density and treatment success (p=0.0001). The cut-off value determined for stone density was 739 HU (p=0.001, sensitivity=70.6%, specificity=60%) (Table 2). It was seen that the stone type was an influential factor affecting the success of treatment (p=0.019) (Table 2).

The overall complication rate was 13.7%. Double J stent placement and ureterorenoscopy were performed for ureteral obstruction and steinstrasse. PNL was applied to complicated kidney stones in the unsuccessful group and postoperative stone-free status was achieved. Complications classified according to Clavien and auxiliary procedures performed are shown in Table 1. The EQ of the device used in this study was 60.1%.

Discussion

Although SWL has been one of the essential treatment option for kidney stone treatment for many years, its place in the list of kidney stone treatment preferences may change due to technological developments in endoscopic devices (6,7). SWL is a non-invasive treatment option with lower complication rates compared to other treatment modalities of kidney stones, but it has lower success rates (2). Hence, the predicted factors for the SWL result should be defined and the proper treatment option should be chosen for patients with upper urinary tract stones.

Habib et al. (8) analyzed the association between stone size and treatment success and reported that the rate of success was 80% for stone diameter <13.5 mm, while this rate reduced to 52.3% for >13.5 mm. In a study where 2.954 cases were analyzed, Abdel-Khalek et al. (9) reported 89.7% stone-freeness for kidney stones of 15 mm and below, while this rate reduced to 78% in stones above 15 mm. Kanao et al. (10) developed

Table 1. Demographic data and treatment outcomes				
	Success	**Failure**	**Total**	**p-value**
Gender				
Male	59 (69%)	27 (31%)	86 (69%)	p=0.632
Female	31 (82%)	7 (18%)	38 (31%)	
Age	43.7±13.3	48.7±15.6	45.1±14.1	p=0.079
Body mass index, (kg/m²)	26.4±4.0	26.5±4.2	26.4±4.0	p=0.557
Side				
Right	51 (80%)	13 (20%)	84 (68%)	p=0.119
Left	39 (65%)	21 (35%)	60 (32%)	
Stone-localization				
Lower calyx	29 (66%)	15 (34%)	44 (36%)	p=0.225
Middle calyx	14 (70%)	6 (30%)	20 (16%)	
Upper calyx	15 (75%)	5 (25%)	20 (16%)	
The renal pelvis	32 (80%)	8 (20%)	40 (32%)	
Stone size (mm)	11.3±3.6	14.7±4.9	12.2±4.3	p=0.0001
Stone burden (mm²)	102.9±65.6	205±131.7	130.9±99.3	p=0.0001
Stone density (HU)*	682.9±254.4	890.6±310.4	739.9±285.2	p=0.0001
Skin to stone distance (mm)	90.6±22.0	91.8±22.8	90.9±22.1	p=0.778
Perirenal tissue density (HU)	-101.7±16.3	-101.6±41	-101.7±25.4	p=0.985
Subcutaneous tissue density (HU)	-104.3±11.2	-106±14.6	-104.7±12.2	p=0.488
Infundibulopelvic angle (°)	43.8±8.4	42.8±8.3	43.5±8.4	p=0.549
Composition				
Calcium oxalate monohydrate (COM)	5 (50%)	5 (50%)	10 (8%)	p=0.019
Calcium oxalate dihydrate (COD)	5 (71%)	2 (29%)	7 (6%)	
COM+COD	59 (79%)	17 (23%)	76 (61%)	
Uric acid	14 (82%)	3 (18%)	17 (14%)	
Struvite	1 (100%)	0 (0%)	1 (1%)	
Brushite	2 (67%)	1 (33%)	3 (2%)	
Cystine	0 (0%)	4 (100%)	4 (3%)	
Carbonate apatite	5 (83%)	1 (17%)	6 (5%)	
Complication (Clavien classification)				
Grade 2				-
UTI*	1 (50%)	1 (50%)	2 (1.6%)	
Grade 3				
UP* obstruction	0 (0%)	2 (100%)	2 (1.6%)	
Steinstrasse	7 (70%)	3 (30%)	10 (8%)	
Auxiliary procedures				
DJ* stent placement	1 (100%)	0 (0%)	1 (0.8%)	-
URS*	7 (70%)	3 (30%)	10 (8%)	
PNL*	0 (0%)	2 (100%)	2 (1.6%)	
Count of session				
1	52 (85%)	9 (15%)	61 (49%)	p=0.001
Multiple	38 (60%)	25 (40%)	63 (51%)	

*: Hounsfield unit, ± mean and standard deviation, UTI: Urinary tract enfection, UP: Ureteropelvic, DJ: Double J, URS: Ureterorenoscopy, PNL: Percutaneous nephrolithotomy

Table 2. Determined cut-off values for stone size, burden and density					
	AUC*	Sensitivity	Specifity	Cut-off	p
Stone size	0.718	64.75%	67.8%	12.95 mm	0.0006
Stone burden	0.786	70.6%	72.2%	121.38 mm^2	0.004
Stone density	0.706	70.6%	60%	739 HU	0.001
AUC: Area under curve, HU: Hounsfield unit					

a nomogram to predict SWL success and reported that stone size, the location of the stone, and the number of stones were the factors affectingthe success rates. Azal Neto et al. (11) published a prospective study investigating the relationship between stone size and SWL success involving 1.902 patients. They reported that the success of treatment decreases for any localization of the kidney in stones larger than 15 mm. In the lower pole, they found that the success of the treatment decreased in stones larger than 10 mm. In this study, similar to the literature, we determined that SWL treatment success reduced with increasing stone size. In the study, the cut-off value determined for stone size was calculated as 12.95 mm (sensitivity=70.6%, specificity=72.2%).

Soliman et al. (12) investigated the results of lower pole kidney stone treatment of different treatment modalities in a prospective study. They reported that the success rate of SWL in lower pole kidney stones was lower. ElSheemy et al. (13) showed in their study that mini-PNL operation is a more effective treatment than SWL for stones of 10-25 mm in the lower calyx of the kidney. Kupeli et al. (14) reported that the stone-free rate was 53.3% in 165 patients who underwent SWL to the lower calyx stones. In our study, although the treatment rate in lower calyceal stones was lower compared to other localizations, statistically significant results could not be obtained due to the small number of patients.

In the study by Obek et al. (15), the SWL success in the isolated lower calyx, middle calyx and upper calyx were analyzed and the success rate was determined to be 63%, 73%, and 71%, respectively. We observed that the success rates of patients with a stone burden more than 2 cm^2 reduced further to 49%, 53%, and 60%, respectively. In the study, Obek et al. (15) concluded that SWL treatment should be the basic treatment option in stones, with a stone burden less than 200 mm^2, independent of localization. Torricelli et al. (3), in a prospective study of 125 patients, determined that stone burden was an important factor for the success of SWL treatment, regardless of localization. Similarly, in this study, it was observed that the stone burden was an essential factor in SWL success and treatment success decreased as the stone burden increased. The cut-off value for stone burden was calculated as 121.38 mm^2 (sensitivity=70.6%, specificity=72.2%).

In the study by El-Nahas et al. (16), where 120 kidney stones were analyzed, the mean BMI of the patients was measured as 28.6±5.3 kg/m^2. It was determined that BMI was a factor influencing the stone fragmentation success and was suggested that alternative treatments should be applied in obese patients (16). In this study, the mean BMI value of the patients was measured as 29.8±4.2 and there was no statistically significant difference between the BMI and the stone fragmentation success. At this point, we have a limitation that should be considered. SWL treatment wasn't applied to the patients weighing more than 130 kg due to technical limitations of our SWL device.

There is contradictory data in the literature concerning the association between IA and SWL success. In the study by Talas et al. (17) on 198 patients, the IA was reported to be one of the essential factors for the passage of residual stone fragments after SWL in lower calyx kidney stones. In the prospective study by Toricelli et al. (3) on 120 patients, it was revealed that the IA did not have a significant relationship with the success of treatment in the lower calyx stones. Similarly, our results yielded that the IA did not affect SWL success.

In a study on 30 patients, Joseph et al. (18) analyzed the association between NCCT attenuation value and stone fragmentation and determined that the SWL success of stones >1000 HU decreased. In the study by Nakasato et al. (19), it was found that the treatment success of stones with >815 HU decreased. Similarly, in our study, it was reported that treatment success decreased as stone density increased. The cut-off value for stone density was determined as 739 HU (sensitivity=70.6% specificity=60%). Although stone density was determined to be an essential factor that predicted SWL success in various studies, the cut-off values were reported in a wide range. One of the most significant reasons for this situation may be that the stone density measurement methods differ. There is no consensus for the stone density calculation. We calculated the stone density from the longest section of the stone that may have affected our results. Studies have shown that ultraslow and full-power SWL are more effective in the shock wave treatment of urinary tract stones with high stone density (20,21). However, the potential negative impact of this approach on the parenchyma and its associated device-dependent factors, such as generator type and focal area size, should not be ignored.

The association between stone composition and stone fragmentation was firstly defined by Dretler in 1988 (22). In some studies, it was determined that the type of stone could

be defined according to the heterogeneity of the stone in NCCT images and the success of SWL could be predicted according to the stone heterogeneity (23,24). Higher energy levels and more sessions were required during SWL treatment in chemically resistant stones. While the fragility of calcium oxalate monohydrate (COM) and cystine stones was low, the fragility of calcium oxalate dihydrate, struvite, and uric acid stones was high (25). In this study, it was concluded that the stone composition was an essential factor affecting the success of treatment. The treatment success of the study was lower in cystine and COM stones.

There are different results in the literature concerning the effect of SSD on SWL success. In the study by Abdelhamid et al. (26), it was determined that treatment success decreased as SSD increased. In the study by Lee et al. (27), it was observed that a factor determining the treatment success was SSD and that the area of the perirenal and pararenal fat tissue and the abdominal circumference was not influential on the treatment success. In the study by Nakasato et al. (19), no significant result was observed between SSD and treatment success. Although El-Nahas et al. (16) determined that obesity was a factor that decreased the success of treatment, SSD was not a factor effecting for treatment success. In our study, the mean BMI value of the patients was measured as 29.8±4.2 and there was no statistically significant difference between the BMI and the stone fragmentation success and between SSD and treatment success. Besides, PTD was also not an effective factor in terms of the success of treatment. To define the effectiveness of SSD in predicting SWL treatment success, extensive prospective studies are needed.

Study Limitations

The study had some limitations. It was a retrospective and non-randomized study. Additionally, the number of patients whose data could be totally accessed was not very high.

Conclusion

In the study, it was determined that stone size, stone burden, and stone density were the essential factors in the success of SWL and the type of stone is an essential marker determining SWL activity. By defining these parameters before treatment, SWL treatment success can become more predictable. Hence, SWL can be recommended for suitable patients as an alternative to the minimally invasive surgery options that have developed recently.

Ethics

Ethics Committee Approval: This study was approved by Baskent University Institutional Review Board (project no: KA16/227) and supported by Baskent University Research Fund.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.V.K., M.R.G., C.Ö., F.K., Concept: M.V.K., M.R.G., C.Ö., F.K., Design: M.V.K., M.R.G., C.Ö., F.K., Data Collection or Processing: M.V.K., M.R.G., C.Ö., F.K., Analysis or Interpretation: M.V.K., M.R.G., C.Ö., F.K., Literature Search: M.V.K., M.R.G., C.Ö., F.K., Writing: M.V.K., M.R.G., C.Ö., F.K.

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

Financial Disclosure: The authors declare that they have no relevant financial.

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CASE REPORT
Pediatric Urology

Doi: 10.4274/jus.galenos.2022.2022.0015
J Urol Surg, 2023;10(1):74-76

A Young Boy with Renal Agenesis and Ectopic Seminal Vesicle: Zinner Syndrome

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Abstract

Zinner syndrome is a rare disorder, and it is associated with unilateral renal agenesis, ipsilateral ejaculatory duct atresia (obstruction), and cystic dilatation of the ipsilateral seminal vesicle. Here, we present an eighteen-year-old male with Zinner syndrome who presented to a urology clinic with perineal/pelvic pain and dysuria. We also emphasize the computed tomography and magnetic resonance imaging findings of Zinner syndrome.

Keywords: Imaging, congenital malformations, renal agenesis

Introduction

Zinner syndrome is a rare disease that is seen in males. It occurs due to a developmental abnormality of the distal part of the Wolffian duct. Zinner first described the Zinner syndrome in 1914 as unilateral renal agenesis, ipsilateral ejaculatory duct obstruction, and ipsilateral seminal vesicle cyst (1-3). It is also accepted as the male equivalent of Müllerian agenesis (Mayer-Rokitansky syndrome) seen in females. Zinner syndrome is associated with unilateral renal agenesis, ipsilateral ejaculatory duct atresia (obstruction), and cystic dilatation of the ipsilateral seminal vesicle (3). The pathogenesis of Zinner syndrome is related to the mesonephric (Wolffian) duct (4). The mesonephric (Wolffian) duct develops into the prostatic part of the urethra, ductus deferens, seminal vesicle, and epididymis owing to testosterone and anti-mullerian hormone (5). An abnormality of development of the distal part of the Wolffian duct can because by atresia (obstruction) of the ejaculatory duct, leading to the dilatation and cysts of the ipsilateral seminal vesicle. Furthermore, the concurrent ureteral budding abnormalities can lead to renal agenesis or dysplasia. These developmental pathologies can result in azoospermia and oligospermia, which cause primer infertility in males (3-5). Also, seminal vesicle cysts and cystic dilatation of the ipsilateral seminal vesicle can have mass effects and pelvic perineal pain (4,5). Diagnosis of Zinner syndrome can be made by ultrasonography or computed tomography (CT) scan; but magnetic resonance imaging (MRI) gives a better resolution of the local anatomy. Treatment is usually conservative, but surgery may be required in selected cases.

Case Report

An eighteen-year-old boy presented to the urologic clinic with pelvic pain and dysuria. Physical examination and laboratory test results, including complete biochemical profile, C-reactive protein, blood count, and urinalysis results, were within normal limits. A urine specimen for culture was obtained. An abdominal ultrasound showed right renal agenesis and a 31x40x52 mm heterogeneous cystic lesion in the right lower quadrant. Unenhanced abdominal CT showed the right renal agenesis and ipsilateral pelvic lesion with well-defined borders (Figure 1). The following pelvic MRI revealed that the ipsilateral pelvic lesion was a cyst with proteinaceous/hemorrhagic content and was compatible with an ectopic and dilated right seminal vesicle (Figure 2). Zinner syndrome should be considered first in the differential diagnosis, characterized by unilateral renal agenesis, ipsilateral ejaculatory duct atresia (obstruction), and cystic

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Received: 08.02.2022 **Accepted:** 07.05.2022

Cite this article as: Yitik AY, Ufuk F, Çelen S. A Young Boy with Renal Agenesis and Ectopic Seminal Vesicle: Zinner Syndrome. J Urol Surg, 2023;10(1):74-76.

dilatation of the ipsilateral seminal vesicle (1). After diagnosis, sperm analysis results were within normal limits, except for mild hematospermia. Laparoscopic surgical resection of the right seminal vesicle was performed due to hematospermia and clinical symptoms in this case. The patient was discharged without complications on the second day after the operation. The one-year follow-up of the patient was uneventful and her clinical complaints wholly regressed. Informed consent was obtained from the patient.

Discussion

Zinner syndrome is an uncommon anomaly, and its frequency is not known precisely. According to a study on ultrasonography, the incidence of seminal vesicle cysts in patients with ipsilateral renal dysplasia or aplasia (agenesis) is 0.0046% (6). The first-line examination of the assessment of Wolffian duct anomaly is the ultrasound owing to its non-invasive, radiation-free, and easily applicable nature. On ultrasound, seminal cysts are seen as a cystic pelvic mass that can demonstrate thick or irregular wall and mural calcifications. The internal echoes depend on hemorrhage or infection (1,3). Excretory urography and kidney scintigraphy can indicate ipsilateral kidney agenesis or dysgenesis. Pelvic MRI is an appropriate tool for the detailed examination of pelvic anomalies. It is a gold standard modality for evaluating pelvic abnormalities due to magnificent soft-tissue resolution and multiplanar visualization without radiation. When an absence of urogenital structures is detected on imaging, it should be cautiously examined for possible other Wolffian duct anomalies such as renal agenesis and seminal vesicle cyst (3). While figuring out the etiology of abdominal pain caused by the pressure effects of the seminal vesicle cyst over the adjacent structures, the Zinner syndrome can be diagnosed as in this study (4,5). However, the patients can admit primering infertility caused by azoospermia and oligospermia (6).

Cystic lesions of the seminal vesicle may imitate other pelvic lesions. That's why an accurate diagnosis is required. The differentiation of the cystic pelvic lesions is mainly based on the position as median, paramedian, or lateral (2). Also, abdominal pain causes, such as acute appendicitis, should be excluded. Ultrasonography or CT should be used for differential diagnosis if needed (5,6). Early diagnosis is principal to prevent complications such as infertility in patients with Zinner syndrome and

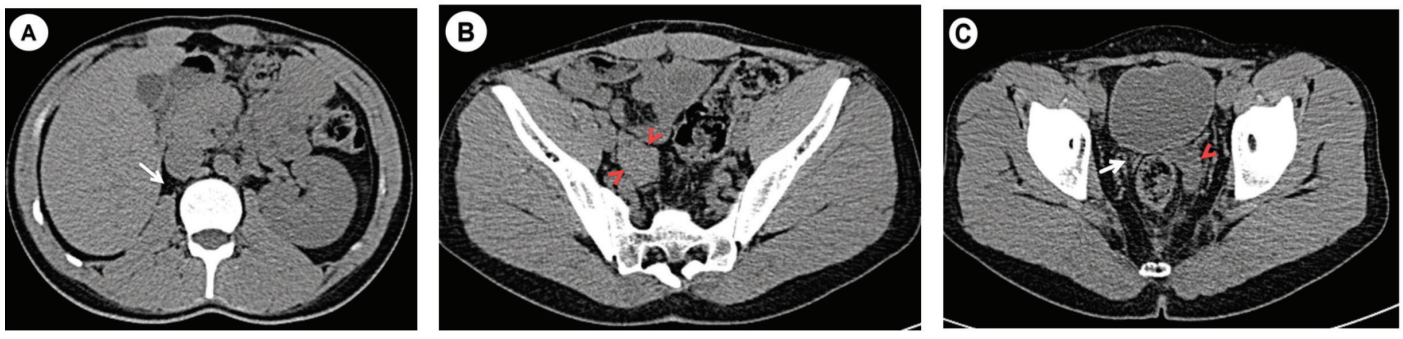

Figure 1. a) Axial unenhanced computed tomography (CT) image at the level of the upper abdomen shows right renal agenesis (arrow). **b)** Axial CT image at the level of the lower abdomen shows well-defined pelvic lesion (arrowheads). **c)** Axial CT image at the level of prostate demonstrates the normal left seminal vesicle (arrowhead) and the absence of the right seminal vesicle (arrow)

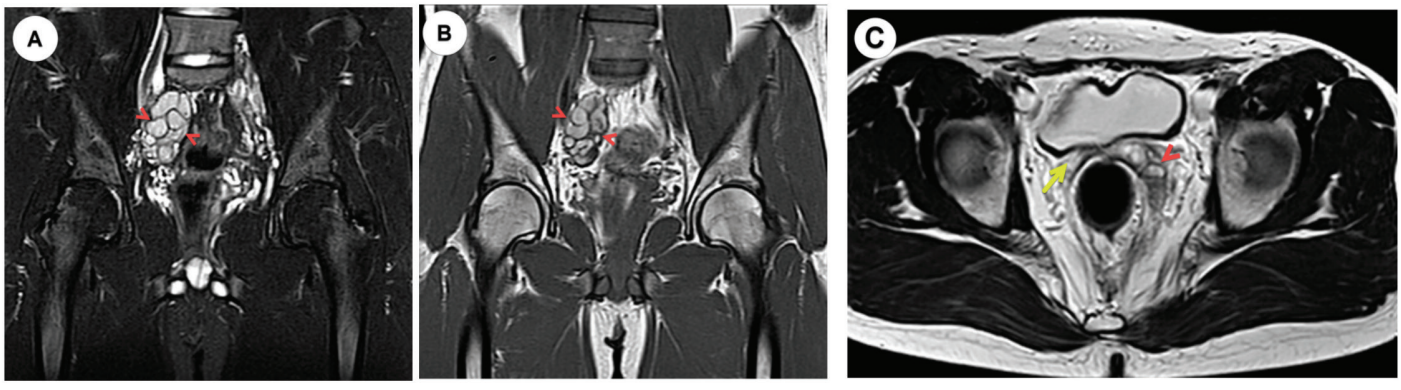

Figure 2. a) T2-weighted and **b)** T1-weighted coronal magnetic resonance (MR) images of the pelvis show the hyperintense pelvic lesion on both sequences is consistent with a proteinaceous/hemorrhagic cyst (arrowheads). **c)** T1-weighted axial MR image at the level of prostate demonstrates the normal left seminal vesicle (arrowhead) and the absence of the right seminal vesicle (arrow). The right pelvic mass is consistent with ectopic and a dilated right seminal vesicle, according to pelvic MR imaging findings

avoid nephrotoxic drugs. surgical excision may be considered depending on the size and location of the seminal vesicle cysts and clinical symptoms. Treatment is often conservative if the patient is asymptomatic (1,5). Moreover, since renal agenesis will occur in a patient with Zinner syndrome, a single kidney should be protected by measures such as avoiding nephrotoxic drugs and nephrotoxic contrast agents.

Conclusion

In conclusion, Zinner syndrome is an unusual anomaly, which includes unilateral kidney agenesis, ipsilateral ejaculatory duct obstruction, and seminal vesicle cyst. Moreover, seminal vesicle ectopia and cystic dilatation may also be seen in patients with Zinner syndrome, as in this case. Zinner syndrome should be kept in mind in the differential diagnosis of young patients with abdominal pain, infertility, and urinary symptoms.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ç., Concept: A.Y.Y., F.U., Design: A.Y.Y., F.U., Data Collection or Processing: A.Y.Y., F.U., S.Ç., Analysis or Interpretation: F.U., Literature Search: A.Y.Y., F.U., Writing: A.Y.Y., F.U.

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

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

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CASE REPORT
Pathology

Doi: 10.4274/jus.galenos.2022.2022.0023
J Urol Surg, 2023;10(1):77-81

Male Urethral Clear Cell Adenocarcinoma: Case Presentation and Literature Review of a Rare Cancer

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Abstract

Primary urethral carcinomas account for less than one percent of all genitourinary cancers. Primary clear cell adenocarcinoma of the urethra (CCAU) is an extremely rare and aggressive tumor which predominantly presents in adult women but has rarely been documented in males. Diagnosis of CCAU is difficult as its clinical presentation shows significant overlap with various other conditions and carcinomas. Controversies remain regarding the histogenesis of CCAU. The histological diagnosis can be challenging and there are no definitive treatment guidelines. English literature to date only describes 17 previous cases of CCAU in males. Here we present an 18th case in a 29-year-old man.

Keywords: Clear cell adenocarcinoma, urethral cancer, nephrogenic metaplasia

Introduction

Urethral malignancies are rare, compromising less than one percent of all genitourinary cancers (1). Clear cell adenocarcinoma of the urethra (CCAU) is the least common subtype, which is an aggressive tumor with a poor five-year survival rate and a strong female predominance (2). Diagnosis of CCAU is difficult as it often clinically presents similar to various other conditions and carcinomas (2). One previous case series of CCAU raised the possibility of association with diverticula, documenting their presence in 12 of 18 cases (3). The histopathological origin of CCAU is poorly understood and many possible theories have been postulated, including origins from mesonephric (4), Müllerian duct (5) or pre-existing areas of nephrogenic metaplasia (6). As the pathophysiology of CCAU is not fully understood there has been no definitive treatment guideline. The literature to date only describes 17 previous cases of CCAU in males. Here we present an 18th case in a 29-year-old man.

Case Report

A 29-year-old male presented with several weeks of macroscopic hematuria and perineal pain. Urine microscopy showed sterile pyuria and the cytology was atypical flexible cystoscopy revealed multiple papillary lesions in his urethra and a normal bladder. Subsequently, rigid cystoscopy, biopsy and diathermy of the urethral tumors were performed. Histopathological assessment demonstrated a clear cell adenocarcinoma, with superficial invasion of the lamina propria. The tumor had a tubulopapillary architecture and comprised large pleomorphic cells with hobnail cytology, eosinophilic cytoplasm, and areas of cytoplasmic clearing (Figure 1). A panel of immunohistochemical (IHC) stains was performed, with the tumour cells showing diffuse strong positive staining for PAX8, CK7, and p53, with MIB1 (Ki-67) staining 75% of tumour nuclei. There was no significant staining within the tumour cells for CK20 or GATA3. The morphology and IHC staining pattern were in keeping with a diagnosis of CCAU.

Magnetic resonance imaging (MRI) showed no significant invasive lesions in the urethra and staging computed tomography (CT) demonstrated no metastatic disease. The patient declined a cystoprostourethectomy and after a multi-disciplinary discussion, underwent a urethrectomy, apical prostatectomy and suprapubic catheter insertion. Despite the MRI findings, histopathology of the excision specimen did show the CCAU invaded the lamina propria of the urethra. No muscularis propria invasion was identified.

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Received: 07.03.2022 **Accepted:** 30.05.2022

Cite this article as: Razi B, Kam J, Maclean F, Gurney H, Arianayagam M. Male Urethral Clear Cell Adenocarcinoma: Case Presentation and Literature Review of a Rare Cancer. J Urol Surg, 2023;10(1):77-81.

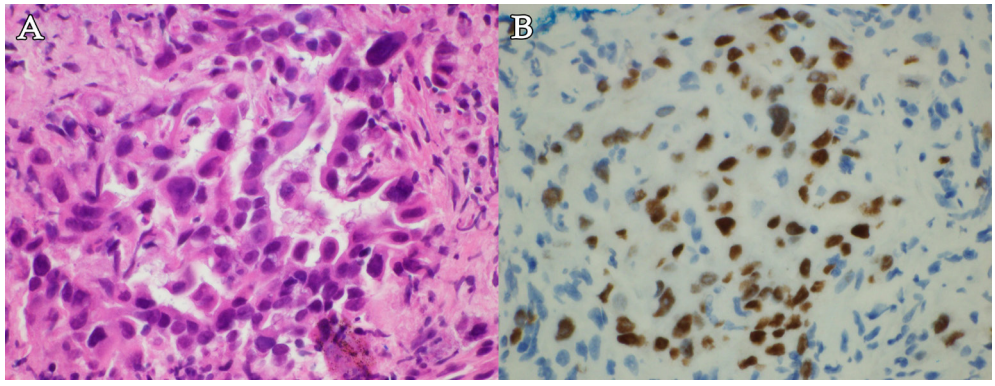

Figure 1. Clear cell adenocarcinoma of the urethra showing hobnailed cells in a tubulopapillary arrangement (A, Haematoxylin and eosin, 600x magnification), showing positivity for PAX8 (B, 600x magnification)

The patient was subsequently placed on a surveillance program, which comprised six-monthly cystoscopy and CT scans. Two and half years later, he was diagnosed with dyspnea. A CT at that time demonstrated mediastinal lymphadenopathy, pericardial and pleural effusions, and abnormal interstitial markings suggestive of diffuse lymphangitic disease within the lungs. Cytology and IHC of the pericardial fluid demonstrated metastatic clear cell adenocarcinoma.

He received four cycles of gemcitabine and cisplatin chemotherapy with complete radiological remission. Twenty months after chemotherapy, he developed metastatic disease to his left adrenal gland and pembrolizumab was started. There was no response and disease progression was shown on positron emission tomography-CT in the adrenal with new metastases in the para-aortic lymph nodes and liver. He was enrolled in a clinical trial and completed 6 cycles of enfortumab vedotin with further progression. Further gemcitabine and cisplatin treatment was associated with a significant radiological response, but isolated relapse occurred in the paraaortic nodes eight months later, treated with radiotherapy. Fifteen months further recurrence occurred in the kidney and liver that again responded platinum-based chemotherapy. Next-generation sequencing of the primary urethral tumour DNA revealed a mutation in SMARCB1 (p.T9Dfs*61NM_001007468.1 c.23dup, reflected by lack of staining for INI-1/SMARCB1 IHC). After further progression, he was started on tazemetostat, an inhibitor of enhancer of zeste-homolog-2 (EZH2), without response. He is currently relatively well and active, and on platinum-based chemotherapy awaiting a suitable phase 1 trial. Written and informed consent was obtained from the patient for the publication.

Discussion

CCAU is a rare and aggressive carcinoma that predominantly affects females in 60-70 s (2). As with our case, CCAU typically present like a urothelial carcinoma with non-specific irritative or obstructive urinary symptoms including hematuria, frequency and dysuria. Histopathological features characteristic of CCAU include hobnail cells, clear cytoplasm and pleomorphic nuclei and mitotic figures (2,3,7). CCAU tumour cells exhibit a classic triad of tubulocystic, papillary and diffuse growth patterns, in variable proportions (2). The mainstay treatment for CCAU is surgical resection and in cases with pelvic lymph node involvement, radiotherapy may be of benefit, however there is a paucity of the literature surrounding the effectiveness of chemotherapy.

The histogenesis of CCAU is unclear, it was first described in 1973 by Konnak (4), who used the term "mesonephric carcinoma" postulating a mesonephric origin. However, most authors have suggested that CCAU most likely arises from a Müllerian (paramesonephric) origin (5,8,9) or areas of nephrogenic metaplasia, due to the morphologic and IHC overlap with the latter (6,10). Nephrogenic metaplasia/adenoma is a benign condition which is believed to arise in areas of chronic irritation or infection, and is most commonly seen in adult males (2,3,11). Interestingly, in renal transplant patients, nephrogenic adenomas have been shown to originate from the tubular epithelium of the donor kidney (12). In contrast, Kawano et al. (13), hypothesized that CCAU in females is an entirely separate entity, arising from the para-urethral ducts. Additionally, there appears to be an association between CCAU and urethral diverticulum, with possibly up to 56% of cases in females presenting in such a manner (3).

The relationship between nephrogenic metaplasia and clear cell adenocarcinoma remains controversial. Generally, nephrogenic metaplasia is usually thought of as benign though some evidence exists for its malignant potential (11). For example, Hartmann et al. (10), presented molecular evidence of the progression of nephrogenic metaplasia to clear cell adenocarcinoma in the urinary bladder. To date, in English literature, there have only been 17 reported cases of urethral clear cell adenocarcinoma in males (Table 1) with no clear demonstrable relationship

Table 1. Summary of Urethral clear cell adenocarcinoma in male patients

Reference	Age	Symptoms	Immunohistochemistry/ Special stains	Postulated origin	Therapy	Relapse	Metastases	Survival
Cantrell et al. (8)	68	Painless haematuria	Positive: PAS	Mesonephric or Mullerian	Pelvis lymphadenectomy + Radiation	20 months	Thoracic vertebrae, pulmonary hilar adenopathy	2.6 years
Ingram and DePauw (19)	38	Recurrent urethral stricture	NR	Nephrogenic metaplasia	Surgery	Nil	Nil	Alive, 5 years post-surgery
Oliva and Young (3)	46	Urinary retention	NR	NR	Biopsy + radiation	NR	NR	NR
Seseke et al. (6)	57	Urinary retention	Positive: PAS	Nephrogenic metaplasia	Total urethrectomy	10 months	Pulmonary	2.5 years
Gögus et al. (15)	44	Urinary retention	Negative: PSA	NR	Radical cystoprostatectomy and urethrectomy + chemotherapy	5 months	Para-aortic lymphadenopathy	10 months
Varachhia et al. (20)	68	Periurethral abscess	NR	NR	Drainage/debridement of abscess only	NR	Nil	2 months
Liu et al. (18)	37	Urinary hesitancy	Positive: CK7, CAM 5.2 Negative: CK20, AFP, CDX-2, PSA	NR	Surgery + palliative chemotherapy	15 months	Iliac, inguinal, supraclavicular, mediastinal, and hilar lymphadenopathy, pulmonary	2.4 years
Gandhi et al. (16)	55	Recurrent urinary tract infections	Positive: PSA, PSAP, CA125 Negative: p63, CK20	Paraurethral	Radical cysto-prostatourethrectomy + chemotherapy	NR	NR	NR
Sugimura et al. (21)	56	Haematuria	Positive: CK7, PAX-8, CK20, CK-HMW Negative: p63, PSA	NR	Radical cystectomy	NR	NR	Alive, 5 months post-surgery
Lin et al. (22)	31		Positive: PAX-8 Negative: TTF-1	Oncogenic (PI3K/ AKT/mTOR)	Radical cystectomy and urethrectomy	28 months	Lung	NR
Grosser et al. (17)	29	NR	Positive: PAX-8	NR	Urethrectomy + chemotherapy	NR	Mediastinal lymphadenopathy, lung and adrenal	Alive, 3 years post-surgery
Grosser et al. (17)	45	NR	Positive: PAX-8	NR	Transurethral resection + radiotherapy (for recurrence)	NR	NR	NR
Grosser et al. (17)	47	NR	Positive: PAX-8	NR	Cystoprostatectomy and lymph node dissection, sigmoid colon and rectum resection	NR	Extension to bladder and rectum	10 months
Grosser et al. (17)	36	NR	Positive: PAX-8	NR	Planned surgery	NR	Nil	Lost to follow-up
Our case	29	Haematuria	Positive: PAX8, CK7, and p53, with MIB1 75% Negative: CK20, GATA3, INI1/SMARCB1	Nephrogenic metaplasia	Urethrectomy, apical prostatectomy, SPC + chemotherapy + immunotherapy	18 months	Mediastinal, para-aortic and coeliac lymphadenopathy, adrenal, liver	Alive, 7 years post-surgery

NR: Not reported [3 further male cases were not included as no details were provided (23)]

to nephrogenic metaplasia. Here we present an interesting case of a male patient with evidence of both CCAU and nephrogenic metaplasia, which unfortunately progressed to distant metastasis. Furthermore, our case is the only one in the literature in which demonstrates a mutation in SMARCB1 and loss of INI1. Mehra et al. (14), demonstrated a dysregulation in different genetic/molecular pathways (ATM, ARID2). Whether nephrogenic metaplasia exists concurrently with CCAU or serves as a precursor to CCAU requires further study.

Despite the limited number of reported cases of CCAU in males, the prognosis is poor. Of the 17 previously reported cases, only three reported long-term survival past three years. Most of these cases presented with either irritative or obstructive symptoms and were treated with surgery and radiotherapy or chemotherapy. Seven patients progressed to distant metastases despite therapy. Only four patients received cisplatin-based chemotherapy; however three patients succumbed to progressive disease (15-18). In this study, the patient's tumor seemed extremely sensitive to platinum-based chemotherapy but resistant to anti-PD-1 immunotherapy and a novel EZH2 inhibitor. This case report demonstrates to our knowledge the 18th case of CCAU in a male patient who appears responsive to cisplatin-gemcitabine chemotherapy, partially responsive to immunotherapy, and is also the longest surviving CCAU patient in the literature.

Conclusion

Our case contributes to the current limited literature that shows that CCAU is an aggressive cancer and often presents with lower urinary tract symptoms. These patients should be closely monitored with regular surveillance for the development of local and distant metastases and managed with a multi-disciplinary input. Further studies are required to identify its relationship to nephrogenic metaplasia, which may reveal more robust treatment options.

Ethics

Informed Consent: Written and informed consent was obtained from the patient for the publication.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: J.K., F.M., H.G., M.A., Concept: B.R., J.K., F.M., H.G., M.A., Design: B.R., J.K., F.M., H.G., M.A., Data Collection or Processing: B.R., J.K., F.M., H.G., M.A., Analysis or Interpretation: B.R., J.K., F.M., H.G., M.A., Literature Search: B.R., J.K., F.M., Writing: B.R., J.K., F.M., H.G., M.A.

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

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

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CASE REPORT
Reconstructive

Doi: 10.4274/jus.galenos.2022.2022.0021
J Urol Surg, 2023;10(1):82-84

Ventral and One-sided Dorsolateral Onlay Buccal Mucosa Graft Urethroplasty for Simultaneous Penile and Bulbar Urethral Stricture: A Case Report and Review of Literature

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Abstract

Buccal mucosa graft (BMG) urethroplasty is one of the most commonly used augmentation techniques in urethral stricture. In this case report, we present a patient who had urethral strictures in 2 different localizations; 1 cm in the proximal penile urethra and 3 cm in the mid-bulbar urethra. We applied two different BMG techniques as one-sided dorsolateral onlay and ventral onlay. Our case report indicates that according to stricture nature, different BMG techniques can be performed safely in simultaneous urethral strictures. In this case report, we presented the techniques and reviewed the literature.

Keywords: Buccal mucosa graft, ventral onlay, dorsolateral onlay, simultaneous urethral stricture

Introduction

Today, the incidence of urethral stricture has grown with the increase in retrograde endoscopic procedures (1). The anterior urethra is the most frequently affected part in urethral strictures (2). Simultaneous urethral strictures with different localizations are rare (3). Open urethroplasty is an effective treatment option for the management of anterior urethral strictures (4). Buccal mucosa graft (BMG) urethroplasty is one of the most commonly used augmentation techniques. Ventral and one-sided dorsal onlay techniques are frequently used and offer satisfactory results (5,6). In this case report, we present a patient who underwent dorsolateral one-sided BMG urethroplasty due to mid-penile urethral stricture and then underwent ventral onlay and dorsolateral one-sided BMG urethroplasty surgery due to simultaneous proximal penile and mid-bulbar urethral stricture. Our aim was to present the techniques and review the literature.

Case Report

A seventy-two-year-old male patient with a history of one-sided dorsolateral onlay BMG urethroplasty due to mid-penile urethral stricture was admitted to our clinic with voiding symptoms. The patient, whose etiology of urethral stricture was trans-urethral resection of the prostate, had a history of 4 direct vision internal urethrotomies (DVIU) before previous urethroplasty. In the uroflowmetry of the patient, the maximum flow (Q^{max}) was 7.1 mL/s, the mean flow (Q^{mean}) was 6.5 mL/s. In the retrograde urethrography (RUG) it was observed that there was no stricture in the localization of the previous urethroplasty, but there were strictures in 2 different localizations, 1 cm in the proximal penile urethra and 3 cm in the mid-bulbar urethra as it is demonstrated in Figure 1. BMG urethroplasty was planned for the simultaneous strictures in two different localizations.

Surgical Procedure

After general anesthesia, the patient was placed in the extended lithotomy position. Retrograde endoscopic evaluation was performed on the patient with a 9.5 fr semi-rigid ureteroscope. It was observed that there was no stenosis in the localization of the previous urethroplasty. In the proximal penile urethra, a 1 cm stricture area was passed, then the mid-bulbar stricture was observed. A guide-ware stent was delivered to the bladder. Afterwards, perineal vertical incision was made. Bulbospongiosus

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Received: 01.03.2022 **Accepted:** 21.06.2022

Cite this article as: Kutluhan MA, Ünal S, Özayar A, Okulu E, Kayıgil Ö. Ventral and One-sided Dorsolateral Onlay Buccal Mucosa Graft Urethroplasty for Simultaneous Penile and Bulbar Urethral Stricture: A Case Report and Review of Literature. J Urol Surg, 2023;10(1):82-84.

muscle was identified and a midline incision was performed. The bulbar urethra was applied. Penile invagination was performed through a perineal incision. The penile urethra was dissected. A penile urethral stricture localization was detected by urethral catheter. A one - sided dorsolateral dissection was performed and a stricture was incised. Afterwards, bulbar urethral stricture localization was identified with a urethral catheter. A longitudinal ventral incision until healthy tissue encountered was performed. BMG harvested from the left inner cheek was trimmed. 1 cm graft was fixed dorsolaterally to the corpus cavernosum in penile urethral stricture localization then one edge of the opened urethral mucosa and graft was sutured with 4/0 vicryl sutures. In bulbar urethral stricture localization three-cm graft sutured to the opened urethral mucosa ventrally (Figure 2). Urethral incisions were closed on 16 fr silicon urethral catheter with interrupted sutures then corpus spongiosum was closed in bulbar urethral stricture localization. After three weeks, there was no urinary leakage in the RUG, and the urethral catheter was removed (Figure 1). Three months after surgery, Q^{max} was 15,1 mL/s and Q^{mean} was 10,2 mL/s in uroflowmetry. The patient was satisfied with regard to lower urinary tract symptoms.

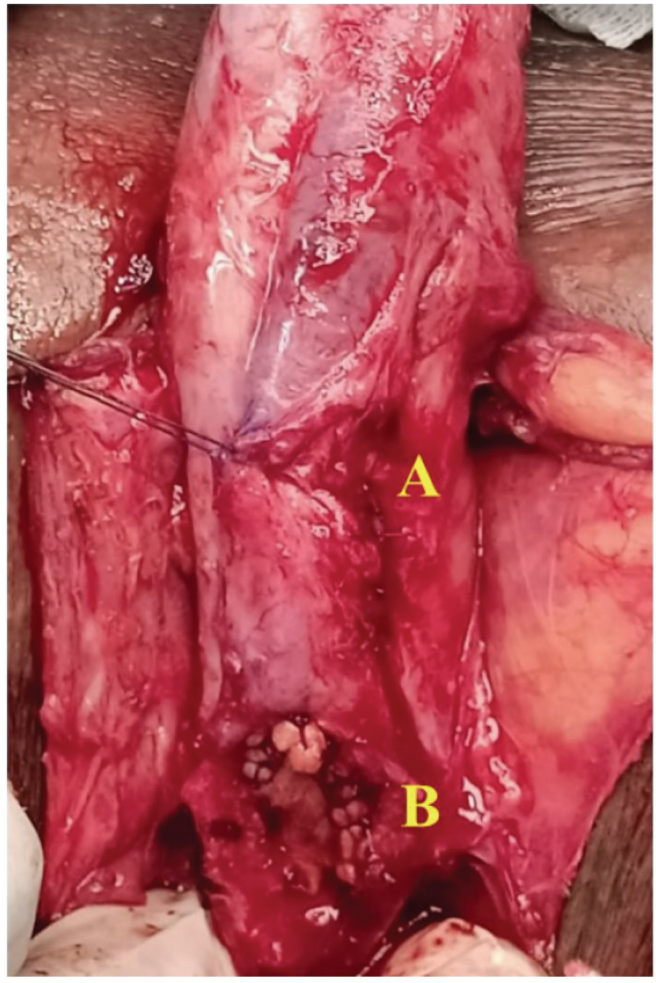

Figure 2. Intraoperative view. Penile invagination and urethral dissection was performed. **A:** One sided dorsolateral onlay BMG, urethra was closed with interrupted 4/0 vicrly sutures, **B:** Ventral onlay BMG, urethra was closed with interrupted 4/0 vicrly sutures

Discussion

DVIU has a lower success rate in complex urethral strictures than in short segment bulbar strictures (7). Therefore, BMG urethroplasty is used as an effective treatment option in complex urethral strictures. Kulkarni et al. (8) described the one-sided dorsolateral onlay graft technique for the first time. It has been shown that patient-reported outcomes of one-sided dorsolateral BMG urethroplasty are high in anterior urethral strictures (6). In another study by Zumrutbas et al. (9), it was shown that functional results were good for patients who

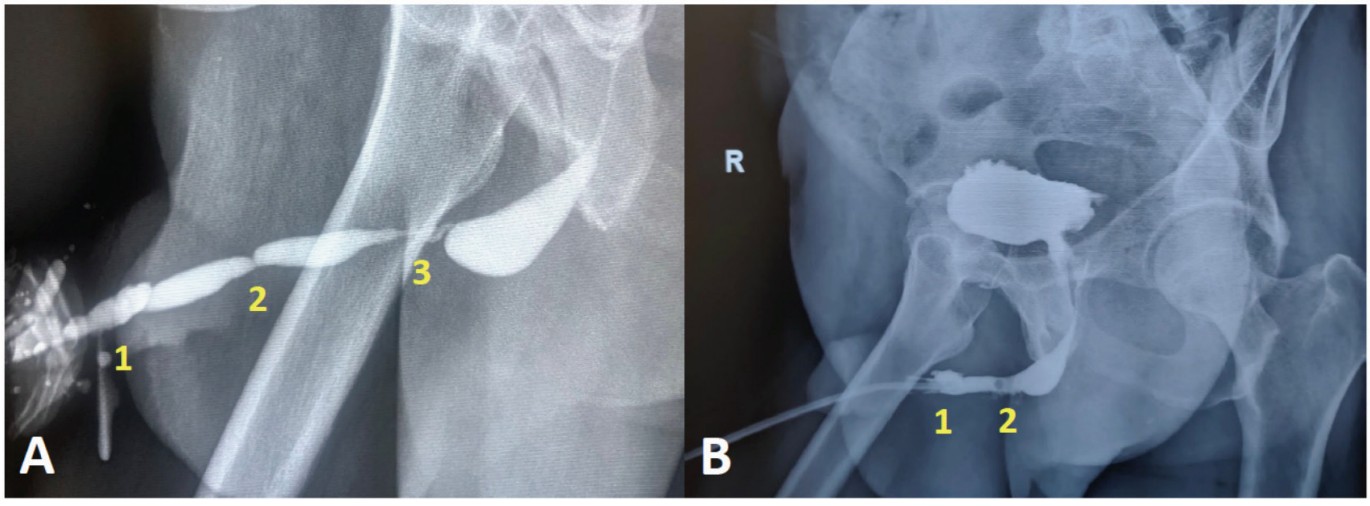

Figure 1. A; 1: Previous urethroplasty localization, **2:** 1 cm proximal penile urethral stricture, **3:** 3 cm mid-bulbar urethral stricture, **B; 1:** Postoperative proximal penile graft, **2:** Postoperative mid-bulbar graft, no urinary leakage in both side

underwent one-sided dorsolateral BMG urethroplasty due to panurethral stricture. However, ventral onlay BMG urethroplasty is a frequently preferred technique in bulbar urethral strictures Mellon and Bihrle (5) showed that ventral onlay BMG urethroplasty has good long-term functional results and low complication rates in bulbar urethral strictures. The ventral approach in the proximal bulbar urethra provides direct access to the urethral lumen and a clear visualization of the entire stricture. Also, corpus spongiosum tissue is thick in proximal bulbar urethra, which provides good blood supply to the BMG. Additionally, the ventral onlay technique is easier than the dorsal or dorsolateral onlay technique. In one-sided dorsolateral onlay technique, corpus cavernosum directly supplies BMG. Also, one-sided nervous supply of urethra is preserved. Additionally, much less bleeding occurs in contrast to the ventral approach. Dorsal approach is preferred in penile urethral strictures because the spongiosum tissue is thinner.

Simultaneous urethral strictures at different locations are relatively rare in clinical practice. In the case series in the literature, it is seen that urethral strictures usually develop in a single site either as a short or long segment. We detected proximal penile and mid-bulbar urethral strictures in a patient who had previously undergone one-sided dorsolateral onlay BMG urethroplasty due to penile urethral stricture. We applied two different BMG techniques (One sided dorsolateral and ventral onlay) to the patient. There is only one case report about simultaneous multiple strictures treated with different BMG techniques. Favorito et al. (3) reported that they applied dorsal inlay and ventral onlay BMG technique to a patient with simultaneous penile and bulbar urethral strictures. In our clinical practice, the single stage one-sided dorsolateral BMG technique is the technique we frequently prefer in penile urethral strictures, and we applied the same technique for penile urethral stricture in this patient. In the literature, the ventral onlay BMG technique has good results in the bulbar urethral stricture (5) and we preferred the ventral onlay BMG technique for bulbar urethral stricture in this patient. Augmented anastomotic urethroplasty can be performed in bulbar urethral strictures and it was shown that augmented anastomotic urethroplasty was independently associated with stricture recurrence (10). We prefer this technique for appropriate bulbar urethral strictures. But, we did not apply the non-transecting anastomosis technique in this patient because we detected that the dorsal urethral mucosa was sufficient at the stricture site of the bulbar urethra.

Conclusion

In conclusion, our case report indicates that according to stricture nature, different BMG techniques can be performed safely in simultaneous urethral strictures. One-sided dorsolateral and ventral onlay BMG techniques are simple to perform and yield good functional results. We think that this case report encourages urologists who are unfamiliar with reconstructive urethral surgery.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.K., Ö.K., Concept: E.O., Design: A.Ö., Data Collection or Processing: S.Ü., Writing: M.A.K.

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

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

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