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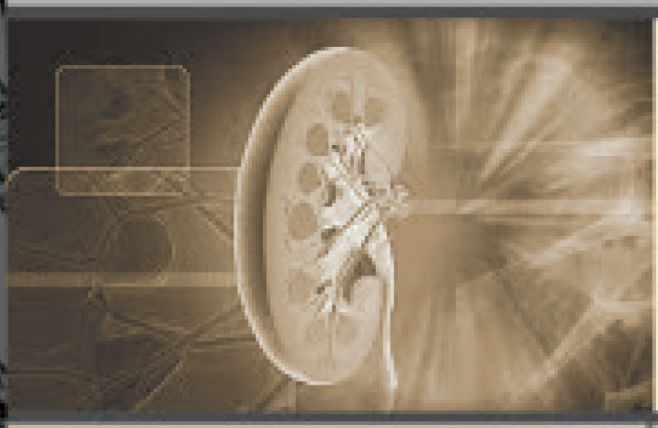

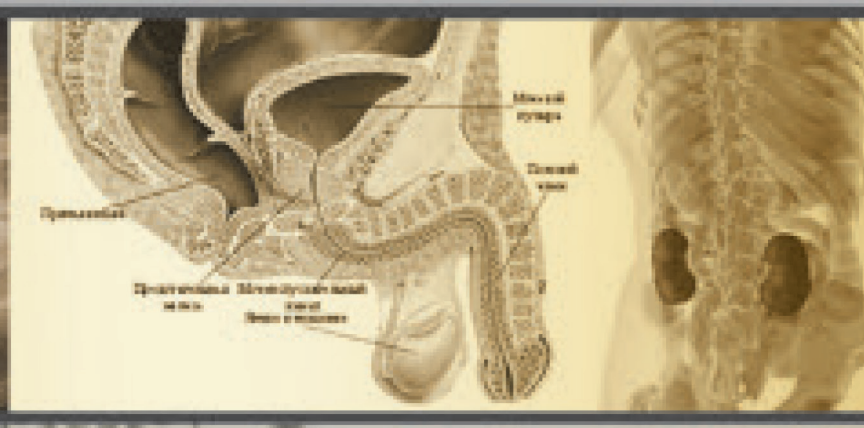

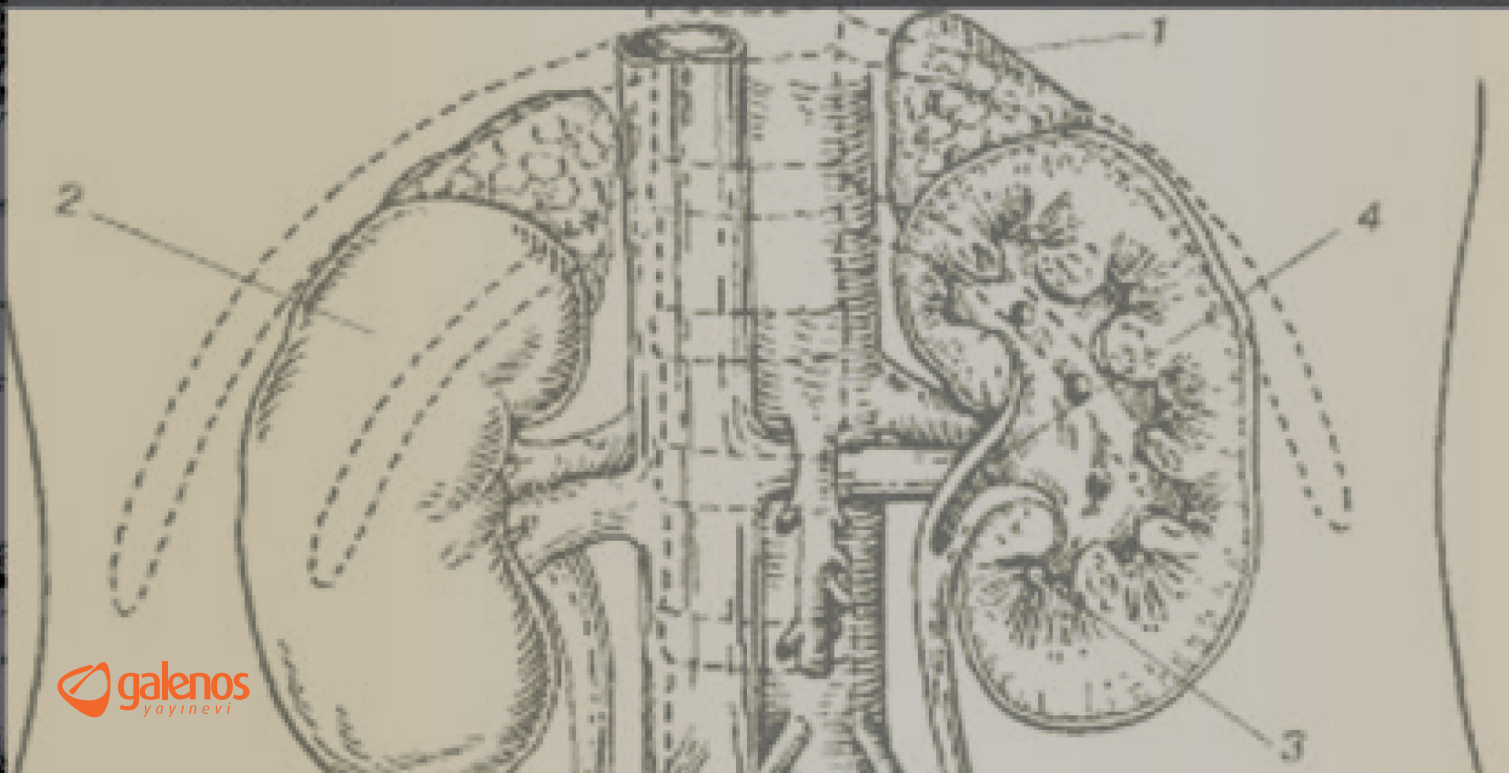

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Top 100 Articles on Artificial Intelligence in Urology

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Abstract

Artificial intelligence (AI) is rapidly increasing its importance in many fields today, including medicine and even urology. In this article, we have compiled the top 100 articles on this topic to provide insights into and guide future research for researchers. We selected the best-matched articles from 2019-2024 by typing "AI in urology" into the search bar on PubMed's website. We accepted the terms deep learning, machine learning, and neural networks. We have excluded the editorial letter and comments from the study. We reviewed 231 articles and selected the top 100 articles. We categorized the articles based on the date of printing, publication types, related sub-specialties, journal names, the quartile indexes of these journals, the number of references, and citations, the country of affiliation of the first author, and the number of centers involved. Every year, researchers are delving deeper into this topic. Currently, the majority of articles are review articles. High-quality journals are publishing studies on this topic. Researchers from America and Europe are the leading figures in this field. In AI, researchers focus the most on uro-oncology, which is the subspecialty of urology. We anticipate a substantial increase in the use of AI in urology in the future. It is imperative to acknowledge that there are numerous disadvantages, in addition to the advantages. Numerous original articles are necessary.

Keywords: Artificial intelligence, machine learning, deep learning, neural network

Introduction

In the realm of medicine, artificial intelligence (AI) is swiftly becoming prominent, and its impact on urology is profound. Validated and optimized AI leads to a speedier, more personalized, efficient, and focused search compared with traditional methods (1). The field of AI continues to advance rapidly. The patient-doctor relationship, as well as patient outcomes, is improving (2). The ability of AI to efficiently process vast quantities of data, in combination with the shift towards electronic patient records, results in increasingly larger "big data" sets. In the future, AI will be able to analyze and detect novel diagnostic and treatment patterns (3). Current advances in computer science have already led to the study and automated optimization of multiple, highly complex non-medical processes. If applied correctly, the development of AI models can lead to more effective processing and analysis of patient-related data, as well as optimized diagnosis and therapy for urological patients (4).

AI may soon automate and standardize many facets of routine work. In the near future, the most promising approach appears to be a model that enhances pathologists with second-review or real-time AI systems (5). To make patient-specific disease predictions, AI systems have combined clinical and histologic information. AI will likely play a major role in histopathological examination (6). This is a promising approach that has several possible clinical applications, resulting in increased speed and/or quality of pathology reports (7). Machine learning (ML) algorithms, fueled by vast datasets of medical images and patient records, are adept at detecting subtle abnormalities that might escape human observation. AI algorithms are proving invaluable in the interpretation of bladder and kidney scans, enabling clinicians to pinpoint pathology swiftly and accurately. This method has effectively utilized automatic tumor detection and grading in histopathological image analysis to assess the risk of recurrence, metastasis, or survival (8). It has grown in use over the years and continues to evolve, contributing to the decision-making process for modern cancer treatment (9).

Although deep learning (DL) enables the investigation of large data sets, the implementation of AI still faces considerable obstacles, such as heterogeneous data infrastructure between different health care organizations and the need for collaboration between computer scientists and surgeons. Modalities such as cystoscopy and robotic video/image-based data have shown promise, but initial studies require additional

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research to establish more robust results and better ways to incorporate AI in an effort to improve patient outcomes (10). Most studies included a small sample of patients from a single institution, and most models did not undergo proper external validation. Further research through larger and well-designed studies is required to develop reliable AI tools (11).

In this study, we compiled research on AI in urology. We aimed to highlight AI's advantages and disadvantages, showing which areas it is most needed or lacking in urology, thereby guiding researchers in their future studies.

Materials and Methods

We entered the term "AI in urology" into PubMed's search bar, selected the "between 2019 and 2024" date range, and then sorted the articles using the "best matched" section. We accept the following terms in articles: "neural network", "DL", or "ML". We clicked on all available text and included all article types, with the exception of editorial letters and comments. After checking the articles to confirm their relevance to urology, we excluded unrelated papers. We scanned the first 231 articles on the list to identify the first 100 that met our inclusion criteria. No language restriction was applied.

On the Web of Science (WoS) websites, we verified the journals' quartile scores. We categorized the articles based on the date of printing, publication types, related sub-specialties, journal names, the quartile indexes of these journals, the number of references and citations, the country of affiliation of the first author, and the number of centers involved. We classified the articles by sub-specialties based on the European Association of Urology 2024 guidelines. The WoS website checked how many citations the articles had recently received.

This study did not seek ethical committee approval because it was a bibliometric study without any human subjects.

Limitations

We evaluated the Top 100 articles using the best-matched tab for keywords in PubMed, potentially excluding high-quality articles that did not match the relevant keywords from the list.

Results

The distribution of the top 100 articles in the study by year indicates that there were 3 articles in 2019, 13 in 2020, 16 in 2021, 19 in 2022, 28 in 2023, and 21 in 2024 up to this point (Table 1). The dominant type of article was a review study (n=59). The remainder consisted of 23 original articles, 9 research supports, 6 multicenter studies, 1 clinical study, 1 comparative study, and 1 meta-analysis (Table 2). The publications appeared in 53 different journals. It is evident that certain journals prioritize articles related to AI over others. During this period, Current Opinion in Urology holds the top rank with 15 publications about AI, followed by Urologic Clinics of North America with 9 publications, and Current Urology Reports with 6 publications (Table 3). Notably, 58% of these journals published their articles in the first quartile (Q1), 30% in the second quartile (Q2), 20% in the third quartile (Q3), and 2% in the fourth quartile (Q4) (Table 4). The average number of citations was 6.88 (range 0-58). All of the articles with 0 or 1 citation were published in 2023 or 2024. The first authors were from 28 different countries. The United States is clearly at the forefront of this ranking (n=61), followed by England (n=12), Germany (n=7), the Netherlands (n=6), Canada (n=5), and France (n=5), and these are followed by others with 1 or 2 articles (Table 5).

We found that based on their subspecialties, 53% of the articles focused on oncology. Out of these, 26 articles focused on prostate cancer (PCa), including topics such as pathology (n=6), genomics (n=3), follow-ups (n=4), radiology (n=9), education (n=2), and limitations (n=2). Additionally, 13 articles addressed bladder cancer (BCa), including diagnostic cystoscopy (n=3), cytology (n=3), histopathology (n=3), radiogenomics (n=1), lymph node metastases (n=2), and one article each on general oncology, kidney cancer (KCa), and quality of life (QoL). There were 17 articles on patient care, 10 articles on stone disease, 7 articles on endourology and robotic surgery, and 4 articles on men's health [lower urinary tract symptoms (n=1), infertility (n=2), and erectile dysfunction (n=1)]. There are 3 articles on surgical training and pediatrics, 2 articles on transplantation, and 1 article on neuro-urology and QoL (Table 6).

Table 1. Number of articles by years

	(n)
2019	3
2020	13
2021	16
2022	19
2023	28
2024	21

Table 2. Type of articles

	(n)
Review	59
Original article	23
Research support	9
Multicenter study	6
Clinical study	1
Comparative study	1
Meta-analysis	1

Table 3. The journals	
	(n)
Actas Urológicas Españolas	1
American Society of Clinical Oncology Educational Book	1
Annals of Surgical Oncology	1
Archivos Espanoles de Urologia	1
BJU International	2
BMC Cancer	1
BMC Medical Informatics and Decision Making	1
BMC Medicine	1
BMJ Open	1
Canadian Journal of Urology	1
Cancer Cytopathology	1
Cell Reports Medicine	1
Computer Methods and Programs in Biomedicine	1
Contrast Media Mol Imaging	1
Current Opinion in Urology	15
Current Urology Reports	6
Der Urologe	1
European Journal of Nuclear Medicine and Molecular Imaging	1
European Urology	2
European Urology Focus	3
European Urology Oncology	1
International Brazilian Journal of Urology	2
International Journal of Impotence Research	1
International Journal of Molecular Sciences	1
International Journal of Surgery	2
International Journal of Urology	1
International Urology and Nephrology	1
Investigative and Clinical Urology	2
JCO Clinical Cancer Informatics	1
Journal of Endourology	1
Journal of Nephrology	1
Journal of Pathology	1
Journal of Pediatric Urology	1
Journal of the National Cancer Institute	1
Journal of Translational Medicine	1
Journal of Urology	2
Lancet Digital Health	1
Lancet Oncology	1
Medicina (Lithuania)	1
Military Medical Research	1
Minerva Urology and Nephrology	3
Nature Reviews Urology	1
New England Journal of Medicine	1
PLoS One	1
Prostate	1
Prostate Cancer and Prostatic Diseases	3
Radiology	1
Urologe	2
Urologic Clinics of North America	9
Urologic Oncology	3

Table 3. Continued	
	(n)
Urologie	2
Urology Practice	1
World Journal of Urology	5

Table 4. The quartile numbers of the journals	
	(n)
Q1	58
Q2	30
Q3	10
Q4	2

Table 5. First author's country	
	(n)
USA	35
Germany	13
China	11
Italy	7
UK	5
France	5
Austria	2
Belgium	2
Canada	2
India	2
Japan	2
Korea	2
Netherlands	2
Singapore	2
Türkiye	2
Brasil	1
Greece	1
Kazakhstan	1
Russia	1
Spain	1
Taiwan	1

Table 6. Relevant subspeciality	
	n
Endourology and robotic surgery	7
Men's health	4
Neuro-urology	1
Oncology-bladder	13
Oncology-general	10
Oncology-kidney	3
Oncology-prostate	26
Oncology-quality of life	1
Patient care	17
Pediatric	3
Stone disease	10
Surgical training	3
Transplantation	2

Discussion

AI's primary application in urology is in the field of genitourinary cancers. Upon examining the statistics, it is evident that the majority of the articles fall within the field of urological oncology. Reviewing all the articles reveals the use of AI in diagnosis, particularly in pathological, radiological, and genomic contexts, focusing on PCa and BCa. Focusing on PCa, AI was applied for the prediction of prostate biopsy results. ML algorithms performed predicted recurrence-free probability and diagnostic evaluation for BCa. For KCa and testis cancer, anecdotal experiences were reported for staging and prediction of disease recurrence (12). Suarez-Ibarrola et al. (13) used radiomics and texture feature analysis for BCa studies. They focused on image-based cytology and algorithms for treatment response, tumor recurrence, and patient survival. PCa studies aim to develop Gleason score prediction, magnetic resonance imaging computer-aided diagnosis prediction, surgical outcomes prediction, and biochemical recurrence prediction. They looked into how ML and DL could be used in renal cell cancer, to differentiate between benign and malignant masses, determine the Fuhrman nuclear grade, and develop molecular signatures (13). By analyzing data using various methods, ML-based programs appear to be able to prevent undiagnoses, or missed diagnoses, but it is indisputable that a significant number of original studies are still required.

Perhaps one of the areas where AI is currently most beneficial is education. Regarding the simulation technology, many clinicians, residents, and medical students benefit from these developments. Khanna et al. (14) created a fully automated AI tool for robotic-assisted radical prostatectomy surgical video annotation. Automated surgical video analysis has immediate practical applications in surgeon video review, surgical training and education, quality and safety benchmarking, medical billing and documentation, and operating room logistics.

AI has also contributed to patient care. The plan is to provide more cost-effective services through the use of statistics on patient care both inside and outside the hospital. Reducing readmissions, strengthening patient-doctor relationships, and providing higher-quality services are among the primary goals of using AI in this field. Wendler et al. (15) discussed the role of various technologies at different stages of the surgical workflow, including surgical decision and planning, target localization and excision guidance, and surgical verification at the back table. Stai et al. (16) conducted a survey to compare confidence in human and computer-based diagnosis. Most participants express confidence in AI in providing medical diagnoses, sometimes even over human physicians. Despite their general concerns, participants mistakenly believe that surgical AI is already in use. There is currently no evidence that AI can identify the critical tasks of robot-assisted surgery that determine patient outcome. There is an urgent need for research on large datasets and external validation of the AI algorithms used (17).

Researchers also have expectations for AI in the field of men's health. Researchers use a variety of AI- and ML-based methods to assess sperm parameters and DNA integrity or damage, and to ensure the success of conventional testicular sperm extraction in patients with non-obstructive azoospermia. While AI and ML hold promise in accurately assessing semen analysis and providing correct information to clinicians, it is essential to address challenges such as data quality, standardization, and ethical considerations (18). Xiong et al. (19) reviewed 30 articles to summarize the current status, merits, and limitations of applying AI in diagnosing and predicting ED. The results showed that AI contributed to developing novel diagnostic questionnaires, equipment, expert systems, image classifiers, and predictive models.

There is substantial evidence that pediatric urologic publications using AI methodology have exponentially increased in recent years. While these studies show enormous promise for better understanding of disease and patient care, urologists should be realistic about the challenges arising from the nature of pediatric urologic conditions and practice in order to continue to produce high-impact research (20). For instance, the world of pediatric urology has been slow to fully accept robotic surgery, largely due to its initial application for adult use and its inherent high cost. However, as previously shown, it has now become the gold standard for adolescent pyeloplasty in the United States (21).

As the years passed, the transition from open surgery to endourology occurred in parallel with the use of instruments in urology, and this process subsequently evolved into minimally invasive interventions. With technological advancements in automated systems, AI is increasingly gaining prominence. In the coming years, we anticipate a gradual decrease in human factors' role in medicine. Currently, reviews predominate, but over time, original studies should contribute to the field of urology. Furthermore, prestigious academic journals are publishing AI-related results. As countries increase their investments in science and technology, it is not surprising to see a rise in the amount of research conducted on this topic. However, the clinical use of AI has not yet fully settled. Currently, clinicians only use AI to conduct detailed data analyses in clinical settings. Additionally, despite the availability of numerous computer programs, clinicians have yet to demonstrate proficiency in using them. We hope that in the future, AI can go beyond detailed data analyses used in diagnosis and instrumental technological advancements in surgery.

Conclusion

AI is currently at the center of attention, especially for young researchers, and stands out as one of the most popular topics. It is not surprising that clinicians want to benefit from the indispensable innovations that technology offers in every field. Not only is it quite natural for expectations to be high, but time will also tell whether AI can truly provide superhuman contributions.

Footnotes

Authorship Contributions

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

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References

1. Stenzl A, Sternberg CN, Ghith J, Serfass L, Schijvenaars BJA, Sboner A. Application of artificial intelligence to overcome clinical information overload in urological cancer. BJU Int. 2022;130:291-300. [Crossref]
2. Hung AJ, Chen AB, Cacciamani GE, Gill IS. Artificial intelligence will (MAY) make doctors expendable (in good ways): pro. Eur Urol Focus. 2021;7:683-684. [Crossref]
3. Yang B, Veneziano D, Somani BK. Artificial intelligence in the diagnosis, treatment and prevention of urinary stones. Curr Opin Urol. 2020;30:782-787. [Crossref]
4. Alexa R, Kranz J, Kuppe C, Hayat S, Hoffmann M, Saar M. Künstliche intelligenz in der urologie – chancen und möglichkeiten [Artificial intelligence in urology-opportunities and possibilities]. Urologie. 2023;62:383-388. German. [Crossref]
5. Oszwald A, Wasinger G, Pradere B, Shariat SF, Compérat EM. Artificial intelligence in prostate histopathology: where are we in 2021? Curr Opin Urol. 2021;31:430-435. [Crossref]
6. Busby D, Grauer R, Pandav K, Khosla A, Jain P, Menon M, Haines GK 3rd, Cordon-Cardo C, Gorin MA, Tewari AK. Applications of artificial intelligence in prostate cancer histopathology. Urol Oncol. 2024;42:37-47. [Crossref]
7. Morozov A, Taratkin M, Bazarkin A, Rivas JG, Puliatti S, Checcucci E, Belenchon IR, Kowalewski KF, Shpikina A, Singla N, Teoh JYC, Kozlov V, Rodler S, Piazza P, Fajkovic H, Yakimov M, Abreu AL, Cacciamani GE, Enikeev D; Young Academic Urologists (YAU) Working Group in Uro-technology of the European Association of Urology. A systematic review and meta-analysis of artificial intelligence diagnostic accuracy in prostate cancer histology identification and grading. Prostate Cancer Prostatic Dis. 2023;26:681-692. [Crossref]
8. Wessels F, Kuntz S, Krieghoff-Henning E, Schmitt M, Braun V, Worst TS, Neuberger M, Steeg M, Gaiser T, Fröhling S, Michel MS, Nuhn P, Brinker TJ. Artificial intelligence to predict oncological outcome directly from hematoxylin and eosin-stained slides in urology. Minerva Urol Nephrol. 2022;74:538-550. [Crossref]
9. von Klot CJ, Kuczyk MA. Künstliche intelligenz und neuronale netze in der urologie [Artificial intelligence and neural networks in urology]. Urologe A. 2019;58:291-299. German. [Crossref]
10. Chang TC, Seufert C, Eminaga O, Shkolyar E, Hu JC, Liao JC. Current trends in artificial intelligence application for endourology and robotic surgery. Urol Clin North Am. 2021;48:151-160. [Crossref]
11. Canellas R, Kohli MD, Westphalen AC. The evidence for using artificial intelligence to enhance prostate cancer MR imaging. Curr Oncol Rep. 2023;25:243-250. [Crossref]
12. Checcucci E, Autorino R, Cacciamani GE, Amparore D, De Cillis S, Piana A, Piazzolla P, Vezzetti E, Fiori C, Veneziano D, Tewari A, Dasgupta P, Hung A, Gill I, Porpiglia F; Uro-technology and SoMe Working Group of the Young Academic Urologists Working Party of the European Association of Urology. Artificial intelligence and neural networks in urology: current clinical applications. Minerva Urol Nefrol. 2020;72:49-57. [Crossref]
13. Suarez-Ibarrola R, Hein S, Reis G, Gratzke C, Miernik A. Current and future applications of machine and deep learning in urology: a review of the literature on urolithiasis, renal cell carcinoma, and bladder and prostate cancer. World J Urol. 2020;38:2329-2347. [Crossref]
14. Khanna A, Antolin A, Bar O, Ben-Ayoun D, Zohar M, Boorjian SA, Frank I, Shah P, Sharma V, Thompson RH, Wolf T, Asselmann D, Tollefson M. Automated identification of key steps in robotic-assisted radical prostatectomy using artificial intelligence. J Urol. 2024;211:575-584. [Crossref]
15. Wendler T, van Leeuwen FWB, Navab N, van Oosterom MN. How molecular imaging will enable robotic precision surgery : the role of artificial intelligence, augmented reality, and navigation. Eur J Nucl Med Mol Imaging. 2021;48:4201-4224. [Crossref]
16. Stai B, Heller N, McSweeney S, Rickman J, Blake P, Vasdev R, Edgerton Z, Tejpaul R, Peterson M, Rosenberg J, Kalapara A, Regmi S, Papanikolopoulos N, Weight C. Public perceptions of artificial intelligence and robotics in medicine. J Endourol. 2020;34:1041-1048. [Crossref]
17. Moglia A, Georgiou K, Georgiou E, Satava RM, Cuschieri A. A systematic review on artificial intelligence in robot-assisted surgery. Int J Surg. 2021;95:106151. [Crossref]
18. Panner Selvam MK, Moharana AK, Baskaran S, Finelli R, Hudnall MC, Sikka SC. Current updates on involvement of artificial intelligence and machine learning in semen analysis. Medicina (Kaunas). 2024;60:279. [Crossref]
19. Xiong Y, Zhang Y, Zhang F, Wu C, Qin F, Yuan J. Applications of artificial intelligence in the diagnosis and prediction of erectile dysfunction: a narrative review. Int J Impot Res. 2023;35:95-102. [Crossref]
20. Scott Wang HH, Vasdev R, Nelson CP. Artificial intelligence in pediatric urology. Urol Clin North Am. 2024;51:91-103. [Crossref]
21. Fuchs ME, DaJusta DG. Robotics in pediatric urology. Int Braz J Urol. 2020;46:322-327. [Crossref]

ORIGINAL RESEARCH
General Urology

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Investigation of Clinical and Hematological Parameters Predicting Organ Loss in Testicular Torsion

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

In testicular torsion, which causes physical and psychological damage, the duration of symptoms and the increase in the degree of torsion are the main parameters that cause testicular loss. However, the discussions on the cut-off points of these parameters continue. In this study, we tried to determine the cut-off points of these parameters and also tried to determine the value of new hematological parameters that have not been investigated before in predicting testicular loss.

Abstract

Objective: In this study, we aimed to determine clinical and hematological parameters that may predict testicular viability or testicular loss in patients diagnosed with testicular torsion and undergoing scrotal exploration.

Materials and Methods: Our study included 98 patients aged 1-25 years diagnosed with testicular torsion. Two groups were formed: the testicular salvage group and the unsuccessful testicular salvage group. Demographic, clinical, and hematological parameters of the two groups were compared.

Results: While 52 patients were considered successful testicular salvage, 46 patients were grouped as unsuccessful. Symptom duration and torsion degree were significantly higher in the unsuccessful testicular salvage group than in the successful testicular salvage group ($p<0.001$, respectively). White blood cell, neutrophil, monocyte, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, systemic immune-inflammation index, systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) values were significantly higher in the unsuccessful testicular salvage group ($p=0.001$, $p<0.001$, $p=0.016$, $p=0.002$, $p=0.012$, $p=0.001$, $p=0.001$, $p<0.001$, and $p<0.001$, respectively). The most important predictors for successful testicular salvage were symptom duration and degree of torsion. In the successful salvage of testicular torsion, the threshold for symptom duration was established at 9 hours, while the maximum torsion degree tolerated was set at 270°. Furthermore, $2.21\times10^3/\mu L$ for SIRI and $635.59\times10^6/\mu L^2$ for AISI were determined as the limit values predicting organ loss.

Conclusion: In our study, we found that the most important parameters in predicting organ loss in testicular torsion were the degree of torsion and symptom duration. Hematological parameters in testicular torsion patients may help predict the need for scrotal exploration and potential outcomes such as orchiectomy or testicular atrophy.

Keywords: Testicular torsion, orchidopexy, orchiectomy, haematological tests

Introduction

Testicular torsion is an urgent urological condition characterized by reduced blood flow to the testicle due to the rotation of the testicle and epididymis. Urgent intervention is required to protect the viability of the testicle and prevent testicular loss (1).

The incidence of testicular torsion has been reported to be 1 in 4.000 among male patients up to 25 years of age (2). The critical period to save the testicle after the onset of pain in testicular torsion is 4-8 hours (3). The risk of testicular loss increases with each hour passed. It is 5% within the first 6 hours, 40% after 12 hours, and 80% after 24 hours (4). The most commonly

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used imaging method in the differential diagnosis of testicular torsion is scrotal color Doppler ultrasonography (CDUS), which has high sensitivity and specificity (5).

In the literature, studies examine clinical parameters such as symptom duration and the degree of cord rotation, which predict testicular viability before surgery (6,7). However, most of these studies did not evaluate testicular atrophy, which develops after orchidopexy and is considered unsuccessful testicular salvage. Based on the data obtained in these studies, it can be said that symptom duration and the degree of spermatic cord rotation are significant parameters affecting testicular viability (7,8).

It has been shown that systemic inflammatory markers may increase with hypoxic tissue damage occurring in testicular torsion (9,10). In some studies, hematological parameters of systemic inflammation have been used in the differential diagnosis of epididymo-orchitis and testicular torsion (11,12). A limited number of studies have also used hematological parameters to predict testicular viability in testicular torsion (13,14).

The aim of this study was to identify clinical and hematological parameters that can predict testicular viability or testicular loss in patients diagnosed with testicular torsion who undergo scrotal exploration.

Materials and Methods

The study was conducted at the Urology Clinic of Afyonkarahisar Health Sciences University. Following ethical approval from the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University (2011-KAEK-2, 2024/2, date: 19.04.2024) the data were collected retrospectively. The study was carried out in accordance with the principles of the Helsinki Declaration.

The study included patients who visited the Department of Urology at the Afyonkarahisar Health Sciences University between April 2012 and April 2023, with testicular pain, diagnosed with testicular torsion through examination and CDUS. Symptoms in infant patients were restlessness, crying, and swelling in the testicle. CDUS was performed on all patients before the operation. All patients underwent scrotal exploration, with the diagnosis of testicular torsion confirmed Testicular viability was confirmed using the three-grade bleeding test recommended by Arda and Ozyaylali (15). Patients between the ages of 1 and 25 were included in the study.

Appendiceal testicular torsion, signs of epididymo-orchitis, any malignancy, receiving chemotherapy, hematological disease, hepatic or renal failure, other infection sites, partial blood flow to the testicle, and other testicular pathologies (cryptorchidism, etc.) were the exclusion criteria. Patients with significant differences in testicular volumes, either on preoperative physical examination or CDUS, and patients with clinical varicocele were not included in the study.

A total of 117 patients were included in the study. Twelve patients who did not attend follow-ups regularly for at least 6 months or whose testicular volume was not measured by CDUS were excluded from the study. Additionally, seven patients whose testicular torsion was not confirmed during scrotal exploration were excluded. Thus, the study proceeded with a total of 98 patients. Demographic and clinical data such as age, time from the onset of pain to the operation, seasonality, laterality, CDUS findings (degree of torsion, testicular volume, etc.), and preoperative hemogram values were recorded. The degree of torsion was calculated as rotation measured on CDUS. Symptom duration was the time from the onset of symptoms until the testicle was exposed during exploration. Patients who showed a volume difference of more than 50% between the affected testicle and the contralateral testicle on postoperative CDUS were classified as having testicular atrophy and were included in the unsuccessful testicular salvage group (16,17).

Preoperative complete blood count (CBC) parameters of the patients such as white blood cell (WBC), neutrophil, leymphocyt, monocyte, basophil, eosinophil, haemoglobin, platelet, mean corpuscular volume, mean platelet volume (MPV), platelet distribution width, red cell distribution width (RDW)-coefficient of variation, RDW-standard deviation values were measured. Furthermore, the values of the systemic inflammatory markers obtained from CBC parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and monocyte-to-platelet ratio, systemic immune-inflammation index (SII) (neutrophil*platelet to lymphocyte ratio), systemic inflammation response index (SIRI) (neutrophil*monocyte to lymphocyte ratio), aggregate index of systemic inflammation (AISI) (neutrophil*platelet*monocyte to lymphocyte ratio) were calculated.

As a result, two groups were formed: the successful testicular salvage group, in which orchidopexy was performed, and no more than 50% atrophy was detected compared to the contralateral testicle, and the unsuccessful testicular salvage group, in which orchiectomy was performed, or more than 50% testicular atrophy was detected during follow-up after orchidopexy. Demographic, clinical, and hematological parameters of the two groups were compared.

Statistical Analysis

A statistical program (SPSS for Windows, v21) was used for data analysis. The Kolmogorov-Smirnov test, histogram, and skewness-kurtosis coefficients were used to evaluate whether the data had a normal distribution. Nominal and ordinal variables were compared using the Pearson chi-square test or

Fisher's exact test. The Student's t-test was used for normally distributed variables, while the Mann-Whitney U test was used for parameters that did not have a normal distribution. Independent predictors of organ loss in testicular torsion were examined with the binary logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic decision-making abilities of clinical and hematological parameters in predicting testicular loss. A value of $p<0.05$ was accepted as statistically significant.

Results

While 67 (68.4%) of the 98 patients in the study underwent orchidopexy, the remaining 31 (31.6%) underwent orchiectomy. During follow-ups, 15 (22.4%) of the 67 patients who underwent orchidopexy showed more than a 50% reduction in the affected testicle compared to the contralateral testicular volume. These 15 patients were also included in the unsuccessful testicular salvage group along with those who underwent orchiectomy. As a result, 52 (53.1%) patients were classified as successful testicular salvage, while 46 (46.9%) were classified as unsuccessful.

The mean age of all patients was 15.37±5.45 years, with no significant difference between the groups (p=0.398). Testicular torsion was found on the left side in 62 (63.3%) patients. There was no difference between the groups in terms of the side of torsion and seasonality (p=0.530 and p=0.738, respectively) (Table 1). The follow-up period of all patients ranged from 6 to 48 months. The median follow-up period was 11 months in the detorsion group and 12 months in the orchiectomy group.

The median symptom duration was 5.5 hours in the successful testicular salvage group, which was statistically significantly lower than in the unsuccessful group (p<0.001). The median degree of torsion was 180° in the successful testicular salvage group and 360° in the unsuccessful testicular salvage group, with a statistically significant difference (p<0.001) (Table 1). In addition, the median symptom duration of 15 patients who developed testicular atrophy after detorsion was 17 hours; and the median torsion degree was 360 degrees.

When hematological parameters were analyzed between the groups, WBC, neutrophil, monocyte, NLR, PLR, MLR, SII, SIRI, and AISI values were statistically significantly higher in the testicular salvage failure group. There were no significant differences between the groups in other hematological parameters (Table 1).

Multivariate binary logistic regression analysis was used to identify the possible independent predictors of organ loss in testicular torsion that contributed the most to the outcome. Symptom duration, degree of torsion, WBC, neutrophil, monocyte, NLR, PLR, MLR, SII, SIRI, and AISI values were used as predictors. The model predicting organ loss in testicular torsion was found to fit the data well [Hosmer-Lemeshow test: $\chi^2(8)=8.7$, p=0.364] and could explain 62.1% of the variance (Nagelkerke $R^2=0.621$). The model correctly predicted 88.5% of successful salvages and 80.4% of unsuccessful salvages (84.7% in total). The success of testicular salvage in cases of testicular torsion was strongly related to the symptom duration and the degree of torsion (p=0.001 and p=0.029, respectively) (Table 2).

Table 1. Comparison of demographic and clinical data of the groups

	Successful salvage (n=52) n (%)	**Unsuccessful salvage (n=46) n (%)**	**p**
Age (years)	15.81±4.49	14.87±6.38	0.398
Laterality			
Right	21 (40.4)	15 (32.6)	0.530
Left	31 (59.6)	31 (67.4)	
Symptom duration (h)	5.5 (3-8)*	16 (10-48)*	**<0.001**
Torsion degree (°)	180 (112.5-360)*	360 (360-540)*	**<0.001**
Seasonality			
Winter	17 (32.7)	14 (30.4)	0.738
Spring	11 (21.2)	9 (19.6)	
Summer	12 (23.1)	8 (17.4)	
Autumn	12 (23.1)	15 (32.6)	
WBC count (×10³/µL)	9.71±3.08	12.49±4.66	**0.001**
Neutrophil count (×10³/µL)	6.44±3.03	9.24±4.44	**<0.001**
Lymphocyte count (×10³/µL)	2.45±1.12	2.11±0.92	0.108
Monocyte count (×10³/µL)	0.62±0.31	0.84±0.44	**0.016**

Table 1. Comparison of demographic and clinical data of the groups			
	Successful salvage (n=52) n (%)	**Unsuccessful salvage (n=46) n (%)**	**p**
Basophil count (×10³/μL)	0.035±0.024	0.070±0.18	0.241
Eosinophil count (×10³/μL)	0.11±0.10	0.09±0.11	0.169
Hemoglobin level (g/dL)	14.56±1.52	14.30±1.31	0.364
Platelet count (×10³/μL)	273.80±59.48	293.71±94.11	0.662
MCV (fL)	83.46±3.94	85.32±6.01	0.072
MPV (fL)	9.49±1.16	9.13±1.26	0.151
PDW (fL)	12.23±2.59	13.16±2.84	0.111
RDW-CV (%)	13.20±0.77	13.26±0.99	0.760
RDW-SD (fL)	39.32±2.08	39.97±2.84	0.268
NLR (%)	3.46±2.79	5.56±4.36	**0.002**
PLR (%)	136.83±81.11	158.53±67.50	**0.012**
MLR (%)	0.28±0.15	0.46±0.29	**0.001**
MPR (%)	0.0024±0.0012	0.0030±0.0016	0.085
SII (×10³/μL)	920.41±754.33 697.09 (373.82-1151.58)*	1528.20±67.50 1253.96 (770.54-1828.50)*	**0.001**
SIRI (×10³/μL)	1.94±1.66 1.56 (0.75-2.32)*	5.12±6.18 3.47 (1.61-6.39)*	**<0.001**
AISI (×10⁶/μL²)	508.39±416.06 404.87 (191.52-664.32)*	1463.04±1718.25 1154.75 (501.44-1553.59)*	**<0.001**

*: Median (25-75 percentiles), WBC: White blood cell, MCV: Mean corpuscular volume, MPV: Mean platelet volume, PDW: Platelet distribution width, RDW-CV: Red cell distribution width-coefficient of variation, RDW-SD: Red cell distribution width-standard deviation, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, MPR: Monocyte-to-platelet ratio, SII: Systemic immune-inflammation index (neutrophil*platelet to lymphocyte ratio), SIRI: Systemic inflammation response index (neutrophil* monocyte to lymphocyte ratio), AISI: Aggregate index of systemic inflammation (neutrophil*platelet* monocyte to lymphocyte ratio)

Table 2. Multivariate logistic regression analysis of parameters predicting organ loss in testicular torsion		
Risk factor	**Unsuccessful salvage**	
	OR (95% CI)	**p-value**
Symptom duration (h)	1.076 (1.032-1.121)	**0.001**
Torsion degree (°)	1.004 (1.001-1.007)	**0.019**
WBC count (×10³/μL)	1.132 (0.508-2.523)	0.762
Neutrophil count (×10³/μL)	0.891 (0.319-2.490)	0.825
Monocyte count (×10³/μL)	0.134 (0.001-21.529)	0.438
NLR (%)	2.370 (0.554-10.131)	0.245
PLR (%)	1.005 (0.981-1.031)	0.665
MLR (%)	0.324 (0.000-3517.793)	0.812
SII (×10³/μL)	0.996 (0.989-1.003)	0.254
SIRI (×10³/μL)	0.293 (0.025-3.467)	0.330
AISI (×10⁶/μL²)	1.008 (0.999-1.017)	0.088

OR: Estimated relative risk shown by odds ratio, CI: Confidence interval, WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

ROC analysis was conducted to determine the cut-off values for symptom duration, degree of torsion, NLR, PLR, MLR, SII, SIRI, and AISI score for successful testicular salvage in testicular torsion. The evaluation by ROC analysis revealed that symptom duration, degree of torsion, NLR, PLR, MLR, SII, SIRI, and AISI score had diagnostic value in predicting successful testicular salvage (Figures 1 and 2). The threshold for symptom duration was established at 9 hours, while the maximum torsion-degree tolerated was set at 270° (Table 3). Furthermore, 2.21×10³/μL for SIRI and 635.59×10⁶/μL² for AISI were determined as the limit values predicting organ loss. Other hematological parameters for which limit values were determined are given in the table (Table 4).

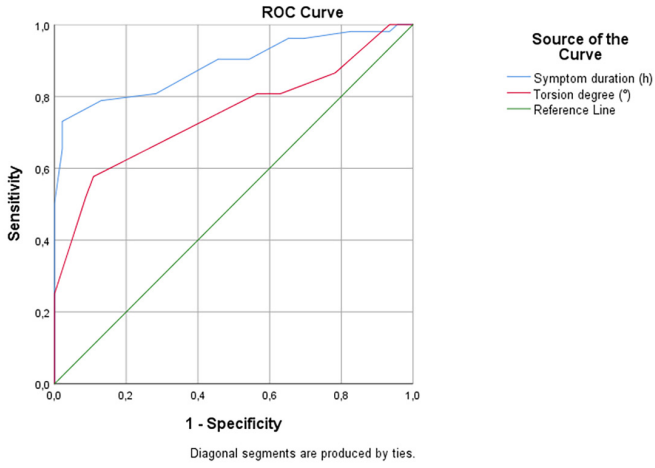

Figure 1. The ROC curve analysis of symptom duration and torsion degree in testicular salvage

ROC: Receiver operator characteristic

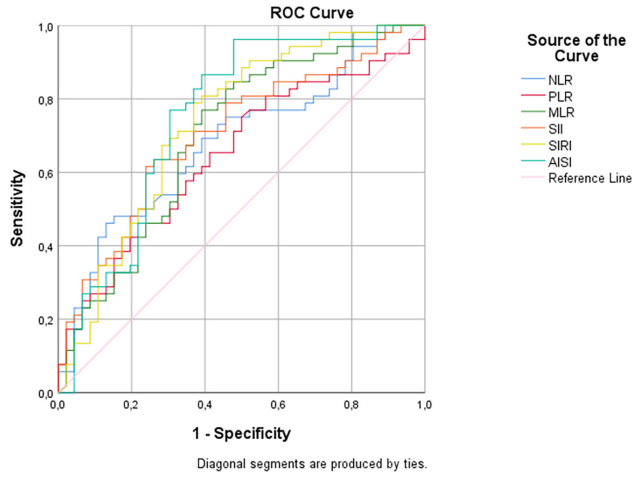

Figure 2. The ROC curve analysis of NLR, PLR, MLR, SII, SIRI and AISI in testicular salvage

ROC: Receiver operator characteristic, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

Table 3. Areas under the ROC curve (AUC), sensitivity and specificity by the optimized cut-off points for symptom duration and torsion degree in testicular loss

Risk factor	AUC (95%)	Cut-off	p	Sensitivity (%)	Specificity (%)
Symptom duration (h)	0.885 (0.818-0.953)	9	<0.001	78.8	87.0
Torsion degree (°)	0.749 (0.651-0.846)	270	<0.001	57.7	89.1

ROC: Receiver operator characteristic, AUC: Areas under the ROC

Table 4. Areas under the ROC curve (AUC), sensitivity and specificity by the optimized cut-off points for SII, SIRI and AISI in testicular loss

Risk factor	AUC (95%)	Cut-off	p	Sensitivity (%)	Specificity (%)
NLR	0.679 (0.573-0.785)	3.10	0.002	63.5	63
PLR	0.647 (0.538-0.756)	126.33	0.012	61.5	60.9
MLR	0.700 (0.595-0.806)	0.30	0.001	65.4	65.2
SII	0.704 (0.601-0.807)	968.17	0.001	65.4	65.2
SIRI	0.734 (0.632-0.835)	2.21	<0.001	69.2	69.6
AISI	0.752 (0.651-0.853)	635.59	<0.001	69.2	69.6

ROC: Receiver operator characteristic, AUC: Areas under the ROC, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, SII: Systemic immune-inflammation index, SIRI: Systemic inflammation response index, AISI: Aggregate index of systemic inflammation

Discussion

In our study, the mean admission time was 5.5 hours in the successful group and 16 hours in the unsuccessful group. Again in our study, the rate of atrophy after orchidopexy was 22.4%. As a result of the ROC analysis performed to determine the cut-off values for testicular salvage, we showed that this limit was 9 hours for symptom duration and 270° for the degree of torsion.

Testicular torsion is a urological emergency that can result in testicular ischemia and organ loss if not promptly diagnosed and treated. In our study, we examined patients who underwent surgical exploration for testicular torsion and subsequently underwent either orchidopexy or orchiectomy. These patients were also enrolled in the 6-month follow-up schedule. Thus, we evaluated whether atrophy developed in patients treated with orchidopexy. Our study holds significance in assessing the long-term outcomes of orchidopexy and evaluating systemic inflammation indices that have not been previously investigated in the literature.

A study evaluating the duration of symptoms and the degree of torsion reported that the only significant variable in multivariate regression analysis was the duration of torsion (16). However,

this study reported a mean duration of hospital stay of 24 hours for the orchidopexy group and 96 hours for the orchiectomy group. These durations were significantly longer than those observed in our study and in many other studies in the literature (8,18). These increased admission times may have affected the results of the study.

In a study examining the prognostic factors for testicular salvage during testicular torsion, the median duration of admittance to the hospital in the successful testicular salvage group (orchidopexy) was found to be 5 hours, and the degree of torsion was 360°, with a mean follow-up period of 8 months. In the unsuccessful group (orchiectomy + atrophy), these values were reported to be 12.5 hours and 540°. The rate of atrophy after orchidopexy was 25.7%. Howe et al. (8) revealed that the most important prognostic factors for testicular salvage were symptom duration and degree of torsion. In the ROC analysis, the cut-off value for symptom duration was identified as 8.5 hours. These results show similarities to our study. We think that it is significant to have similar results in these two studies with similar admission times, degree of torsion and age range.

In their study, Lian et al. (19) showed that 54% of patients who underwent orchidopexy for testicular torsion experienced testicular atrophy. It was also noted that no testicle with a symptom duration longer than 3 days could be salvaged. The median follow-up period in their study was 12.5 months.

In the study by He et al. (13), the participants were divided into two groups: those who underwent orchiectomy and orchidopexy at their first visits. They showed that symptom duration, degree of torsion, and MPV value were significant predictors of orchiectomy. In the study, 20 out of 54 patients returned for follow-up visits after orchidopexy. Although the volume of the affected testicles was reported to decrease in comparison to the contralateral testicle, they suggested that testicular function was preserved due to blood supply in the testicular parenchyma. However, numerous studies have indicated that the function of the affected testicle decreases after torsion, and this deterioration worsens with prolonged torsion duration (20,21).

There is a limited number of studies investigating the value of hematological parameters in testicular torsion (13,14,22). Yucel and Ozlem Ilbey (9) analyzed patients with acute scrotal pain, including 85 patients who underwent orchiectomy or orchidopexy for testicular torsion, 72 patients diagnosed with epididymitis, and 78 healthy men as a control group. According to the findings of their study, NLR and PLR values were observed to be similar between the torsion and epididymo-orchitis groups, but significantly higher than the control group.

Bitkin et al. (11) evaluated three groups: the epididymo-orchitis, torsion, and control groups, and NLR values were higher in the other two groups compared to the control group. PLR value was higher in the epididymo-orchitis group than in the other groups. NLR was shown to be similar between the torsion and epididymo-orchitis groups.

However, it's worth noting that the age groups of the populations in these two studies were statistically different. There are studies showing that neutrophil count is the lowest in the pediatric period and increases with age, whereas lymphocyte count is the highest in the pediatric period and decreases with age (23). Hence, studies incorporating CBC and systemic inflammatory indices with varying age groups could be restrictive. In our study, we included a patient population with comparable age groups.

CDUS has been safely used for many years with high sensitivity in the differentiation of epididymo-orchitis and torsion. Furthermore, it has been reported that erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values can also help in the differentiation of these two pathologies (24). Since hematological parameters are not as precise as scrotal CDUS for the differential diagnosis of testicular torsion and are non-specific, like CRP and ESR, it might be more useful to assess whether these parameters can serve as predictive factors in evaluating surgical success.

Under physiological conditions, an increase in platelet count typically results in a decrease in MPV to maintain hemostasis. Since this non-linear inverse relationship between PLT and MPV values can be disrupted in various pathologies, it is recommended to analyze these two values together. MPV is strongly influenced by many inflammatory diseases, age, gender, dietary habits, and genetic factors (25). He et al. (13) reported that the MPV value was predictive of the need for orchiectomy, while Cicek et al. (22) found that the MPV value was significantly different in the testicular torsion group compared to the healthy group. Güneş et al. (14), on the other hand, found significant differences in NLR, PLT, and PLR values between the testicular torsion group and the control group. However, MPV did not play a role in predicting the diagnosis of testicular torsion. Merder et al. (18) similarly noted that the MPV value did not differ between the groups. In our study, we also found that the MPV value did not show a significant difference between the groups. We believe that more data and research are needed to evaluate the use of MPV, which is influenced by factors such as age, gender, eating habits, and genetics, in testicular torsion.

In our study, WBC, neutrophil, monocyte, NLR, PLR, MLR, SII, SIRI, and AISI values were found to be statistically significant and higher in the unsuccessful testicular salvage group compared to the successful group. In a retrospective study of 60 male patients diagnosed with testicular torsion published in 2018, NLR value was reported to be predictive of testicular salvage.

However, since there was no long-term follow-up in that study, the rate of testicular atrophy was not reported. Therefore, testicular salvage is limited to orchidopexies performed in the first stage (26). In our study, more precise results were obtained by assessing long-term testicular atrophy and incorporating systemic inflammatory indices from recent research.

It should be noted that successful testicular salvage offers psychological benefits in addition to physical ones. Research has shown that testicular loss can cause feelings of shame and unease in some men (27). This increases the importance of early admission and intervention in testicular torsion patients.

Study Limitations

There are some limitations to our study. One of these is that scrotal CDUS was not performed by the same radiologist when evaluating the degree of testicular torsion. Another limitation of our study is its lack of generalizability to the broader population due to its single-center, retrospective design. We believe that this study will pave the way for future multicenter prospective studies, providing a more comprehensive representation of the general population. The strengths of our study are the clear distinction between successful and unsuccessful testicular salvage groups through long-term follow-up data analysis, the analysis of previously unexplored parameters SII, SIRI, and AISI, and the establishment of robust cut-off values for critical factors like symptom duration and degree of torsion.

Conclusion

Our study revealed that the most crucial parameters in predicting organ loss in testicular torsion, which can lead to both psychological and physical damage, are the degree of torsion and symptom duration. This underscores the significance of early diagnosis and treatment. This study, which highlights the value and importance of previously unexplored hematological parameters, will contribute to the literature. We think that hematological parameters and systemic inflammatory indices, which can be easily assessed at the time of initial visit, in patients with testicular torsion, may serve as predictors of scrotal exploration outcomes, potentially leading to orchiectomy or the development of testicular atrophy. It is thought that preoperative evaluation of these parameters by the physician and the provision of information about the potential outcomes of orchiectomy or testicular atrophy to the patients and their relatives will facilitate a smoother and more manageable postoperative process.

Ethics

Ethics Committee Approval: This study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (2011-KAEK-2, 2024/2, date: 19.04.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.G., M.Ş., K.T., Concept: O.G., M.Ş., K.U., Design: M.Ş., K.T., V.M.Y., Data Collection or Processing: K.U., K.T., Analysis and Interpretation: O.G., K.U., V.M.Y., Literature Search: M.Ş., K.T., V.M.Y., Writing: O.G., K.U., V.M.Y.

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

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References

1. Taskinen S, Mäkelä E, Raivio T. Effect of pediatric testicular torsion on testicular function in the short term. J Pediatr Surg. 2020;55:1613-1615. [Crossref]
2. Barada JH, Weingarten JL, Cromie WJ. Testicular salvage and age-related delay in the presentation of testicular torsion. J Urol. 1989;142:746-748. [Crossref]
3. Shunmugam M, Goldman RD. Testicular torsion in children. Can Fam Physician. 2021;67:669-671. [Crossref]
4. Visser AJ, Heyns CF. Testicular function after torsion of the spermatic cord. BJU Int. 2003;92:200-203. [Crossref]
5. Kalfa N, Veyrac C, Baud C, Couture A, Averous M, Galifer RB. Ultrasonography of the spermatic cord in children with testicular torsion: impact on the surgical strategy. J Urol. 2004;172:1692-1695; discussion 1695. [Crossref]
6. Ramachandra P, Palazzi KL, Holmes NM, Marietti S. Factors influencing rate of testicular salvage in acute testicular torsion at a tertiary pediatric center. West J Emerg Med. 2015;16:190-194. [Crossref]
7. Dias AC Filho, Alves JR, Buson H Filho, Oliveira PG. The amount of spermatic cord rotation magnifies the timerelated orchidectomy risk in intravaginal testicular torsion. Int Braz J Urol. 2016;42:1210-1219. [Crossref]
8. Howe AS, Vasudevan V, Kongnyuy M, Rychik K, Thomas LA, Matuskova M, Friedman SC, Gitlin JS, Reda EF, Palmer LS. Degree of twisting and duration of symptoms are prognostic factors of testis salvage during episodes of testicular torsion. Transl Androl Urol. 2017;6:1159-1166. [Crossref]
9. Yucel C, Ozlem Ilbey Y. Predictive value of hematological parameters in testicular torsion: retrospective investigation of data from a high-volume tertiary care center. J Int Med Res. 2019;47:730-737. [Crossref]
10. Zhu J, Song Y, Chen G, Hu R, Ou N, Zhang W, Liang Z, Liu X. Predictive value of haematologic parameters in diagnosis of testicular torsion: evidence from a systematic review and meta-analysis. Andrologia. 2020;52:e13490. [Crossref]
11. Bitkin A, Aydın M, Özgür BC, Irkilata L, Akgunes E, Keles M, Sarıcı H, Atilla MK. Can haematologic parameters be used for differential diagnosis of testicular torsion and epididymitis? Andrologia. 2018;50. [Crossref]
12. Arikan MG, Akgul M, Akdeniz E, Iskan G, Arda E. The value of hematological inflammatory parameters in the differential diagnosis of testicular torsion and epididymorchitis. Am J Clin Exp Urol. 2021;9:96-100. [Crossref]
13. He M, Zhang W, Sun N. Can haematologic parameters be used to predict testicular viability in testicular torsion? Andrologia. 2019;51:e13357. [Crossref]
14. Güneş M, Umul M, Altok M, Akyuz M, İşoğlu CS, Uruc F, Aras B, Akbaş A, Baş E. Predictive role of hematologic parameters in testicular torsion. Korean J Urol. 2015;56:324-329. [Crossref]

15. Arda IS, Ozyaylali I. Testicular tissue bleeding as an indicator of gonadal salvageability in testicular torsion surgery. BJU Int. 2001;87:89-92. [Crossref]

16. Zvizdic Z, Aganovic A, Milisic E, Jonuzi A, Zvizdic D, Vranic S. Duration of symptoms is the only predictor of testicular salvage following testicular torsion in children: a case-control study. Am J Emerg Med. 2021;41:197-200. [Crossref]

17. Niedzielski J, Balinska K, Wilk D, Slowikowska-Hilczer J. The effect of the two-stage laparoscopic Fowler-Stevens operation on testicular growth and risk of atrophy in boys with intra-abdominal testes. Arch Med Sci. 2019;18:666-671. [Crossref]

18. Merder E, Bozkurt M, Ariman A, Sezgin MA, Culha MG, Altunrende F. Comprehensive examination of haematological parameters of patients operated due to testicular torsion. Andrologia. 2020;52:e13674. [Crossref]

19. Lian BS, Ong CC, Chiang LW, Rai R, Nah SA. Factors predicting testicular atrophy after testicular salvage following torsion. Eur J Pediatr Surg. 2016;26:17-21. [Crossref]

20. Heindel RM, Pakyz RE, Reinking LN, Cosentino MJ. The effect of various degrees of unilateral spermatic cord torsion on fertility in the rat. J Urol. 1990;144:366-369. [Crossref]

21. Cosentino MJ, Nishida M, Rabinowitz R, Cockett AT. Histopathology of prepubertal rat testes subjected to various durations of spermatic cord torsion. J Androl. 1986;7:23-31. [Crossref]

22. Cicek T, Togan T, Akbaba K, Narci H, Aygun C. The value of serum mean platelet volume in testicular torsion. J Int Med Res. 2015;43:452-459. [Crossref]

23. Nah EH, Kim S, Cho S, Cho HI. Complete blood count reference intervals and patterns of changes across pediatric, adult, and geriatric ages in Korea. Ann Lab Med. 2018;38:503-511. [Crossref]

24. Asgari SA, Mokhtari G, Falahatkar S, Mansour-Ghanaei M, Roshani A, Zare A, Zamani M, Khosropanah I, Salehi M. Diagnostic accuracy of C-reactive protein and erythrocyte sedimentation rate in patients with acute scrotum. Urol J. 2006;3:104-108. [Crossref]

25. Yazici M, Kaya A, Kaya Y, Albayrak S, Cinemre H, Ozhan H. Lifestyle modification decreases the mean platelet volume in prehypertensive patients. Platelets. 2009;20:58-63. [Crossref]

26. Jang JB, Ko YH, Choi JY, Song PH, Moon KH, Jung HC. Neutrophil-lymphocyte ratio predicts organ salvage in testicular torsion with marginal diagnostic delay. World J Mens Health. 2019;37:99-104. [Crossref]

27. Skoogh J, Steineck G, Cavallin-Ståhl E, Wilderäng U, Håkansson UK, Johansson B, Stierner U; SWENOTECA. Feelings of loss and uneasiness or shame after removal of a testicle by orchidectomy: a population-based long-term follow-up of testicular cancer survivors. Int J Androl. 2011;34:183-192. [Crossref]

ORIGINAL RESEARCH
Urooncology

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Can Laparoscopic Adrenalectomy Be A Reliable Method for Adrenal Masses Larger than 4 Cm?: Our Clinical Outcomes

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

Adrenal masses are now a common pathology in urology clinics, found incidentally or managed under endocrinological guidance. Adrenalectomy is the preferred approach for masses larger than 4 cm in individuals where surgery is considered acceptable. The most crucial factor in surgical selection is the experience of the surgeon. However, considering criteria such as hospital stay, intraoperative complications, cost, postoperative pain, and wound infection, the gold standard in adrenalectomy is laparoscopic adrenalectomy. We hope that this study will contribute to the literature by demonstrating the safe and effective use of laparoscopic adrenalectomy for large adrenal masses.

Abstract

Objective: The laparoscopic approach to large adrenal masses is becoming increasingly common. Our study aims to investigate the reliability and effectiveness of adrenalectomy performed with laparoscopic surgery in adrenal masses larger than 4 cm.

Materials and Methods: Fifty-two patients who underwent transperitoneal laparoscopic adrenalectomy in our clinic between January 2014 and July 2022 were evaluated retrospectively. Each patient's age, gender, hormonal activity status, tumor size and side, hospital stay, amount of bleeding, operation time, complication rates (Clavian classification), pathology results, and surgical margin positivity were evaluated. Thirty patients with tumor size over 4 cm and 22 patients under 4 cm were compared separately.

Results: There was no statistically significant difference between the two groups regarding hospital stay (p=0.11). When the operation time and bleeding amount were compared, no statistically significant difference was found between these two groups (p=0.392, p=0.761; respectively). Although slightly more complications were seen in patients with tumors smaller than 4 cm, no statistical difference was observed (p>0.05). Surgical margin positivity was detected only in one of the patients with a tumor size of less than 4 cm, and this patient was reported to have adenoma. All operations were completed laparoscopically. No complications occurred in Clavien class 3 or above in any of the patients.

Conclusion: Our study and experience unequivocally demonstrate that transperitoneal laparoscopic adrenalectomy is not only effective but also remarkably safe for large (>4 cm) adrenal masses.

Keywords: Laparoscopy, adrenal, large mass

Introduction

Adrenal masses are now a common pathology in urology clinics, incidentally or under endocrinology's guidance. Recently, with the widespread use of radiological imaging, there has been a significant increase in the incidence of adrenal masses. Adrenal masses require a detailed evaluation because they may present with different clinical, laboratory, and radiological features (1). Adrenal masses are hormonally active or inactive; oncologically, they can be benign or malignant. Asymptomatic masses larger than 1 cm that are detected incidentally are called incidentalomas. These masses are generally benign. Its incidence is between 1.5% and 8.5% (2,3). Ten percent of adrenal masses are hormonally active. Hormonally active masses

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are generally symptomatic. They can cause conditions such as Conn syndrome, Cushing syndrome, pheochromocytoma, hypercortisolism, hyperandrogenism, and hyperaldosteronism. From an oncological perspective, 94% of adrenal masses are benign. As the size of the mass increases, the possibility of malignancy and hormonal activity also increases (1,4).

Adrenalectomy is recommended for masses that show malignant characteristics on imaging or for hormonally active masses. Masses that are under 4 cm and non-functional can be monitored since the likelihood of malignancy is low. However, masses larger than 6 cm should be considered malignant and treated surgically. If there is no radiological evidence of malignancy in adrenal tumors between 4-6 cm, follow-up with intermittent imaging can be considered as an option. However, adrenalectomy is still recommended for masses that grow during follow-up. Adrenalectomy is a more recommended approach for masses larger than 4 cm in individuals for whom surgery is deemed appropriate, and the risk of anesthesia is not high (3,5,6).

Adrenalectomy can be performed openly, laparoscopically, or robotically. The most crucial factor in surgical selection is the experience of the surgeon. However, considering criteria such as hospital stay, intraoperative complications, cost, postoperative pain, and wound infection, the gold standard in adrenalectomy stands out as laparoscopic adrenalectomy (7).

While there continues to be uncertainty about which method is more suitable for large masses, this study aimed to investigate the safety and effectiveness of laparoscopic adrenalectomy in adrenal masses >4 cm with respect to complications, operation time, hospital stay, and bleeding volume.

Materials and Methods

Approval was received from the Düzce University Non-invasive Health Research Ethics Committee on 06.09.2021 with decision number 2021/184. A total of 52 patients who had undergone transperitoneal laparoscopic adrenalectomy for the treatment of an adrenal mass at the Düzce University Urology Clinic between January 2014 and July 2022, were retrospectively evaluated and included in the study. The study excluded patients with incomplete observation files, those lost to follow-up, and those who underwent retroperitoneal adrenalectomy, open adrenalectomy, or adrenalectomy during radical nephrectomy.

The two groups, 30 patients with tumor size over 4 cm and 22 under 4 cm, were compared separately. In the endocrinological evaluation, metanephrine, homovanillic acid, 5-hydroxy indole acetic acid, vanillylmandelic acid, adrenaline, noradrenaline, levels were measured in 24-hour urine. Dopamine levels, aldosterone levels, adrenocorticotropic hormone levels, cortisol levels, norepinephrine levels, and epinephrine levels, and complete blood count were also measured with serum tests. Each patient had abdominal computed tomography or magnetic resonance imaging. Decisions about surgery for the patients were made in a multidisciplinary council. Detailed verbal and written consent was obtained from each patient before surgery. In patients with diagnosed or suspected pheochromocytoma, alpha-blocker (doxazosin 4 mg 2x1), and beta-blocker (propranolol hydrochloride 40 mg 1x1), treatment was started with the recommendation of the preoperative endocrinology department. Intravenous fluid replacement was performed before surgery. Ceftriaxone 1 g was administered for prophylaxis before surgery.

All patients underwent laparoscopic adrenalectomy using the transperitoneal method in the lateral decubitus position under general anesthesia. The pneumoperitoneum was created with the help of a Veres needle. A 10 mm trocar was placed 3 cm lateral to the umbilicus. Two more trocars, measuring 5 mm and 10 mm, were placed to form a triangle in relation to each other. In patients who underwent right adrenalectomy, an additional 5 mm trocar was placed for liver retraction. Adrenal vein control was performed with the help of Hem-o-lock or metal clips. A 21f silicone drain was placed in the operation area after the masses were removed with an endo bag.

Each patient's age, sex, hormonal activity status, tumor side and size, hospital stay, amount of bleeding, operation time, complication rates, pathology results, and surgical margin status were recorded. Complications were evaluated with the Clavien-Dindo classification (8).

Statistical Analysis

Statistical analyses were performed using SPSS (version 16). In comparison between groups, continuous variables were evaluated using Mann-Whitney U test or Independent Samples t-test, depending on the data distribution. Categorical variables were examined with appropriate cross-tab statistics. A comparison of qualitative variables was made using chi-square and McNemar tests. The results were evaluated at the 95% confidence interval, and the significance level was $p<0.05$.

Results

The demographic characteristics of the two groups and operation-related data are summarized in Table 1. In the <4 cm group, 17 patients had tumors on the right side, while 5 patients had tumors on the left. In the >4 cm group, 4 patients had tumors on the right side, and 26 patients had tumors on the left. The average tumor size of the <4 cm group was 24.47 mm, and that of the >4 cm group was 67.09 mm. The average ages of the <4 cm group and >4 cm group were 57 and 53.2 years.

Table 1. Demographic characteristics of patients and operation-related data			
	<4 cm group	**>4 cm group**	**p-value**
Number of patients	22	30	
Age (years)	57 (29-68)	53.2 (39-79)	p=0.731
Gender (female/male)	13/9	16/14	
Side (right/left)	17/5	4/26	
Hospitalization period (days)	3.63±1.25 (2-7)	4.35±1.61 (2-7)	p=0.11
Tumor size (millimeters)	24.47±7.40 (12-35)	67.09±28.96 (41-140)	p<0.05
Surgery time (minutes)	192.42±60.47 (60-285)	207.57±51.06 (122-315)	p=0.392
Bleeding amount (mL)	75.78±45.03 (30-200)	80.43±53.04 (20-230)	p=0.761
Hormonal activity (active/inactive)	19/3	17/13	
Complications (none/clavian 1/clavian 2)	16/3/3	23/4/4	p>0.05
Surgical margin positivity (negative/positive)	21/1	30/0	p>0.05
Pathology result	20 Adrenocortical adenoma 1 Pheochromocytoma 1 Metastatic carcinoma	14 Adrenocortical adenoma 3 Adrenocortical hyperplasia 4 Pheochromocytoma 3 Myelolipoma 2 Adrenocortical carcinoma 1 Metastasic carcinoma 2 Pseudocyst 1 Adrenal endothelial cyst	

The average hospitalization day was 3.63 days in the >4 cm group and 4.35 days in the <4 cm group. There was no statistically significant difference between these two groups (p=0.11). The average operation time was 207.57 minutes in the >4 cm group and 192.42 minutes in the <4 cm group. The difference between these two groups was not statistically significant (p=0.392). The average amount of bleeding was found to be 80.43 mL in the >4 cm group 75.78 mL in the <4 cm group, and this difference was not statistically significant (p=0.761).

In the <4 cm group, Clavien class 2 complications were observed in 3 patients, and Clavien class 1 complications were observed in 3 patients. In the >4 cm group, Clavien class 1 complications were reported in 4 patients, and Clavien class 2 complications were reported in 4 patients. However, no significant difference was found between these two groups regarding complications (p>0.05). No complications occurred in any of the patients with Clavien 3 or higher.

As noted in the classification above, postoperative low saturation was detected in 1 patient and improved with triflow exercise. One patient received one unit of an erythrocyte suspension transfusion. One patient was extubated postoperatively, and then intubated again due to low saturation and taken to intensive care, but later their saturation improved spontaneously. One patient developed atrioventricular block during surgery, and improved later. One patient had mild postoperative chest pain, but no problem was detected in the examinations performed afterwards, and it improved spontaneously. A few patients used analgesics due to pain during their postoperative hospitalization.

Hypertensive attacks were observed during the operation in two cases diagnosed with pheochromocytoma. Both attacks occurred during maneuvers applied to the adrenal tissue while releasing the surrounding tissue. In one case with a diameter of 42 mm, the session had to be interrupted three times for approximately 30 minutes each due to hypertensive attacks. Anesthesiologists controlled hypertensive episodes intraoperatively.

In a patient with a 2 cm tumor, the pathology of which was reported as adrenocortical adenoma surgical margin positivity was detected. No positive surgical margins were detected in any of the other 51 patients. All surgeries were completed laparoscopically. In a follow-up of at least 2 years of patients, with malignancy detected in their pathology, port site metastasis, which is considered a feared complication in malignant adrenal masses, was not detected in any patient. No intraoperative or postoperative blood transfusion was performed in either group.

Discussion

Laparoscopic adrenalectomy is currently the preferred surgical method for most patients with adrenal tumors. The laparoscopic method has many advantages compared to open surgery, such as fewer complications, less analgesic need, less blood loss, earlier mobilization, quicker nutritional recovery of the patient, and shorter hospital stay.

The size of the incision made to remove the tumor is proportional to its size. The disadvantages of a large tumor diameter are wound infection due to the lengthening of the incision, delay in

wound healing, and a higher risk of incisional hernia. However, no wound infection, evisceration, or incisional hernia was detected in our patients during the 1-year follow-up. However, because this incision will be much more prominent in open surgery, laparoscopic surgery clearly reduces the incision size in large masses (9).

It is stated that approximately 20-40 cases are needed to complete the learning curve for laparoscopic adrenalectomy. On the other hand, high volume surgeons are defined as those who perform 6 or more cases of adrenalectomy per year (10). While National Comprehensive Cancer Network recommends the open method in adrenocortical carcinomas, regardless of size, European Society of Endocrine Surgeons recommends (weak recommendation) laparoscopic adrenalectomy only in high-volume centers and high-volume surgeons in lesions with suspected adrenocortical carcinoma under 6 cm and without suspicion of invasion. However, adrenocortical cancer does not contraindicate laparoscopic adrenalectomy. In our study, no recurrence was detected in the 3-year follow-up of 2 patients with tumor sizes of 6.5 cm and 7 cm who underwent laparoscopic adrenalectomy, and whose pathology was reported as adrenocortical carcinoma (11,12).

The risk of port metastasis or local recurrence after laparoscopic adrenalectomy in large masses with malignant potential is not fully known, but port site metastasis has rarely been reported. Port site metastases appear to be more common in adrenalectomy performed for metastatic masses. In the study conducted by Micali et al. (13), laparoscopic adrenalectomy was performed on 330 patients, and port site metastases were detected in 4 of these patients. Three of these four metastases had metastatic adrenal masses with a primary origin in another organ. In our study, no port site metastasis was detected in at least a 2-year follow-up of a total of 4 patients diagnosed with adrenocortical carcinoma and with metastatic masses.

The laparoscopic method is generally recommended for adrenal masses under 4 to 5 cm in diameter. Open adrenalectomy is recommended in patients with suspected or known invasion, vein thrombus, or positive surgical margins. However, many publications have shown that laparoscopic adrenalectomy is a safe and effective method for large adrenal masses (>4-5 cm) (14-18). Novitsky et al. (19) reported in their study that laparoscopic adrenalectomy for masses larger than 5 cm is equally effective and safe for both right and left-located tumors. However, it is also suggested that laparotomy may be more effective in locally invasive tumors, and hand-assisted laparoscopy may be considered (9). Although no complications related to the incision site developed in our case series, considering the incision required for specimen removal in large masses (>10 cm), hand-assisted laparoscopy may also be considered as an option in these patients.

Agrusa et al. (20) found that laparoscopic adrenalectomy showed better surgical results compared to open adrenalectomy. However, they stated that it is still controversial whether this technique is safe and applicable for large adrenal masses due to the increased risk of malignant lesions. The study argues that laparoscopic adrenalectomy is safe and appropriate for adrenal masses larger than 5-6 cm, but open surgery should be considered in cases of suspected malignant invasion (20).

Young and Thompson (21) argued that the 3.6% conversion rate to open surgery in laparoscopic adrenalectomy, means the surgeon should be knowledgeable about open adrenalectomy even if they use the laparoscopic method. Therefore, any surgeon who performs laparoscopic adrenalectomy should also be familiar with the open surgical approach. This will make the surgery safer and more effective, and will allow the surgeon to perform it more comfortably.

Study Limitations

The complication rates encountered in this study were lower in both large and small masses compared to the literature. However, more accurate comparisons can be made as the number of patients increases. A limitation of our study is the small number of cases. A larger number of patients would have increased the sample size and therefore the reliability of the study.

Although many complications, such as injuries to the spleen, pancreas, colon, duodenum, kidney, and vascular injuries, have been reported in the literature, there was no organ injury or significant vascular injury in any of our cases (16,17,22-26). This situation suggests that surgeons who have completed the learning curve can perform laparoscopic adrenalectomy on large adrenal masses as safely and effectively as on small adrenal masses.

It is important to acknowledge the limitations of our study. Firstly, it was retrospective and conducted at a single center. Secondly, the sample size was relatively small. Thirdly, the follow-up period was less than three years.

Conclusion

Recently, there has been a trend towards minimally invasive surgery, especially in urology. While open adrenalectomy was previously performed, today the majority of adrenal surgeries are performed laparoscopically or robotically. Considering the cost of robotic surgery, laparoscopic adrenalectomy has an essential place in adrenal gland surgery. Although there is an opinion that laparoscopic adrenalectomy surgery would be complicated in cases of large masses, our study found that the

laparoscopic approach for masses larger than 4 cm and below 4 cm had similar effectiveness and surgical reliability results. However, studies with more patients are needed to support this reliability and effectiveness.

Ethics

Ethics Committee Approval: Approval was received from the Düzce University Non-invasive Health Research Ethics Committee on 06.09.2021 with decision number 2021/184.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

Conflict of Interest: Ali Tekin, MD, is Section Editor in Journal of Urological Surgery. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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References

1. Vaughan E, Blumenfeld J, JD P. The adrenals. Campell's Urology 8th edition. 2002. [Crossref]
2. Abecassis M, McLoughlin MJ, Langer B, Kudlow JE. Serendipitous adrenal masses: prevalence, significance, and management. Am J Surg. 1985;149:783-788. [Crossref]
3. Mantero F, Terzolo M, Arnaldi G, Osella G, Masini AM, Alì A, Giovagnetti M, Opocher G, Angeli A. A survey on adrenal incidentaloma in Italy. Study group on adrenal tumors of the Italian Society of Endocrinology. J Clin Endocrinol Metab. 2000;85:637-644. [Crossref]
4. Angeli A, Osella G, Alì A, Terzolo M. Adrenal incidentaloma: an overview of clinical and epidemiological data from the National Italian Study Group. Horm Res. 1997;47:279-283. [Crossref]
5. Cerfolio RJ, Vaughan ED Jr, Brennan TG Jr, Hirvela ER. Accuracy of computed tomography in predicting adrenal tumor size. Surg Gynecol Obstet. 1993;176:307-309. [Crossref]
6. Young WF Jr. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. Endocrinol Metab Clin North Am. 2000;29:159-185, x. [Crossref]
7. Elfenbein DM, Scarborough JE, Speicher PJ, Scheri RP. Comparison of laparoscopic versus open adrenalectomy: results from American College of Surgeons-national surgery quality improvement project. J Surg Res. 2013;184:216-220. [Crossref]
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-213. [Crossref]
9. Winfield HN, Hamilton BD, Bravo EL, Novick AC. Laparoscopic adrenalectomy: the preferred choice? a comparison to open adrenalectomy. J Urol. 1998;160:325-329. [Crossref]
10. Ginzberg SP, Gasior JA, Kelz LR, Passman JE, Soegaard Ballester JM, Roses RE, Fraker DL, Wachtel H. Adrenalectomy approach and outcomes according to surgeon volume. Am J Surg. 2024;229:44-49. [Crossref]
11. Gaujoux S, Mihai R; joint working group of ESES and ENSAT. European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma. Br J Surg. 2017;104:358-376. [Crossref]
12. Shah MH, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, Chan J, Das S, Dickson PV, Fanta P, Giordano T, Halfdanarson TR, Halperin D, He J, Heaney A, Heslin MJ, Kandeel F, Kardan A, Khan SA, Kuvshinoff BW, Lieu C, Miller K, Pillarisetty VG, Reidy D, Salgado SA, Shaheen S, Soares HP, Soulen MC, Strosberg JR, Sussman CR, Trikalinos NA, Uboha NA, Vijayvergia N, Wong T, Lynn B, Hochstetler C. Neuroendocrine and adrenal tumors, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19:839-868. [Crossref]
13. Micali S, Celia A, Bove P, De Stefani S, Sighinolfi MC, Kavoussi LR, Bianchi G. Tumor seeding in urological laparoscopy: an international survey. J Urol. 2004;171:2151-2154. [Crossref]
14. Kazaryan AM, Mala T, Edwin B. Does tumor size influence the outcome of laparoscopic adrenalectomy? J Laparoendosc Adv Surg Tech A. 2001;11:1-4. [Crossref]
15. Gill IS. The case for laparoscopic adrenalectomy. J Urol. 2001;166:429-436. [Crossref]
16. Gagner M, Pomp A, Heniford BT, Pharand D, Lacroix A. Laparoscopic adrenalectomy: lessons learned from 100 consecutive procedures. Ann Surg. 1997;226:238-246; discussion 246-247. [Crossref]
17. Henry JF, Sebag F, Iacobone M, Mirallie E. Results of laparoscopic adrenalectomy for large and potentially malignant tumors. World J Surg. 2002;26:1043-1047. [Crossref]
18. Gan L, Peng L, Meng C, Zheng L, Zeng Z, Ge S, Wang Z, Li K, Li Y. The role of laparoscopic adrenalectomy in the treatment of large pheochromocytomas (>6 cm): a meta-analysis and systematic review. Int J Surg. 2023;109:1459-1469. [Crossref]
19. Novitsky YW, Czerniach DR, Kercher KW, Perugini RA, Kelly JJ, Litwin DE. Feasibility of laparoscopic adrenalectomy for large adrenal masses. Surg Laparosc Endosc Percutan Tech. 2003;13:106-110. [Crossref]
20. Agrusa A, Romano G, Frazzetta G, Chianetta D, Sorce V, Di Buono G, Gulotta G. Laparoscopic adrenalectomy for large adrenal masses: single team experience. Int J Surg. 2014;12(Suppl 1):S72-S74. [Crossref]
21. Young WF Jr, Thompson GB. Role for laparoscopic adrenalectomy in patients with Cushing's syndrome. Arq Bras Endocrinol Metabol. 2007;51:1349-1354. [Crossref]
22. Prinz RA. A comparison of laparoscopic and open adrenalectomies. Arch Surg. 1995;130:489-492; discussion 492-494. [Crossref]
23. Thompson GB, Grant CS, van Heerden JA, Schlinkert RT, Young WF Jr, Farley DR, Ilstrup DM. Laparoscopic versus open posterior adrenalectomy: a case-control study of 100 patients. Surgery. 1997;122:1132-1136. [Crossref]
24. Conzo G, Gambardella C, Candela G, Sanguinetti A, Polistena A, Clarizia G, Patrone R, Capua FD, Offi C, Musella M, Iorio S, Bellastella G, Pasquali D, Bellis AD, Sinisi A, Avenia N. Single center experience with laparoscopic adrenalectomy on a large clinical series. BMC Surgery. 2018;18:1-7. [Crossref]
25. Wang L, Liu B, Wu Z, Yang Q, Chen W, Sheng H, Xu Z, Xiao L, Wang C, Sun Y. Comparison of single-surgeon series of transperitoneal laparoendoscopic single-site surgery and standard laparoscopic adrenalectomy. Urology. 2012;79:577-583. [Crossref]
26. Fassnacht M, Tsagarakis S, Terzolo M, Tabarin A, Sahdev A, Newell-Price J, Pelsma I, Marina L, Lorenz K, Bancos I, Arlt W, Dekkers OM. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European network for the study of adrenal tumors. Eur J Endocrinol. 2023;189:G1-G42. [Crossref]

ORIGINAL RESEARCH
Basic Science

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Mitigation of Renal Injury in Wistar Rats Using Adipose Tissue-derived Mesenchymal Stromal Cells and Simvastatin

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

Ischemia-reperfusion injury (IRI) remains one of the primary risk factors contributing to adverse outcomes in kidney transplantation. Combining adipose-derived mesenchymal stem cells and simvastatin enhances renal function after IRI, indicating synergy. Neutrophil gelatinase-associated lipocalin was identified as a potential early biomarker for renal IRI.

Abstract

Objective: Renal ischemia-reperfusion injury (IRI) is a major cause of acute kidney injury, negatively impacting short- and long-term kidney transplantation results. No effective treatment is available to protect or treat IRI currently. We aimed to investigate the role of pre-injury oral simvastatin and adipose tissue-derived mesenchymal stem cells (MSC) infusion, alone or in combination, to prevent and treat renal IRI, and to evaluate neutrophil gelatinase-associated lipocalin (NGAL) as an early biomarker for IRI in a rat model.

Materials and Methods: The study was conducted on adult male Wistar rats (n=75, 8-12 weeks old). Rats were divided into the following groups: healthy group (H) (no surgery, no treatment); control (C) (lesion animals + no treatment); oral simvastatin + lesion animals (S); MSC infusion + lesion animals (SC); MSC infusion + oral simvastatin + lesion animals [stem cells plus simvastatin (SC+S)]. Blood samples were collected at days 0, 15, and 30 for measurement of serum creatinine (Cr) and on day 1 for measurement of NGAL protein. The animals were followed up for 30 days, at which time a histopathological analysis was performed.

Results: The model used was able to establish IRI, as NGAL levels were significantly higher in the interventional groups. Cr increased at 15 days and returned to baseline, showing a pattern that was significant in the SC+S group. The combination of MSC and simvastatin resulted in lower renal IRI morphologic scores.

Conclusion: The combination of pre-injury oral simvastatin and MSC infusion synergistically prevents experimental renal IRI.

Keywords: Basic science, reconstructive urology, transplantation and vascular surgery

Introduction

Chronic kidney disease is a highly prevalent disease. Data from the global database on donation and transplantation reveal a high rate of patients using replacement therapies such as renal transplantation and dialysis (1-3). A comparison of these two substitutive therapies reveals the superiority of renal transplantation in terms of quality of life and other aspects (4). However, renal transplantation promotes ischemic tissue injury, experienced by the organ during transplantation, the so-called

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renal ischemia-reperfusion injury (IRI). An inopportune injury can jeopardize renal function during warm ischemia during partial nephrectomy. Considering both circumstances renal transplantation and partial nephrectomy to mitigate IRI are essential (5-9).

For decades now, several clinical protocols and drugs have been used with the aim of reducing renal tissue degradation. Considering the post-transplant scenario, losses of implanted grafts are occurring (2). Therefore, promising therapeutic alternatives, such as stem cell (SC) therapies and anti-oxidative stress drugs, are now being studied (6,10,11).

Mesenchymal stromal cells (MSC) are adult and multipotent cells that can differentiate into mesodermal cell lines (12). These cells have important properties such as the production and release of anti-inflammatory and immunomodulatory molecules, growth factors, and angiogenic factors (10). Their low immunogenicity allows these cells to be widely used in research and allogeneic transplants without the need for compatibility tests (13,14). The use of MSC or their extracellular vesicles as a treatment for IRI resulted in better renal function and faster recovery of renal epithelial cells, decreased cellular apoptosis, and increased anti-inflammatory cytokines, antioxidants, and renal-specific growth factors in acute renal tubular necrosis (11,12,14-17).

Simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, was previously demonstrated to modulate inflammation and oxidative stress in experimental models. In addition to the known beneficial effects of simvastatin on cholesterol reduction, recent studies have shown a potential renoprotective effect during warm ischemia (18-20).

However, to date, studies investigating the combined use of simvastatin and adipose tissue-derived mesenchymal stromal cells (ADSCs) to prevent kidney damage have not been performed. These therapies used synergistically led to beneficial results in bone fracture recovery and ADSC growth acceleration (21,22).

Therefore, our study aims to investigate the potential use of simvastatin and ADSC in improving renal function when used either alone or in combination, as a form of warm IRI treatment in an experimental model. Additionally, we aim to evaluate neutrophil gelatinase-associated lipocalin (NGAL) as an early biomarker for IRI.

Materials and Methods

All procedures performed in this study involving human subjects were in accordance with the ethical standards of the Research Ethics Committee (approval number 31647514.7.0000.0020, date: 09.06.2015 - Pontifical Catholic University of Puerto Rico Ethics Committee) and with the 1964 Helsinki Declaration or comparable ethical standards. All procedures performed in this study involving animals were in accordance with the ethical standards of the Ethics Committee for Animal use PUC-PR (approval number 0882, date: 05.06.2014 - Pontifical Catholic University of Puerto Rico Ethics Committee).

ADSC samples were isolated from the liposuction of two healthy human donors who agreed to participate in the study and signed the informed consent form.

Animals

Adult male Wistar rats (*Rattus norvegicus*) were used (n=75) with a mean age of 8-12 weeks and averaging 300 g of body mass. The rats were housed in polypropylene cages measuring 41×34×16 cm, with four rats per cage. Temperature, humidity, and light were controlled (18-21 °C, 55-65% relative humidity, 12-hour light-dark cycle). They had ad libitum access to standard rodent feed (NUVITAL®, PR - Brazil) and water. The bedding material, consisting of pine wood shavings (Inbrasfama, PR - Brazil), was replaced daily. Prior to the commencement of the experimental protocol, the animals underwent a ten-day acclimatization period.

All efforts were made to minimize suffering while also minimizing the number of animals used. Sixty animals underwent the ischemia/reperfusion surgical procedure (as described below). Rats were divided into six groups. The control group (group C, n=15) underwent the surgical procedure but did not receive any therapeutic intervention, as they were inoculated with a sterile infusion of DMEM-F12 (Dulbecco's Modified Eagle Medium/ Nutrient Mixture F-12) culture medium (Gibco™ Invitrogen Corporation, NY, USA) below the renal capsule. Additionally, a group was used as a control, aiming to investigate the potential use of the accuracy of NGAL as an IRI biomarker. A healthy group (group H, n=15) was kept under the same conditions but was not submitted to the surgical procedure or receive any treatments. In the remaining three groups, the ischemia/reperfusion surgical procedures were performed, along with simvastatin (Pharmacy of Manipulation, Viaflora, Curitiba) and/or ADSC infusions, oral simvastatin (S, n=15), ADSC infusion (SC, n=15), ADSC infusion + oral simvastatin (SC+S, n=15) (Figure 1).

Experimental Warm Renal Dysfunction Model (Surgical Procedure)

This experiment was designed to investigate whether Simvastatin and ADSC, alone or in association, would prevent renal degradation. After analgesia with morphine (DIMORF®, Cristalia, SP - Brazil) 2.5 mg/kg and anesthesia with ketamine (Ketamin®, Cristalia, SP-BR) 75 mg/kg combined with xylazine (ANASEDAN®, Ceva, SP-BR) 10 mg/kg, the renal I/R procedure was performed according to Cai et al. (23), with modifications. Briefly, a xiphopubic incision was made,

followed by moving away viscera and locating and dissecting the right kidney. The right renal vascular pedicle and ureter were ligated, and a right nephrectomy was performed. The left kidney was then located and dissected. The left renal hilum was clamped using a Bulldog clamp (Kent Scientific Corporation©, CT, USA) for 60 minutes. After observing kidney reperfusion for five minutes, the peritoneal cavity was reviewed, and the abdominal wall was closed using a continuous suture.

Cell Isolation and Culture of Adipose-derived Mesenchymal Stem Cells

A total of 200 mL of adipose tissue were obtained from donors who underwent liposuction. ADSCs were isolated using the enzymatic digestion method according to Rebelatto et al. (24). Briefly, the adipose tissue was washed with phosphate-buffered saline (PBS) (Gibco™ Invitrogen Corporation, NY, USA), and the tissue was digested with collagenase type I (Gibco™ Invitrogen Corporation, NY, USA) at 37 °C for 30 minutes. The material was subsequently filtered through a 100-µm filter (BD FALCON™, BD Biosciences Discovery Labware, Belford, USA). Next, a homemade red blood cell lysis buffer was used, followed by another wash with PBS. The cells were cultured in 75 cm^2 flasks with DMEM-F12 medium supplemented with 10% fetal bovine serum, penicillin (100 units/mL), and streptomycin (100 µg/mL) (Gibco™ Invitrogen Corporation, NY, USA). The culture medium was replaced twice a week. When the cultures reached approximately 80-90% confluency, cells were dissociated using 0.25% trypsin/EDTA (Invitrogen, Auckland, NZ) and replated (passage 1). When the optimal number of cells for transplantation was reached, the cell viability test was performed using the vital dye 7-amino-actinomycin D (7-AAD) and Annexin-V (BD Pharmingen®, Becton Dickinson and Company, NJ, USA).

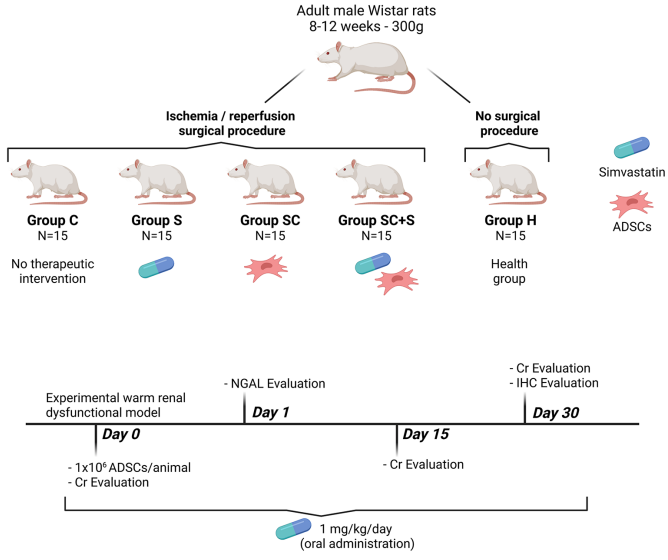

Figure 1. Study design and schematic representation of the days before and after the treatment until the end of the experiments

NGAL: Neutrophil gelatinase-associated lipocalin, ADSCs: Adipose tissue-derived mesenchymal stromal cells, Cr: Creatinine, IHC: Immunohistochemistry, SC+S: Stem cells plus simvastatin

Immunophenotypic analysis was performed by staining 5×10^5 ADSC cells. The cells were incubated with conjugated monoclonal antibodies against the following antigens: CD90, CD29, CD73, CD166, CD105, and CD34 (all PE-conjugated), CD29, CD45 [peridinin chlorophyll protein (PerCP)-conjugated]; CD14 and CD19 (both fluorescein isothiocyanate isomer-conjugated); and human leukocyte antigen-DR isotype (HLA-DR) (PerCP-conjugated). All antibodies are from Becton Dickinson, San Diego, CA, USA. The incubations were performed at room temperature for 30 min. Isotype-identical antibodies served as controls. After incubation, the cells were washed with PBS and fixed with PBS containing 1% paraformaldehyde (Exodo Cientifica/F09640SO, Sumare, SP, Brazil). The FACSCalibur flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA) was used for data acquisition, and FlowJo software (FlowJo, Ashland, OR, USA) was used for flow cytometry analysis.

Treatments

The S, SC, and SC+S groups received simvastatin, ADSC infusion, and both, respectively. Oral simvastatin (1 mg/kg/day) was administered for 30 days through the gavage technique. ADSC ($1x10^6$ cells/animal) were infused directly into the medial portion of the renal capsule five minutes after organ reperfusion.

Biomarkers

Blood samples were obtained from jugular vein punctures at days 0 (preoperative values) and after 15 and 30 for checking serum creatinine (Cr) and on day 1, to check NGAL serum concentration in order to demonstrate acute IRI. Serum NGAL protein was measured by enzyme-linked immunosorbent assay (ELISA) using Abcam's Rat Lipocalin-2 ELISA Kit (ab119602) (Abcam©, Cambridge, UK), according to the manufacturer's instructions. This experiment was designed to investigate NGAL serum concentration as a biomarker for an experimental IRI model (25,26). The absorbance was read with a 450 nm filter.

According to the manufacturer's instructions, Cr was quantified to evaluate kidney function using the Laborclin serum Cr detection kit (cat. #742071; Laborclin Laboratory Products LTDA, Pinhais, PR, BR). The output was read in the semi-automated biochemical analyzer, Quick Lab Drake (Drake©, São José do Rio Preto, SP, BR).

Renal Histopathology

At the end of 30 days, histochemical evaluations were performed using hematoxylin/eosin (HE). Histological fixation was properly performed, sections were made and stained with HE and analyzed under light microscopy (Nikon/E100/Tokyo/Japan). Histopathological analysis of renal tissue was performed

according to the criteria described by Jablonski et al. (27) and Kocak et al. (28). Because the glomeruli of the animals showed no significant histopathological alterations, the renal damage was characterized as tubular necrosis, following the score described (Table 1).

Statistical Analysis

The quantitative variables are described as mean ± standard deviation, median ± interquartile, and/or minimum and maximum when appropriate. NGAL protein and Cr were compared using the Kruskal-Wallis test. A non-parametric test (Friedman test) was used to compare Cr concentration within each group at time points 0, 15, and 30 days. The Kruskal-Wallis was also applied to compare renal histopathology, followed by Dunn's multiple comparison test. Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA). Statistical significance was accepted at $p<0.05$.

Results

Serum NGAL Protein

We tested blood samples from the study groups, then compared these to a healthy group (no surgery, no treatment). NGAL levels were significantly higher in all interventional groups compared to healthy rats ($p<0.05$). NGAL was also different in the comparisons Healthy × other groups ($p<0.05$), Control vs. SC ($p=0.003$), and SC vs. S ($p=0.028$) (Kruskal-Wallis non-parametric test). Figure 2 demonstrates NGAL concentrations 24 hours after surgery. The study successfully demonstrated that NGAL serum concentration was directly associated with acute IRI.

Histopathological Analysis

The combination SC+S group had a median histopathological score of 2, indicating tissue injury confined to the renal cortex. Control, S, and SC groups were classified with a median score of 3. Score 3 indicates that the necrotic lesions of the tubular cells extend to the renal medulla and are thus considered more severe lesions. Group S ($p>0.05$) and SC ($p>0.05$), both with a score of 3, failed to exhibit reduced renal tubular changes when compared to the control. However, the combination SC+S group showed a significant decrease in renal tubular damage with a score of 2 ($p<0.0001$) (Figure 3).

Table 1. Classification of renal injury

Score	Criteria
0	Normal histology
1	Necrosis of individual cells
2	Necrosis of adjacent cells of the proximal convoluted tubules, confined to the renal cortex
3	Necrosis of the proximal tubules extending across the cortex
4	Necrosis affecting all segments of proximal convoluted tubules

Source: Adapted from Kocak et al. (28)

In addition to tubular necrosis, persistent qualitative aspects were observed, which involved the abnormal congestion of tubular capillaries and the presence of an inflammatory process (Figure 4).

Adipose Tissue-Derived Mesenchymal Stromal Cell Expansion and Characterization

The 7-AAD assay (viability of 92.33%) and Annexin V assay (apoptosis of 5.91%) results demonstrated that the cells were viable. Visual observation under bright field microscopy showed that cells had fibroblastic morphology and the capacity to adhere to plastic (Figure 5A). Immunophenotypic characterization of surface antigens from adipose tissue-derived MSCs exhibited positive signals for CD29, CD73, CD90, CD105, and CD166 in >95% of the cells, and negative or reduced (<2%) expression of CD14, CD19, CD34, CD45, and HLA-DR (Figure 5B), in accordance with the minimum criteria established by the International Society for Cellular and Gene Therapy (29).

Serum Creatinine

The analysis showed no significant difference in Cr concentration between the groups at baseline (day 0) ($p=0.751$). Control and S groups showed elevated Cr on day 15. Such alteration persisted until day 30 ($p<0.05$). However, considering both groups infused with SC (group SC only and SC+S), a decrease in Cr was observed on day 30 regardless of a negative Cr increase on day 15. The observed improvement was statistically significant in the combination (SC+S) group ($p<0.05$), where Cr levels returned to baseline. Nevertheless, this improvement in Cr levels was not significant in the SC group. These data are shown in Figure 6.

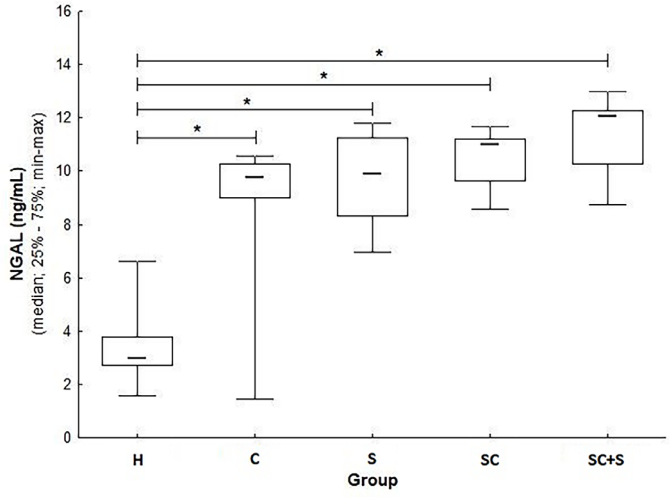

Figure 2. Serum NGAL protein concentration in the groups: healthy (H), control (C), S, SC and SC+S 24 hours after the ischemic process

NGAL: Neutrophil gelatinase-associated lipocalin, Min-max: Minimum-maximum, SC+S: Stem cells plus simvastatin, S: Simvastatin, SC: Stem cells

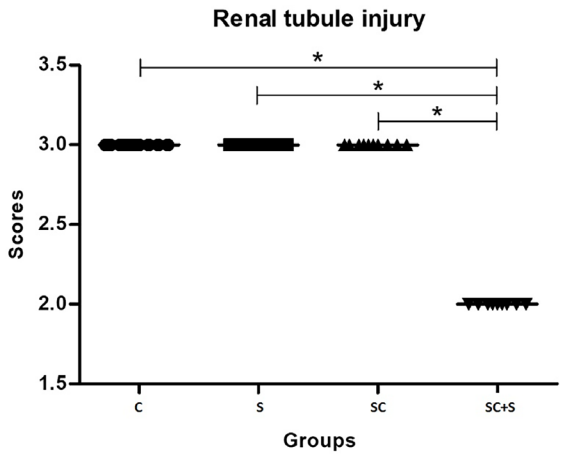

Figure 3. Renal histopathology in the groups: control (untreated animals), S, SC and SC+S submitted to ischemia-reperfusion ($p<0.0001$). The combination SC+S group showed a significant decrease in renal tubular damage compared to the other groups studied

SC+S: Stem cells plus simvastatin, S: Simvastatin, SC: Stem cells

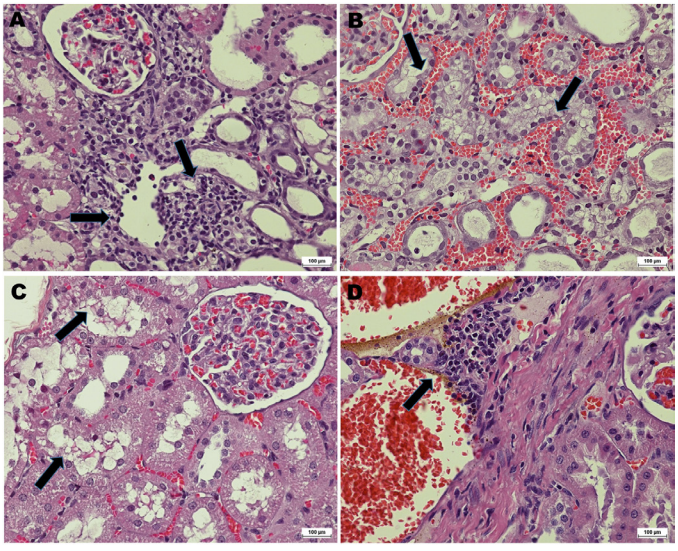

Figure 4. Qualitative histopathological aspects characteristic of tissue lesions at 40x magnification are specifically demonstrated in images A, B, and D. The histological technique used was hematoxylin/eosin. The C image specifically demonstrates the points analyzed in the characterization of the score of Jablonski et al. (27). Arrows indicate (A) mononuclear infiltrate, (B) congestion of red blood cells in the capillaries, (C) areas of necrosis in proximal convoluted tubules, such as vacuolization of epithelial cells, nuclear degradation derived from cell death and intratubular material, and (D) migration of inflammatory cells together with congestion of blood capillaries

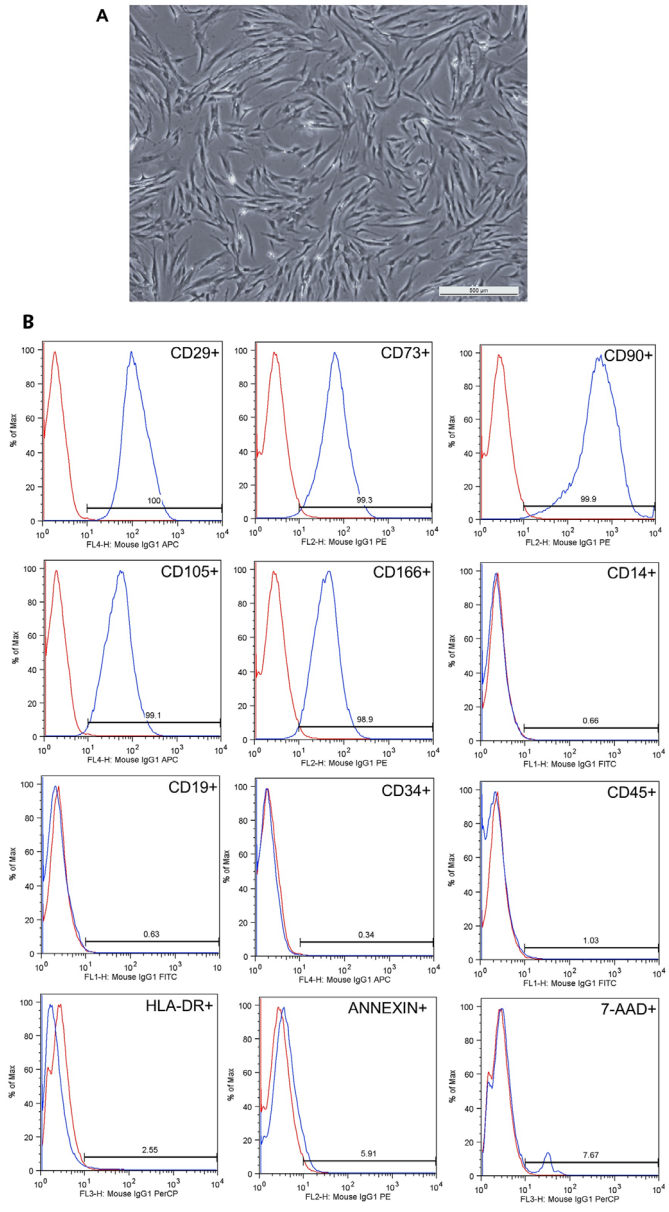

Figure 5. Adipose tissue-derived mesenchymal stem cells (MSCs) in culture and immunophenotypic characterization at passage 3. A. Representative fields showing the fibroblast-like morphology of the MSCs (magnification 50x, scale bars 500 µm). B. Representative flow cytometry analysis of cell surface markers of MSCs. The isotype control is shown as a red line histogram

Discussion

Renal injury related to ischemia and reperfusion is a consequence of warm ischemia after arterial clamping during partial nephrectomy or kidney transplantation. IRI is associated with short- and long-term postoperative complications. Treatment options to prevent or treat IRI are limited (6). In the current study, we show that a combination of ADSC and simvastatin resulted in less histological injury as well as a significant functional improvement in Cr levels in an IRI experimental model.

It has been hypothesized that NGAL could be a biomarker for IRI. Although not all studies have been consistent, there is a

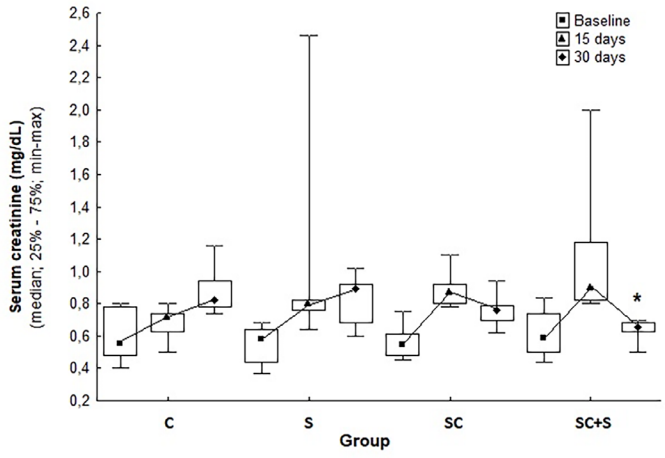

Figure 6. Serum creatinine concentration in the groups: control (untreated animals), S, SC and SC+S

SC+S: Stem cells plus simvastatin, S: Simvastatin, SC: Stem cells

general trend towards the observed outcome (25,28,30). Our results demonstrated a significant NGAL increase in all groups subjected to acute IRI compared to healthy animals. This increase in serum NGAL associated with renal damage was consistent with the findings of Corbacıoglu et al. (31) (year). Those authors successfully differentiated acute from chronic renal injury using serum NGAL. The NGAL responses, as an early biomarker of acute renal injury, we reported here are promising, but further studies involving this protein are needed. NGAL protein was not followed. Therefore, we do not yet know if the infusion of SC plus simvastatin directly into the renal capsule could generate a faster IRI recovery.

Serum Cr level was used as a standard marker of renal function. In our C and S groups, we observed a continuous increase in Cr on day 1, day 15, up to 30 days after the IRI. These data demonstrated that simvastatin alone has no therapeutic effect on the S group. Considering both groups, SC and SC+S, after an elevation in Cr on the 15th day compared with the baseline level, a subsequent reduction was observed by the 30th day. An initial reduction in glomerular filtration rate followed by an improvement was suggested. This improvement was statistically significant in the SC+S group. In this group, Cr at day 30 was similar to baseline (median at baseline of 0.59 mg/dL, median at 30 days of 0.65 mg/dL). Regardless of conflicting results, it remains to be seen if simvastatin has a potential benefit on renal function. Our findings demonstrate that simvastatin could have a synergistic role in conjunction with MSC, as we do not observe a significant reduction in Cr with ADSC infusion alone.

Particularly, there are no studies showing the beneficial effect of the combination of simvastatin and MSC in the treatment of renal injury. However, the beneficial effects of this combination have been described in the recovery of bone fractures and the acceleration of *in vitro* cell growth of SC extracted from dental pulp when exposed to simvastatin (22,32,33). Recently, Jang et al. (34) observed the same synergistic effect of bone marrow-derived MSC and simvastatin in treating induced hepatic fibrosis in rats. Through secretion of cytokines and growth factors, MSCs show immunomodulatory activity, inhibiting the activation and proliferation of immune cells, such as T-cells, B-cells, and natural killer cells, while promoting the induction of regulatory T-cells, resulting in anti-inflammatory properties. Moreover, MSCs possess the intrinsic capacity to migrate to injured tissues and release paracrine factors that promote tissue regeneration and reduce apoptosis (34). Simvastatin mitigates oxidative stress by enhancing antioxidant enzyme activity and reducing the production of reactive oxygen species. Additionally, it inhibits the expression of pro-inflammatory cytokines and adhesion molecules, improves endothelial function, and increases the bioavailability of nitric oxide (33).

Regarding the histological analysis, de Matos et al. (35) showed that cellular changes associated with inflammation, fibrosis, and necrosis occurred in the tubular epithelium after the ischemic procedure. In our study, we reported the distribution of tubular lesions for quantitative analysis because the glomeruli were intact. In consequence, tubular aspects characteristic of cell necrosis was observed, such as cell atrophy and cell and nuclear vacuolation, loss of the brush border of the epithelium of the proximal convoluted tubules, and migration of the cell nucleus and necrotic material to the center of the tubules.

Additionally, we found that the combination SC+S group had a higher mean histopathological score. According to our histological observations, repetitive events were frequent and indicative of tissue damage, such as inflammatory infiltrate and congestion of blood vessels with abnormal red blood cells, consistent with what has been previously described (36). The SC+S group was classified as having lesions confined to the cortex which are considered milder lesions than the other groups. The SC+S group underwent the same ischemic process as the other study groups and obtained a lower score. We postulate that the combined treatment effectively reduced tissue injury through synergistic anti-inflammatory and antioxidant mechanisms, which is consistent with our Cr data.

Study Limitations

In interpreting our results, we must acknowledge strengths and limitations. A strength is undoubtedly the use of standardized outcomes such as Cr and a histological Likert score. Secondly, it was clear that NGAL serum levels are associated with IRI in this experimental model and could represent a potential early biomarker of IRI as previously proposed (24). Unfortunately, several questions arose during our study. Firstly, we did not follow NGAL or accurately investigate its role as a prognostic factor for the recovery of renal function. Secondly, we have

no insight on how the protective effects of simvastatin could synergistically act with SC to promote a faster recovery of the IRI. In light of these considerations, we suggest that future studies clarify those issues.

Conclusion

Our findings indicate that the NGAL protein is associated with renal injury induced by the renal ischemia/reperfusion experimental model, suggesting it could be further explored as an early biomarker of IRI. Furthermore, the combined pleiotropic effects of simvastatin and the modulating inflammatory effects of MSC may result in a cross-potentiation, leading to improved renal function after IRI.

Ethics

Ethics Committee Approval: All procedures performed in this study involving human subjects were in accordance with the ethical standards of the Research Ethics Committee (approval number 31647514.7.0000.0020, date: 09.06.2015 - Pontifical Catholic University of Puerto Rico Ethics Committee) and with the 1964 Helsinki Declaration or comparable ethical standards. All procedures performed in this study involving animals were in accordance with the ethical standards of the Ethics Committee for Animal Use PUC-PR (approval number 0882, date: 05.06.2014 - Pontifical Catholic University of Puerto Rico Ethics Committee).

Informed Consent: ADSC samples were isolated from the liposuction of two healthy human donors who agreed to participate in the study and signed the informed consent form.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.M., D.B., L.F., Concept: F.M., D.B., A.S., S.A.B.d.M., Design: F.M., D.B., S.A.B.d.M., P.R.S.B., Data Collection or Processing: F.L.H., A.S., Analysis or Interpretation: F.M., D.B., A.S., C.L.K.R., R.P-F., Literature Search: F.L.H., D.B., S.A.B.d.M., L.F., Writing: F.L.H., L.F., R.P-F.

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

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References

1. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. PLoS One. 2016;11:e0158765. [Crossref]
2. Bello AK, Levin A, Lunney M, Osman MA, Ye F, Ashuntantang GE, Bellorin-Font E, Benghanem Gharbi M, Davison SN, Ghnaimat M, Harden P, Htay H, Jha V, Kalantar-Zadeh K, Kerr PG, Klarenbach S, Kovesdy CP, Luyckx VA, Neuen BL, O'Donoghue D, Ossareh S, Perl J, Rashid HU, Rondeau E, See E, Saad S, Sola L, Tchokhonelidze I, Tesar V, Tungsanga K, Turan Kazancioglu R, Wang AY, Wiebe N, Yang CW, Zemchenkov A, Zhao MH, Jager KJ, Caskey F, Perkovic V, Jindal KK, Okpechi IG, Tonelli M, Feehally J, Harris DC, Johnson DW. Status of care for end stage kidney disease in countries and regions worldwide: international cross sectional survey. BMJ. 2019;367:l5873. [Crossref]
3. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2020;395:709-733. [Crossref]
4. Ju A, Chow BY, Ralph AF, Howell M, Josephson MA, Ahn C, Butt Z, Dobbels F, Fowler K, Jowsey-Gregoire S, Jha V, Locke JE, Tan JC, Taylor Q, Rutherford C, Craig JC, Tong A. Patient-reported outcome measures for life participation in kidney transplantation: a systematic review. Am J Transplant. 2019;19:2306-2317. [Crossref]
5. Buys-Gonçalves GF, Abreu LAS, Gregorio BM, Sampaio FJB, Pereira-Sampaio MA, de Souza DB. Antioxidants as renoprotective agents for ischemia during partial nephrectomy. Biomed Res Int. 2019;2019:8575398. [Crossref]
6. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Ischemia/reperfusion. Compr Physiol. 2016;7:113-170. [Crossref]
7. Mir MC, Pavan N, Parekh DJ. Current paradigm for ischemia in kidney surgery. J Urol. 2016;195:1655-1663. [Crossref]
8. Malek M, Nematbakhsh M. Renal ischemia/reperfusion injury; from pathophysiology to treatment. J Renal Inj Prev. 2015;4:20-27. [Crossref]
9. Heldwein FL, McCullough TC, Souto CA, Galiano M, Barret E. Localized renal cell carcinoma management: an update. Int Braz J Urol. 2008;34:676-689; discussion 689-690. [Crossref]
10. Lange C, Tögel F, Ittrich H, Clayton F, Nolte-Ernsting C, Zander AR, Westenfelder C. Administered mesenchymal stem cells enhance recovery from ischemia/reperfusion-induced acute renal failure in rats. Kidney Int. 2005;68:1613-1617. [Crossref]
11. Cao H, Qian H, Xu W, Zhu W, Zhang X, Chen Y, Wang M, Yan Y, Xie Y. Mesenchymal stem cells derived from human umbilical cord ameliorate ischemia/reperfusion-induced acute renal failure in rats. Biotechnol Lett. 2010;32:725-732. [Crossref]
12. Arslan F, Lai RC, Smeets MB, Akeroyd L, Choo A, Aguor EN, Timmers L, van Rijen HV, Doevendans PA, Pasterkamp G, Lim SK, de Kleijn DP. Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress and activate PI3K/Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/reperfusion injury. Stem Cell Res. 2013;10:301-312. [Crossref]
13. Walczak P, Zhang J, Gilad AA, Kedziorek DA, Ruiz-Cabello J, Young RG, Pittenger MF, van Zijl PC, Huang J, Bulte JW. Dual-modality monitoring of targeted intraarterial delivery of mesenchymal stem cells after transient ischemia. Stroke. 2008;39:1569-1574. [Crossref]
14. Semedo P, Wang PM, Andreucci TH, Cenedeze MA, Teixeira VP, Reis MA, Pacheco-Silva A, Câmara NO. Mesenchymal stem cells ameliorate tissue damages triggered by renal ischemia and reperfusion injury. Transplant Proc. 2007;39:421-423. [Crossref]
15. Lian Q, Zhang Y, Zhang J, Zhang HK, Wu X, Zhang Y, Lam FF, Kang S, Xia JC, Lai WH, Au KW, Chow YY, Siu CW, Lee CN, Tse HF. Functional mesenchymal stem cells derived from human induced pluripotent stem cells attenuate limb ischemia in mice. Circulation. 2010;121:1113-1123. [Crossref]
16. Ohtaki H, Ylostalo JH, Foraker JE, Robinson AP, Reger RL, Shioda S, Prockop DJ. Stem/progenitor cells from bone marrow decrease neuronal death in global ischemia by modulation of inflammatory/immune responses. Proc Natl Acad Sci U S A. 2008;105:14638-14643. [Crossref]

17. Miyasaki DM, Senegaglia AC, de Moura SAB, Leitolis A, Capriglione LGA, Fracaro L, Boldrini Leite LM, Utumi PH, Fragoso FYI, Meyer F, Correa A, Brofman PRS. Treatment of chronic kidney disease with extracellular vesicles from mesenchymal stem cells and CD133+ expanded cells: a comparative preclinical analysis. Int J Mol Sci. 2022;23:2521. [Crossref]

18. Kostapanos MS, Liberopoulos EN, Elisaf MS. Statin pleiotropy against renal injury. J Cardiometab Syndr. 2009;4:E4-E9. [Crossref]

19. Birnbaum GD, Birnbaum I, Ye Y, Birnbaum Y. Statin-induced cardioprotection against ischemia-reperfusion injury: potential drug-drug interactions. Lesson to be learnt by translating results from animal models to the clinical settings. Cardiovasc Drugs Ther. 2015;29:461-467. [Crossref]

20. Weitz-Schmidt G, Welzenbach K, Brinkmann V, Kamata T, Kallen J, Bruns C, Cottens S, Takada Y, Hommel U. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med. 2001;7:687-692. [Crossref]

21. Incontri Abraham D, Gonzales M, Ibarra A, Borlongan CV. Stand alone or join forces? Stem cell therapy for stroke. Expert Opin Biol Ther. 2019;19:25-33. [Crossref]

22. Yang YJ, Qian HY, Huang J, Li JJ, Gao RL, Dou KF, Yang GS, Willerson JT, Geng YJ. Combined therapy with simvastatin and bone marrow-derived mesenchymal stem cells increases benefits in infarcted swine hearts. Arterioscler Thromb Vasc Biol. 2009;29:2076-2082. [Crossref]

23. Cai J, Yu X, Xu R, Fang Y, Qian X, Liu S, Teng J, Ding X. Maximum efficacy of mesenchymal stem cells in rat model of renal ischemia-reperfusion injury: renal artery administration with optimal numbers. PLoS One. 2014;9:e92347. Erratum in: PLoS One. 2014;9:e101336. [Crossref]

24. Rebelatto CK, Aguiar AM, Moretão MP, Senegaglia AC, Hansen P, Barchiki F, Oliveira J, Martins J, Kuligovski C, Mansur F, Christofis A, Amaral VF, Brofman PS, Goldenberg S, Nakao LS, Correa A. Dissimilar differentiation of mesenchymal stem cells from bone marrow, umbilical cord blood, and adipose tissue. Exp Biol Med (Maywood). 2008;233:901-913. [Crossref]

25. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol. 2003;14:2534-2543. [Crossref]

26. Faria P, Beckwith JB, Mishra K, Zuppan C, Weeks DA, Breslow N, Green DM. Focal versus diffuse anaplasia in Wilms tumor--new definitions with prognostic significance: a report from the National Wilms Tumor Study Group. Am J Surg Pathol. 1996;20:909-920. [Crossref]

27. Jablonski P, Howden BO, Rae DA, Birrell CS, Marshall VC, Tange J. An experimental model for assessment of renal recovery from warm ischemia. Transplantation. 1983;35:198-204. [Crossref]

28. Kocak C, Kocak FE, Akcilar R, Bayat Z, Aras B, Metineren MH, Yucel M, Simsek H. Effects of captopril, telmisartan and bardoxolone methyl (CDDO-Me) in ischemia-reperfusion-induced acute kidney injury in rats: an experimental comparative study. Clin Exp Pharmacol Physiol. 2016;43:230-241. [Crossref]

29. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for cellular therapy position statement. Cytotherapy. 2006;8:315-317. [Crossref]

30. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A; NGAL meta-analysis investigator group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;54:1012-1024. [Crossref]

31. Corbacıoglu SK, Cevik Y, Akinci E, Uzunosmanoglu H, Dagar S, Safak T, Oncul V, Guvendi M. Value of plasma neutrophil gelatinase-associated lipocalin (NGAL) in distinguishing between acute kidney injury (AKI) and chronic kidney disease (CKD). Turk J Emerg Med. 2017;17:85-88. [Crossref]

32. Mohammadian M, Sadeghipour HR, Kashani IR, Jahromi GP, Omidi A, Nejad AK, Golchoobian R, Boskabady MH. Evaluation of simvastatin and bone marrow-derived mesenchymal stem cell combination therapy on airway remodeling in a mouse asthma model. Lung. 2016;194:777-785. [Crossref]

33. Okamoto Y, Sonoyama W, Ono M, Akiyama K, Fujisawa T, Oshima M, Tsuchimoto Y, Matsuka Y, Yasuda T, Shi S, Kuboki T. Simvastatin induces the odontogenic differentiation of human dental pulp stem cells in vitro and in vivo. J Endod. 2009;35:367-372. [Crossref]

34. Jang YO, Kim SH, Cho MY, Kim KS, Park KS, Cha SK, Kim MY, Chang SJ, Baik SK. Synergistic effects of simvastatin and bone marrow-derived mesenchymal stem cells on hepatic fibrosis. Biochem Biophys Res Commun. 2018;497:264-271. [Crossref]

35. de Matos AC, Câmara NO, de Oliveira AF, Franco MF, Moura LA, Nishida S, Pereira AB, Pacheco-Silva A. Functional and morphologic evaluation of kidney proximal tubuli and correlation with renal allograft prognosis. Transpl Int. 2010;23:493-499. [Crossref]

36. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest. 2011;121:4210-4221. [Crossref]

ORIGINAL RESEARCH
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The Effect of Bladder Outlet Obstruction on Bladder Cancer Recurrence and Progression

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

It is known that the risk of bladder tumour detection is higher in patients with benign prostatic obstruction (BPO). In this study, the effect of BPO on the recurrence and progression of existing bladder cancer was investigated.

Abstract

Objective: To investigate the effect of bladder outlet obstruction (BOO) on cancer recurrence and progression in patients with non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: A retrospective analysis was conducted on 256 male patients diagnosed with primary NMIBC at Kartal Dr. Lütfi Kırdar City Hospital between 2010 and 2018. Patients were divided into two groups according to the presence of BOO (BOO group, n=123; control group, n=133). Demographic and pathological data, as well as intravesical treatments, recurrence and progression status of both groups were recorded and compared according to cystoscopy findings in five years of follow-up.

Results: Patients with BOO were older and had higher rates of comorbidities, larger prostate volumes, higher prostate-specific antigen levels, and more frequent cystoscopic findings of trabeculation and diverticula (p<0.001). Initial pathology showed higher rates of T1 stage and high-grade tumors in the BOO group (50% *vs.* 24%, p=0.003 and 42.6% *vs.* 21%, p=0.008, respectively). A multivariate logistic regression model indicated that BOO was not an independent variable to predict any initial bladder cancer pathology, recurrence, or progression rate (p>0.05). The presence of trabeculation in cystoscopy was found to be an independent predictor of the initial diagnosis of high-grade/carcinoma *in situ* urothelial carcinoma, with an odds ratio of 4.62 (95% confidence interval, 1.3-17; p=0.021), following adjustment for potential confounding variables.

Conclusion: Findings of this study indicate that BOO does not affect disease recurrence or progression, nor does it affect the pathological features of the tumour at the time of diagnosis. Conversely, increased bladder trabeculation resulting from BOO may be associated with a higher-grade tumor at the time of initial diagnosis.

Keywords: Bladder cancer, bladder outlet obstruction, benign prostatic hyperplasia

Introduction

Bladder cancer (BLCA) is one of the most prevalent cancers worldwide, with an estimated increase in incidence of approximately 30-40% over the past few decades, particularly among men aged 64-75 years (1). Bladder outlet obstruction (BOO) is a prevalent pathology among men of similar age categories, typically resulting from conditions such as benign prostatic hyperplasia (BPH). The prevalence of BPH is known to be 70-80% in men aged 70 and over (2). Although BPH and BLCA are distinct diseases with disparate pathophysiological alterations, epidemiological profiles, and risk factors (3,4), it has

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been demonstrated that the incidence of BLCA in patients with BOO is 20-30% higher than in those without BOO (5).

It is postulated that BOO plays a pivotal role in the pathogenesis of BLCA, resulting in significant alterations to bladder histology and physiology. BOO is associated with a number of histological changes, including hypertrophy and hyperplasia of the detrusor muscle, fibrosis, increased collagen deposition, and chronic inflammation (6). These conditions may trigger cancer development by causing cellular stress and DNA damage (7). Additionally, increased intravesical pressure and high poliovirus receptor (PVR) can trigger malignant transformation by causing mechanical stress in bladder epithelial cells and prolonged contact with carcinogenic substances (8). It has been demonstrated that conditions that cause BOO, particularly BPH, may increase the risk of BLCA by triggering increased intravesical pressure (5). Nevertheless, there is evidence that establishes a causal relationship between the two diseases. In a mendelian randomization study by Du et al. (9), genetically predicted BPH was associated with a higher risk of BLCA in all histological subtypes. Similarly, many population-based cohort studies have shown that lower urinary tract symptoms (LUTS) or BOO is associated with a high incidence of BLCA (2,5,7,10-12). However, few studies have investigated the effect of LUTS or BOO on cancer recurrence or progression after local treatment of BLCA (13). Important risk factors for recurrence and progression of BLCA include tumor characteristics as well as patient factors such as age, comorbidities, initial response, and non-response to intravesical therapies (14). The objective of this study was to examine the impact of BOO and associated cystoscopic findings on the recurrence and progression of BLCA over a five-year period.

Materials and Methods

Data Collection

A total of 256 male patients diagnosed with primary non-muscle invasive bladder cancer (NMIBC) between 2010 and 2018, who were followed for five years at the Urology Department of Kartal Dr. Lütfi Kırdar City Hospital, were included in this study. Data on the patients were reviewed retrospectively. Patients were divided into two groups based on the presence of BOO (Group 1: BOO, Group 2: Control). The inclusion criteria for the BOO group were defined as the presence of an obstructive uroflowmetry test with a voided volume over 150 cc and a maximum flow rate (MFR) below 15 mL/s, or a MFR between 15-20 mL/s accompanied by at least 6 months of α-blocker medication use, for the purposes of this study. The control group consisted of patients with a MFR of 20 mL/s or above. Patients who did not comply with the BLCA clinical follow-up protocol, underwent surgery for BOO, in the past or during the follow-up period, or had a uroflowmetric voiding volume below 150 mL were excluded from the study. Accordingly, 123 patients were included in the BOO group and 133 in the control group, making a total of 256 patients included in the study. The findings of the digital rectal examination (DRE) were recorded in accordance with the grading system proposed by Barnes et al. (15). Accordingly, prostate penetration of 1-2 cm into the rectum was classified as grade I, greater than 2 but less than 3 cm as grade II, greater than 3 but less than 4 cm as grade III, and greater than 4 cm as grade IV. The demographic data, medical histories, prostate-specific antigen levels, uroflowmetry values, cystoscopy findings, pathology results, and intravesical treatments were documented. The recurrence rate, time to recurrence, and progression during follow-up were recorded and compared between the two groups. Patients who underwent radical cystectomy/chemoradiotherapy due to MIBC development or Bacillus Calmette-Guérin (BCG) non-response or incomplete transurethral resection (TUR) were enrolled. The follow-up data of these patients after this stage, were not included in the study. Those who had at least one diverticulum larger than 3 cm and/or extensive trabeculation according to cystoscopy findings in the first or subsequent months were enrolled.

Clinical Management and Follow-Up

Patients were treated according to the European Association of Urology (EAU) guidelines for NMIBC (16). All patients underwent initial imaging of the upper urinary tract with CT urography or renal USG. After the initial transurethral resection of bladder tumor (TURBT), resection was performed within 6 weeks in patients with the relevant indication (Re-TURBT). Early intravesical chemotherapy (mitomycin-C) was administered to eligible patients within the first 6 hours. Patients were stratified according to EAU-NMIBC prognostic factor risk groups. The low-risk group was typically followed without adjuvant intravesical chemo/immunotherapy, while patients in the high-risk group received at least one-year adjuvant intravesical BCG induction cycle 2-4 weeks after re-TURBT. The intermediate-risk group received either routine clinical follow-up or at least one six-week course of adjuvant intravesical mitomycin-C.

Clinical follow-up after TURBT was performed with cystoscopy and urine cytology every 6 months for the first 2 years and annually thereafter in the low-risk group; in the intermediate- and high-risk groups, follow-up was every 3 months for the first 2 years, then every 6 months, and annually after the 5th year. Upper system imaging was performed every 1-2 years. Recurrence and progression status were determined according to the final histopathologic diagnosis obtained from repeat TURBT or urinary tract biopsy during follow-up.

This study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (approval number: 2024/010.99/6/20,

date: 26.07.2024). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Statistical Analysis

Continuous variables were presented as median (interquartile range), and categorical variables were presented as patient numbers and percentages (%). The Mann-Whitney U test was used for the comparison of continuous variables, while the chi-square test or Fisher's exact test was used for the comparison of categorical variables. Logistic regression analysis was performed to evaluate the relationship between tumor aggressiveness and BOO/cystoscopic parameters, adjusting for potential confounding variables such as age and comorbidities. The results were reported as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was considered at $p<0.05$, and all analyses were conducted using Statistical Package for the Social Sciences.

Results

Various clinical (Table 1) and pathological parameters (Table 2) were compared in patients with BLCA, categorized by the presence or absence of BOO. Patients with BOO were older than controls (69 *vs.* 61 years, p=0.001). Additionally, the rate of comorbidities was higher in patients with BOO (1 or 2 comorbidities: 73% *vs.* 38%, p=0.001). DRE grading of BPH showed higher grades in patients with BOO (grade 3: 52% *vs.* 8%, p=0.001). Prostate volume was also larger in patients with BOO (45 cc *vs.* 25 cc, p=0.001). Total prostate-specific antigen levels were higher in patients with BOO (2.1 ng/dL vs. 1 ng/dL, p=0.001). According to uroflowmetry results, the MFR value was lower in patients with BOO (11.7 mL/s *vs.* 24.5 mL/s, p=0.001). Cystoscopy findings showed more frequent trabeculation (63% *vs.* 5%, p=0.001) and diverticula (32% *vs.* 3%, p=0.001) in patients with BOO. The use of α-blockers was also more common in patients with BOO (50% *vs.* 2%, p=0.001) (Table 1).

Regarding cancer parameters, patients with BOO had higher stage (T1: 50% *vs.* 24%, p=0.003) and more advanced grade [high grade/carcinoma *in situ* (CIS): 42.6% *vs.* 21%, p=0.008] tumors at initial diagnosis. Despite the median follow-up period being 61 months for both groups, there were no statistically significant differences between the groups in terms of follow-up duration, number of recurrences, time to first recurrence, recurrence rate, and initiation rate of intravesical therapy. Although the progression rate was higher in patients with BOO, the difference was not statistically significant (16.4% *vs.* 6%, p=0.059) (Table 2).

Table 3 shows the relationship between tumor aggressiveness and presence of BOO, trabeculations, and diverticula, which were investigated in a multivariate logistic regression model, following

Table 1. Characteristics, findings related with voiding functions of the patients with bladder cancer and its subgroups according to having bladder outlet obstruction or not

	Total (n=256)	Control (n=133)	BOO (n=123)	p
Age (years)	65 (14)	61 (12)	69 (12)	**0.001**
BMI (kg/m²)	25 (5)	25 (5)	24 (5.5)	**0.76**
Comorbidities, n (%)				
None	93 (36%)	72 (54%)	21 (17%)	**0.001**
1 or 2	141 (55%)	51 (38%)	90 (73%)	
3 or more	22 (9%)	10 (8%)	12 (10%)	
Smoking status	178 (70%)	95 (72%)	83 (68%)	**0.87**
Digital rectal grading of BPH, n (%)				
Grade 1	29 (11%)	26 (20%)	3 (2%)	**0.001**
Grade 2	132 (52%)	94 (71%)	38 (31%)	
Grade 3	75 (29%)	11 (8%)	64 (52%)	
Grade 4	20 (8%)	2 (2%)	18 (15%)	
Prostate volume (cc)	32 (22)	25 (10)	45 (26)	**0.001**
Total PSA (ng/dL)	1.4 (1.8)	1 (0.8)	2.1 (3)	**0.001**
MFR (mL/sn) in uroflowmetry	18.6 (9.9)	24.5 (7.1)	11.7 (4.9)	**0.001**
Cystoscopy findings n (%)				
Trabeculation	84 (33%)	6 (5%)	78 (63%)	**0.001**
Diverticule	43 (17%)	4 (3%)	39 (32%)	
Usage of alfa blockers, n (%)	64 (25%)	3 (%2)	61 (50%)	**0.001**

Data are presented as median (interquartile range for continuous variables and number of patients (%) for categorical variables. P<0.05 is a significant diffences between the groups, PSA: Prostate-specific antigen, BOO: Bladder outlet obstruction, BPH: Benign prostatic hyperplasia, BMI: Body mass index, MFR: Maximum flow rate

adjustment for potential confounding variables, including age, comorbidities, smoking status and tumor size and number of tumors at first cystoscopy. The presence of trabeculation was an independent predictor of tumor recurrence and the initial diagnosis of high-grade/CIS urothelial carcinoma (OR 4.62; 95% CI, 1.3-17; p=0.021). The parameters related to bladder functions could not be associated with the categories determining tumor aggressiveness (p>0.05).

Table 2. A comparison of the findings in primary pathology and the recurrence and progression status in follow-up between the groups

	Control (n=133)	BOO (n=123)	p
Cancer parameters at first diagnosis			
Size (mm)	30 (20)	30 (20)	0.96
Number	2 (3)	2 (1)	0.11
Stage			
Ta	101 (75%)	62 (50%)	**0.003**
T1	32 (24%)	61 (50%)	
Grade			
Low grade	106 (79%)	70 (57.4%)	**0.008**
High grade/CIS	28 (21%)	52 (42.6%)	
Cancer parameters at follow-up			
Follow-up period (months)	61 (12)	61 (12)	0.79
No. recurrens	2.5 (3)	2 (2)	0.09
Time to first recurrence (months)	12 (12)	12 (18)	0.29
Annual recurrens rate	0.33 (0.58)	0.40 (0.47)	0.11
Progression in stage, n (%)	8 (6%)	20 (16.4%)	0.059
Intravesical treatment			
No	71 (53%)	64 (52%)	0.441
Mitomycin	22 (17%)	13 (10%)	
BCG	40 (30%)	46 (38%)	

Data are presented as median (interquartile range for continuous variables and number of patients (%) for categorical variables. P<0.05 is a significant diffences between the groups, BOO: Bladder outlet obstruction, BCG: Bacillus Calmette-Guérin, CIS: Carcinoma *in situ*

Table 3. Relationship between tumor aggresiveness and bladder outlet obstruction and cystoscopic parameters via multivariate logistic regression analysis

	Bladder outlet obstruction		Presence of trabeculation		Presence of diverticule	
	No (n=133)	Yes (n=123)	No (n=172)	Yes (n=84)	No (n=212)	Yes (n=44)
T1 stage at first diagnosis **No. pts (%)** **Adjusted OR[a] (95% CI)** **P-value**	32 (24%) Reference	60 (49%) 2.21 0.131	50 (29%) Reference	42 (50%) 2.36 0.170	73 (34%) Reference	19 (45%) 0.56 0.366
High grade/CIS at first diagnosis **No. pts (%)** **Adjusted OR[a] (95% CI)** **P-value**	28 (21%) Reference	52 (43%) 1.41 0.538	39 (23%) Reference	41 (48%) **4.62** **0.021**	63 (29%) Reference	17 (41%) 0.49 0.280
Recurrence rate more than 0.5/year **No. pts (%)** **Adjusted OR[a] (95% CI)** **P-value**	41 (30%) Reference	42 (34%) 1.25 0.67	56 (33%) Reference	27 (31%) 1.44 0.56	74 (35%) Reference	9 (18%) 0.25 0.054
Progression in stage **No. pts (%)** **Adjusted OR[a] (95% CI)** **P-value**	8 (6%) Reference	20 (16%) 4.2 0.054	18 (11%) Reference	10 (12%) 0.83 0.83	26 (12%) Reference	2 (5%) 0.11 0.09

[a]: Adjustment for potential confounding variables, including age, comorbidities, smoking status and tumor size and count in first cystoscopy, OR: Odds ratio, CI: Confidence interval, CIS: Carcinoma *in situ*

Discussion

The association between BOO/BPH and urologic cancers has received increasing attention in recent years. The frequent co-occurrence of these pathologies, especially in elderly males, has stimulated studies to investigate the potential link between them. Recently, a meta-analysis of observational studies was published (12) that clarified the conflicting results regarding the association between BPH and BLCA. Accordingly, BPH was shown to increase the risk of BLCA. Upon examination of the included studies, the most frequently cited mechanism is that the elevated intravesical pressure observed in patients with BPH, may result in lower urinary tract damage, prolonged exposure to urinary carcinogens due to high residual urine, and potential carcinogenesis (12,17). The only mendelian randomization study investigating causality in this regard was published by Du et al. (9). The results of this study indicated that BPH exhibited a weak positive effect on the occurrence of BLCA (OR: 1.095, 95% CI: p=0.003); however, no causal effect was identified for BLCA on BPH. In contrast to the aforementioned studies, our investigation focused on the presence of BOO and its effect on response to treatment in patients with NMIBC. We sought to determine whether BOO was associated with differences in pathologic variables at diagnosis and/or influenced the recurrence and progression of the disease over time.

In our study, we employed uroflowmetric evaluation (18), which is regarded as one of the most efficacious non-invasive tests for the diagnosis of BOO (8). The observation that the prostate size of the patients included in the BOO group was significantly higher indicates that BPH is a significant condition affecting these patients. In a study by Ham et al. (19), men with concurrent bladder urothelial carcinoma and BPH underwent simultaneous TURBT and transurethral resection of the prostate (TURP). It has been demonstrated that the recurrence of BLCA can be reduced by the treatment of BPH, with a 60-month recurrence-free probability of 52%, compared to 43%. However, there was no significant difference in the progression rates. A similar study corroborated this finding, demonstrating that in men with BLCA and BPH/BOO, the 5-year recurrence rate was lower in patients who had TURBT and TURP performed in the same setting compared to TURBT alone (56% *vs.* 80%, p<0.01) (20). Given that the methodology of these studies was based on dependent groups, a comparison with our data would be erroneous. If a urothelial tumor develops in the context of elevated intravesical pressure and augmented carcinogen exposure as a consequence of BOO, a reduction in the incidence of recurrence or progression following BOO treatment may be anticipated. Nevertheless, this issue continues to be a source of debate since there are studies indicating that individuals who have undergone surgical or medical treatment for BPH may be at an elevated risk of developing cancer compared to those who have not. Kang et al. (10) published a cohort study investigating the risk of BLCA in 79,280 patients hospitalized with a diagnosis of BPH. The findings indicate that BPH is not associated with an increased risk of BLCA. However, among men who underwent TURP, particularly those with other genitourinary tract conditions (such as bladder stones or infections), the risk of BLCA was elevated. The authors proposed that this is due to chronic bladder inflammation caused by recurrent urinary infection, high residual urine, or retention in treated patients (21,22). To eliminate the confounding effect of prostate surgery on BLCA and thereby more clearly demonstrate the effect of BOO on recurrence and progression, we excluded these patients from our study.

In their 2019 study, Lin et al. (2) observed that patients with BOO exhibited higher stage and grade of primary BLCA. This finding suggests that BOO may not only increase the risk of BLCA but also affect tumor aggressiveness. Similarly, in our study, the first pathology data following TURBT revealed that both the T1 tumor and high-grade tumor rates were higher in the BOO group. However, this patient group was older, had more comorbidities, and had larger tumor sizes and higher multifocality rates. It was unavoidable that these covariates would have resulted in the development of more advanced-stage disease. Consequently, we conducted a multivariate regression analysis to ascertain whether BOO was a predictor of grade and stage at the time of initial diagnosis of BLCA, which failed to prove it as an independent variable.

The relationship between LUTS occurring after TURB and BLCA recurrence was investigated in a study by Lunney et al. (13). It was shown that moderate or severe LUTS (defined as International Prostate Symptom Score ≥8) occurring within 30 days after TUR was an independent predictor for NMIBC recurrence (OR: 19.1). However, from a different perspective, there are no clear data in the literature on the effect of chronic LUTS or BOO on BLCA recurrence. The data we obtained in this study suggest that there is no association between BOO and BLCA recurrence and progression. The limited number of studies showing the effect of BOO on cancer recurrence and progression increases the importance of this study in terms of its contribution to the literature.

Bladder trabeculation is a phenomenon that develops in patients with chronic increased intra-bladder pressure. It causes bladder smooth muscle cell proliferation and hypertrophy, which are followed by fibroproliferative changes in the bladder wall (23). A similar mechanism, whereby the bladder mucosa herniates through weak gaps in the muscular layer, is observed in acquired diverticula (24). It is hypothesized that diverticula and trabeculations, which are bladder structural disorders diagnosed cystoscopically in the developmental stages of the three-stage model of BOO-induced bladder remodeling

(hypertrophy, compensation, and decompensation) (25), may also play a role in the development of BLCA. According to our hypothesis, these may have a detrimental effect on recurrence and progression, or affect TURBT success by reducing wall thickness and contributing to heterogeneity. Given the low prevalence of diverticula in our study population, the statistical reliability of our findings may be limited. However, multivariate regression analysis of 84 patients revealed that the probability of high-grade/CIS pathology being present at the time of diagnosis was 4.6 times higher compared to patients without any trabeculation. Nevertheless, our findings indicated that it had no effect on recurrence and progression. In a multicentre observational study investigating the association of detrusor wall thickness (DWT) with BLCA (26); patients with DWT >2.5 mm were significantly older, had larger and more tumors and experienced more prior NMIBC than patients with a DWT ≤2.5 mm. At univariate analysis, DWT >2.5 was a predictive risk factor for cancer recurrence and progression: OR: 4.9 (95% CI: 2.5-9.5), p=0.001, and OR: 2.21 (95% CI: 1.71-4.73), p=0.001. One of the reasons for the discrepancy between the results of this study and our own is that an increase in DWT does not necessarily coincide with an increase in trabeculation. Trabeculations are most prevalent in the decompensated stage, when bladder contractility is reduced due to the presence of fibrosis (27). This decline may negate the impact on progression and recurrence. However, it is essential to recognise that further investigation through histopathological or clinical urodynamic studies is necessary to elucidate the intricate mechanisms at play. To the best of our knowledge, this is the first study to investigate the effect of the presence of trabeculation and diverticula on initial pathology, as well as recurrence and progression.

Study Limitations

This study has several limitations. First, given the retrospective design of the study, the lack of homogenization between groups due to higher tumor grade and stage may have caused bias through reverse causality, although multivariate analysis was performed in men with NMIBC and concurrent BOO. Furthermore, since we used MFR as the main inclusion criterion for BOO, patients with underactive bladders were also likely to be evaluated in the BOO group. In addition, we could not investigate the effect of residual urine on BLCA recurrence and progression because PVR data was incomplete. Finally, we could not investigate the relationship between BOO subgroups and urothelial carcinoma due to the limited number of patients in our study population.

Conclusion

The existing literature has suggested the relationship between BOO and BLCA through observational studies. However, the underlying pathophysiology remains unclear due to the limited number of studies on causality. This study adds to the existing literature by demonstrating the prevalence of BOO in BLCA patients. It shows that BOO is not associated with the primary stage of BLCA, nor is it linked to recurrence or progression. However, bladder trabeculation may be associated with a higher primary grade of BLCA. Further research is needed to evaluate the long-term effects of BOO on BLCA development and progression, with larger studies and longer follow-up periods. Future studies should also focus on elucidating the molecular mechanisms underlying this association.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (approval number: 2024/010.99/6/20, date: 26.07.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.C., E.D., A.C., C.Ç., F.N., Concept: U.C., F.N., Design: U.C., F.N., Data Collection or Processing: U.C., E.D., A.C., C.Ç., Analysis or Interpretation: U.C., A.C., Literature Search: U.C., Writing: U.C., E.D., C.Ç., F.N.

Conflict of Interest: Fehmi Narter MD is editor-in-chief in Journal of Urological Surgery. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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References

1. Taylor JA 3rd, Kuchel GA. Bladder cancer in the elderly: clinical outcomes, basic mechanisms, and future research direction. Nat Clin Pract Urol. 2009;6:135-144. [Crossref]
2. Lin YH, Hou CP, Juang HH, Chang PL, Chen TH, Chen CL, Tsui KH. Association between bladder outlet obstruction and bladder cancer in patients with aging male. J Clin Med. 2019;8:1550. [Crossref]
3. Chughtai B, Forde JC, Thomas DD, Laor L, Hossack T, Woo HH, Te AE, Kaplan SA. Benign prostatic hyperplasia. Nat Rev Dis Primers. 2016;2:16031. [Crossref]
4. Lenis AT, Lec PM, Chamie K, Mshs MD. Bladder cancer: a review. JAMA. 2020;324:1980-1991. [Crossref]
5. Fang CW, Liao CH, Wu SC, Muo CH. Association of benign prostatic hyperplasia and subsequent risk of bladder cancer: an Asian population cohort study. World J Urol. 2018;36:931-938. [Crossref]
6. Gao Y, Liu P, He F, Yang X, Wu R, Chen W, Li L, Yang Z. Fibroblast growth factor 2 promotes bladder hypertrophy caused by partial bladder outlet obstruction. Front Cell Dev Biol. 2021;9:630228. [Crossref]

7. Di Gianfrancesco L. The association between postvoid residual and response to standard therapy in male and female patients with non-muscle-invasive bladder cancer. Curr Urol. 2023;17:251-256. [Crossref]
8. Chen SF, Lee CL, Kuo HC. Change of detrusor contractility in patients with and without bladder outlet obstruction at ten or more years of follow-up. Sci Rep. 2019;9:18887. [Crossref]
9. Du W, Wang T, Zhang W, Xiao Y, Wang X. Genetically supported causality between benign prostate hyperplasia and urinary bladder neoplasms: a mendelian randomization study. Front Genet. 2022;13:1016696. [Crossref]
10. Kang D, Chokkalingam AP, Gridley G, Nyren O, Johansson JE, Adami HO, Silverman D, Hsing AW. Benign prostatic hyperplasia and subsequent risk of bladder cancer. Br J Cancer. 2007;96:1475-1479. [Crossref]
11. Tseng CH. Benign prostatic hyperplasia is a significant risk factor for bladder cancer in diabetic patients: a population-based cohort study using the National Health Insurance in Taiwan. BMC Cancer. 2013;13:7. [Crossref]
12. Dai X, Fang X, Ma Y, Xianyu J. Benign prostatic hyperplasia and the risk of prostate cancer and bladder cancer: a meta-analysis of observational studies. Medicine (Baltimore). 2016;95:e3493. [Crossref]
13. Lunney A, Haynes A, Sharma P. Moderate or severe LUTS is associated with increased recurrence of non - muscle - invasive urothelial carcinoma of the bladder. Int Braz J Urol. 2019;45:306-314. [Crossref]
14. Shen Z, Xie L, Chen T, Tian D, Liu X, Xu H, Zhang Y, Wu Z, Sha N, Xing C, Ding N, Hu H, Wu C. Risk factors predictive of recurrence and progression for patients who suffered initial recurrence after transurethral resection of stage pT1 bladder tumor in chinese population: a retrospective study. Medicine (Baltimore). 2016;95:e2625. [Crossref]
15. Barnes RW, Bergman RT, Hadley HL. Endoscopy. 1959;6. [Crossref]
16. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, Gontero P, Liedberg F, Masson-Lecomte A, Mostafid AH, Palou J, van Rhijn BWG, Rouprêt M, Shariat SF, Seisen T, Soukup V, Sylvester RJ. European Association of Urology Guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). Eur Urol. 2022;81:75-94. [Crossref]
17. Kadlubar FF, Dooley KL, Teitel CH, Roberts DW, Benson RW, Butler MA, Bailey JR, Young JF, Skipper PW, Tannenbaum SR. Frequency of urination and its effects on metabolism, pharmacokinetics, blood hemoglobin adduct formation, and liver and urinary bladder DNA adduct levels in beagle dogs given the carcinogen 4-aminobiphenyl. Cancer Res. 1991;51:4371-4377. [Crossref]
18. Lee KS, Song PH, Ko YH. Does uroflowmetry parameter facilitate discrimination between detrusor underactivity and bladder outlet obstruction? Investig Clin Urol. 2016;57:437-441. [Crossref]
19. Ham WS, Kim WT, Jeon HJ, Lee DH, Choi YD. Long-term outcome of simultaneous transurethral resection of bladder tumor and prostate in patients with nonmuscle invasive bladder tumor and bladder outlet obstruction. J Urol. 2009;181:1594-1599; discussion 1599. [Crossref]
20. Karaguzhin SG, Merinov DS, Martov AG. [One-stage transurethral resection of the urinary bladder and the prostate in patients with superficial cancer of the urinary bladder combined with benign prostatic hyperplasia]. Urologiia. 2005:17-21. [Crossref]
21. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeney LA, La Vecchia C, Shariat S, Lotan Y. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63:234-241. [Crossref]
22. Nesi G, Nobili S, Cai T, Caini S, Santi R. Chronic inflammation in urothelial bladder cancer. Virchows Arch. 2015;467:623-633. [Crossref]
23. Selby B, Hidas G, Chuang KW, Soltani T, Billimek J, Kaplan S, Wehbi E, Khoury A. Development and validation of a bladder trabeculation grading system in pediatric neurogenic bladder. J Pediatr Urol. 2020;16:367-370. [Crossref]
24. Halaseh SA, Leslie SW. Bladder diverticulum. Uropathology, second edition 2023:195-196. [Crossref]
25. Bosch R, Abrams P, Averbeck MA, Finazzi Agró E, Gammie A, Marcelissen T, Solomon E. Do functional changes occur in the bladder due to bladder outlet obstruction? - ICI-RS 2018. Neurourol Urodyn. 2019;38(Suppl 5):S56-S65. [Crossref]
26. Cicione A, Manno S, Ucciero G, Cantiello F, Damiano R, Lima E, Posti A, Balloni F, De Nunzio C. A larger detrusor wall thickness increases the risk of non muscle invasive bladder cancer recurrence and progression: result from a multicenter observational study. Minerva Urol Nefrol. 2018;70:310-318. [Crossref]
27. Kim SJ, Kim J, Na YG, Kim KH. Irreversible bladder remodeling induced by fibrosis. Int Neurourol J. 2021;25(Suppl 1):S3-S7. [Crossref]

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The Role of the Incontinence Severity Index in the Treatment of Stress Urinary Incontinence

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

Urinary incontinence symptoms are quite common among women. It has a significant impact on quality of life and creates financial burdens on both personal and social levels. Stress urinary incontinence (SUI) is considered the most common type of transurethral urinary incontinence, especially in women of menopausal and reproductive age. Various quality of life questionnaires, such as the International Incontinence Consultation Questionnaire, the incontinence severity index (ISI), and the Incontinence Impact Questionnaire, have been developed to assess the impact of SUI on quality of life, but their results may vary. We believe that evaluating the effects of medical and surgical treatment of SUI on the ISI will offer valuable insights in monitoring the diagnosis and treatment response.

Abstract

Objective: To evaluate the effects of medical and surgical treatment of stress urinary incontinence (SUI) on incontinence severity index (ISI).

Materials and Methods: In our study, 64 patients aged 30-60 years, who were admitted to our hospital with symptoms of SUI between 2018 and 2023, underwent medical or surgical treatment for SUI, and met the inclusion criteria, were included. Women included in the study were divided into three groups: those who received medical treatment, those who underwent Burch colposuspension, and those who received tension-free obturator tape (TOT).

Results: When ISI measurements were categorized between the groups in the pre-treatment period, it was found that the rate of patients with slight and moderate SUI was significantly higher in the medical treatment group (p=0.018 and p=0.044, respectively). The rate of patients with severe SUI was found to be significantly lower in the medical treatment group (p=0.032). When the groups were evaluated individually, the post-treatment ISI score was found to be significantly lower than the pre-treatment ISI score in all groups (p<0.001). The difference between pre-treatment and post-treatment ISI scores (ΔISI) was found to be significantly higher in the TOT group and Burch colposuspension group compared to the medical treatment group (p<0.001).

Conclusion: ISI is useful in assessing the severity of incontinence in patients with SUI and the effectiveness of treatment after treatment. For ISI to be widely used as an alternative, prospective use with a larger number of patients and longer follow-up periods is needed.

Keywords: TOT, Burch colposuspension, incontinence severity index, stress urinary incontinence

Introduction

Urinary incontinence symptoms are quite common among women. It has a significant impact on quality of life and creates personal and social financial burdens. Urinary incontinence is evaluated in two groups (1). Stress urinary incontinence (SUI) is defined as the involuntary loss of urine during situations where bladder pressure exceeds the pressure at which the urethra can remain closed, and when intra-abdominal pressure is increased (e.g., coughing) (2). SUI is considered the most common type of urinary incontinence, especially in women of menopausal and reproductive age (3). The prevalence of SUI has a wide spectrum, ranging from 4% to 35% in the literature. Although the clinical definition of SUI has been established by the International

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Continence Society, its epidemiologic definition remains undefined, resulting in variable reported prevalence rates (4).

The occurrence and progression of SUI are associated with age, overweight, diabetes, and obstetric trauma (5). In addition, vaginal births, menopause, and hormone therapy are known to affect functionality at the lower urethral level (6). The multifactorial risk of SUI is evident, with different criteria shown to have a very complex effect on its development (7-9). Although urodynamic studies are useful in diagnosing SUI and excluding detrusor overactivity, they are not routinely recommended for all cases. They require expertise and have cost-related disadvantages (10-13). In patients with uncomplicated SUI, preoperative urodynamic evaluation has not been shown to improve the outcome of continence surgery. However, urodynamic testing provides additional information about lower urinary tract function that can guide physicians in making the right treatment choice (14,15).

Various quality of life questionnaires, such as the International Incontinence Consultation Questionnaire score, the incontinence severity index (ISI), and the Incontinence Impact Questionnaire, have been developed to assess the impact of SUI on quality of life, but their results may vary (16-18). ISI is a simple questionnaire with only two questions (frequency of urine leakage and its quantity). Its score is calculated, and patients are categorized as having slight (score 1-2), moderate (score 3-7), severe (score 8-9), and very severe (score 12) SUI (19). Although there are approaches that include treatment of mild-to-moderate SUI, lifestyle changes, pelvic floor exercises, and duloxetine therapy, surgical options are recommended as the gold standard of treatment, with Burch colposuspension or tension-free vaginal tapes or polypropylene tapes, including tension-free obturator tapes (TOT) (20-23). In addition, rectus fascial slings are used in the treatment of SUI (24). The aim of our study was to evaluate the effects of medical and surgical treatment of SUI on ISI scores.

Materials and Methods

This study was designed as a retrospective observational study. The study was initiated after receiving ethics committee approval (date: 09.10.2024, approval number: KA-24/338 - Başkent University Rectorate Medicine and Health Sciences Research Board) from the hospital. The study was designed according to the Helsinki Declaration, and informed consent was obtained from all patients.

In our study, 64 patients aged 30-60 years who were admitted to our hospital with symptoms of SUI between 2018 and 2023, who underwent medical or surgical treatment for SUI, and who met the inclusion criteria were included. Women included in the study were divided into three groups based on the type of treatment received: medical treatment, Burch colposuspension, and TOT. Patients in the medical treatment group were those who did not opt for surgical options. Pre-treatment and post-treatment ISI scores of all patients were compared. ISI scores of all patients were compared between groups according to treatment type. Women with urge urinary incontinence, overactive bladder diagnosis, neurogenic bladder diagnosis, other causes of incontinence, active urinary tract infection, total uterovaginal prolapse, and malignancy were excluded from the study.

Incontinence history, obstetric history, physical examination, and gynecologic examination findings of all patients were retrospectively reviewed from patient files. All patients suspected of having stress incontinence were questioned about their Bonney test results. ISI scores of all patients who were diagnosed as having stress incontinence and therefore started on medical treatment or underwent surgery were evaluated.

The ISI questionnaire seeks answers to two questions, asking how often patients experience urinary incontinence and how much urine they lose each time (19). In the ISI scoring, severity levels are defined as mild, moderate, severe, and very severe (19). ISI scoring was chosen because it is easy to apply and positive results regarding its effectiveness have been reported in previous studies. Inclusion criteria for the study were defined as being aged 30-60 years, having SUI confirmed through clinical examinations, Bonney tests, and voiding diaries. All patients diagnosed as having SUI and requesting medical treatment were advised to consume less fluids, lose weight, and do pelvic floor exercises, along with taking 20 mg duloxetine daily. Patients requesting surgery were subjected to Burch colposuspension or TOT after detailed evaluations. Routine examination records of all patients were reviewed at the end of the 3rd month and the 6th month. ISI scores of all patients at the end of the 6th month were evaluated retrospectively from the hospital database for each group.

Statistical Analysis

Statistical analysis was conducted using the SPSS 26.0 software package, (IBM Inc., Chicago, IL, USA). Descriptive statistics such as mean, standard deviation, and range values were computed from continuous variables. The normality of the data distribution was evaluated using the Kolmogorov-Smirnov and the Shapiro-Wilk tests. For the variables that showed approximately normal distribution, the independent Student's t-test was used to compare mean values of two groups. For the same group, pre- and post-values were compared using the paired t-test. Fisher's exact and chi-square tests were used in the categorical data analysis. To find correlations between two variable parameters, Pearson's correlation coefficient was

computed, and comparisons among subgroups were performed using analysis of variance.

Results

The mean age of the women included in the study was 40.25±9.64 years, and the mean body mass index score was 25.1±4.46 kg/m^2. The mean parity of the women was 2.16±1.18, and the mean gravidity was 2.81±1.34. Of the women included in the study, 30 (46.8%) were smokers and 40 (62.5%) were university graduates. No significant difference was found between the groups in terms of demographic characteristics (Table 1).

When ISI measurements were categorized in the pre-treatment period, it was found that the rate of patients with slight and moderate SUI was significantly higher in the medical treatment group (p=0.018 and p=0.044, respectively). The rate of patients with severe SUI was found to be significantly lower in the medical treatment group (p=0.032) (Table 2).

The overall pre-treatment ISI score of all participants was 7.78±2.86. The mean pre-treatment ISI score was 5.50±1.32 in the medical treatment group, 9.04±1.88 in the TOT group, and 8.38±1.76 in the Burch colposuspension group, with the medical treatment group having a significantly lower score (p<0.001). No significant difference was observed between the pre-treatment ISI scores of the TOT and Burch colposuspension groups (p>0.05). The mean post-treatment ISI score was 2.11±0.78. The mean post-treatment ISI score was 2.26±0.88 in the medical treatment group, 2.09±0.76 in the TOT group, and 2.05±0.79 in the Burch colposuspension group. No significant difference was observed between the groups (p=0.68). When the groups were evaluated within themselves, the post-treatment ISI score was found to be significantly lower than the pre-treatment ISI score in all groups (p<0.001). The difference between pre-treatment and post-treatment ISI score (ΔISI) in the TOT group and Burch colposuspension group was found to be significantly higher than in the medical treatment group (p<0.001) (Table 3).

Discussion

In our study, ISI scores were evaluated before and after treatment in different treatment modalities. A significant decrease in ISI scores was observed in all treatment groups compared with the pre-treatment period. However, when the patients in the surgical group were evaluated among themselves, no significant difference was found in terms of treatment response between the surgical methods.

Although the ISI score also decreased significantly in the medical treatment group in the post-treatment period, a more limited decrease was observed in ΔISI scores compared with the surgical groups. The ISI scoring system is important in evaluating the presence and severity of SUI before and after treatment because it is very cost-effective and can be easily performed even in small hospitals, unlike high-cost urodynamic studies (12,13).

Table 1. Comparison of demographic characteristics of participants

	All patients (n=64)	Medical treatment (n=22)	Tension-free obturator tape (n=21)	Burch colposuspension (n=21)	p-value
	Mean ± standard deviation				
Age (year)	40.25±9.64	40.1±9.76	39.95±9.52	40.42±9.68	0.78
Body mass index (kg/m^2)	25.1±4.46	25.2±4.62	25.3±4.36	24.9±4.51	0.28
Gravidity	2.81±1.34	2.76±1.30	2.86±1.38	2.82±1.37	0.42
Parity	2.16±1.18	2.12±1.22	2.19±1.16	2.13±1.19	0.56
Smoking n (%)	30 (46.8%)	10 (45.4%)	11 (52.3%)	9 (42.8%)	0.18
Education n (%)					
High school	24 (37.5%)	9 (40.9%)	8 (38%)	7 (33%)	0.11
University	40 (62.5%)	13 (59.1%)	13 (62%)	14 (67%)	

Table 2. Evaluation of pre-treatment incontinence severity index scores according to groups in patients with stress urinary incontinence

Incontinence severity index	All patients n (%)	Medical treatment n (%)	Tension-free obturator tape n (%)	Burch colposuspension n (%)	p-value
Slight (1-2)	2 (3.1%)	2 (9.1%)	-	-	0.018
Moderate (3-6)	18 (28.2%)	7 (31.9%)	5 (23.9%)	6 (28.6%)	0.044
Severe (8-9)	34 (53.1%)	10 (45.4%)	12 (57.1%)	12 (57.1%)	0.032
Very severe (12)	10 (15.6%)	3 (13.6%)	4 (19%)	3 (14.3%)	0.066

Table 3. Comparison of incontinence severity index scores within and between groups				
	Pre-treatment incontinence severity index score	Post-treatment incontinence severity index score	ΔISI score	p-value
	Mean ± standard deviation			
All patients	7.78±2.86	2.11±0.78	5.67±1.33	<0.001
Medical treatment	5.50±1.32	2.26±0.88	2.24±0.84	<0.001
Tension-free obturator tape	9.04±1.88	2.09±0.76	6.95±1.54	<0.001
Burch colposuspension	8.38±1.76	2.05±0.79	6.33±1.46	<0.001
p-value	<0.001	0.68	<0.001	
ISI: Incontinence severity index				

When all treatment modalities were evaluated in our study, there were two (3.1%) patients in the slight group, 18 (28.2%) patients in the moderate group, 34 (53.1%) patients in the severe group, and 10 (15.6%) patients in the very severe group. In the study conducted by Nygaard et al. (25), when ISI categories were evaluated, 9.2% were observed in the slight group, 37.8% in the moderate group, 64.6% in the severe group, and 85.3% in the very severe group. In evaluations made using ISI in women with SUI, mild incontinence was found at a rate of 64%, moderate incontinence was 13.25%, and severe incontinence was 22.75% (26). In the literature, a wide spectrum of results has been revealed in ISI assessments used for the evaluation of SUI. This difference in data may have occurred due to the different demographic and obstetric histories of the patients depending on the study inclusion criteria.

The review by Rodrigues-Amorim et al. (27) provided substantial evidence supporting duloxetine in the treatment of SUI. In the study conducted by Jost and Marsalek (28) duloxetine was shown to be effective in reducing incontinence attacks and improving quality of life in women with SUI. In our study, a significant decrease in the severity of incontinence was found in women with SUI who used duloxetine, consistent with the literature. In addition, the positive results of the treatment were clearly demonstrated in ISI evaluations, which was the main criterion of our study.

In the study conducted by Frick et al. (29), a significant improvement was found in ISI results in women who underwent TOT surgery for SUI in the post-treatment period. Therefore, it was stated that it could be preferred as the primary outcome measure in the evaluation of SUI treatment. Ye et al. (30) showed that Burch colposuspension was an effective procedure for SUI and the therapeutic effect was largely maintained during the long follow-up period. Similarly, in our study, significant improvement in incontinence symptoms was found in patients who underwent Burch colposuspension for SUI; the findings were confirmed by ISI evaluations.

To our knowledge, our study is the first in the literature to compare TOT surgery, Burch colposuspension surgery, and medical treatment through ISI evaluations between comparably sized patient populations. Surgery is generally preferred for successful improvement of symptoms in patients with moderate-to-severe SUI (3). Serati et al. (31) stated that "the best surgery includes retropubic urethropexy (Burch colposuspension) and pubovaginal slings". They were dismissive of midurethral slings, saying that they played a marginal and almost experimental role in the field However, there are studies in the literature evaluating the effectiveness of the Burch colposuspension and TOT operations, referring to the positive aspects of both methods (32-35). In our study, no significant difference was found in terms of the effect of TOT and Burch colposuspension surgeries on ISI measurements.

Study Limitations

The main limitation of our study is that it is retrospective, and only the data from the 6th month post-treatment of all patients in the medical and surgical treatment groups are available. Another limitation is that the data on the long-term effectiveness of the treatment methods, both individually and in comparison, with each other, have not yet been obtained. The strength of our study is that it is one of the few studies performing three different methods using equal numbers of patients, evaluating ISI scores. The evaluation of the effect of medical and surgical treatment on ISI can be considered another strength.

Conclusion

ISI is useful in assessing the severity of incontinence in patients with SUI and the effectiveness of treatment after SUI treatment. Considering the cost and difficulties in the applicability of urodynamic tests, prospective studies with larger patient numbers and longer follow-up periods are needed for ISI to be widely used as an alternative.

Ethics

Ethics Committee Approval: The study was initiated after receiving ethics committee approval (date: 09.10.2024, approval

number: KA-24/338 - Başkent University Rectorate Medicine and Health Sciences Research Board) from the hospital.

Informed Consent: Informed consent was obtained from all patients.

Footnotes

Authorship Contributions

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

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References

1. Aoki Y, Brown HW, Brubaker L, Cornu JN, Daly JO, Cartwright R. Urinary incontinence in women. Nat Rev Dis Primers. 2017;3:17042. Erratum in: Nat Rev Dis Primers. 2017;3:17097. [Crossref]
2. D'Ancona C, Haylen B, Oelke M, Abranches-Monteiro L, Arnold E, Goldman H, Hamid R, Homma Y, Marcelissen T, Rademakers K, Schizas A, Singla A, Soto I, Tse V, de Wachter S, Herschorn S; Standardisation Steering Committee ICS and the ICS Working Group on Terminology for Male Lower Urinary Tract & Pelvic Floor Symptoms and Dysfunction. The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol Urodyn. 2019;38:433-477. [Crossref]
3. Irwin GM. Urinary incontinence. Prim Care. 2019;46:233-242. [Crossref]
4. Luber KM. The definition, prevalence, and risk factors for stress urinary incontinence. Rev Urol. 2004;6 (Suppl 3):S3-S9. [Crossref]
5. Lin YH, Chang SD, Hsieh WC, Chang YL, Chueh HY, Chao AS, Liang CC. Persistent stress urinary incontinence during pregnancy and one year after delivery; its prevalence, risk factors and impact on quality of life in Taiwanese women: an observational cohort study. Taiwan J Obstet Gynecol. 2018;57:340-345. [Crossref]
6. Swain D, Parida SP, Jena SK, Das M, Das H. Prevalence and risk factors of obstetric fistula: implementation of a need-based preventive action plan in a South-eastern rural community of India. BMC Womens Health. 2020;20:40. [Crossref]
7. Kowalik CG, Dmochowski RR, De EJB. Surgery for female SUI: the ICI algorithm. Neurourol Urodyn. 2019;38(Suppl 4):S21-S27. [Crossref]
8. Wesnes SL, Seim E. Birthweight and urinary incontinence after childbirth: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol X. 2020;8:100115. [Crossref]
9. Sharma JB. Urinary problems. In: textbook of gynecology. 1st ed. New Delhi: Avichal Publishing Company; 2018. p. 392-429. [Crossref]
10. Pal M, Halder A, Bandyopadhyay S. Approach to a woman with urinary incontinence. Urol Ann. 2020;12:4-8. [Crossref]
11. Matharu GS, Assassa RP, Williams KS, Donaldson M, Matthews R, Tincello DG, Mayne CJ. Objective assessment of urinary incontinence in women: comparison of the one-hour and 24-hour pad tests. Eur Urol. 2004;45:208-212. [Crossref]
12. Nambiar AK, Lemack GE, Chapple CR, Burkhard FC; European Association of Urology. The role of urodynamics in the evaluation of urinary incontinence: the European Association of Urology recommendations in 2016. Eur Urol. 2017;71:501-503. [Crossref]
13. Yande SD, Joglekar OV, Joshi M. Role of urodynamics in stress urinary incontinence: a critical appraisal. J Midlife Health. 2016;7:119-125. [Crossref]
14. Serati M, Braga A, Torella M, Soligo M, Finazzi-Agro E. The role of urodynamics in the management of female stress urinary incontinence. Neurourol Urodyn. 2019;38(Suppl 4):S42-S50. [Crossref]
15. Colli E, Artibani W, Goka J, Parazzini F, Wein AJ. Are urodynamic tests useful tools for the initial conservative management of non-neurogenic urinary incontinence? a review of the literature. Eur Urol. 2003;43:63-69. [Crossref]
16. Uren AD, Cotterill N, Pardoe M, Abrams P. The international consultation on incontinence questionnaires (ICIQ): an update on status and direction. Neurourol Urodyn. 2020;39:1889-1896. [Crossref]
17. Sandvik H, Espuna M, Hunskaar S. Validity of the incontinence severity index: comparison with pad-weighing tests. Int Urogynecol J Pelvic Floor Dysfunct. 2006;17:520-524. [Crossref]
18. Skorupska K, Grzybowska ME, Kubik-Komar A, Rechberger T, Miotla P. Identification of the urogenital distress inventory-6 and the incontinence impact questionnaire-7 cutoff scores in urinary incontinent women. Health Qual Life Outcomes. 2021;19:87. [Crossref]
19. Sargın MA, Yassa M, Taymur BD, Ergun E, Akca G, Tug N. Adaptation and validation of the Michigan incontinence severity index in a Turkish population. Patient Prefer Adherence. 2016;10:929-935. [Crossref]
20. Mariappan P, Alhasso A, Ballantyne Z, Grant A, N'Dow J. Duloxetine, a serotonin and noradrenaline reuptake inhibitor (SNRI) for the treatment of stress urinary incontinence: a systematic review. Eur Urol. 2007;51:67-74. [Crossref]
21. Veit-Rubin N, Dubuisson J, Ford A, Dubuisson JB, Mourad S, Digesu A. Burch colposuspension. Neurourol Urodyn. 2019;38:553-562. [Crossref]
22. Nilsson CG, Palva K, Aarnio R, Morcos E, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013;24:1265-1269. [Crossref]
23. Ulrich D, Tammaa A, Hölbfer S, Trutnovsky G, Bjelic-Radisic V, Tamussino K, Aigmüller T. Ten-year followup after tension-free vaginal tape-obturator procedure for stress urinary incontinence. J Urol. 2016;196:1201-1206. [Crossref]
24. Elsersy MA. Tension-free transobturator vaginal tape and autologous rectus fascia transobturator vaginal sling for the treatment of urinary stress incontinence: a prospective clinical study. Int J Reprod Contracept Obstet Gynecol. 2017;6:1174-1179. [Crossref]
25. Nygaard I, Girts T, Fultz NH, Kinchen K, Pohl G, Sternfeld B. Is urinary incontinence a barrier to exercise in women? Obstet Gynecol. 2005;106:307-314. [Crossref]
26. Yang J, Cheng JW, Wagner H, Lohman E, Yang SH, Krishingner GA, Trofimova A, Alsyouf M, Staack A. The effect of high impact crossfit exercises on stress urinary incontinence in physically active women. Neurourol Urodyn. 2019;38:749-756. [Crossref]
27. Rodrigues-Amorim D, Olivares JM, Spuch C, Rivera-Baltanás T. A systematic review of efficacy, safety, and tolerability of duloxetine. Front Psychiatry. 2020;11:554899. [Crossref]
28. Jost WH, Marsalek P. Duloxetine in the treatment of stress urinary incontinence. Ther Clin Risk Manag. 2005;1:259-264. [Crossref]
29. Frick AC, Ridgeway B, Ellerkmann M, Karram MM, Paraiso MF, Walters MD, Barber MD. Comparison of responsiveness of validated outcome measures after surgery for stress urinary incontinence. J Urol. 2010;184:2013-2017. [Crossref]
30. Ye Y, Wang Y, Tian W, Zhang Z, Liang S, Song X, Guo J, Gao Q, Shi H, Sun Z, Chen J, Lang J, Zhu L. Burch colposuspension for stress urinary incontinence: a 14-year prospective follow-up. Sci China Life Sci. 2022;65:1667-1672. [Crossref]

31. Serati M, Salvatore S, Uccella S, Artibani W, Novara G, Cardozo L, Bolis P. Surgical treatment for female stress urinary incontinence: what is the gold-standard procedure? Int Urogynecol J Pelvic Floor Dysfunct. 2009;20:619-621. [Crossref]

32. Sievert KD, Abufaraj M, Kernig K, Drager DI, Blaganje M, Hakenberg O, Mansy K, Liedl B, Tarcan T, de Ridder D. Sling surgery for female incontinence. Eur Urol Suppl. 2018;17:109-118. [Crossref]

33. Albo ME, Richter HE, Brubaker L, Norton P, Kraus SR, Zimmern PE, Chai TC, Zyczynski H, Diokno AC, Tennstedt S, Nager C, Lloyd LK, FitzGerald M, Lemack GE, Johnson HW, Leng W, Mallett V, Stoddard AM, Menefee S, Varner RE, Kenton K, Moalli P, Sirls L, Dandreo KJ, Kusek JW, Nyberg LM, Steers W; Urinary Incontinence Treatment Network. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007;356:2143-2155. [Crossref]

34. Rogers RG. Clinical practice. Urinary stress incontinence in women. N Engl J Med. 2008;358:1029-1036. [Crossref]

35. Brazzelli M, Javanbakht M, Imamura M, Hudson J, Moloney E, Becker F, Wallace S, Omar MI, Shimonovich M, MacLennan G, Ternent L, Vale L, Montgomery I, Mackie P, Saraswat L, Monga A, Craig D. Surgical treatments for women with stress urinary incontinence: the ESTER systematic review and economic evaluation. Health Technol Assess. 2019;23:1-306. [Crossref]

ORIGINAL RESEARCH
Basic Science

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Evaluation of the Efficacy of Colchicine, Pirfenidone and Prednisolone in Preventing Stricture Due to Inflammation as a Result of Urethral Mucosal Damage in Rats

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

Urethral stricture is a disease characterized by fibrotic scar formation causing narrowing of the urethra, decreased urethral volume, and failure of normal voiding function, and can frequently recur despite endoscopic or open surgical treatment. We administered pirfenidone, colchicine, and corticosteroids orally to prevent proliferation, excessive fibrosis, and scarring during the healing process of urethral stricture. This is the only study in the literature comparing three oral pharmacological agents with known anti-inflammatory and antifibrotic properties to prevent recurrence of urethral stricture. As a result of clinical studies, we believe that the use of these agents before and after all interventions for urethral stricture should be included in clinical practice.

Abstract

Objective: To evaluate the effectiveness of oral use of drugs with anti-inflammatory and antifibrotic properties that are used in the treatment of many diseases in clinical practice in rats with stenosis caused by urethral damage.

Materials and Methods: Forty male rats were equally divided into 5 groups. After anesthesia, penectomy was performed in group 1 without any other procedure. Urethral stenosis was created in rats in the groups 2, 3, 4, and 5. The rats in group 2 underwent penectomy at the end of 6 weeks. Groups 3, 4, and 5 were treated with colchicine, prednisolone, and pirfenidone, respectively by gavage for 6 weeks and underwent penectomy. Inflammation, fibrosis, and urethral lumen area were evaluated histopathologically in urethral tissue or all animals.

Results: The urethral lumen area increased in group 4, although this incease was not statistically significant compared to group 2. In addition, prednisolone lead to a significant decrease in the inflammation and fibrosis scores compared to group 2. We also found that there was a significant decrease in inflammation and fibrosis scores and a significant increase in the urethral lumen area in groups 3,5 compared to group 2. Moreover, the group 3 had a significant increase in matrix metalloproteinase-9 expression compared to group 2. Bone morphogenetic protein-2 expression was increased especially in groups 3,5.

Conclusion: We concluded that oral administration of colchicine or pirfenidone prevented the formation of urethral stenosis in rats to a large extent. The oral steroid treatment also reduced the formation of urethral stenosis, although not as effectively as colchicine or pirfenidone.

Keywords: Functional urology, pathology, reconstructive urology

Introduction

The urethra is a tube-shaped canal with two open ends that allows urine, which is stored in the bladder, to be excreted from the body. The typical length of the urethra is 18-20 cm in men and 3-4 cm for women. Since the urethra is much longer in men than in women, urethral stricture is more commonly seen in men. It is a disease characterized by narrowing in the urethra, decreased urethral volume, and abnormal voiding function due to fibrotic wound formation. Etiology of the disease usually

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includes trauma, infections, and previous surgical interventions. Cellular changes in the extracellular matrix of the urethral spongiosis tissue are involved in the pathogenesis of urethral stricture (1). Here, the normal connective tissue is replaced by dense fibers lined with fibroblasts. Histopathological studies have shown a decrease in the ratio of collagen type III to collagen type I (1). This change is accompanied by a decrease in the smooth muscle to collagen ratio and a marked increase in nitric oxide synthesis in the constricted fibrotic region (2).

Male patients with symptomatic urethral stricture often present to the outpatient clinic due to symptoms such as difficulty urinating, inability to empty the bladder completely, and weak urine flow. The location, size, and length of the urethral stricture are important factors when considering various treatment options. Treatment methods include endoscopic treatments (urethral dilation, internal urethrotomy, injectable materials, laser urethrotomy, and urethral stents) and open surgical reconstructions (urethroplasties, end-to-end anastomotic urethroplasty, onlay free graft, and pedicle flap) (3). However, in some cases, effective results cannot be obtained with these methods, and the disease can recur. It is often emphasized that healing the damaged tissue in urethral stricture would require stopping the bleeding and properly balanced modelling that will not cause infection, proliferation, excessive fibrosis, and scarring (1-3). Therefore, anti-inflammatory agents or antifibrotics can be used for the treatment of urethral stricture. The final feature is progressive fibrosis resulting from extracellular matrix control in which matrix metalloproteinase (MMP) is believed to play an important role. In the evaluation of the antifibrotic and anti-inflammatory effect, MMP-9, which is effective in inhibiting granulation tissue formation, and bone morphogenetic protein (BMP-2), which has an anti-fibrogenic function in multiple organs, are also known to be active in this mechanism (4,5). However, there are a limited number of studies about this subject.

In this study, we aimed to evaluate the use, efficacy, and advantages of drugs such as colchicine, corticosteroids, and pirfenidone. These drugs are used in the treatment of many diseases in clinical practice, due to their anti-inflammatory and antifibrotic properties, in terms of non-recurrence of urethral stricture.

Materials and Methods

Forty male Albino-Wistar rats (220-450 g) were used in this study. All procedures were carried out in a room with a constant temperature (22±2 °C) with a 12-hour light-dark cycle. Institutional guidelines and the Guide for Care and Use of Laboratory Animals of the National Research Council were followed while handling the rats. All procedures were performed in compliance with the provisions of the 1986 Strasbourg Universal Declaration on Animal Welfare and by the approval of the local ethics committee (approval number: HADYEK 23, date: 15.01.2018 - Gaziosmanpaşa University Rectorate Animal Experiments Ethics Committee). The animals were divided into 5 groups with 8 animals in each group. A sharp tip device is made by twisting the 21-gauge syringe needle approximately 1 mm backward. The urethral stricture model was created by rotating this device 360 degrees and back and forth in an approximately 2 cm section starting from about 0.5 cm proximal to the urethral meatus towards the anterior urethral mucosa (Figure 1). The animals were anesthetized with 50 mg/kg IP ketamine hydrochloride and 10 mg/kg IP xylazine. After the anesthesia injection, group 1 underwent penectomy without any other procedure. Urethral stricture was created in rats in groups 2, 3, 4, and 5. The rats in group 2 underwent penectomy at the end of 6 weeks. Groups 3, 4, and 5 were treated with 1 mg/kg colchicine, 0.5 mg/kg prednisolone, and 50 mg/kg/day pirfenidone, respectively by gavage for 6 weeks and underwent penectomy at the end of 6 weeks (6-8). After all the procedures, the animals were sacrificed by cervical dislocation under ketamine, and xylazine anesthesia.

Histopathological Evaluation

Rats' penises were immediately put into a 4% buffered neutral (pH: 7.2) formalin solution for 48 hours after being resected to be fixed. Since it is known that there are bone and cartilage pieces in some areas of the rat penis, the penises were postfixed in decalcification solution with EDTA.

After the fixation process, the penises were divided into two right from the midpoint in one move of a sharp scalpel. Afterwards, the tissue was rinsed under running water, dehydrated with

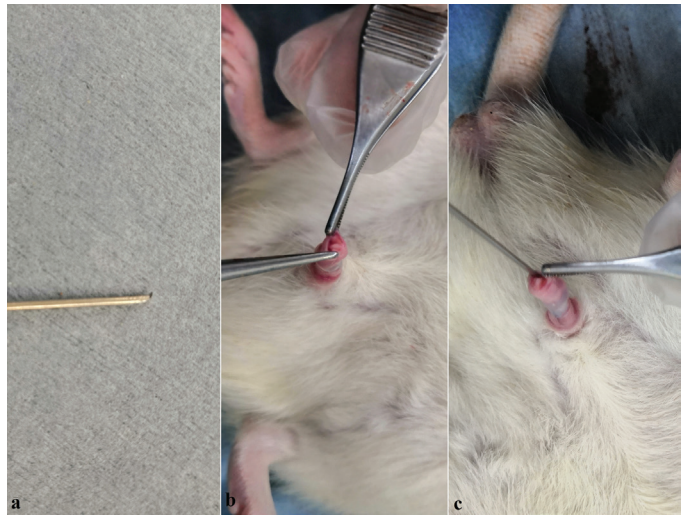

Figure 1. a. Sharp tip tool created by twisting the 21 gauge syringe needle approximately 1 mm back, b. Urethral meatus of rat, c. Creation of urethral mucosal damage

increasing alcohol concentrations (70%, 80%, 90%, 96%, and 100%) for 5 minutes each. Then the samples were cleared in increasing xylene concentrations and were incubated in 3 different paraffin series at 60 °C. The samples were then buried upright in a clean paraffin block. Serial consecutive sections of 5 µm thickness were taken from the blocked tissue with a rotary microtome (Leica RM2135, Germany). The penis tissue sections were placed in poly-L-lysine slides and used for hematoxylin-eosin staining, triple staining, and immunohistochemical analysis.

Hematoxylin-Eosin Staining

The tissue sections of rat penile tissue fixed with formalin and embedded in paraffin blocks were cut into 5 µm thick sections, stained with hematoxylin for 10 minutes after deparaffinization and rehydration procedures. Slides were rinsed in water for 5 minutes, and then immersed in acid alcohol and rinsed under running water. After incubating for 3 minutes in eosin dye solution, the slides were immersed in distilled water, which was changed several times to remove excess dye. The sections were then passed through the increasing concentrations of alcohol (80%, 90%, 95%, and 100%). After incubating in xylene (3x15 min), the sections were sealed with entellan drops and covered with coverslips. Histological analyses of the prepared hematoxylin, eosin-stained slides were done using a light microscope (Nikon Eclipse 200; Nikon).

Triple Staining (Modified Masson Trichrome)

The paraffin from the penile tissue sections of 5 µm thickness was melted by incubating the sections in a 60°C oven, then they were deparaffinized in a xylene series, and rehydrated with decreasing concentrations of alcohol followed by distilled water. The slides were incubated in Weigert's hematoxylin solution for 10 minutes. Then, the slides were rinsed under running tap water for 5 minutes and immersed in distilled water. Next, the slides were dipped into acid fuchsin solution for 1 minute and then immersed in distilled water two times and incubated in phosphotungstic acid solution for 10-15 minutes. Soaked in phosphotungaustic acid solution. Tissue sections were dipped in distilled water twice, soaked in aniline blue solution for 1 minute, and then immersed in distilled water. Then, after dipping through increasing concentrations of alcohol (80, 90, 96, and 100%) and 3 separate xylene series, the slides were closed with entellan and covered with a coverslip, in preparation for microscopic analysis.

Histopathologic Analysis

Histopathological evaluations were performed by a histologist blinded to the study. Hematoxylin-eosin-stained preparations were scored by semi-quantitative inflammation scoring criteria after microscopic analyses (9). Modified Masson Trichrome-stained preparations were scored according to semi-quantitative fibrosis scoring criteria (9). For both scoring procedures, the weighted averages of the 8 sections from each animal and the 5 different areas in each section were scored under a microscope with a 40x objective. The calculated mean inflammation and fibrosis score values of each group were compared statistically.

Immunohistochemical Analysis

Five-µm-thick tissue sections were immunohistochemically stained with BMP and MMP primary antibodies to detect expression of BMP and MMP molecules. Immunohistochemical staining procedures were carried out as follows: 5 µm thin tissue sections were incubated in a 60 °C oven, to melt the paraffin, and sequentially passed through three different xylene series for deparaffinization, followed by alcohol washes of decreasing concentration (100%, 90%, 80%, and 70%) and rehydrated with distilled water. After the microwave antigen retrieval treatment in 10 mM citric acid, endogenous peroxidase blockade was performed by incubating the slides in 3% hydrogen peroxide (H_2O_2) solution for 10 minutes. The slides were washed with phosphate buffer solution (PBS) three times for 5 minutes each, and the perimeter was outlined with a hydrophobic pen (PAP pen). The non-immune blocking serum was applied and the slides were kept in a humid dark environment for 15 minutes. After the blocking agent was removed, BMP and MMP primary antibodies (1:100; Abcam, Cambridge, UK) were added to the slides. The slides were incubated overnight in a closed humid box at 4 °C. After 3 washes with PBS (5 min each), the slides were incubated with biotinylated secondary antibody (goat immunoglobulin G) in a humid, dark environment for 45 minutes at room temperature. This was followed by three PBS washes (5 min each), and secondary antibody (streptavidin-horseradish peroxidase conjugated reagent) was applied, after which the slides were incubated in a dark and humid environment for 30 minutes. After 3 PBS washes (5 min each), coloring was achieved using aminoethyl carbazole chromogen solution. Following contrast with hematoxylin, the sections were passed through distilled water and were covered with a coverslip with a water-based (aqueous mounting reagent) closure solution. For negative control slides, PBS was used instead of primary antibody.

The immune staining intensities were analyzed based on the staining intensity scoring criteria using a light microscope (Nikon Eclipse 200; Nikon) at 40x magnification in the NIS-Element program (Hasp ID: 6648AA61; Nikon) (10). For this purpose, the immunostained and unstained areas of the urethra were categorized based on the intensity of the staining reaction in five sections for each protein, using immunohistochemistry. The obtained weighted group average results were converted to H-score values with the formula [∑Pi (i + 1)]. In the formula, represents the staining intensity score, while Pi is the percentage of stained cells.

Statistical Analysis

IBM SPSS 22 Windows statistical software was used for statistical comparison of the results. The Kruskal-Wallis test was used in the comparison of the groups' mean urethral lumen area. The comparison of groups' means values of inflammation scores, fibrosis scores, and immunohistochemical H scores was conducted using one-way ANOVA, and multiple comparisons were made with Tukey's HSD. A p-value of less than 0.05 was considered significant.

Results

Histopathological Results

Histomorphometric (Urethral Lumen Area) Findings

The result of the analysis indicated that the urethral lumen area of group 2 (G2) decreased significantly compared to control (G1) and other groups (p=0.001). The results of the treatment groups were calculated to be similar to the control (p=0.1420) (Figure 2).

Inflammation Findings

The analyses of hematoxylin-eosin-stained preparations based on inflammation scale criteria showed that the inflammation score was significantly increased in the stricture-only group (G2), while in the control group it was normal (p=0.001). The inflammation scores of the treated groups were similar (p=0.19) and higher than the control (p=0.01), but lower than the stricture only group (G2) (Figure 3).

Fibrosis Findings

The histopathological analysis of triple stained slides showed normal urethrae in G1. It was found that fibrosis score increased significantly in G2 compared to the control (G1) (p=0.001). In treatment groups (G3, G4, G5), the score was significantly lower compared to G2 (p=0.01), but significantly higher than the control group (G1) (p<0.001) (Figure 4).

Immunohistochemical Findings

The immunohistochemical analyses showed that expression of BMP-2 was significantly decreased in G2 compared to G1 (p=0.007). In treatment groups, especially in G3 and G5, there was a significant increase in BMP-2 expression compared to G2 (p=0.03).

MMP-9 expression was similarly found to be decreased in G2 and increased in treatment groups (p=0.01). However, this increase was not statistically different from G1 and G2 (p=0.11) (Tables 1 and 2) (Figure 5).

Discussion

Urethral stricture is a complex pathology characterized by the narrowing of the urethral lumen with varying depths and lengths. Histopathologically, it manifests as spongiofibrous tissue and scarring and can be seen in male patients at any age (1). The prevalence of urethral stricture is between 0.6-1.4%, and 15-20% of adult males have been reported to be affected by this pathology at some time in their lives (11). Urethral stricture occurs mostly as idiopathic, iatrogenic, inflammatory, and, to a lesser extent, secondary to trauma (12). There are many invasive treatment approaches for urethral stricture. Although the success rates with treatment methods such as urethroplasty are around 90% in the first year, it decreases to 60-70% by the 5th year (13). Failure of dilatations due to urethral stricture is up to 80% (14). Yi et al. (15) evaluated 80 patients who had undergone balloon dilatation for bulbomembranous stricture

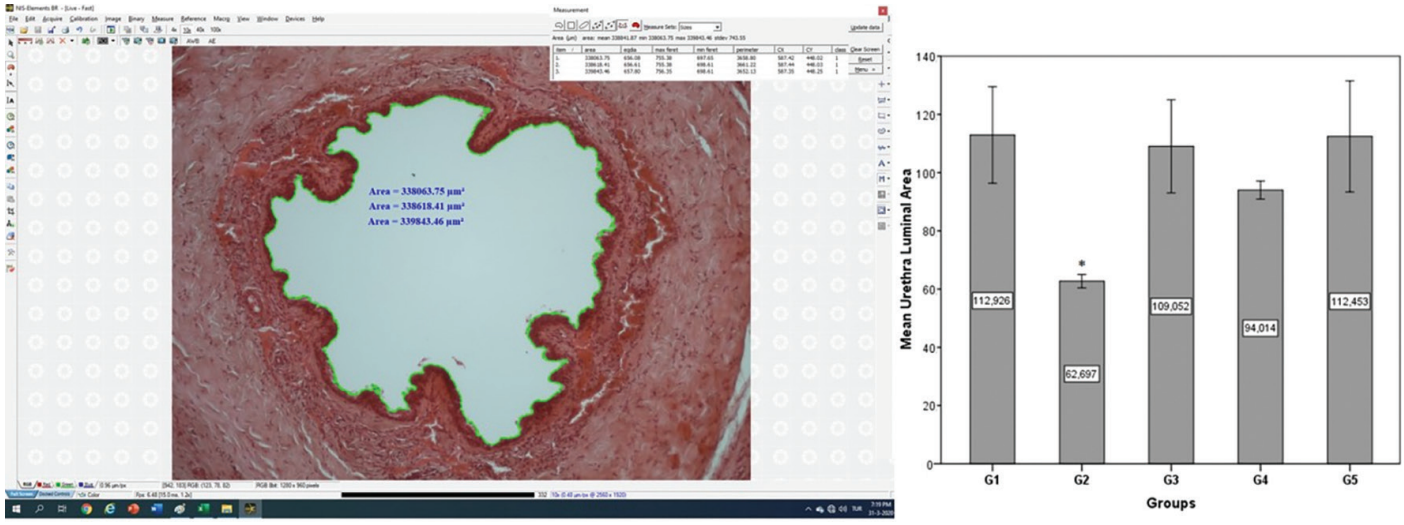

Figure 2. Screen shot from an example of urethral lumen area measurements and graphical view of the mean values of urethral lumen areas of the groups. *: p<0.05 vs. others (Kruskal-Wallis Mann-Whitney test)

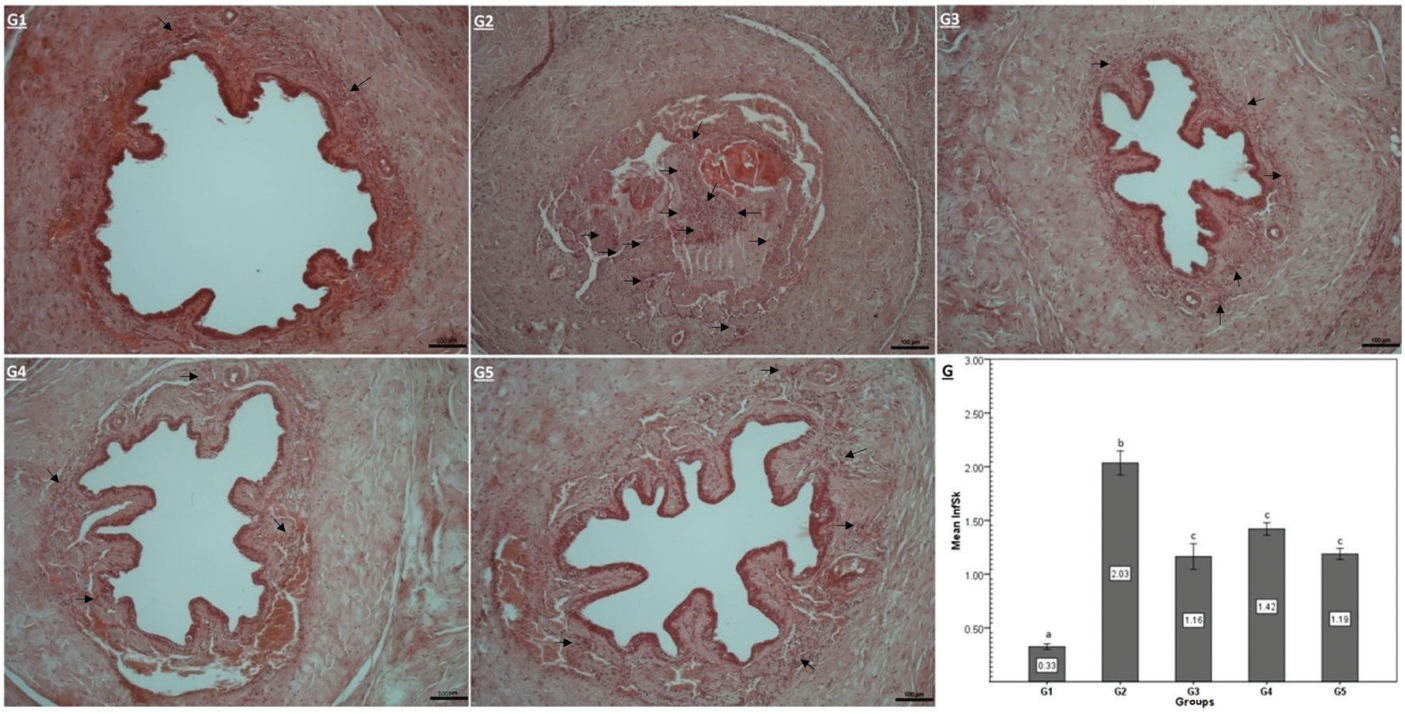

Figure 3. Representative hematoxylin eosin-stained urethra images from each group. Arrows indicate areas with inflammatory cell density. G1-G5, working groups (Bar: 100 µm); G is the values of inflammation scores group environment. Letters on the bars show statistical similarities and differences (b: $p<0.05$ vs. G1, c: $p<0.05$ vs. G1 and G2 One-Way ANOVA, Tukey HSD)

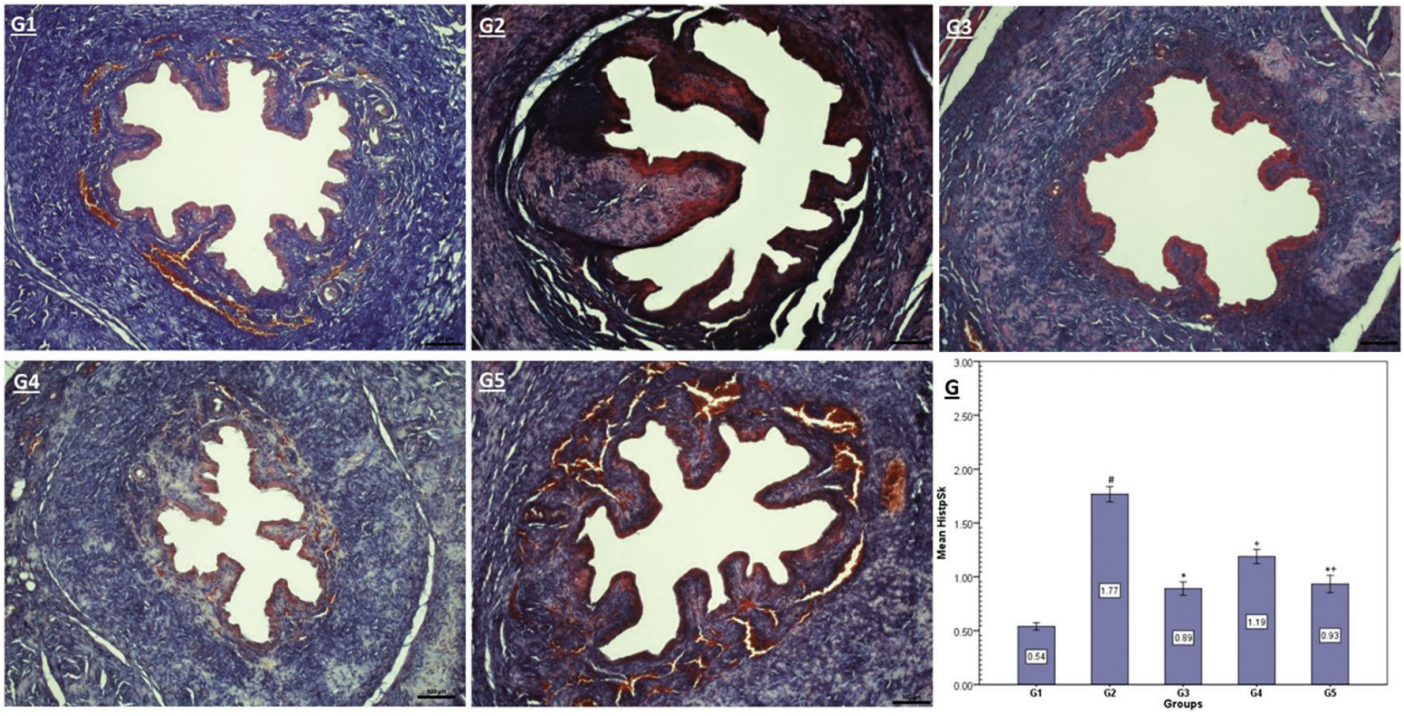

Figure 4. Representative modified masson trichrome painted urethra images (Bar: 100 µm) from each group. G1-G5, working groups; G fibrosis scores are group mean values. The icons on the graphic bars show statistical similarities and differences (#: $p<0.05$ vs. G1, *: $p<0.05$ vs. G1 and G2 One-Way ANOVA, Tukey HSD)

Table 1. The mean Hsc values (±: SEM) of the immunohistochemical staining intensities of the BMP and MMP expressions of the groups

	G1	G2	G3	G4	G5
BMP Hsc	117.71±9.3^{A}	72.71±8.4^{B}	82.42±8.0^{AC}	77.84±10.2^{BC}	89.58±7.1^{AC}
MMP Hsc	99.77±12.3^{a}	74.65±11.5^{b}	81.72±3.2^{ab}	67.22±13.3^{ab}	72.59±8.6^{ab}

G1-G5 are working groups. Capital letters on values represent statistical similarities and differences for BMP, and small letters for MMP. BMP: Bone morphogenetic protein, MMP: Matrix metalloproteinase, Hsc: H-score, SEM: Standard error of mean

Table 2. Mean values of urethra lumen area, inflammation score and fibrosis score of the study groups

	G1	G2	G3	G4	G5
Urethra luminal area (μm²)	112925,51±16575.8	62697,44±2310.7	109051,64±16019	94014,38±3120.1	112452,67±19090.1
Inflammation grade	0.33±0.02	2.03±0.11	1.16±0.11	1.42±0.05	1.19±0.05
Fibrosis grade	0.54±0.03	1.77±0.07	0.89±0.06	1.19±0.06	0.93±0.08

A. Inflammation grading scale (6)
Grade - Amount of inflammation
0 - None
1 - Giant cells, occasional lymphocytes, and plasma cells
2 - Giant cells, plasma cells, eosinophils, neutrophils
3 - Many inflammatory cells, microabscesses

B. Fibrosis grading scale (7)
Grade - Amount of fibrosis
0 - None
1 - Minimal, loose
2 - Moderate
3 - Florid, dense

C. Criteria for grading immunohistochemical staining intensities (10)
Score - Immune reactivity
0+ / None staining
1+ / Minimal staining
2+ / Moderate staining
3+ / Strong staining

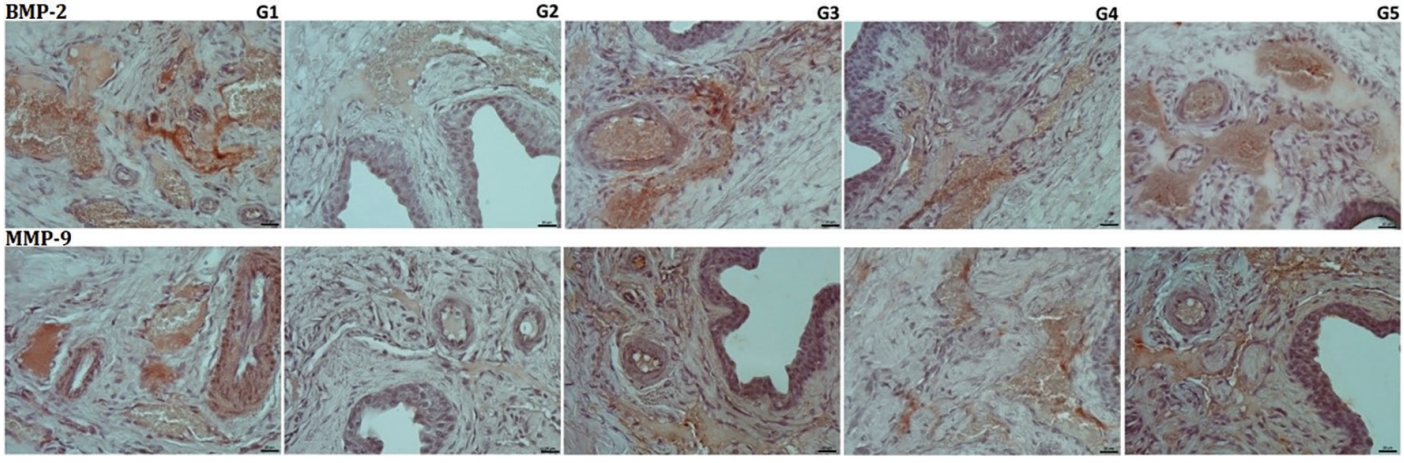

Figure 5. Representative images for top-line BMP-2 and low-order MMP-9 expressions from immunohistochemically stained preparations from each group (Bar: 20 μm, IHC-AEC)

BMP-2: Bone morphogenetic protein, MMP-9: Matrix Metalloproteinase, IHC: Immunohistochemistry, AEC: Amino ethyl carbochol

and observed that 33.8% of the patients redeveloped stricture during the mean follow-up period of 8.4 months. Long-term balloon dilatation success varies between 35 and 70%. Success rates of a single session of optic urethrotomy are only 8% (16). Other urethral surgeries are based on highly complicated techniques and/or can result in higher rates of complications (13,14). Urethral stricture is a disease that significantly impairs quality of life due to lower urinary tract complaints, recurrent infections, sexual dysfunction, and hematuria. Since it may require many urological interventions, it is important to treat urethral stricture with as minimally invasive methods as possible.

Studies on alternative methods, such as medical treatment approaches or tissue engineering, aiming to increase success in the treatment of urethral stricture are increasing. Recently, some studies have suggested using steroids. It is known that corticosteroid therapy, which can be used in the treatment of urethral stricture, reduces collagen production (17). Yıldırım et al. (18) treated half of the 83-patient cohort, whose mean age was 56.4 years, with 40 mg suburethral methyl prednisolone during internal urethrotomy, and observed that stricture recurred in 19 (46%) cases. They reported that the rate of recurrence was significantly lower in the steroid group than the control group. In a meta-analysis in which Zhang et al. (19) examined 8 studies, the time until relapse was longer in 203 cases who underwent internal urethrotomy and steroid injection than in patients that did not receive steroids. In the case-control study involving 72 cases with bulbar urethral stricture, patients were divided into two groups: those who received oral steroid treatment (n=36, deflazocort 6 mg tablets) after urethrotomy and those who did not (n=36) (20). At the end of the six months on average, the maximum flow rates in the first and second groups were determined as 18.2 mL/sec and 13.7 mL/sec, respectively, and recurrence of urethral stricture was lower in those receiving steroid therapy (20). In many studies, except for one, various steroids were given locally by invasive methods (17-19). In our study, the urethral lumen area increased, although not statistically significant, in the rats given oral prednisolone treatment compared to the stricture-only group (G2). Moreover, prednisolone treatment significantly decreased the inflammation and fibrosis scores compared to the G2 group.

In urology, pirfenidone has been used for urethral stricture, for reducing the effect of kidney damage, and in prostate cancer cell cultures (21-23). Transforming growth factor (TGF)-beta (β)1 is known to stimulate fibroblast differentiation and increase extracellular matrix production. Pirfenidone prevents fibrosis by reducing the effect of TGF-β1, and therefore is widely used in the treatment of pulmonary fibrosis. In addition, pirfenidone has been shown to inhibit cell proliferation and collagen I synthesis in intestinal cells, and is effective in reducing fibrosis in many organs (24). In a study conducted in rabbits with urethral stricture, it was reported that catheters coated with nanoparticle/pirfenidone complexes reduced urethral stricture and fibrosis (21). In our study, we also found that there was a significant decrease in inflammation and fibrosis scores, and a significant increase in the urethral lumen area in rats treated with pirfenidone compared to the stenosis-only group.

The use of antifibrotic agents appears to be a rational approach in the treatment of urethral stricture. Colchicine is an alkaloid chemically known as colchicinum-N-(5,5,7,-tetrahydro-1,2,3,-tetramethoxy-9-oxobenzo [alpha] heptalen-7-yl) acetamide. It has been used as an antifibrotic agent because it inhibits procollagen secretion and prevents its conversion into collagen (25). It has also been used to reduce fibrosis in the liver, lung, and kidney as well as serosal adhesions due to its antifibrotic and anti-inflammatory effects (26,27). Colchicine disrupts microtubule formation and binds to tubulin to inhibit microtubule polymerization (28). In a retrospective study evaluating 84 patients who received 1 g of oral colchicine per day and underwent internal urethrotomy due to urethral stricture, it was reported that the recurrence rate of urethral stricture was significantly reduced (29). In our study, we also found that there was a significant decrease in inflammation and fibrosis scores and a significant increase in the urethral lumen area in rats treated with oral colchicine compared to the stricture-only group (G2).

The main features of urethral stricture include epithelial damage, fibroblast proliferation, inflammation, and production of increased extracellular matrix. The ultimate feature is progressive fibrosis due to extracellular matrix deposition, in which MMP is believed to play an important role (1). MMPs are a group of proteinases known to regulate the remodeling of the extracellular matrix and are therefore important in the process of fibrosis and scarring that cause urethral stricture. A drug called verapamil has been reported to prevent excessive formation of urethral scars by inhibiting proliferation of urethral scar fibroblasts and increasing MMP activity in human cell culture (30). MMP-9 has been reported to be effective in inhibiting granulation tissue formation caused by metallic stent placement in the rat urethral model (4). In our study, MMP-9 expression was significantly increased in the group treated with colchicine compared to the stricture-only group (G2).

TGF-β1 is a protein with a wide range of biological functions in cell growth, differentiation, and extracellular matrix production. TGF-β1 plays a supportive role in the development of fibrosis in the kidney, lung, liver, and pancreas (31). Meanwhile, BMP-2 has an anti-fibrogenic function in multiple organs. It antagonizes TGF-β1-induced fibrogenic signals in renal fibroblasts and is effective in the treatment of rat renal fibrosis caused by unilateral ureteral obstruction (32). Wound healing in human skin has been reported, to be partly through induction of BMP-2 (33). Similarly, in a study with mice, mutual regulation between BMP-2 and TGF-β1 signal axes, has been reported to elucidate the anti-fibrogenic mechanism of BMP-2 in the pathogenesis of liver fibrosis (5). In our study, the increase of BMP-2 expression, especially in G3 and G5, supports the notion of the antifibrotic effect of colchicine and pirfenidone in immunohistochemistry.

Study Limitations

Since this study is an animal experiment, we cannot use methods such as endoscopy, radiological imaging, or uroflowmetry in the creation of urethral stricture or in the evaluation of healing.

The sample size of the experimental groups is also one of the limitations of the study. In addition, we cannot use the medical treatments applied in the study before and after opening the urethral stricture with the endoscopic methods in use at our current urology clinic.

Conclusion

We concluded that oral administration of colchicine or pirfenidone prevents the formation of urethral stricture to a large extent, and that oral steroid treatment reduces this formation, albeit not as effectively as colchicine or pirfenidone. Colchicine reduced fibrosis via BMP and contributed to partial urethral remodeling via MMP. Based on these findings, we believe that using these agents before and after endoscopic surgery or dilatation of the urethra in clinical practice following necessary clinical studies.

Ethics

Ethics Committee Approval: All procedures were performed in compliance with the provisions of the 1986 Strasbourg Universal Declaration on Animal Welfare and by the approval of the local ethics committee (approval number: HADYEK 23, date: 15.01.2018 - Gaziosmanpaşa University Rectorate Animal Experiments Ethics Committee).

Informed Consent: Not necessary.

Footnotes

Authorship Contributions

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

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

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References

1. Tritschler S, Roosen A, Füllhase C, Stief CG, Rübben H. Urethral stricture: etiology, investigation and treatments. Dtsch Arztebl Int. 2013;110:220-226. [Crossref]
2. Cavalcanti AG, Yucel S, Deng DY, McAninch JW, Baskin LS. The distribution of neuronal and inducible nitric oxide synthase in urethral stricture formation. J Urol. 2004;171:1943-1947. [Crossref]
3. Verla W, Oosterlinck W, Spinoit AF, Waterloos M. A comprehensive review emphasizing anatomy, etiology, diagnosis, and treatment of male urethral stricture disease. Biomed Res Int. 2019;2019:9046430. [Crossref]
4. Park JH, Kim JH, Kim EY, Kim J, Song HY, Kim WJ, Lee D, Park J, Kim S. Bioreducible polymer-delivered siRNA targeting MMP-9: suppression of granulation tissue formation after bare metallic stent placement in a rat urethral model. Radiology. 2014;271:87-95. [Crossref]
5. Chung YH, Huang YH, Chu TH, Chen CL, Lin PR, Huang SC, Wu DC, Huang CC, Hu TH, Kao YH, Tai MH. BMP-2 restoration aids in recovery from liver fibrosis by attenuating TGF-β1 signaling. Lab Invest. 2018;98:999-1013. [Crossref]
6. Marcovici I, Rosenzweig BA, Brill AI, Scommegna A. Colchicine and post-inflammatory adhesions in a rabbit model: a dose-response study. Obstet Gynecol. 1993;82:216-218. [Crossref]
7. Cinar O, Bolat MS, Erdem S, Kaymaz E, Demirkiran ED, Girgin R, Bulut E, Akduman B, Mungan NA. The effect of an antifibrotic agent, pirfenidone, on penile erectile function in an experimental rat model of ischemic priapism. Int J Impot Res. 2020;32:232-238. [Crossref]
8. Khelik IA, Berger DJ, Mochel JP, Seo YJ, Palerme JS, Ware WA, Ward JL. Clinicopathologic, hemodynamic, and echocardiographic effects of short-term oral administration of anti-inflammatory doses of prednisolone to systemically normal cats. Am J Vet Res. 2019;80:743-755. [Crossref]
9. Hooker GD, Taylor BM, Driman DK. Prevention of adhesion formation with use of sodium hyaluronate-based bioresorbable membrane in a rat model of ventral hernia repair with polypropylene mesh--a randomized, controlled study. Surgery. 1999;125:211-216. [Crossref]
10. Godbole GB, Modi DN, Puri CP. Regulation of homeobox A10 expression in the primate endometrium by progesterone and embryonic stimuli. Reproduction. 2007;134:513-523. [Crossref]
11. Mundy AR, Andrich DE. Urethral strictures. BJU Int. 2011;107:6-26. [Crossref]
12. Fenton AS, Morey AF, Aviles R, Garcia CR. Anterior urethral strictures: etiology and characteristics. Urology. 2005;65:1055-1058. [Crossref]
13. Levy M, Gor RA, Vanni AJ, Stensland K, Erickson BA, Myers JB, Voelzke BB, Smith TG 3rd, Breyer BN, McClung C, Alsikafi NF, Fan Y, Elliott SP; Trauma and Urologic Reconstructive Network of Surgeons (TURNS). The impact of age on urethroplasty success. Urology. 2017;107:232-238. [Crossref]
14. Pansadoro V, Emiliozzi P. Internal urethrotomy in the management of anterior urethral strictures: long-term followup. J Urol. 1996;156:73-75. [Crossref]
15. Yi YA, Rozanski AT, Shakir NA, Viers BR, Ward EE, Bergeson RL, Morey AF. Balloon dilation performs poorly as a salvage management strategy for recurrent bulbar urethral strictures following failed urethroplasty. Transl Androl Urol. 2020;9:3-9. [Crossref]
16. Santucci R, Eisenberg L. Urethrotomy has a much lower success rate than previously reported. J Urol. 2010;183:1859-1862. [Crossref]
17. Giovannini UM. Treatment of scars by steroid injections. Wound Repair Regen. 2002;10:116-117. [Crossref]
18. Yıldırım ME, Kaynar M, Ozyuvali E, Badem H, Cakmak M, Kosem B, Cimentepe E. The effectiveness of local steroid injection after internal urethrotomy to avoid recurrence. Arch Ital Urol Androl. 2016;87:295-298. [Crossref]
19. Zhang K, Qi E, Zhang Y, Sa Y, Fu Q. Efficacy and safety of local steroids for urethra strictures: a systematic review and meta-analysis. J Endourol. 2014;28:962-968. [Crossref]
20. Gupta S, Roy S, Pal DK. Efficacy of oral steroids after optical internal urethrotomy in reducing recurrence of urethral strictures. Turk J Urol. 2018;44:42-44. [Crossref]
21. Meng W, Jiang Z, Wang J, Chen X, Chen B, Cai B, Zhou Y, Ma L, Guan Y. Inhibition of urethral stricture by a catheter loaded with nanoparticle/pirfenidone complexes. Front Bioeng Biotechnol. 2023;11:1254621. [Crossref]
22. Ishii K, Sasaki T, Iguchi K, Kato M, Kanda H, Hirokawa Y, Arima K, Watanabe M, Sugimura Y. Pirfenidone, an anti-fibrotic drug, suppresses the growth

of human prostate cancer cells by inducing G_1 cell cycle arrest. J Clin Med. 2019;8:44. [Crossref]

23. Lima-Posada I, Fontana F, Pérez-Villalva R, Berman-Parks N, Bobadilla NA. Pirfenidone prevents acute kidney injury in the rat. BMC Nephrol. 2019;20:158. [Crossref]
24. Cui Y, Zhang M, Leng C, Blokzijl T, Jansen BH, Dijkstra G, Faber KN. Pirfenidone inhibits cell proliferation and collagen I production of primary human intestinal fibroblasts. Cells. 2020;9:775. [Crossref]
25. Diegelmann RF, Peterkofsky B. Inhibition of collagen secretion from bone and cultured fibroblasts by microtubular disruptive drugs. Proc Natl Acad Sci U S A. 1972;69:892-896. [Crossref]
26. Solak Y, Siriopol D, Yildiz A, Yilmaz MI, Ortiz A, Covic A, Kanbay M. Colchicine in renal medicine: new virtues of an ancient friend. Blood Purif. 2017;43:125-135. [Crossref]
27. Yıldız İ, Koca YS, Emek AK, Gelen T. To Investigate the effect of colchicine in prevention of adhesions caused by serosal damage in rats. Surg Res Pract. 2015;2015:315325. [Crossref]
28. Andreu JM, Perez-Ramirez B, Gorbunoff MJ, Ayala D, Timasheff SN. Role of the colchicine ring A and its methoxy groups in the binding to tubulin and microtubule inhibition. Biochemistry. 1998;37:8356-8368. [Crossref]
29. Sinanoglu O, Kurtulus FO, Akgün FS. Long-term effect of colchicine treatment in preventing urethral stricture recurrence after internal urethrotomy. Urol J. 2018;15:204-208. [Crossref]
30. Zeng M, Chen J, Huang L, Xue R, Xiang X, Zeng F, Wang G, Tang Z. [Effect of calcium channel blockers on primary cultured human urethra scar fibroblasts]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2016;41:1317-1322. Chinese. [Crossref]
31. Kimura T, Saito T, Yoshimura M, Yixuan S, Baba M, Ji G, Muramatsu M, Kawata S. Association of transforming growth factor-beta 1 functional polymorphisms with natural clearance of hepatitis C virus. J Infect Dis. 2006;193:1371-1374. [Crossref]
32. Yang YL, Ju HZ, Liu SF, Lee TC, Shih YW, Chuang LY, Guh JY, Yang YY, Liao TN, Hung TJ, Hung MY. BMP-2 suppresses renal interstitial fibrosis by regulating epithelial-mesenchymal transition. J Cell Biochem. 2011;112:2558-2565. [Crossref]
33. Yan C, Grimm WA, Garner WL, Qin L, Travis T, Tan N, Han YP. Epithelial to mesenchymal transition in human skin wound healing is induced by tumor necrosis factor-alpha through bone morphogenic protein-2. Am J Pathol. 2010;176:2247-2258. [Crossref]

VIDEO ARTICLE
Urooncology

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Laparoscopic Partial Nephrectomy Tips and Tricks

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Abstract

This video article presents tips and techniques for laparoscopic partial nephrectomy (LPN), emphasizing the importance of preoperative assessment with advanced imaging techniques like 3-dimensional reconstruction. The transperitoneal approach, precise trocar placement, and intraoperative ultrasound guidance are highlighted for optimal surgical outcomes. The role of renorrhaphy, with considerations for suturing techniques and materials, is discussed, particularly focusing on nephron-sparing strategies. The benefits of minimizing warm ischemia time are reviewed alongside the value of zero ischemia techniques. LPN remains a highly effective nephron-preserving procedure for managing small renal masses.

Keywords: Endourology, general urology, urooncology

Introduction

Partial nephrectomy (PN) should be recommended for clinically stage T1 or "resectable" T2 tumors rather than radical nephrectomy if technically feasible. Technical preference for PN depends on the expertise of the surgeon (1). Laparoscopic and robotic PN have shown comparable surgical margin status and oncological outcomes relative to open surgery in appropriately selected patients (2). Current data indicate that the advantages of minimally invasive surgery are evident in the short-term perioperative period and are comparable to open surgery during intermediate and long-term assessments (3). In experienced hands, laparoscopic partial nephrectomy (LPN) indeed works as an effective nephron-preserving platform despite a more difficult learning curve (4). In this video article, we aim to present LPN's technical details and tips on all steps.

Preoperative Assessment

Comprehensive preoperative evaluation is essential for optimizing outcomes and minimizing complications in patients undergoing PN. High-resolution multiphasic contrast-enhanced tomography or magnetic resonance imaging assesses the tumor's location, size, and relationship to surrounding structures. The tumor's proximity to the renal vasculature and collecting system is crucial for surgical planning. 3D reconstruction techniques enable patients to grasp organ structures' spatial and anatomical relationships more effectively than conventional images.

Scoring systems such as the RENAL nephrometry score (5) aid in assessing tumor complexity and assist surgeons in refining nephron-sparing strategies during surgery and in preoperative discussions with patients. The RENAL score also has significant correlations with clinical outcomes, including longer warm ischemia times, increased complications, more aggressive pathological features, and higher tumor grades (6).

Positioning and Trocar Placement

We prefer the transperitoneal approach, which offers a larger operative field and facilitates easier anatomical orientation. A modified lateral decubitus position aids colon medialization, allowing the intestines to naturally fall away from the kidney. The pneumoperitoneum is established using a closed technique, with the optical trocar typically inserted at the pararectal line or umbilicus, depending on the patient's anatomical characteristics. The remaining trocars are placed in a triangular configuration based on the tumor's location, whether polar or central, and at the upper or lower pole of the kidney.

Vascular and Perirenal Dissection

Following the medialization of the colon, duodenum, and spleen, Gerota's fascia is incised next to the gonadal vein.

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After the ureter is identified and suspended, the fascia is carefully dissected to the inferior margin of the renal vein. The inferior pole is subsequently elevated to enhance visibility. Mobilization is enhanced by liberating the plane between the kidney and the adrenal gland. The renal vein and artery are separately dissected and secured with silicone tapes. Dissection is conducted cautiously due to vascular abnormalities and the risk of perforating branches. We employ ultrasonic energy devices, such as Thunderbeat®, for vascular and perirenal fat dissection. Intraoperative ultrasonography is essential for directing accurate parenchymal dissection, particularly in cases with adherent perirenal fat (7), avoiding tumor capsule rupture, and defining margins. Tumor margin scoring is performed using hook cautery. The application of intraoperative ultrasound is especially vital for executing PN in endophytic tumors.

Resection and Renorraphy

Recent literature demonstrates that the most important determinant of functional outcomes after PN is the preservation of vascularized renal parenchyma (8). Efforts to optimize this parameter during tumor excision and reconstruction should be prioritized as long as oncological outcomes are not compromised. In short, preserving nephron mass is crucial for maintaining kidney function. Resection, enucleoresection, and enucleation are the three main resection techniques. The choice of technique depends on the tumor's location, shape, relationship to the collecting system and vessels, and the surgeon's experience. The tumor's relationship with these anatomical structures plays a critical role in selecting the surgical strategy and can directly impact the surgical outcomes.

We primarily prefer enucleation, when technically feasible, to maximize the preservation of normal renal parenchyma. The concept of tumor enucleation (blunt excision of the tumor with minimal margin during nephron-sparing surgery) was originally developed in familial renal cell carcinoma (RCC) patients who require multiple surgeries throughout their lifetime due to multiple tumors to preserve as much renal parenchyma as possible (9). This technique maximizes renal tissue preservation, making it a suitable strategy for repeat surgeries. It was later evaluated in the sporadic RCC population, and several studies reported similar oncological outcomes compared to traditional PN (10). In traditional PN, a deliberate margin of normal renal parenchyma surrounding the tumor is excised, while enucleation minimizes this margin. However, most studies comparing enucleation and traditional PN have been retrospective, with no standard pathological review applied. Additionally, the selection of enucleation is often based on favorable imaging characteristics such as homogeneity and encapsulation (11). Enucleation involves blunt dissection along the tumor pseudo capsule, a structure in many but not all renal cancers. When present, the pseudo capsule may contain invasive cancer in up to one-third of cases, with its impact on prognosis being unclear (12). Given these concerns, careful evaluation of tumor growth patterns and its interface with normal parenchyma through preoperative radiological imaging is necessary to assess the feasibility of successful enucleation.

In PN, safe resection should be followed by quality reconstruction. Renorrhaphy techniques during minimally invasive PN have evolved for several reasons. In the early LPN series, renorrhaphy focused on minimizing complications through proper hemostasis and closure of the collecting system. Today, "nephron-sparing renorrhaphy" aims to maximize the volume of vascularized parenchyma preserved, thus ensuring better long-term renal function. This approach prioritizes bleeding control and preservation of the kidney's functional tissue (13).

Renorrhaphy can be performed in two layers (medullary and cortical) or in a single layer. A systematic review evaluating suturing techniques found no difference in complications between single- and double-layer renorrhaphy but emphasized that single-layer closure was more advantageous for preserving kidney function (14). The same review found no significant difference in complications between interrupted and continuous suturing but reported that the duration of surgery was longer in the interrupted suture group (14). We prefer a double-layer running fashion; in medullar renorraphy, we prefer monofilament sutures with a Hem-o-lok™ clip at the end. In the cortical renorraphy, we use a 2/0 absorbable, braided suture with a sliding clip technique (15).

In terms of suture material, both barbed and monofilament sutures can be used for medullary renorrhaphy. While barbed sutures shorten the duration of renorrhaphy, we prefer monofilament sutures in complex masses to prevent tension and tearing in the tissue. Monofilament sutures offer an advantage in wide-based cases as they can be tightened from both ends.

The European Association of Urology guidelines recommend limiting warm ischemia time to 20-25 minutes (1). Although warm ischemia time is important, as previously mentioned, complete tumor resection and renorrhaphy should be prioritized. Zero ischemia (off-clamp) techniques may improve functional outcomes, but they are not always feasible and may reduce the surgical field visibility during PN (16).

In patients undergoing off-clamp PN, the long-term estimated glomerular filtration rate was higher (mean difference =7 mL/min/1.73 m^2) than those undergoing on-clamp PN. Meta-analyses comparing ischemia techniques have shown that zero ischemia is associated with higher positive surgical margin rates (5.6% *versus* 3.8%, $p<0.01$) and local recurrence (3.1% *versus* 1.8%, $p=0.13$) compared to warm ischemia (17).

Conclusion

Minimally invasive PN has proven to be a safe and effective procedure for managing renal masses, offering similar oncological outcomes to open surgery while preserving renal function. Advances in laparoscopic and robotic techniques and intraoperative imaging tools have further enhanced surgical precision and outcomes. Preserving vascularized renal parenchyma remains a critical factor in maintaining long-term renal function. Continued focus on optimizing surgical techniques, such as nephron-sparing renorrhaphy and enucleation, will ensure that PN remains the gold standard in nephron-sparing surgery for appropriate cases.

Video 1.

Ethics

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

Footnotes

Authorship Contributions

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

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References

1. Ljungberg B. European Association of Urology guidelines on renal cell carcinoma: the 2022 update. Eur Urol. 2022;82:399-410. [Crossref]
2. Campbell SC. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part I. J Urol. 2021;206:199-208. [Crossref]
3. Auffenberg GB, Curry M, Gennarelli R, Blum KA, Elkin E, Russo P. Comparison of cancer-specific outcomes following minimally-invasive and open surgical resection of early-stage kidney cancer from a national cancer registry. J Urol. 2020;203:1094-1100. [Crossref]
4. Ellison JS, Montgomery JS, Wolf JS, Hafez KS, Miller DC, Weizer AZ. A matched comparison of perioperative outcomes of a single laparoscopic surgeon versus a multisurgeon robot-assisted cohort for partial nephrectomy. J Urol. 2012;188:45-50. [Crossref]
5. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009;182:844-853. [Crossref]
6. Veccia A. Predictive value of nephrometry scores in nephron-sparing surgery: a systematic review and meta-analysis. Eur Urol Focus. 2020;6:490-504. [Crossref]
7. Gülşen M, Özden E, Çamlıdağ İ, Öner S, Bostancı Y, Yakupoğlu YK, Yılmaz AF, Sarıkaya Ş. Intraoperative ultrasound can facilitate laparoscopic partial nephrectomy in adherent perinephric fat. J Laparoendosc Adv Surg Tech A. 2023;33:480-486. [Crossref]
8. Wu J, Suk-Ouichai C, Dong W, Zhang Z, Tanaka H, Wang Y, Caraballo E, Remer EM, Li J, Isharwal S, Abouassaly R, Campbell SC. Vascularized parenchymal mass preserved with partial nephrectomy: functional impact and predictive factors. Eur Urol Oncol. 2019;2:97-103. [Crossref]
9. Walther MM, Thompson N, Linehan W. Enucleation procedures in patients with multiple hereditary renal tumors. World J Urol. 1995;13:248-250. [Crossref]
10. Minervini A. Impact of resection technique on perioperative outcomes and surgical margins after partial nephrectomy for localized renal masses: a prospective multicenter study. J Urol. 2020;203:496-504. [Crossref]
11. Lu Q, Ji C, Zhao X, Fu Y, Guo S, Liu G, Zhang S, Li X, Gan W, Guo H. Histopathologic analysis of tumor bed and peritumoral pseudocapsule after in vitro tumor enucleation on radical nephrectomy specimen for clinical T1b renal cell carcinoma. Urol Oncol. 2017;35:603.e15-603.e20. [Crossref]
12. Jacob JM, Williamson SR, Gondim DD, Leese JA, Terry C, Grignon DJ, Boris RS. Characteristics of the peritumoral pseudocapsule vary predictably with histologic subtype of T1 renal neoplasms. Urology. 2015;86:956-961. [Crossref]
13. Porpiglia F, Bertolo R, Amparore D, Fiori C. Nephron-sparing suture of renal parenchyma after partial nephrectomy: which technique to go for? Some best practices. Eur Urol Focus. 2019;5:600-603. [Crossref]
14. Bertolo R, Campi R, Mir MC, Klatte T, Kriegmair MC, Salagierski M, Ouzaid I, Capitanio U; Young Academic Urologists Kidney Cancer Working Group of the European Urological Association. Systematic review and pooled analysis of the impact of renorrhaphy techniques on renal functional outcome after partial nephrectomy. Eur Urol Oncol. 2019;2:572-575. [Crossref]
15. Benway BM, Wang AJ, Cabello JM, Bhayani SB. Robotic partial nephrectomy with sliding-clip renorrhaphy: technique and outcomes. Eur Urol. 2009;55:592-599. [Crossref]
16. Cacciamani GE. Impact of renal hilar control on outcomes of robotic partial nephrectomy: systematic review and cumulative meta-analysis. Eur Urol Focus. 2019;5:619-635. [Crossref]
17. Greco F. Ischemia techniques in nephron-sparing surgery: a systematic review and meta-analysis of surgical, oncological, and functional outcomes. Eur Urol. 2019;75:477-491. [Crossref]

VIDEO ARTICLE
Pediatric Urology

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Zinner Syndrome: A Rare Case Report

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Abstract

Over 200 cases of seminal vesicle cysts linked to ipsilateral renal agenesis have been reported in the literature, indicating Zinner syndrome. This condition occurs when the ureteric buds fail to meet the metanephros, leading to cystic dilatation in the ipsilateral seminal vesicle along with unilateral renal agenesis. Here, we are discussing a 17-year-old boy who presented with lower urinary tract symptoms predominantly flow symptoms, was evaluated thoroughly, and robotic surgery was selected as the best minimally invasive treatment.

Keywords: Zinner syndrome, general urology, radiology, seminal vesicle cyst

Introduction

More than 200 cases of seminal vesicle cysts associated with ipsilateral renal agenesis have been reported. These cases are indicative of Zinner syndrome (ZS), a rare congenital condition characterized by cystic seminal vesicles and ejaculatory duct obstruction in association with ipsilateral renal agenesis (1).

Embryology

Due to inadequate migration, the ureteric bud emerging from the proximal section of the Wolffian duct cannot join the metanephros (1).

The inability of the ureteric buds to migrate from the mesonephric duct is the underlying reason for the failure to meet metanephros. As a result, cystic dilatation develops in the ipsilateral seminal vesicle due to ejaculatory duct blockage and ipsilateral renal agenesis caused by the failure of metanephric blastoma to differentiate (2).

Case Presentation

A 17-year-old boy presented with chief complaints of voiding lower urinary tract symptoms for 3 months. Local examination of the genitalia and abdomen was normal, and the digital rectal examination (DRE) was also normal.

Ultrasound revealed left atrophic kidney (5 cm), left dilated ureter, and the remaining anatomy was normal.

Computed tomography (CT) scan abdomen findings are depicted in Figures 1, 2 and 3. Semen analysis revealed oligospermia. All blood tests were normal.

Patients and relatives were counseled regarding left nephroureterectomy with cystic lesion excision robotically.

Materials and Methods

Surgery (Voice Over Included with Video)

Initially in the lithotomy position, cytoscopy showed normal urethra, right ureteric orifice normal, left ureteric orifice could not be localized, left poster-lateral bladder wall bulging toward the lumen, possibly due to extraluminal compression by the cystic structure. The bladder mucosa was normal.

Position changed to right lateral position: atrophic kidney dissected with vasculature clipped and cut, and ureter dissected until bladder.

Position changed to Lithotomy with head low position-the ureter was found to be ending in the left cystic structure, possibly the left seminal vesicle, dissected and cut at the base. An abdominal drain was placed. Specimens were retrieved in bags by Pfannenstiel incision. The postoperative period was uneventful.

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Figure 1. Non-functional left kidney

Figure 2. Atrophic left kidney with dilated ureter opening in the cystic leaves seminal vesicle

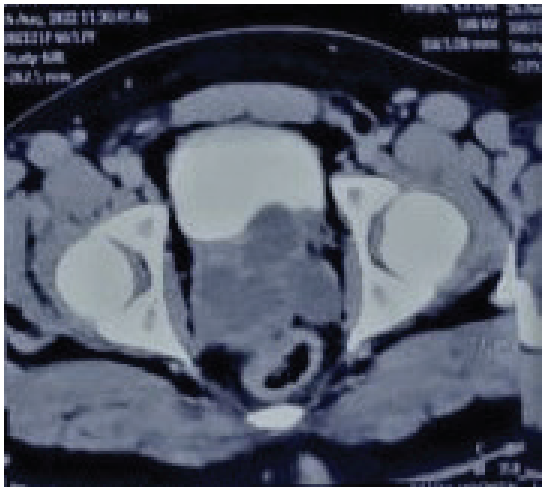

Figure 3. Left seminal vesicles could not be identified separately from the cystic structure

Discussion

Zinner's syndrome is a rare congenital disease characterized by the association of ipsilateral renal agenesis or dysplasia, ectopic uretera, and ipsilateral seminal vesicle cysts, first described by Zinner in 1914 (3).

It is thought that Mayer-Rokitansky-Küster-Hauser syndrome affects females and ZS affects males. An ectopic ureter may develop when the ureteric bud emerges distally from the urogenital sinus. It might empty into the seminal vesicle cyst, vas deferens, ejaculatory duct, or bladder neck. Seminal vesicles and dilated tubules may become cysts as a result of ejaculatory duct occlusion (2).

Therefore, aberrant ureteric bud development is a cause of ZS. Abdominal pain, fullness, and micturition-related symptoms, such as dysuria, hematuria, urgency, and obstructed urination are typical presenting features. Signs become more noticeable during peak sexual or reproductive activity, particularly in the second and third decades (4), although they can sometimes appear without symptoms (2).

The ipsilateral ureter and kidney are confirmed to be absent on CT urogram, but the origin of the cyst is typically not confirmed. The best method is magnetic resonance imaging, which also allows analysis of the cyst contents, which are typically pure liquid and appear hypointense on T1 and hyperintense on T2 (5). DRE may or may not reveal a clinically significant finding. In our case, there was no clinically aberrant finding however (6) had shown a cystic mass palpable per rectally.

Clinical assessment determines how ZS should be managed (3). The patient's symptoms, cyst size, and presence of comorbidities all influence how the patient is managed. It is possible to use observation management in patients who are asymptomatic or have minimal symptoms (6). For patients with minor symptoms, conservative treatment with antibiotics, transurethral needle aspiration of the cyst, or transurethral aspiration combined with substance instillation (alcohol and minocycline) is appropriate (7). Despite being simple to perform, conservative transrectal aspiration carries a significant risk of infection and recurrence; if it proves fruitless, it should not be repeated (6). The cornerstone of treatment for symptomatic patients is surgery (2). The condition can be treated surgically using an open, laparoscopic, or robotic technique.

The advantages of a robotic approach over conventional laparoscopy include the ability to manipulate instruments more easily in a small working space and to move with greater precision and degrees of freedom. This allows the calibrated use of thermal energy, which lowers the risk of blood loss and nerve injury. Because seminal vesicles are located deep in the pelvis,

better vision with higher magnification and three-dimensional imaging is key to vesiculectomy (3).

Given its positive outcomes, robotic surgery can be regarded as the gold standard for surgical therapy in these patients (3). The surgeon can simultaneously manage the upper and lower which significantly lowers the morbidity associated with making two separate incisions (3).

Prolonged follow-up is required because seminal vesicle diseases are prone to recurrence due to potential coexisting ejaculatory duct abnormalities or its development following surgery. Because of this, transurethral resection of the ejaculatory duct should be taken into consideration (8).

Conclusion

This case presents an adult seminal vesicle cyst, renal dysplasia linked to an ipsilateral incomplete duplicated ectopic ureter, and an uncommon congenital defect of the genitourinary tract. With good surgical and cosmetic outcomes, the robotic-assisted laparoscopic approach was selected as the best minimally invasive method for treating this patient's unusual congenital cystic malformation.

Video 1.

Ethics

Informed Consent: Written informed consent was obtained from the patient and parents regarding the surgery and publication of information on this case in scientific meetings/journals.

Footnotes

Authorship Contributions

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

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

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References

1. Hofmann A, Vauth F, Roesch WH. Zinner syndrome and infertility-a literature review based on a clinical case. Int J Impot Res. 2021;33:191-195. [Crossref]
2. Kumar S, G KI, Khalil-Khan A, Arul Pitchai ADP, Sathiamoorthy R, Raju E. Zinner syndrome. Cureus. 2022;14:e31308. [Crossref]
3. Altobelli E, Bove AM, Falavolti C, Sergi F, Nguyen HT, Buscarini M. Robotic-assisted laparoscopic approach in the treatment for Zinner's syndrome associated with ipsilateral megaureter and incomplete double-crossed ectopic ureter. Int Urol Nephrol. 2013;45:635-638. [Crossref]
4. Slaoui A, Regragui S, Lasri A, Karmouni T, El Khader K, Koutani A, Ibn Attya A. Zinner's syndrome: report of two cases and review of the literature. Basic Clin Androl. 2016;26:10. [Crossref]
5. Abakar D, Badi FE, Sabiri M, El Manjra S, Lezar S, Essodegui F. Zinner syndrome. Eur J Case Rep Intern Med. 2021;8:002628. [Crossref]
6. Djordjevic D, Dragicevic S, Vukovic M. Radical surgical treatment of a large seminal vesicle cyst that can cause acute urinary retention in a patient with zinner syndrome: a case report and review of literature. J Urol Surg. 2021;8:291-293. [Crossref]
7. Aslan S. Rare cause of chronic pelvic pain in young men: magnetic resonance imaging findings of Zinner's syndrome. J Urol Surg. 2019;6:331-334. [Crossref]
8. Dilek İE, Ediz E, Şenoğlu Y. Is the laparoscopic approach adequate for Zinner syndrome? one patient, two cases. J Urol Surg. 2024;11:243-247. [Crossref]

CASE REPORT
General Urology

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Ureterocele in Adults: A Case Study and Review of Clinical Presentations and Management Options

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Abstract

Ureterocele is a cystic dilatation of the distal ureter and is a rare cause of urinary tract obstruction. It is commonly found in infants and young children and is more prevalent in females than in males. This report presents the case of a 59-year-old woman who suffered right flank pain and was diagnosed with ureterocele. The patient was treated with endoscopic surgery and unroofing of the ureterocele.

Keywords: Ureterocele, flank pain, unroofing ureterocele

Introduction

Ureterocele is a cystic dilatation of the submucosal distal ureter and is an uncommon cause of urinary tract obstruction. Ureterocele occurs more frequently in infants and early children than in adults and teenagers, and it affects females more frequently than males (1,2). The prevalence rate of ureterocele is 1 per 4000 children, with the prevalence being 4 times higher in females where the left side is slightly dominant and 10% of the cases are bilateral (3,4).

The common symptoms of ureterocele range from incontinence, recurrent urinary tract infections (UTIs), failure to thrive, urinary tract calculus, and irregular flank pain. Without proper early diagnosis and treatment during childhood, ureterocele could present along with secondary complications such as pyonephrosis, urosepsis, stones, urinary retention, or chronic renal failure. Hence, an individualized treatment is needed for ureterocele patients (5). Ureterocele incisions, open technique, endoscopic therapy, and transurethral diathermy incision are among the available therapeutic methods that have produced positive results (6). Endoscopic surgery and unroofing can be performed to relieve obstruction and prevent complications such as UTIs and renal damage (7,8).

Ureteroceles are classified on the basis of their location and association with other anatomical abnormalities. The classification system of the American Academy of Pediatrics is commonly used, where the uretroceles are classified into intravesical ureteroceles (occur at the normal vesicoureteric junction position, bilateral and occur mostly in adults) and extravesical ureteroceles (occur abnormally low and medial, close to the bladder neck or urethra, predominantly associated with a duplex kidney) (9). The latter type might result in blockage of the entire renal tract due to prolapse into the bladder (10-12). In 1954, Ericsson classified ureterocele as (1) simple ureterocele, in which the orifice is located on the trigone, and (2) ectopic ureterocele, in which the orifice is located at the bladder neck or posterior urethra (13,14). Furthermore, Bruézière classified ureterocele intothe following: 1) type A, intravesical ureterocele on a single ureter; 2) type B, ectopic ureterocele on a single ureter; 3) type C, intravesical ureterocele on pyeloureteral duplicity; and 4) type D, ectopic ureterocele on pyeloureteral duplicity (15).

Understanding the different types and classifications of ureteroceles is important for accurate diagnosis and appropriate management. This case report highlights the uncommon occurrence of ureterocele in adults. Despite the absence of urinary issues, the study underscores the significance of considering ureterocele as a potential urinary tract blockage in adult patients presenting with flank pain. In addition, with various symptoms and presentations of ureterocele, this case could be used as a perspective of a case with a single symptom of right flank pain in adults.

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Case Presentation

We present the case of a 59-year-old woman who presented with right flank pain and was diagnosed with ureterocele. Laboratory investigation showed normal results. To test the condition of this woman, computed tomography (CT) intravenous pyelogram (IVP) was performed and showed dilatation of the right distal ureter or ureterovesical junction suggestively as ureterocele, as shown in Figure 1 and Figure 2. After diagnosis, the patient underwent endoscopic surgery and unroofing of the ureterocele. The patient had no complaints during the postoperative control session.

Treatment options for ureterocele include upper pole partial nephrectomy, endoscopic incision, complete bladder reconstruction, and non-operative (conservative) treatment (16). The choice of treatment should be individualized for each case.

Discussion

Ureteroceles depicts a particular clinical challenge in terms of diagnosis and management because of the various types and presentations; hence, the treatment has to be customized based on the individual needs of each case. With various types and presentations, the cause of ureterocele remains controversial. There are two arguments regarding the etiology of ureterocele: one is congenital and the other is an acquired lesion. The congenital argument is supported by more evidence than the acquired argument (17).

One of the widely accepted theories regarding the pathogenesis of ureterocele is the regression failure of the Chwalla membrane, a membrane between the urogenital sinus and the developing ureteral bud. Chwalla proposed the etiology of ureterocele, where the development of ureterocele is caused by the obstruction of a membrane closing the mouth of the ureter in the embryo. However, this does not justify the stenotic case of ureterocele because it does not clarify the presence of a patulous ureteric orifice in the urethra (13). Considering that ureteroceles in duplex systems only affect the upper bud and not the lower bud, the etiology foundation of uretroceles is correlated to their location on the mesonephric duct (Wolffian duct) (18). A previous study stated that ureterocele is caused by malformation of the ureteral and urogenital sinus (19). On the other hand, acquired ureterocele is hypothesized by an

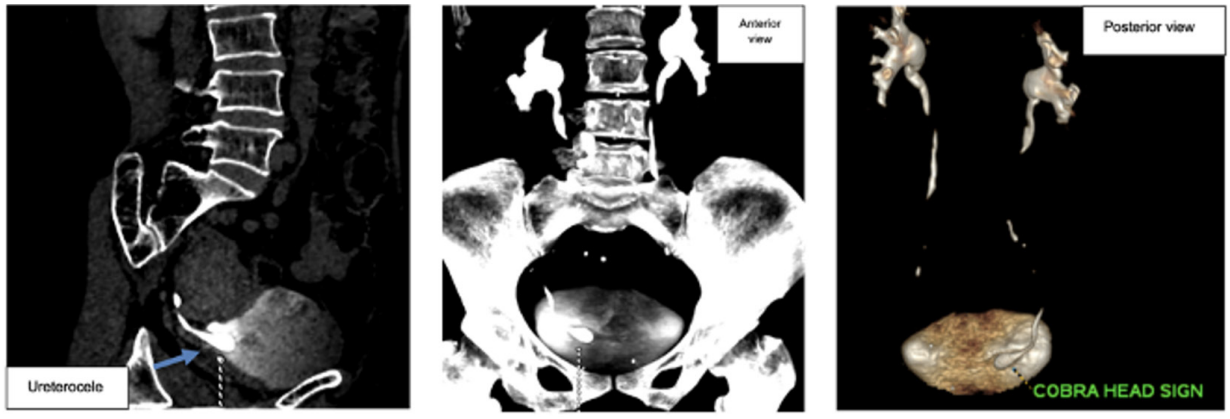

Figure 1. CT-IVP imaging

CT-IVP: Computed tomography intravenous pyelogram

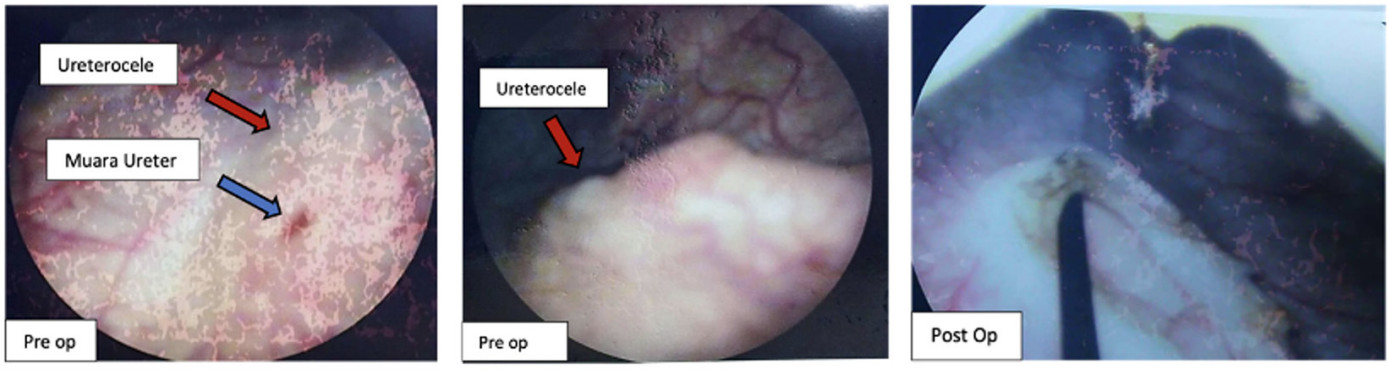

Figure 2. Endoscopic imaging showed an ureterocele on the right UVJ

UVJ: Ureterovesical junction

increase in intramural pressure and mucosal herniation of the ureter, which is caused by a sequel of distal obstruction such as calculus (20).

The diagnosis of ureterocele in pediatric patients can be made through imaging studies such as ultrasound, voiding cystourethrography, or IVP. Treatment options for ureterocele in pediatric patients depend on the severity of symptoms and the presence of complications. Conservative management may be considered for asymptomatic cases, whereas surgical intervention, such as endoscopic incision or complete reconstruction at the bladder level, may be necessary for symptomatic cases or those with complications.

The management of ureterocele is varied. The management option is based on the patient's presentation, age, ureterocele type, presence of contagion or infection, stones, and duplex kidney (5). Operative treatment options for ureteroceles include incision, multiple punctures, unroofing, and resection (21). Endoscopic procedure as a minimally invasive approach provides early decompression for ureterocele patients (22). A previous study stated that minimally invasive procedures have been proven to be safe, effective, and successfully managed in ureteroceles patients (5,21-27).

While previous studies found that minimally invasive surgery is considered successful without recurrent symptoms, other studies found that some cases of ureteroceles need secondary surgery after minimally invasive procedures (24,27,28). Minimally invasive procedures, such as endoscopic incision, are not considered a definitive management for ectopic ureterocele patients with duplex systems and preoperative reflux (26). Nevertheless, experts agree that the management of uretroceles aims to prevent UTIs, relieve the blockage of renal parenchyma, prevent and treat VUR, and minimize surgical procedures and morbidity (13).

In this case, the patient underwent endoscopic surgery and unroofing of the ureterocele. Endoscopic incision is a minimally invasive surgery that requires making a minor surgical cut in the ureterocele to relieve the obstruction and improve urine drainage. After endoscopic incision of the ureterocele, the patient may experience relief of symptoms and improvement in urinary flow. The procedure resulted in no postoperative complaints from the patient.

The clinical presentation of ureterocele in adults is usually incidental, but it can sometimes present with intermittent flank pain, recurrent UTI, or calculus. The patient only complained about flank pain, and CT IVP showed dilatation of the right distal ureter and an indication of cobra head abnormality. This case could be a reference to diagnose patients with flank pain complaint properly, so further symptoms of ureteroceles could be avoided.

Study Limitations

The limitation of this research is that it is based on a single case study, which may limit the generalizability of the findings. Case studies provide valuable insights into individual cases but may not represent the broader population. Therefore, the conclusions drawn from this research should be interpreted with caution and further studies are needed to validate the findings and establish more robust conclusions. Further research is needed to enhance our understanding of ureterocele and optimize its management strategies.

Conclusion

The case reported a 59-year-old woman who presented with right flank pain and was diagnosed with ureterocele. After endoscopic incision and unroofing of the ureterocele to relieve the symptoms, the patient is declared asymptomatic. It is important to note that ureterocele in adults is a rare condition, and its diagnosis and management can be challenging because of its variable presentations. Follow-up is necessary to monitor for recurrence of symptoms or complications. Overall, the diagnosis and management of ureterocele require a comprehensive approach, considering the patient's age, symptoms, and individual characteristics.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.G.P.P., E.O., A.P.A., Concept: A.G.P.P., E.O., A.P.A., Design: A.G.P.P., E.O., A.P.A., Analysis or Interpretation: A.G.P.P., E.O., A.P.A., Literature Search: A.G.P.P., Writing: A.G.P.P.

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

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References

1. Belhassen S, Elezzi A, Hidouri S, Laamiri R, Mosbahi S, Ksiaa A, Sahnoun L, Mekki M, Belguith M, Nouri A. Urétérocèle sur uretère simplex chez l'enfant: aspects cliniques et thérapeutiques [Ureterocele associated with simplex ureter in children: clinical and therapeutic features]. Pan Afr Med J. 2021;38:345. French. [Crossref]
2. Wang J, Zhao Y, Chen Z, Geng H, Fang X. Ureterocele with duplex collecting systems and febrile urinary tract infection risk. Pediatr Surg Int. 2023;39:200. [Crossref]

3. Misseri R, Rink RC. Chapter 58. Complications of ureteral reimplantation, antireflux surgery, and megaureter repair. In: complications of urologic surgery (fourth edition) [Internet]. 2010. p. 685-695. [Crossref]
4. Schultza K, Todab LY. Genetic basis of ureterocele. Curr Genomics. 2016;17:62-69. [Crossref]
5. Chowdhary SK, Kandpal DK, Sibal A, Srivastava RN. Management of complicated ureteroceles: different modalities of treatment and long-term outcome. J Indian Assoc Pediatr Surg 2014;19:156-161. [Crossref]
6. Abrahamsson LO, Rosenkilde Olsen P, Mathiesen FR. Ureterocele in adults. A follow-up study of 28 adult patients treated with transurethral diathermy incision. Scand J Urol Nephrol. 1981;15:239-242. [Crossref]
7. Cooper CS. Ureterocele treatment & management. Medscape, 2020. [Crossref]
8. Nast KJ, Marietti-Shepherd S, Kaplan G. Scissor ureterocele unroofing endoscopic technique: a novel technique for minimally invasive ureterocele treatment. Videourology. 2017;31:vid.2017.0007. [Crossref]
9. Society for Maternal-Fetal Medicine; Ghaffari N. Ectopic ureterocele. Am J Obstet Gynecol. 2021;225:B14-B15. [Crossref]
10. Xie D. Ureterocele: review of presentations, types and coexisting diseases. Int Arch Urol Complic. 2017;3. [Crossref]
11. Niknejad M, Gaillard F. Ureterocele. In: radiopaedia.org. Radiopaedia.org; 2008. [Crossref]
12. Timberlake MD, Corbett ST. Minimally invasive techniques for management of the ureterocele and ectopic ureter: upper tract versus lower tract approach. Urol Clin North Am. 2015;42:61-76. [Crossref]
13. Shokeir AA, Nijman RJ. Ureterocele: an ongoing challenge in infancy and childhood. BJU Int. 2002;90:777-783. [Crossref]
14. Ali SI, Iqbal N, Kala MS, Dobs MIL, Raffay EA, Khan M, Ali T, Iftikhar MJ, Sethuraman HP, Akhter S. Management of ureteroceles: review article. J Biol Today's World [Internet] 2020;9:1-4. [Crossref]
15. Oueslati A, Saadi A, Chakroun M, Zaghbib S, Bouzouita A, Derouiche A, Slama MRB, Ayed H, Chebil M. Endoscopic meatotomy in the treatment of ureterocele: results in adult patients. Pan Afr Med J. 2020;36:243. [Crossref]
16. Hariwibowo R, Rahardjo HE. Endoscopic incision of protruding right ureterocele in a single collecting system: a case report. Med J Indones. 2017;25:240-244. [Crossref]
17. Wershub LP, Kirwin TJ. Ureterocele, its etiology, pathogenesis and diagnosis. Am J Surg. 1954;88:317-327. [Crossref]
18. Tanagho EA. Embryologic basis for lower ureteral anomalies: a hypothesis. Urology. 1976;7:451-464. [Crossref]
19. Jain S, Chen F. Developmental pathology of congenital kidney and urinary tract anomalies. Clin Kidney J. 2018;12:382-399. [Crossref]
20. Chauhan G, Levy I, Samuel SW. Ureterocele as a cause of chronic intractable abdominal pain. BMJ Case Rep. 2021;14:e245262. [Crossref]
21. Subihardi LME, Rahman IA, Yogiswara N, Rizaldi F, Tarmono. Prolapsed ureterocele mimicking a vulval mass in young female with complete duplex system and ureteral stone: a case report. Int J Surg Case Rep. 2023;106:108087. [Crossref]
22. Caione P, Gerocarni Nappo S, Collura G, Matarazzo E, Bada M, Del Prete L, Innocenzi M, Mele E, Capozza N. Minimally invasive laser treatment of ureterocele. Front Pediatr. 2019;7:106. [Crossref]
23. Quitral VM, Mena DJA, Manriquez CL, Mela SMJ, Ammann RR, Navarrete ML, Montedónico S. Minimally invasive treatment of pediatric obstructive ureterocele: a 20-year experience. J Pediatr Surg Open. 2023;4. [Crossref]
24. Yuri P, Utama ETP. A complete duplicated collecting system with giant ureterocele in adult: case report. Int J Surg Case Rep. 2021;79:49-52. [Crossref]
25. Katwal S, Ghimire A, Shrestha K, Kansakar R, Amatya S. Unraveling recurrent urinary tract infection in adulthood: a rare case report of unilateral partial duplex collecting system with ureterocele. Ann Med Surg (Lond). 2023;85:5214-5218. [Crossref]
26. Byun E, Merguerian PA. A meta-analysis of surgical practice patterns in the endoscopic management of ureteroceles. J Urol. 2006;176:1871-1877; discussion 1877. [Crossref]
27. Aikins K, Taghavi K, Grinlinton M, Reed P, Price N, Upadhyay V. Cystoscopic transurethral incision in simplex and duplex ureteroceles-is it the definitive procedure? J Pediatr Urol. 2019;15:560.e1-560.e6. [Crossref]
28. Coplen DE, Barthold JS. Controversies in the management of ectopic ureteroceles. Urology. 2000;56:665-668. [Crossref]

CASE REPORT
Urooncology

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Robot Assisted Bladder Diverticulectomy Seven Year After Radical Prostatectomy

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Abstract

The impact of radical prostatectomy on the natural history of the neurogenic bladder is not well understood. Neurogenic bladder can manifest as detrusor sphincter dyssynergia. When left untreated, neurogenic bladder can cause bladder hypotonia. Chronically high volumes and pressures can result in the formation of bladder diverticula. Diverticula, if present, are usually located at the lateral walls of the bladder. In this case, a 77-year-old man with a neurogenic bladder presented with a symptomatic bladder diverticulum at the dome, which developed years after radical prostatectomy. A complex history made him a candidate for definitive treatment; thus, a diverticulectomy was performed. The history and operative and pathological findings are discussed.

Keywords: Neurogenic bladder, robotic diverticulectomy, radical prostatectomy, clean intermittent catheterization, cystogram

Introduction

Bladder diverticula are out-pouches of the bladder mucosa that occur through defects in the detrusor muscle fibers (1). This mucosal herniation can occur because of congenital or acquired factors. In the congenital variant, they are often located superolateral to the ureteral orifice and are associated with vesicoureteral reflux. In adults, bladder diverticula are associated with increased pressure in the bladder, either due to obstruction or detrusor sphincter dyssynergia (DSD). They are usually asymptomatic at initial presentation but can cause urinary tract infections (UTIs) or stone disease over time (1). Approximately 1% of urothelial carcinomas are found within bladder diverticula, and such cases have a poorer prognosis (2). 90% of all cases of bladder diverticula occur in adults, with men being disproportionately affected with a 9:1 ratio (1).

Spinal cord injury causes neurogenic bladder and DSD (3). Dyssynergia results from the loss of coordination between detrusor contraction and urinary sphincter relaxation (4). This can cause ineffective bladder emptying, leading to increased bladder volumes and pressures. Over time, the detrusor can stretch and become hypocontractile (5). Bladder diverticula can also occur because of an untreated neurogenic bladder (1,6). They are usually located along the lateral walls of the bladder, which is the area most prone to deformity caused by elevated intravesical pressure (1). Clean intermittent catheterization (CIC) is commonly prescribed in patients with high post-void residual (PVR) volumes of urine in the bladder.

Robot-assisted laparoscopic prostatectomy (RALP) is known to carry a risk of postoperative stress urinary incontinence as a sequala of the procedure (7,8). However, in patients with preexisting neurological injuries before surgery, postoperative management of voiding dysfunction can be more complex. In neurogenic bladder cases, PVRs may decrease after RALP because the sphincter will no longer be present.

However, in this case, the patient did not require CIC before RALP. Years later, he developed very large diverticulum causing significant morbidity requiring CIC and ultimately requiring definitive management with diverticulectomy. There have been three previous reports in which patients presented with

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bladder outlet obstruction and lower urinary tract symptoms and were found to have both prostate cancer (PCa) and large bladder diverticula. Sequential, combined, surgical treatments for both conditions have been shown to be safe (9,10). To our knowledge, there has been no previous documentation of robotic diverticulectomy performed several years after RALP. Here, we explore such a case and its clinical outcomes.

Case Presentation

This is a 77-year-old male, with a remote history of cervical spine injury from a bicycle accident, as well as a history of PCa status post RALP seven years prior, who presented to our clinic complaining of chronic UTIs, which led to hospital admission for urosepsis. He was subsequently found to have highly elevated PVRs and bladder diverticula. Of note, magnetic resonance imaging during the pre-RALP workup reported only small diverticula. Urodynamic studies from the past year show a maximum flow rate of 2.8, voided volume of 50 cc, PVR of 360 cc, and pressure readings consistent with DSD. He had previously experienced intraperitoneal perforation of his bladder at an outside hospital, from which he recovered well with conservative management. However, it could not be visualized with cystoscopy and was considered possibly walled off. At this time, it was considered whether the diverticulum seen on computed tomography scan (Figure 1) was a true diverticulum or a contained perforation. Cystoscopy revealed diffuse inflammatory changes on the posterior and right lateral walls of the bladder. Severe trabeculations and numerous small diverticula were observed. Figure 2 shows images from the cystogram performed at that time, which shows a large volume of urine retained in the diverticulum during the voiding phase. At follow-up appointments, he requested definitive management. He was scheduled for robotic bladder diverticulectomy.

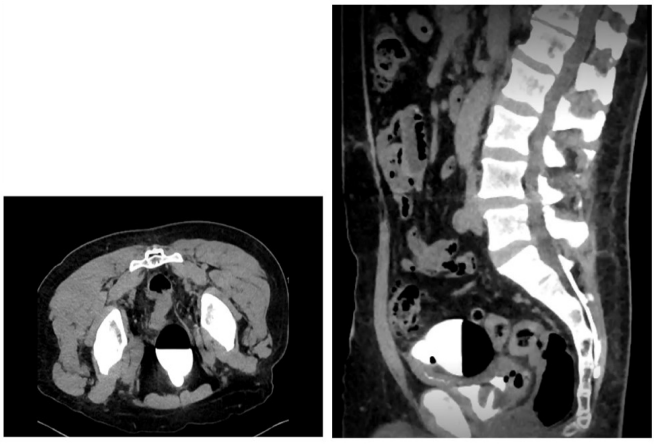

Figure 1. Axial and sagittal CT images showing the diverticulum's anterior and superior position along the bladder wall

CT: Computed tomography

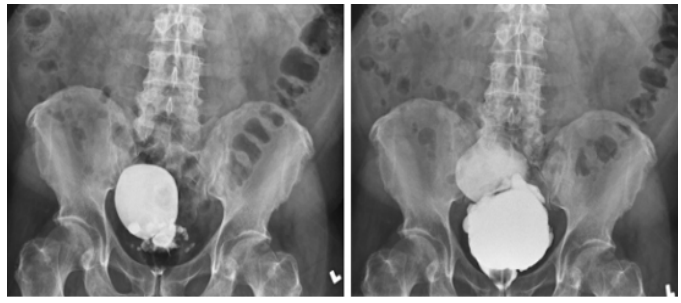

Figure 2. Cystogram images showing filling (right) and voiding (left) phases

Operative Report Summary

On the day of surgery, the patient was taken to the operating room and induced under general anesthesia. He was positioned in the supine position in Trendelenburg. A cystoscope was used to try to identify the main diverticulum, but this was not successful.

We proceeded to identify the diverticulum using the robot. He created a circular mucosal incision around the diverticular neck, dissected posteriorly, and then progressed laterally and anteriorly (Figure 3). The specimen (diverticulum) was retrieved and manually examined before being sent for surgical pathology. The bladder was closed in 2 layers. 2-0 Stratafix suture was used to close the detrusor and mucosal layers, with careful approximation of the mucosal edges. Imbricating sutures were placed using 2-0 V-loc suture. The bladder was distended with 300 mL, and a watertight closure was confirmed. A JP drain was inserted, and the urethral catheter was left in place.

The patient tolerated the procedure well and was accompanied to the recovery room in a stable condition. The estimated blood loss was 50 mL. The patient was discharged on hospital day 3 with a Foley catheter. A cystogram performed 2 weeks after surgery showed no evidence of diverticulum.

Pathologic Examination

The diagnosis was confirmed by pathological assessment. Histopathological examination showed a pouch-like structure lined with urothelium. The underlying subepithelial tissue showed well-organized, thickened muscularis mucosae, thus distinguishing this entity from a pseudodiverticulum of the bladder.

Discussion

The unusual features of this case include the enormous size and atypical location (at the dome) of the bladder diverticulum. Despite the patient using CIC preoperatively, he was unable to empty his bladder sufficiently because of the large volume of urine trapped in the diverticulum, as was seen on the voiding phase of his cystogram. The patient's previous bladder

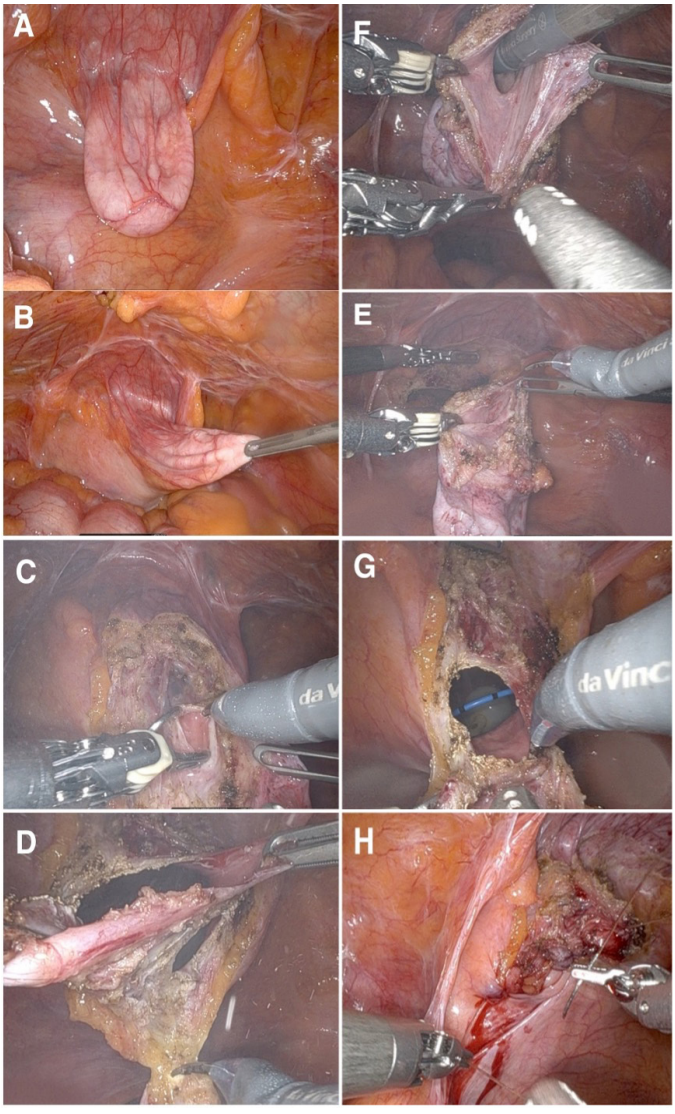

Figure 3. Intraoperative images. A. Intraperitoneal appearance of diverticulum; B. Diverticulum on tension; C. Incision and dissection to mucosa; D. En bloc resection; E. Specimen; F. Specimen with robotic arm inside defect; G. Neck of diverticulum (foley and stents seen); H. Bladder reconstruction

perforation made it difficult to assess from imaging alone whether this abnormal pouch was a contained perforation or a true diverticulum. The location at the dome points toward the contained perforation. However, intraoperatively, there were visual features of the tissue that pointed more toward the diverticulum and not a contained perforation. For example, the neck of the diverticulum was smooth and circular. In the case of a contained perforation, a larger, irregular neck is usually observed. The walls of the diverticulum itself were smooth and regular. Perforations are usually thickened and irregular. Finally, there were no adhesions attached to the structure, which are commonly seen in perforations. For these reasons, the etiology was considered to be bladder diverticulum secondary to neurogenic bladder and not due to a contained perforation. The diagnosis was confirmed by pathological assessment.

The lesson to be learned from this case is that patients with underlying neurogenic bladder, who undergo RALP, may have a change in their bladder function that may not follow the usual predicted pattern. This patient was never found to have bladder neck contracture or lower urinary tract stricture. Additionally, he did not require CIC before he underwent RALP. This suggests that the pathophysiological mechanisms causing the diverticula likely continued or might have even been enhanced by RALP. The most likely pathophysiological mechanism underlying the development of the larger diverticulum is DSD secondary to the neurogenic bladder. One may expect that RALP relieved the dyssynergia by compromising the integrity of the sphincter. However, the sequelae developed anyway. This case suggests that close monitoring of patients with preexisting neurogenic bladder could be beneficial because bladder function evolves after radical prostatectomy. Post-RALP uroflowmetry and urodynamics are reasonable tests for complex cases. Providers may carry a low threshold to start CIC when PVRs are elevated or in cases of compromised bladder voiding efficiency (11).

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: V.W., A.R., A.T., Concept: A.M., K.P.K., M.K.C., A.T., Design: A.M., K.P.K., M.K.C., S.B., V.W., A.R., A.T., Data Collection or Processing: A.M., K.P.K., Analysis or Interpretation: A.M., K.P.K., M.K.C., S.B., V.W., A.R., A.T., Literature Search: A.M., K.P.K., M.K.C., S.B., Writing: A.M., K.P.K., M.K.C., S.B., V.W., A.R., A.T.

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

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References

1. Halaseh SA, Leslie SW. Bladder diverticulum. 2023 May 30. In: statPearls [Internet]. Treasure Island (FL): Statpearls Publishing; 2025 Jan. [Crossref]
2. Voskuilen CS, Seiler R, Rink M, Poyet C, Noon AP, Roghmann F, Necchi A, Aziz A, Lavollé A, Young MJ, Marks P, Saba K, van Rhijn BWG, Fransen van de Putte EE, Ablat J, Black PC, Sosnowski R, Dobruch J, Kumar P, Jallad S, Catto JWF, Xylinas E, Hendricksen K; Young Academic Urologists' Working Group on Urothelial Carcinoma of the European Association of Urology. Urothelial

carcinoma in bladder diverticula: a multicenter analysis of characteristics and clinical outcomes. Eur Urol Focus. 2020;6:1226-1232. [Crossref]

3. Bacsu CD, Chan L, Tse V. Diagnosing detrusor sphincter dyssynergia in the neurological patient. BJU Int. 2012;109(Suppl 3):31-34. [Crossref]
4. Feloney MP, Leslie SW. Bladder sphincter dyssynergia. 2022 Nov 28. In: statPearls [Internet]. Treasure Island (FL): Statpearls Publishing; 2023 Jan. [Crossref]
5. Leslie SW, Tadi P, Tayyeb M. Neurogenic bladder and neurogenic lower urinary tract dysfunction. 2023 Jul 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. [Crossref]
6. Sacco E, Prayer-Galetti T, Pinto F, Fracalanza S, Betto G, Pagano F, Artibani W. Urinary incontinence after radical prostatectomy: incidence by definition, risk factors and temporal trend in a large series with a long-term follow-up. BJU Int. 2006;97:1234-1241. [Crossref]
7. Trofimenko V, Myers JB, Brant WO. Post-prostatectomy incontinence: how common and bothersome is it really? Sex Med Rev. 2017;5:536-543. [Crossref]
8. Loughlin KR, Prasad MM. Post-prostatectomy urinary incontinence: a confluence of 3 factors. J Urol. 2010;183:871-877. [Crossref]
9. Yoshimura I, Uchida H, Nakayama A, Takatama K, Yoshida T. Robot-assisted bladder diverticulectomy sequentially followed by robot-assisted radical prostatectomy: a case series. J Robot Surg. 2019;13:227-230. [Crossref]
10. Ploumidis A, Skolarikos A, Sopilidis O, Chalikopoulos D, Alivizatos G, Wiklund P. Sequential robotic-assisted bladder diverticulectomy and radical prostatectomy. Technique and review of the literature. Int J Surg Case Rep. 2013;4:81-84. [Crossref]
11. Chapple C, Abrams P, Lam T, Mangera A, Belal M, Curtis C, Emkes J, Hillery S, Irwin K, Logan K, Weston P, Yates A. A consensus statement on when to start clean intermittent self-catheterization: an untapped resource? Neurourol Urodyn. 2024;43:459-463. [Crossref]