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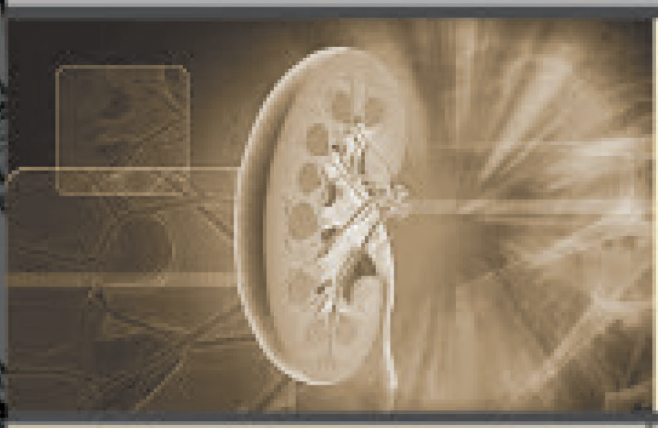

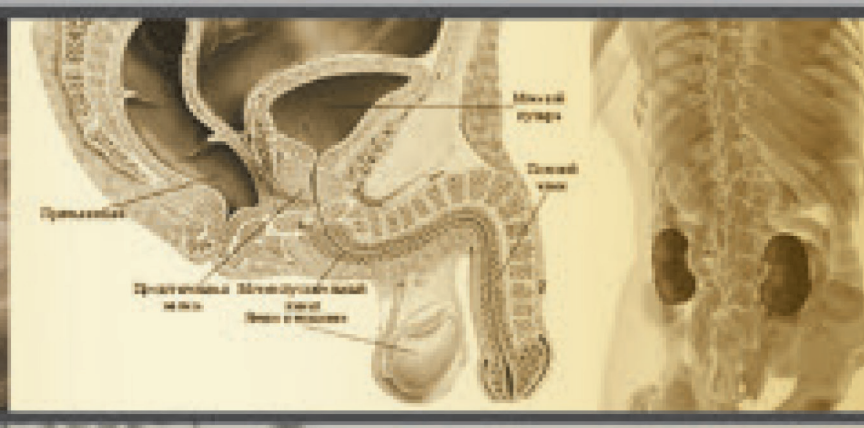

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Ali Tekin

Mehmet Ali Aydınlar Acıbadem Üniversitesi Atakent Hastanesi

Turgut Özal Bulvarı No: 16 34303 Kucukcekmece-Istanbul, Turkiye

Issuing Body

Galenos Yayınevi Tic. Ltd. Şti.

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Phone : +90 212 621 99 25

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3. Complete Book

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

4. Chapter in Book

Pearle MS, Lotan Y Urinary lithiasis: etiology, epidemiology, and pathogenesis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell-Walsh Urology, 10th ed. Philadelphia, Elsevier&Saunders, 201, pp 1257-1323.

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5. Abstract

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

6. Letter to the Editor

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

7. Supplement

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

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ORIGINAL RESEARCH
Andrology

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Effects of Normal Morphology Sperm Count on Fertilization Time in Infertile Couples with Teratospermic Males: An Evaluation with an Embryoscope

Elif Ganime Aygun[1], Emine Karabük[2]

[1]Acıbadem Mehmet Ali Aydınlar University, Atakent Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkiye
[2]Acıbadem Mehmet Ali Aydınlar University, Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Turkiye

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

Embryo development depends on both egg and sperm quality. This study examines the effects of sperm morphology on embryo development. Emphasizes that factors other than the visual evaluation in sperm are effective in embryo development.

Abstract

Objective: Incubation of the embryo is the vital step in assisted reproductive techniques. Embryoscope systems are incubators that keep the embryo stable and allow for continuous observation without opening the lid. Therefore, the embryo is not displaced and goes through a temperature or air change. The primary aim of this study was to explore the effects of normal morphology sperm count on two pronucleus formation time following intracytoplasmic sperm injection in infertile couples with teratospermic males. The secondary aim was clinical pregnancy.

Materials and Methods: Sixty-seven couples undergoing in vitro fertilization were included in this retrospective cohort study. First, intracytoplasmic sperm injection was performed to metaphase II-oocytes. Then, the embryos were placed in an embryoscope (a time-lapse system) for observation. The time that embryos demonstrated two pronuclei were recorded. Demographic and reproductive data were obtained and analyzed.

Results: A statistically significant weak correlation was detected between sperm morphology the two pronucleus formation times (r=0.295, p=0.017). Severely decreased normal sperm count was significantly associated with pregnancy with less decreased normal sperm count (p>0.024). Moreover, decreased two pronucleus formation time was significantly associated with pregnancy.

Conclusion: A statistically significant, albeit weak, correlation was detected between sperm morphology with two pronucleus formation time. Furthermore, having a lower normal sperm count was related to a higher pregnancy rate than having a higher normal sperm count. Lastly, reduced two pronucleus formation time was significantly associated with pregnancy.

Keywords: Embryoscopes, fertilization, infertility, in vitro fertilization, pregnancy, sperm, time-lapse imaging

Introduction

There has been a breakthrough in assisted reproductive techniques with the discovery of in vitro fertilization in 1978. This discovery has enabled approximately three to four times assisted pregnancies than spontaneous pregnancies. As a result, multiple embryo transfers were carried out to increase this number even more. However, this has led to various complications for the mother and the baby, such as ectopic and multiple pregnancies (1,2). Subsequently, physicians started practicing single embryo transfers. Therefore, a need for improving embryo selection was born, and technological advances pursued this need appropriately.

Current studies demonstrate the impact of the sperm on the embryo quality in addition to the oocyte (3,4). Evaluation of the movement, DNA fragmentation, morphological abnormalities of the sperm are determining factors in proper fertilization, implantation, embryo development, and subsequently,

Correspondence: Elif Ganime Aygun MD, Acıbadem Mehmet Ali Aydınlar University, Atakent Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkiye
E-mail: elif.aygun@acibadem.com **ORCID-ID:** orcid.org/0000-0003-3737-7250
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pregnancy (5-7). Therefore, the morphology of the sperm is crucial when it comes to focusing on embryo development. Additionally, studies have demonstrated the relationship between sperm quality and embryo development (8). Especially, abnormalities in the morphology of the sperm could cause fertilization defects and low cleavage-stage problems (9).

Incubation of the embryo is the vital step in assisted reproductive techniques. Furthermore, no evidence of conventional techniques being superior to embryoscope has able be shown by systematic reviews and meta-analysis (10,11). Embryoscope systems are incubator systems that keep the embryo stable and allow for the continuous observation of embryo development without the need to open the lid. Therefore, the embryo is not displaced and go through a heat change. It is one of the most significant advantages of embryoscopes over conventional methods (12,13). Furthermore, the time-lapse imaging technology that enables continuous recording utilized by embryoscopes could shed light on the relationship between sperm parameters and embryo development and extend the currently limited literature (14).

The primary aim of this study was to explore the effects of normal morphology sperm count on two pronucleus formation time following intracytoplasmic sperm injection in infertile couples with teratospermic males. The secondary aim of the study was to achieve clinical pregnancy.

Materials and Methods

This study was authorized by the Acibadem Mehmet Ali Aydinlar University Research Ethics Committee (ATADEK) with the decision number: 2021-21/06 on 04/11/2021. The study was conducted at Acibadem Mehmet Ali Aydinlar University Atakent Hospital, Department of Obstetrics and Gynecology, Istanbul (Turkey), between 2015 and 2016. All methods were performed following the relevant guidelines and regulations.

Study Design

A research question and hypothesis were developed:

Research Question: In a population of infertile couples with teratospermic males, is normal morphology sperm count associated with two pronucleus formation time following intracytoplasmic sperm injection?

Study Hypothesis: In a population of infertile couples with teratospermic males, increased normal morphology sperm count is associated with decreased two pronucleus formation time following intracytoplasmic sperm injection

The study was designed as a retrospective cohort study. Age, karyotypic analysis, sperm morphology, number of oocytes, two pronucleus formation time, the status of pregnancy, and the genetic testing status of the parents were obtained and analyzed. The data were collected from the hospital's electronic health record system.

The primary aim of this study was to explore the effects of normal morphology sperm count on two pronucleus formation time following intracytoplasmic sperm injection in infertile couples with teratospermic males. The secondary aim of the study was to achieve clinical pregnancy.

Selection and Description of Participants

The inclusion criterion for couples was infertility (failure to conceive after one year of unprotected coitus) were

- For males:
  - Having >10% motile sperm in semen
  - Having ≤4% normal morphology sperm
  - Being older than 18 years old
- For females
  - Being 18-43 years old The exclusion criteria were
- For males:
  - Azoospermia (zero sperm present under light microscopy evaluation)
  - Any genetic defects (determined by karyotypic analysis)
- For females:
  - Being older than 43 years old (due to extremely low chances of fertilisation success)
  - Severe ovarian failure (zero antral follicle count on transvaginal ultrasonography and FSH >x15 IU/L and LH >10 IU/L and/or amenorrhea) (due to extremely low chances of fertilisation success)
  - Severe endometriosis (detected by vaginal examination and transvaginal ultrasonography or diagnostic laparoscopy) (due to extremely low chances of fertilisation success)
  - Any genetic defects (determined by karyotypic analysis)

Sperm Evaluation

Semen samples were collected from males by masturbation after three days of sexual abstinence. First, the samples were treated with ORIGIO® Sperm Wash (reference number: 84050060A; Måløv, Denmark) with a 1:1 ratio in Falcon conical tubes and centrifuged at 1500 revolutions per minute for 10 min at 37 ^{o}C to concentrate the sperm. Afterwards, the fluid on the top is removed using a micropipette. Finally, the sperm was left and evaluated using a light microscope. The scoring of normal morphological sperm to all sperm was made between 1 and 4%.

Oocyte Collection

Ovulation was induced in females with 225-450 IU of gonadotropin antagonists [recombinant follicle-stimulating hormone (rFSH) or rFSH and recombinant luteinising hormone

(rLH), depending on the number of antral follicles chosen patient by patient basis]. When follicles were measured to 18 mm by transvaginal ultrasound, recombinant human chorionic gonadotropin alpha (rHCG-α) (Ovitrelle 250 microgram/0.5 millilitres) was administered subcutaneously to facilitate oocyte expulsion. Afterwards, under general anesthesia, transvaginal ultrasound-guided oocyte pickup was performed. Then, the metaphase II-oocytes were determined under a light microscope, and were placed in Petri dishes containing a single-step medium (CooperSurgical, Inc; Connecticut, United States of America).

Fertilization

Intracytoplasmic sperm injection was performed to metaphase II-oocytes using a micromanipulation microscope system (Leica Microsystems, Wetzlar, Germany). Afterwards, the embryos were transferred to 20 microliter droplets single step mediums, and lastly, mineral oil was added. Then, the embryos were placed in an EmbryoScope+ time-lapse system (Vitrolife, Gothenburg, Sweden) for observation. The time that embryos demonstrated two pronuclei were recorded. The embryos are followed up until the blastocyst stage (E5), and then they are either implanted, frozen, or underwent trophectoderm biopsy.

Statistical Analysis

Descriptive statistics are presented using mean, standard deviation, median (and minimum-maximum) for continuous variables. Additionally, frequencies (N) and percentages (%) are used to represent categorical variables.

Non-parametric statistical methods were used for values with skewed distribution. For comparison of two non-normally distributed groups, the Mann-Whitney U test was used.

Spearman's rho correlation analysis is used to investigate the relationship between two non-normally distributed continuous variables.

Statistical significance is accepted when the two-sided p-value is lower than 0.05. Statistical analysis was performed using the STATA/SE 17.0 software.

Results

Sixty-seven patients were included. A single metaphase II-oocyte was selected from the females of the couples (n=67), and ICSI was applied. Table 1 presents the characteristics of the study population.

Primary Outcome (Correlation between normal morphology sperm and two pronucleus formation time)

Table 2 presents the correlation analysis between two pronucleus formation times and normal morphology sperm. The Spearman's rho correlation is interpreted as when the "r" correlation coefficient gets close to 1; the correlation gets stronger. The r-values between 0-0.3 are accepted as a weak correlation.

A statistically significant weak correlation was detected between sperm morphology with two pronucleus formation times (p=0.017) (Table 2 and Figure 1).

Secondary Outcome (Pregnancy)

Table 3 compares pregnancy groups according to normal morphology sperm and two pronucleus formation time.

More decreased normal sperm count was significantly associated pregnancy than less decreased normal sperm count (p>0.024). Figure 2 and Figure 3 display the boxplots for pregnancy, normal morphology sperm count, and two pronucleus formation time. Moreover, decreased two pronucleus formation time was significantly associated with pregnancy. However, subgroup analysis of sperm morphology and fertilization time did not detect statistical significance (p=0.067) (Table 4).

Discussion

The primary goal of this study was to investigate whether normal morphology sperm count affected the time it took for two pronuclei to develop after intracytoplasmic sperm injection in infertile couples with teratospermic males. Normal sperm morphology and two pronucleus formation times were found to have a statistically significant weak correlation. Additionally, the study's secondary goal was to achieve clinical pregnancy. Paradoxically, having a lower normal sperm count was related

Table 1. Characteristics of the study population

Parameters	n (%)	Mean + SD	Median (min-max)
Age (Female)	67 (100)	34.2±4.1	35 (23-41)
Normal morphology sperm count (%)	66 (98.5)	2.02±0.92	2 (1-4)
Number of oocytes	67 (100)	11.9±9.3	10 (0-40)
Two pronucleus formation time (hour)	66 (98.5)	17.2±0.9	17 (16-19)
Pregnancy Status	67 (100)		
Pregnancy	45 (67.2)		
No pregnancy	20 (29.8)		
Anembryonic pregnancy	2 (3)		

n: Number, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2. Correlation of two pronucleus formation time with age and normal morphologysperm

Correlation		Two pronucleus formation time
Normal morphology sperm	**r**	0.295
	p	**0.017**

(r: correlation coefficient) Spearman's rho correlation

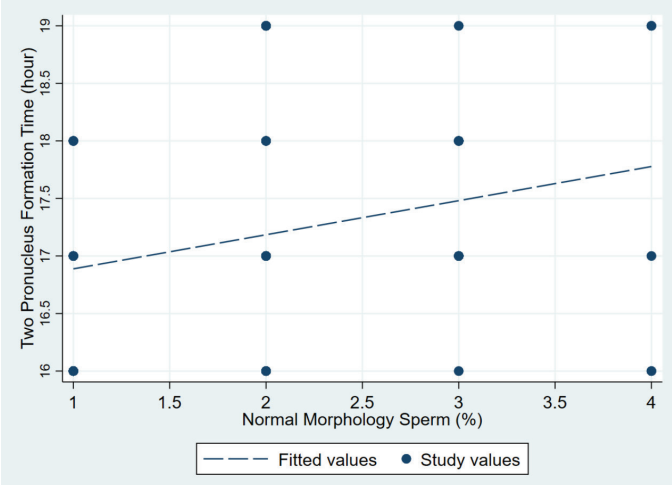

Figure 1. Scatterplot displaying the relationship between normal morphology sperm count and two pronucleus formation time

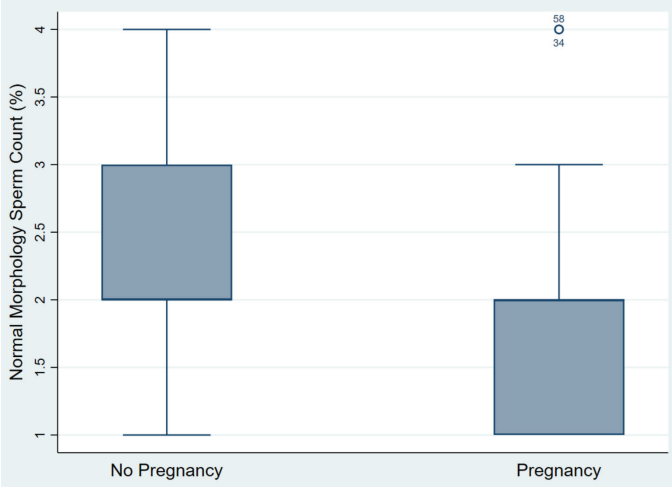

Figure 2. Boxplot of the normal morphology sperm count and pregnancy

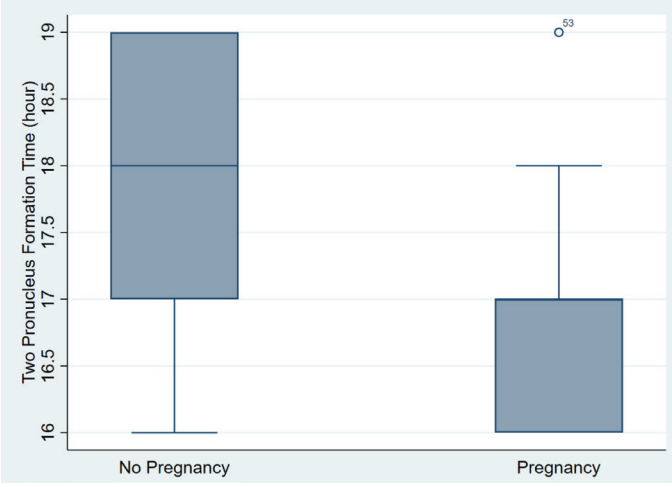

Figure 3. Boxplot of the two pronucleus formation time and pregnancy

to a higher pregnancy rate than having a higher normal sperm count.

Many sperm-related factors, including morphology, are known, and more are being investigated to affect many stages of pregnancy, including fertilization, early cleavage of the embryo, and the foetus's formation. It highlights that the oocyte is not the only factor in fertilization and embryo development, and the sperm holds similar significance (15). Abnormal sperm morphology directly affects fertilization failure and pregnancy (8,16,17). Additionally, it is recorded as an essential factor in spontaneous miscarriages (18). A novel study by Nikovola et al. (19) recently investigated morphology among many sperm parameters and concluded that morphological abnormalities of the sperm were closely associated with embryo morphokinetics. Concurrent with this, the results suggest that normal sperm morphology and two pronucleus formation time, albeit weak, have a statistically significant correlation (Table 2).

Previous studies demonstrated a positive correlation between earlier fertilization (two pronucleus formation time) and normal sperm morphology. Moreover, normal sperm was detected to provide adequate implantation and clinical pregnancy results in couples undergoing ICSI (20,21). In contrast, the current study demonstrated that more decreased normal sperm count was significantly associated with decreased two pronucleus formation time and pregnancy than less decreased normal sperm count (Table 3). In another study, no statistically significant difference was detected in clinical pregnancy, embryo implantation, and miscarriage rates between poor morphology and normal morphology sperm (22). The selection of the sperm is a semiquantitative technique entirely at the discretion of the embryologist. Finding quality sperm for ICSI in in vitro fertilization procedures is challenging as the expression "finding a needle in a haystack" goes. Therefore, maximum effort is given to select the best quality sperm among the poor morphologic sperm. In this study, it could be attributed to the fact that a limited number of patients with higher normal morphology sperm count was present (Table 4) and could be considered a limitation in this regard. However, selecting the best sperm in the pool of bad morphology sperm could positively impact the pregnancy rate. The current study's authors' ongoing works on incorporating artificial intelligence into sperm selection could transform this process into a fully quantitative technique.

Time-lapse imaging technology has emerged recently in embryo selection in the form of embryoscopes. It, expectedly, increases clinical pregnancy and live birth rates (23,24). Embryoscopes are incubator systems that allow for the continuous observation of embryo development and keep the embryo stable without opening the lid. Therefore, the embryo is not displaced and protected from trauma and air content, and the temperature inside the incubator does not change. These are the most

Table 3. Comparison between pregnancy groups					
Pregnancy	**No (n=20)**		**Yes (n=45)**		**p**
	Mean + SD	**Median (min-max)**	**Mean + SD**	**Median (min-max)**	
Normal morphology sperm count (%)	2.42±0.96	2 (1-4)	1.84±0.85	2 (1-4)	**0.024**
Two pronucleus formation time (hour)	17.84±1.17	18 (16-19)	16.89±0.77	17 (16-19)	**0.001**
(N: Number, SD: Standard deviation, Min: Minimum, Max: Maximum). Mann-Whitney U test					

Table 4. Subgroup analysis of sperm morphology and fertilization time									
	Normal Morphology Sperm Count (%)								
	1 (n=22)		**2 (n=26)**		**3 (n=12)**		**4 (n=5)**		**p**
	Mean + SD	**Median (min-max)**	**Mean + SD**	**Median (min-max)**	**Mean + SD**	**Median (min-max)**	**Mean + SD**	**Median (min-max)**	
Two pronucleus formation time (hour)	16.73±0.83	16.5 (16-18)	17.38±1.02	17 (16-19)	17.5±0.79	17.5 (16-19)	17.4±1.52	17 (16-19)	0.067
(N: Number, SD: Standard deviation, Min: Minimum, Max: Maximum). Kruskal Wallis test									

significant advantages of embryoscopes (12,13). The current study utilized embryoscopes and detected a significant association between pregnancy and two pronucleus formation time. Moreover, prolonged fertilization time was determined to have negative effects on pregnancy. Parallel to the current results, recent studies suggested that the delay in two pronucleus formations could cause implantation failures (19).

The current study holds an essential place in investigating the sperm-related issues in in vitro fertilization. The cytoplasm of the sperm and oocyte's and the interactions between the two play a crucial role in embryo development. Moreover, conducting sub-abnormality analyses, screening DNA fragmentation defects, and even analysing histone and protamine of the sperm might yield positive and decisive results regarding pregnancy. To summarize, sperm-related factors have vital importance in assisted-reproductive techniques and require further investigation.

Study Limitations

The first limitation of this study was its limited sample size. Secondly, the statistical analyses were made based on morphological observations. Moreover, the utilization of ICSI enabled the best sperm to be selected under a light microscope and injected into the oocyte. Thus, it could alone have a positive effect on embryo development in males with teratospermia. Lastly, quantitative analyses such as sub-abnormality analyses, screening for DNA fragmentation defects & histone and protamine were not performed.

Conclusion

In conclusion, a statistically significant weak correlation was detected between sperm morphology with two pronucleus formation times (primary outcome). Furthermore, having a lower normal sperm count was related to a higher pregnancy rate than having a higher normal sperm count. Lastly, decreased two pronucleus formation time was significantly associated with pregnancy. However, subgroup analysis of sperm morphology and fertilization time did not detect statistical significance. Therefore, further studies with larger sample sizes investigating additional sperm parameters in infertile couples must be conducted to fully explore the roots of sperm-related issues.

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Ethics

Ethics Committee Approval: This study was authorized by the Acibadem Mehmet Ali Aydinlar University Research Ethics Committee (ATADEK) with the decision number: 2021-21/06 on 04/11/2021.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL RESEARCH
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Turkish Validation of the Hallym Post Micturition Dribble Questionnaire (HPMDQ) and Evaluation of Bulbar Urethral Massage Response

Murat Gül[1], Mehmet Gökhan Çulha[2], Kadir Bocu[1], Ali Furkan Batur[1,3], Emre Altıntaş[1], Mehmet Kaynar[1], Serdar Göktaş[1], Özcan Kılıç[1]

[1]Selçuk University Faculty of Medicine, Department of Urology, Konya, Turkiye
[2]University of Health Sciences Turkiye, Okmeydanı Training and Research Hospital, Clinic of Urology, İstanbul, Turkiye
[3]University Hospitals Cleveland Medical Center, Urology Institution, Cleveland, Ohio, United States

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

Quality of life scales, questionnaires and scoring systems have been used in many areas of modern medicine to provide reproducible and accurate measurements. Post-micturition dribble (PMD) is common as an isolated symptom in men, hallym post micturition dribble questionnaire (HPMDQ) has been developed as the only measurement tool for this symptom. This study could lead to the validation of HMPDQ in different countries. Moreover, thanks to this validation study, a valid questionnaire was obtained for Turkish studies on PMD. The effectiveness of bulbar urethral massage used in the treatment of PMD can be evaluated more objectively with this questionnaire.

Abstract

Objective: As the evidence has been increasing about the post-micturition dribble (PMD) symptom, widely accepted lower-urinary tract symptoms (LUTS) questionnaires fail to assess PMD alone. In this study, our primary aim was to evaluate the validity and reliability of the Turkish version of the hallym post micturition dribble questionnaire (HPMDQ). The secondary objective is to appraise the relationship between PMD and other LUTS and the effectiveness of bulbar urethral massage in patients with PMD.

Materials and Methods: The final draft of the Turkish HPMDQ and International Prostate Symptome score (IPSS) were compared for male patients who were admitted to the urology outpatient clinic between June 2020 and September 2020. The responses of 103 patients were analysed. Fifty-five people being affected by PMD were offered bulbar urethral massage for one month and then re-applied with the questionnaires.

Results: The kappa coefficient for the total score of the Turkish HPMDQ score was 0.789. Considering the relationship between the HPMDQ and the IPSS, the HPMDQ's total score correlated significantly with that of the total IPSS (p=0.660, p<0.001), the voiding symptoms of the LUTS (p=0.621, p<0.001), and post-void residual volume (p=0.614, p<0.001) but not with the storage symptoms of the LUTS (p=0.245). The mean value of HPMDQ-Q5, evaluating the treatment response of bulbar urethra massage, was 1.81+1.02, suggesting an effective treatment of PMD.

Conclusion: The Turkish version of HPMDQ was observed as a reliable tool for evaluating patients with PMD. This study also showed that bulbar urethral massage is an effective method to relieve PMD.

Keywords: Post-micturition dribble, questionnaire, Turkish validation, incontinence

Introduction

Post-micturition dribble (PMD) and the sensation of incomplete emptying are considered the post-micturition symptoms (PMS). PMD is defined as the involuntary loss of urine generally just after leaving the toilet in men or immediately after a person has finished urinating (1). The exact pathophysiological mechanism for PMD is unclear and it can be found in men without any underlying pathognomonic findings (2). The prevalence rate of PMD in men is positively associated with advanced age and was reported to a wide range between 5.5% and 58.1% (3,4). PMD was also shown to account for much of the PMS in men (5) and

Correspondence: Ali Furkan Batur MD, Selçuk University Faculty of Medicine, Department of Urology, Konya, Turkiye
Phone: +90 505 816 11 76 **E-mail:** alifurkanbatur@gmail.com **ORCID-ID:** orcid.org/0000-0001-7945-7326
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it was postulated that PMD is perhaps one of the most common lower urinary tract symptoms (LUTS) (5,6).

The universally accepted questionnaires, such as the Danish Prostatic Symptom score (DAN - PSS - 1), and the International Prostate Symptom score (IPSS) developed for diagnosis, treatment, follow-up of LUTS (7,8). PMS has always been evaluated together with other LUTS in these questionnaires. However, an isolated questionnaire for PMD was lacking and out of the researchers' interest. As the recent epidemiologic studies, including TAMUS and EpiLUTS demonstrated higher rates of PMD prevalence (4,9,10), Jeong et al. (11) Developed and validated a five-item questionnaire, Hallym Post Micturition Dribble Questionnaire (HPMDQ), as a symptom assessment tool for PMD in 2019. This questionnaire's original language is Korean and has not yet been validated in any other language, but the authors also published the English version in the same study (11).

Our primary aim in this study was to evaluate the reliability and validity of the Turkish version of the HPMDQ. The secondary purpose was to evaluate the relationship between PMD and other LUTS using this questionnaire and to show whether there is a correlation between HPMDQ scoring and IPSS.

Materials and Methods

The validation and reliability study of HPMDQ Turkish was conducted between June 2020 and September 2020 at the urology outpatient clinic. This study was approved by the Selcuk University Faculty of Medicine Ethics Committee with the decision number 2020/260. In addition, written informed consent was obtained from each participant, and detailed information about the study was included.

HPMDQ

HPMDQ is the first developed questionnaire specific to PMD. Question-1(Q1) evaluates the frequency of dribbling, question-2(1.1) [Q2 (1.1)] evaluates the amount of dribbling, question-3(Q3) evaluates the discomfort the dribbling caused, question-4(Q4) evaluates the quality of life and question-5(Q5) evaluates the post-treatment improvement. Each question consists of four answers scoring between 0 to 3 points (11). In the case of Q5, it is applied only after the suggested treatment.

IPSS

The first official tool to systematically evaluate and measure LUTS is the American Urology Association Symptom Index (AUA-7). It consists of seven items that question frequency, urgency, nocturia, weak stream, intermittent stream, straining, and incomplete emptying sensation. Each item has five different responses rated between 0 and 5 points and with a total score of 35 points (12). Later on, the World Health Organization's International Consultation on Benign Prostatic Hyperplasia (BPH) added a quality of life item to AUA-7 and constituted the IPSS (8). IPSS is a self-administered questionnaire, and with this aspect, it is an easy-to-apply screening and diagnostic tool. This symptom inquiry index, whose original version is in English, has been translated into their languages by many countries, validated, and widely used for LUTS (13).

The Translation Process

Before beginning translation, a author in developing and validating the original HPMDQ (Lee WK) was contacted to request his approval to translate the English version of the questionnaire into Turkish (Supplementary File 1). Having secured this permission, the translation process began, involving extensive linguistic transformation in multiple stages. First, the HPMDQ was sent to a professional translation centre to be translated into Turkish by two independent native Turkish-speaking translators fluent in English. Arrangements were also made for two urologists (MG and MGÇ) work with the translators to provide medical advice regarding the development of the Turkish text. Thereafter, the translated text was rearranged to make it more understandable and to cover different educational and socio-cultural levels. In the next step, the final Turkish version of the HPMDQ was interpreted back into English by two independent translators who speak professional Turkish and whose native language is English. These translations were subsequently revised, and minimal corrections were made. For verification, a pilot test was then trialed with five participants with PMD and the final alterations were performed. At this point, the Turkish HPMDQ was considered ready for use (Supplementary File 2).

Study Design and Inclusion Criteria

Study participants were recruited from the Selcuk University urology outpatient clinic, between June and September 2020. Men who could read and write in Turkish were included in the study, were mentally capable, and were aged 18 years or over. Patients under 18 years, female patients, patients unable to read or write in Turkish and those with a history of LUTS-related surgery (e.g., transurethral resection or internal urethrotomy) or taking active LUTS treatment, or having illness that was related to LUTS such as urinary tract infections, bladder stones and urethral strictures were excluded from the study. Clinical secretaries oversaw the completion of forms before the face-to-face interviews. Patients diagnosed with PMD were recommended bulbar urethral massage after voiding, and they were asked to complete the Turkish HPMDQ again one month later.

Statistical Analysis

The reliability and validity of the Turkish HPMDQ were measured using internal consistency and test–retest statistical tools. To calculate the overlap in the HPMDQ response scores of the same people at different time points (i.e., initially and one month later), the intraclass correlation coefficient (ICC) was calculated for the aggregate scoring and the weighted Cohen's kappa was calculated for the scoring of each item. Concurrent validity was evaluated using correlation with the outer criteria (IPSS). Correlation coefficients of 0.1 weak, 0.3 medium and 0.5 strong were used, as proposed by Cohen.

Statistical analysis was completed using the IBM Statistical Package for the Social Sciences, version 22.0 (IBM SPSS Statistics). The level of significance was set at $p<0.05$, internal consistency reliability was evaluated using Cronbach's alpha, and test-retest reliability was assessed using the Wilcoxon signed-rank test. Spearman correlation analysis was used for simultaneous external validity. Consistency and reliability are assumed to be sufficient for values >0.70.

Results

In total, 367 patients completed the Turkish HPMDQ and IPSS forms. Of these, 103 patients met the inclusion criteria, and their Turkish HPMDQs and IPSSs were evaluated. Of the participants, n=55 (52.3%) was affected by PMD (Q1≥1) and n=48 (45.7%) were found to be completely dry. The demographic data and clinical findings of the participants are summarized in Table 1. For the HPMDQ, Cronbach's alpha was 0.903, mean inter-item correlation was 0.727 an intraclass correlation coefficient was 0.903 (confidence interval 95%: 0.869-0.931) (Table 2).

No significant difference was found between the test and retest scores for the Turkish HPMDQ; the responses to each item mostly overlapped. The Turkish translation of this questionnaire thus has medium to good reliability. While the kappa coefficient for the individual item scores was 0.628-0.838, it was 0.789 for the total score for the Turkish HPMDQ (Table 3). The relationship between the HPMDQ and the IPSS, which is the most widely used tool for evaluating LUTS, was also investigated. Considering the concurrent validity, it was observed that the HPMDQ's total score correlated significantly with that of the total IPSS ($p=0.660$, $p<0.001$), the voiding symptoms of the LUTS ($p=0.621$, $p<0.001$), and post-void residual volume ($p=0.614$, $p<0.001$) but not with the storage symptoms of the LUTS ($p=0.245$) (Table 4). The mean value of HPMDQ-Q5, evaluating the treatment response of bulbar urethra massage, was 1.81+1.02, suggesting an effective treatment of PMD.

Table 1. Demographic and clinical data of patients

Patient characteristics and findings (n=103)	Mean ± SD	Min-Max
Age	49.74±15.99	18-85
Prostate volume (mL)	60.59±27.67	27-155
Q_{max} (mL/s)	15.03±5.86	1.70-32
Q_{ave} (mL/s)	7.33±2.74	2.40-12
Post-voiding residual urine (mL)	59.22±51.68	0-200
IPSS total score	8.55±7.68	0-30

IPSS: International Prostate Symptom Score; Q_{max}: Maximum flow rate; Q_{ave}: Average flow rate, SD: Standart deviation

Discussion

According to the International Continence Society, PMD is described as "non-volitional loss of urine instantly after he or she has completed passing urine, generally leaving after the toilet for men or after outgoing the toilet for women" (1). It is a symptom of LUTS, but cannot be assessed with in the widely used symptom questionnaires such as IPSS, DAN-PSS-1 (14). These questionnaires have been validated to evaluate BPH or obstructive pathologies affecting the lower urinary system; nevertheless, they do not contain a query for PMD (12,15). Therefore, current literature is insufficient to evaluate PMD and lacks detailed reports of PMD compared with other urinary symptoms. Recently, Jeong et al. (11) Have developed a multidimensional tool (HPMDQ) to evaluate PMD; however, further studies must prove its clinical utility.

In this study, data obtained from patients PMD patients living in Turkey were used to evaluate the reliability and validity of the Turkish version of the HPMDQ. Test-retest reliability and inter-item correlation were calculated to evaluate the reliability of the HPMDQ. The IIC for this study was 0.727, which ensured sufficient circumstances for clinical trials. For each matter in HPMDQ, weighted kappa parameters varying between 0.628 and 0.838 were found. The lowest weighted kappa parameter was for PMD, and the highest was for the fourth question (quality of life). The Cronbach α value calculated as 0.903 was used for internal consistency and the questionnaire was found to be valid.

Table 2. Internal consistency analysis for each HPMDQ item and total score (n=103)

Items	Mean ± SD
HPMDQ Q-1	0.90±1.15
HPMDQ Q-2	1.17±1.39
HPMDQ Q-3	0.79±0.98
HPMDQ Q-4	1.07±1.25
Total	3.92±4.12

HPMDQ: The Hallym Post Micturition Dribble Questionnaire; SD: Standart deviation, Cronbach Alpha: 0.903, Inter-Item correlations: 0.727, Intraclass correlation coefficient: 0.903 (CI 95%: 0.869-0.931), CI: Confidence interval

Most of the previously published reports on PMD were related to its prevalence rather than its clinical significance. The prevalence of PMD in the male population has varied over a wide range in the literature. This could be caused by the various tools that were used to evaluate the PMD. Besides, some studies categorized patients as symptomatic if they had symptoms at least "sometimes", but some other studies defined the symptomatic patients as having symptoms at least "fairly often" (5,9). Nevertheless, more recent studies have shown that the prevalence rate of PMD are around 30-60% (4,9,10,16). In the HPMDQ development study, the prevalence rate of PMD in 2134 patients was found 51%, which is consistent with our findings as the 52.3% of the participants were symptomatic.

Previous studies have also shown that PMD is positively associated with aging men and BPH, but this symptom can also occur in young adults and impair the quality of life (16,17). While the enlargement of the prostate in aging men explains the pathophysiological mechanism of PMD, its occurrence in young and middle age indicates that other factors are interwoven in its pathophysiology. In a urodynamic study, it has been shown that the bulbocavernosus contraction insufficiency at the end of micturition causes PMD with pooling of urine in the bulbar urethra (18). In several different studies, it was thought that the weakening of the urethra-corpora cavernosal reflex with a similar mechanism could cause both erectile dysfunction and PMD and that these two diseases were found to be related to each other (19,20).

Regarding the clinical significance of PMD, the data on literature is scarce. In the BACH study, post micturition symptoms were more closely associated with voiding symptoms than the storage symptoms (5). Similarly, Jeong et al. (11) found that the HPMDQ total score was significantly correlated with the voiding symptoms of LUTS, PVR and prostate size but not with the irritative (storage) symptoms of LUTS. In a Japanese-men based study, PMD did not show a significant association with prostate volume and peak flow rate (16). In our study, PMD showed a significant correlation with total IPSS score, voiding symptoms of LUTS and PVR, indicating that the Turkish version of HPMDQ can reflect PMD well, as in the original development study.

Considering the treatment options for PMD, bulbar urethral massage and pelvic floor exercise (PFE) are the recommended treatment strategies. The rationale behind these treatments is based on the hypothesis that weakened pelvic floor muscle might induce PMD. It was shown that while bulbar urethral massage may show immediate treatment effect, PFE may need a longer time to take effect (3 to 6 months) (21,22). In this study, we recommended bulbar urethral massage method to patients and found that it is an effective and safe method for relieving PMD. Currently, no pharmacological treatment has been established to relieve PMD, but recently a 75 mg udenafil has been introduced as an effective treatment for PMD (23).

Several factors may limit the extrapolation and transferability of the findings from this study. First, we did not include female patients as PMD is seen in males more common and the original

Table 3. Test-retest reliability analysis for the Turkish HPMDQ

PMD (+) (n=55)	First test score	Re-test score	Weighted kappa coefficient
HPMDQ Q-1	1.69±0.77	1.04±0.84	0.829*
HPMDQ Q-2	2.18±1.17	2.12±1.03	0.628*
HPMDQ Q-3	1.47±0.88	1.02±0.73	0.793*
HPMDQ Q-4	2.00±1.02	2.00±0.98	0.838*
Total	7.35±2.53	5.62±2.63	0.789*

PMD: Post micturition dribble, HPMDQ: The Hallym Post Micturition Dribble Questionnaire, *p<0.001

Table 4. Spearman correlation analysis and concurrent validity between HPDMQ and IPSS

Items	p/r value	IPSS	Prostate volume	Q_{max}	PVR
HPMDQ Q-1	p	<0.001	0.024	0.041	0.003
	r	0.652	0.399	-0.363	0.501
HPMDQ Q-2	p	<0.001	0.015	0.144	<0.001
	r	0.520	0.427	-0.264	0.615
HPMDQ Q-3	p	<0.001	0.035	0.006	0.017
	r	0.650	0.374	-0.476	0.418
HPMDQ Q-4	p	<0.001	0.080	0.251	0.005
	r	0.559	0.314	-0.209	0.484
HPMDQ Q-5	p	0.027	0.122	0.268	0.452
	r	0.218	-0.279	0.202	0.138
Total	p	<0.001	0.009	0.035	<0.001
	r	0.660	0.453	-0.373	0.614

IPSS: International Prostate Symptom Score; Q_{max}: Maximum flow rate; PVR: Post-void residual urine (mL)

symptom assessment tool (HPMDQ) was developed for male patients with LUTS (11). Second, we did not use a paper test to evaluate the quantity of PMD, instead we relied on the self-assessments of the patients with PMD. Third, to evaluate the fifth question, only bulbar urethral massage was suggested as a treatment method. Although PFE was shown to be more effective than bulbar urethral massage in relieving PMD, bulbar urethral massage has also proven itself as a simple and effective self-help technique in the literature (24,25).

Conclusion

The Turkish version of the HMPDQ, which allows the evaluation of different aspects of PMD (frequency, severity, amount and discomfort), has been developed and has been identified as a reliable tool in evaluating patients with PMD. PMD was also significantly correlated with IPSS scores, which generally assess the severity of LUTS. This study also showed that bulbar urethra massage is an effective method to relieve PMD. This simple questionnaire would aid researchers in clinical studies and facilitate the understanding of medical applications' responses to among Turkish-speaking patients with PMD.

Ethics

Ethics Committee Approval: This study was approved by the Selcuk University Faculty of Medicine Ethics Committee with the decision number 2020/260.

Informed Consent: Written informed consent was obtained from each participant, and detailed information about the study was included.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Supplementary File 1. The Hallym Post Micturition Dribble Questionnaire (HPMDQ)
1. Over the last month, how often have you experienced dribbling after voiding when you feel you have finished urination?
0: not at all
1: 1 out of 3 times
2: 2 out of 3 times
3. almost always or always
2.(1.1) How much is dribbled urine after voiding?
1: immediately after voiding, a little
2: immediately after voiding, a lot
3: after wearing underwear, a little
4: after wearing underwear, a lot
3. Do you feel frustrated because of dribbling after voiding, when you feel you have finished urination?
0: not at all
1: slightly
2: moderately
3: a lot
4. If you were to spend the rest of your life with dribbling after voiding when you feel you have finished urination, how would you feel about that?
0: not dissatisfied
1: slightly dissatisfied
2: moderately dissatisfied
3: very dissatisfied
5. Compared to before treatment, have you experienced improvement in dribbling after voiding when you feel you have finished urination?
0: not at all
1: slightly
2: moderately
3: a lot

Supplementary File 2. Turkish validation of the Hallym Post Micturition Dribble Questionnaire (HPMDQ)
Türkçe Hallym İdrar Yapma Sonrası Damlama Anketi
1. Geçtiğimiz ay, ne sıklıkla idrarınızın bittiğini hissetmenize rağmen işeme sonrası damlama yaşadınız?
0: Hiç olmadı
1: 3 'te birinde
2: 3 'te ikisinde
3: Neredeyse her zaman ya da her zaman
2.(1.1) İdrarınızı yaptıktan sonra damlayan idrar miktarı nedir?
1: İdrar yaptıktan hemen sonra, biraz
2: İdrar yaptıktan hemen sonra, çok
3: İç çamaşırı giydikten sonra, biraz
4: İç çamaşırı giydikten sonra, çok
3. İdrarınızın bittiğini hissetmenize rağmen, işeme sonrası damlama için kendinizi rahatsız hissettiğiniz oldu mu?
0: Hiç olmadı
1: Biraz oldu
2: Kısmen oldu
3: Çok oldu
4. Farz edelim ki hayatınızın geri kalanını işemeniz bitmiş hissetmenize rağmen idrar yaptıktan sonra damlama ile geçireceksiniz, bu düşünce sizi nasıl hissettirir?
0: Olumsuz etkilemez
1: Biraz memnuniyetsiz olurum
2: Kısmen memnuniyetsiz olurum
3: Çok memnuniyetsiz olurum
5. Aldığınız tedavi öncesine göre, işemenizin bittiğini hissetmenize rağmen işeme sonrası idrar damlaması durumunda düzelme yaşadınız mı?
0: Hiç olmadı
1: Biraz oldu
2: Kısmen oldu
3: Çok oldu

ORIGINAL RESEARCH
Reconstructive

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Evaluation of Functional, Objective and Sexual Outcomes and Patient Reported Quality of Life After Anterior Urethral Reconstruction

Sabby Dias, Vijay Patidar, Rohit Namdev, Sandeep Kumar, Shivanand Prakash, Hari Shankar, Sameer Trivedi

Department of Urology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

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

Traditionally used parameters to define the success of urethral reconstruction have been under scrutiny in several recently published studies which have the importance of subjective assessment using patient reported quality of life measures and evaluation of sexual function following urethral reconstruction. However, there is still sparse data regarding the role of subjective and sexual function assessment in evaluating outcomes of urethral reconstruction. This study evaluates and underscores the role of patient reported outcome measures as a complement to the established objective parameters and highlights the importance of assessing sexual function in patients undergoing urethral reconstruction.

Abstract

Objective: To assess patient satisfaction and quality of life after urethroplasty using clinician driven and patient reported outcome measures.

Materials and Methods: We prospectively evaluated fifty-one men with anterior urethral stricture who underwent urethroplasty. Patient demographics, maximum flow rate and post-void residual urine, International Prostate Symptom Score (IPSS), urethral stricture surgery patient-reported outcome measure (USS-PROM), five-item International Index of Erectile Function (IIEF-5), Male Sexual Health Questionnaire Short Form (MSHQ EjD SF), were collected before surgery and compared with outcomes 1 year after surgery.

Results: Fifty-one men with anterior urethral stricture underwent 18 (35.3%) anastomotic urethroplasties and 33 (64.7%) augmentation urethroplasties. Of 47 men who were available at follow-up, Qmax improved from preoperative mean of 4.4 to 18.3 [-13.86; 95% confidence interval (CI) (-15.1) - (-12.6); p<0.001], post-void residual urine volume (PVR) from 115.1 to 22.1 (93.0; 95% CI 75.2 - 111; p<0.001), IPSS from 20.93 to 3.55 (17.3; 95% CI 16.1 - 18.6; p<0.001). 38 (80.9%) patients were "very satisfied", 3 (6.4%) patients were "satisfied", 5 (10.6%) patients were "unsatisfied" and 1 (2.1%) patient was "very unsatisfied" with the surgery as per USS-PROM. IIEF-5 was insignificantly improved from preoperative mean of 20.72 to 20.89 [-0.17; 95% CI (-0.6) - 0.3; p=0.47] and MSHQ-EjD SF was significantly improved from 10.2 to 11.2 [-0.1; 95% CI (-1.2) - (-0.7); p<0.001].

Conclusion: Patient-reported outcome measurements play an important role in evaluating the outcome of urethroplasty in men with urethral stricture disease and should be used concomitantly with objective measurements of Qmax and PVR. This helps in evaluating the outcomes of surgery in the form of patient satisfaction and quality of life.

Keywords: Urethroplasty, urethral stricture surgery patient-reported outcome measure, sexual function

Introduction

The urethral stricture is a high complexity disease that impacts affected men by progressive symptoms and the need for repeated surgical interventions. Outcome measures of urethroplasty, considered a gold standard for managing urethral stricture disease, are predominantly clinician driven indicators of technical success (1). These measures are not always aligned with symptomatic and health-related quality of life improvements. The definition of urethroplasty success varies widely, which makes comparisons between different studies difficult (2,3).

Correspondence: Sameer Trivedi MD, Department of Urology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India
Phone: +91 9839861656 **E-mail:** drsameertrivedi@gmail.com **ORCID-ID:** orcid.org/0000-0001-8308-9220
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The need for a subjective assessment after urethroplasty was studied in 2002 by Kessler et al. (4) In urethroplasty, patient-reported outcome measure (PROM) is an upcoming tool to score the outcome of urethroplasty based on patient-centered, subjective information complementary to the objective information provided by uroflowmetry, urethrography and urethroscopy.

Jackson et al. (5) in 2011 designed and validated the first PROM to assess condition-specific quality of life as well as health-related quality of life for patients undergoing urethral stricture surgery (USS-PROM). It is a composite instrument comprising lower urinary tract symptoms (LUTS) domain, a generic health status domain, and a treatment satisfaction question. Various validated translations of USS-PROM have been reported and implemented in routine clinical practice (6,7).

Persisting *de novo* erectile dysfunction (ED) has been described in 1% of the patients after urethroplasty (8). An abridged five-item version of the 15-item International Index of Erectile Function was developed (IIEF-5) to diagnose the presence and severity of ED (9).

The Male Sexual Health Questionnaire (MSHQ) was developed in 2004 to assesses sexual function and satisfaction in older men with urogenital symptoms of LUTS and sexual dysfunction (10). The abridged version, MSHQ-EjD Short Form, was developed and validated for assessing ejaculatory dysfunction in 2007 (11). Ejaculatory function is often better after urethroplasty than before, provided the continuity of the bulbospongiosus muscle is actively restored during the multilayered closure of the perineum (12,13).

Very few studies have included International Prostate Symptom Score (IPSS), USS-PROM (including Health-related quality of life domains, and a treatment satisfaction question), IIEF-5 and MSHQ-EjD SF in combination to assess the outcomes of urethral reconstruction in a single study. This study aimed to evaluate patient-reported outcomes to better describe patients' perception of success, considering urinary bother scores, quality of life, erectile, ejaculatory and sexual function.

Materials and Methods

Between January 2018 and January 2019, 51 consecutive men with anterior urethral strictures who underwent urethroplasty in the Department of Urology at a tertiary level academic institute were included in the study after seeking approval from the Institute Ethical Committee and Institutional Review Board. Patients were followed up for minimum 1-year post-surgery. The Local Institutional Ethics Committee (no: 2018/EC/781, date: 31.01.2018) approved this study.

Inclusion Criteria

Men with anterior urethral strictures undergoing urethroplasty,

Age 18 to 65 years.

Exclusion Criteria

Patients who had previously undergone urethroplasty,

Patients with neurogenic bladder,

Patients with BPH.

Pre-operative Assessment

Patients' data were collected in terms of age, presenting complaints including LUTS, co-morbid conditions, and prior history of urinary tract infection, catherization, urological intervention, surgery, and trauma. Patients underwent a thorough physical examination with an assessment of meatus and glans, presence of lichen sclerosus like changes, palpation of urethra, genitalia and digital rectal examination. Pre-operative routine tests were conducted in the form of urine routine and microscopic examination, culture and sensitivity testing, hemogram, and renal function tests. Uroflowmetry was obtained from patients not on a suprapubic catheter. The maximum flow rate (Qmax) along with voided volume and flow pattern was noted. Ultrasonography was performed to assess the upper tracts, bladder wall changes and post-void residual urine volume (PVR). A combined retrograde urethrogram and voiding cystourethrography was performed to assess the stricture length and location. Cysto-urethroscopy was performed to identify the site of stricture and to assess the elasticity of the urethra along with the degree of spongiofibrosis. In selected cases, pediatric endoscopes were used to visually inspect and assess the caliber of the urethral lumen. IPSS, USS-PROM, IIEF-5 and MSHQ-EjD SF were collected preoperatively.

The USS PROM questionnaire incorporates LUTS and Health-related quality of life (HRQoL) domains, and a treatment satisfaction question. The IIEF-5 questionnaire was used to assess the presence and severity of ED. MSHQ-EjD Short Form, which consists of three ejaculatory function items and one ejaculation bother item was used for assessing ejaculatory dysfunction.

Operative Assessment

Surgical procedures performed for urethral reconstruction included anastomotic urethroplasty and augmentation urethroplasty using oral mucosal grafts. The site and length of stricture along with the degree of spongiofibrosis was noted. The site, size, number and length of grafts required for augmentation urethroplasty were noted.

Augmentation procedures included were dorsal inlay graft (Asopa), dorsal onlay graft (Barbagli), dorsolateral graft

(Kulkarni), and combined dorsal plus ventral graft urethroplasty. Dorsal inlay graft (Asopa) urethroplasty was used for cases where the urethra is densely adherent to the underlying corpora cavernosa as a consequence of repeated optical urethrotomies or urethral dilatations and strictures with relatively wider caliber (urethral lumen more than 10 Fr), while dorsal onlay graft urethroplasty (Barbagli) or dorsolateral graft (Kulkarni technique) was used for narrow strictures (urethral lumen less than 10 Fr). Combined dorsal plus ventral graft urethroplasty was used for very tight strictures (urethral lumen less than 6 Fr).

Patients underwent pericatheter urethrogram 3 weeks after the surgery, following which the trial of void was given. The suprapubic catheter was removed 1 week after a successful trial of the void.

Postoperative Follow-up Assessment

IPSS, uroflowmetry and PVR were evaluated at 3 months following urethroplasty. Uroflowmetry, PVR, IPSS, USS-PROM, IIEF-5, and MSHQ-EjD SF scores were collected at 1 year follow up and compared with preoperative scores. Patients with persisting symptoms and/or those requiring subsequent procedures were noted. Technical success was defined as patients who did not require re-intervention. Patient satisfaction according to the USS-PROM was also assessed.

Statistical Analysis

Qualitative data are represented in the form of frequency and percentage. Quantitative data were presented using mean, range & 95% Confidence Interval. Comparison between quantitative data pre- & post-surgery was done using Paired t-test. Association between qualitative variables was assessed using Chi-Square test with Continuity Correction for all 2 X 2 and Fisher's Exact test for all 2 X 2 tables where p-value of chi-square test was not valid due to small counts.

Results are graphically represented where deemed necessary. Appropriate statistical software, including MS Excel and SPSS 25, were used for statistical analysis. A graphical representation was done in MS Excel 2016.

Results

Baseline characteristics of the 51 patients included in the study are given in Table 1.

Urine cultures were positive in 7 (13.8%) patients - *E. coli* in 6 (11.8%) patients and *E. faecalis* in 1 (2%). Patients were started on antibiotic therapy according to their sensitivity.

Operative Findings

Details of the surgical procedures are provided in Table 2. Meatal narrowing was seen in 15 (29.4%) patients who underwent the meatal reconstruction using oral mucosal grafts. A unilateral lingual mucosal graft was taken in seven (13.7%) patients while bilateral strips of lingual mucosal grafts were required in 24 (47.1%) patients. In 2 (3.9%) patients, bilateral lingual mucosal grafts along with buccal mucosal grafts were required. The mean length of the graft used was 10.7cm [range 4-18; 95% confidence interval (CI) 9.4-12.1]. The mean duration of surgery was 135 minutes (range 90-180 min).

Complications

Three (5.8%) patients who had undergone lingual mucosal graft augmentation urethroplasty complained of transient difficulty in chewing and swallowing, which subsided in 3 days. Four (7.8%) patients developed urethral discharge and were treated as per the culture and sensitivity report.

Table 1. Baseline characteristics

Age (mean)	38.16 years (95% CI 34.1-42.1)
18 to 45 years	35 (68.6%)
46 to 65 years	16 (31.4%)
Duration of complaints (mean)	39.88 months (95% CI 29.6-50.1)
Etiology	
Lichen sclerosus	16 (31.4%)
Infection	4 (7.8%)
Iatrogenic	10 (19.6%)
Trauma	9 (17.6%)
Idiopathic	12 (11.5%)
Suprapubic catheter	7 (13.7%)
Previous intervention	
DVIU	11 (21.6%)
Dilatations	11 (21.6%)
Comorbidity	
Hypertension	3 (5.9%)
Diabetes	2 (3.9%)
PVR (mean) in 44 (86.3%) patients	112.07 mL (95% CI 89-135)
Qmax (mean) in 44 (86.3%) patients	4.57 mL/sec (95% CI 3.8-5.2)
Location of stricture	
Penile	12 (23.5%)
Bulbar	12 (23.5%)
Peno-bulbar	27 (52.9%)
Penile + bulbar urethra	18 (35.3%)
Pan urethral (meatus + penile + bulbar urethra)	9 (17.6%)
Length of stricture (mean)	7.59 cm (range 1-18; 95% CI 6.0-9.1)

CI: Confidence interval, PVR: Post-void residual urine volume, DVIU: Direct vision internal urethrotomy

Re-intervention

Four (7.8%) patients required reintervention at a mean of 3.5 months (range 2-9) following urethroplasty. One patient underwent redo EEA urethroplasty, another required direct vision internal urethrotomy (DVIU), while two patients required urethral dilation.

Follow-up at One Year

At one year following surgery, 4 patients (7.8%) were lost to follow up. Baseline and post-operative parameters in the 47 patients are shown in Table 3.

On subgroup analysis, there was no significant change in mean IIEF-5 scores in patients undergoing anastomotic (pre 19.47; post 19.53; p=0.85) or augmentation urethroplasty (pre 21.43; post 21.67; p=0.47). There was significant improvement in MSHQ-EjD SF score (pre 9.8; post 10.8; p=0.001) and MSHQ-EjD SF BOTHER score (pre 1.9; post 1.2; p=0.01) in patients undergoing anastomotic urethroplasty. Similarly, there was significant improvement in MSHQ-EjD SF score (pre 10.4; post 11.4; p<0.001) and MSHQ-EjD SF BOTHER score (pre 1.7; post 0.67; p<0.001) in patients undergoing augmentation urethroplasty.

Of the 47 patients available at follow-up, 14 (82.3%) out of 17 patients who underwent anastomotic urethroplasty, were "very satisfied" or "satisfied" while 3 (17.6%) were "unsatisfied" or "very unsatisfied" with the surgery, as per USS-PROM (Table 4). 27 (90%) of 30 patients who underwent augmentation urethroplasty, were "very satisfied" or "satisfied" with the surgery, while 3 (10%) patients were "unsatisfied" or "very unsatisfied". On statistical analysis, there was no significant difference in the treatment satisfaction rates between the two groups (p=0.67).

There was greater improvement in Qmax, IPSS, USS PROM and MSHQ-EjD SF scores in patients who were "Very satisfied" or "Satisfied" with urethroplasty compared to patients who were "Unsatisfied" or "Very unsatisfied" (Table 5).

Table 2. Types of surgery

Anastomotic urethroplasty	**18 (35.3%) patients**
Excision and primary anastomosis (EPA) urethroplasty	17 (33.3%)
Non-transecting urethroplasty	1 (2%)
Length of stricture (mean)	1.7 cm (95% CI 1.4-2.0)
Augmentation urethroplasty	**33 (64.7%) patients**
Dorsal onlay graft urethroplasty (Barbagli)	20 (39.2%)
Dorsal inlay graft urethroplasty (Asopa)	11 (21.6%)
Dorsolateral graft urethroplasty (Kulkarni)	1 (2%)
Dorsal plus ventral graft urethroplasty	1 (2%)
Length of stricture (mean)	10.7 cm (95% CI 9.3-12.1)
Lingual mucosal graft	31 (60.8%)
Lingual and buccal mucosal combined graft	2 (3.9%)

CI: Confidence interval

Discussion

The surgical management of urethral stricture is challenging and the diverse etiology, varied stricture characteristics and sundry surgical procedures described in the literature make the assessment of surgical outcomes a difficult task. There is a lack of consensus on the optimal protocol to be followed for the evaluation of urethroplasty outcomes. Meeks et al. (14) demonstrated an average of 3.15 different diagnostic tests for this purpose after surgery. Variable follow-up protocols and lack of standardization make comparisons between different studies difficult.

Kessler et al. (4) highlighted that subjective measures should be included in the assessment of urethroplasty outcomes. In their study, of the 30 patients who were considered a failure from a surgeon's perspective, 24 were subjectively satisfied or very satisfied with the surgical outcome. The recently published OPEN trial, comparing patient reported outcomes following open urethroplasty and endoscopic urethrotomy, has re-emphasized the importance of patient-centered evaluation of outcomes following surgical intervention for urethral strictures (15). Assessment of patient satisfaction after reconstruction is critical for patient counseling (4,16). This study evaluated the 1-year outcome of 51 patients who underwent urethroplasty for urethral stricture disease.

Uroflowmetry parameters like Qmax are commonly used for evaluating outcomes of urethral reconstruction, but these can be unreliable markers. Erickson et al. (1) demonstrated that uroflowmetry can be used to screen for postoperative stricture recurrence only when the voiding curve and urinary symptoms were also evaluated. Studies have shown that patient reported outcomes, as represented by the USS-PROM, IPSS, and QoL scores, were not diminished by the lesser improvement in Qmax (17,18). In our study, 2 (4.2%) patients despite having Qmax below 15 mL/sec (mean 14.3 mL/sec) were satisfied with the surgery as per USS-PROM and did not require reintervention.

IPSS is the most frequently used questionnaire in the evaluation of urethroplasty outcomes (3), however, it lacks specificity for urethral stricture disease and is considered inadequate for patients with urethral strictures (19). In our study, there was significant improvement in the mean IPSS score (pre 20.9; post 3.5; p<0.001) and IPSS QoL (pre 4.5; post 0.7; p<0.001).

To standardize patient-centered evaluation of interventions for urethral strictures, Jackson et al. (5) developed and validated USS-PROM. Studies have reported a significant decrease in USS PROM LUTS score and Peeling's stream picture scores, improvement in USS-PROM LUTS Likert type condition-specific QoL, EQVAS score and EQ-5D index score post urethroplasty (5,7).

In our study, there was a significant decrease in the USS PROM LUTS score (pre 14.3; post 2.1; <0.001) and Peeling's voiding picture score (pre 3.4; post 1.2; p<0.001). While comparing USS-PROM LUTS Likert type condition-specific QoL in 40 patients who were not on suprapubic catheter and who completed the follow-up after the surgery, 39 (97.5%) patients had ≥1 scale point improvement, 36 (90%) patients had ≥2 scale point improvement, and 16 (40%) patients reported a 3-scale point improvement while 1 (2.5%) patient had no improvement. There was significant improvement in the mean USS-PROM EQ 5D Visual analog scale score (pre 69.66; post 84.3; p<0.001) and USS-PROM EQ-5D index score (pre 0.78; post 0.95; p<0.001).

In a study by Jackson et al. (20), 87% patients were ''satisfied'' or ''very satisfied'' with the outcome of their urethroplasty as per USS-PROM treatment satisfaction question. In our study, 38 (80.9%) patients were "very satisfied", 3 (6.4%) patients were "satisfied", 5 (10.6%) patients were "unsatisfied" and 1 (2.1%) patient was "very unsatisfied" with the surgery. Overall, 87.3% of patients were "satisfied" or "very satisfied" with urethroplasty. There was no significant difference in treatment satisfaction between patients undergoing anastomotic urethroplasty and augmentation urethroplasty (p=0.67). Similarly, there was no significant difference in the treatment satisfaction between the two age groups at 18 45 and 46 to 65 (p=0.08). Of 6 patients (12.7%) who were "Unsatisfied" of

Table 3. Baseline and postoperative mean of PVR, Qmax, IPSS, IPSS QoL, IPSS, IIEF-5 and MSHQ EjD

n=47	Preop	Postop	Mean Diff	95% CI Diff		p
PVR (mL)	115.2	22.1	93.07	75.2	111	<0.001
Qmax (mL/sec)	4.48	18.33	-13.9	-15.1	-12.6	<0.001
IPSS	20.93	3.55	17.37	16.1	18.69	<0.001
IPSS QoL	4.55	0.77	3.787	3.44	4.13	<0.001
Urethral stricture surgery patient-reported outcome measure (USS-PROM)						
LUTS SCORE	14.3	2.15	12.15	11.1	13.22	<0.001
Peeling's stream picture score	3.48	1.23	2.25	2.02	2.47	<0.001
LUTS QOL	2.48	0.2	2.27	2.04	2.5	<0.001
EQ-5D VAS	69.66	84.3	-14.6	-16	-13.3	<0.001
EQ-5D TTO	0.78	0.95	-0.16	-0.2	-0.14	<0.001
International index of erectile function (IIEF-5)						
IIEF-5	20.72	20.89	-0.17	-0.64	0.3	0.471
Male Sexual Health Questionnaire Short Form (MSHQ EjD)						
MSHQ-EjD SF	10.25	11.28	-1.03	-1.26	-0.79	<0.001
MSHQ-EjD SF bother/satisfaction	1.75	0.8	0.95	0.72	1.17	<0.001

PVR: Post-void residual urine volume, CI: Confidence interval, USS: Urethral stricture surgery, PROM: Patient-reported outcome measure, IPSS: International Prostate Symptom Score, MSHQ-EjD SF: Male Sexual Health Questionnaire Ejaculatory Dysfunction Short Form, LUTS: Lower urinary tract symptoms, IIEF-5: Abridged five-item International Index of Erectile Function

Table 4. USS PROM treatment satisfaction

USS-PROM treatment satisfaction	Frequency	Percent
Very satisfied	38	80.9
Satisfied	3	6.4
Unsatisfied	5	10.6
Very unsatisfied	1	2.1
Among patients who were "Unsatisfied" or "Very unsatisfied"		
The urinary condition did not improve	4	66.7
The urinary condition improved but there was some other problem	2	33.3
The urinary condition did not improve and there was some other problem as well	0	0.0

USS: Urethral stricture surgery, PROM: Patient-reported outcome measure

"Very unsatisfied" with the outcome of surgery, 4 patients (66.7%) stated that "The urinary condition did not improve" and 2 patients (33.3%) stated that "The urinary condition improved but there was some other problem". Both of these patients had reported bothersome sexual dysfunction following urethroplasty. There was a significant difference in post- surgery IIEF- 5 in "Unsatisfied/Very unsatisfied" group (18.0) versus "Very satisfied/Satisfied" group (21.3) (p=0.008), whereas, there was no difference in post- surgery MSHQ-EjD SF (p=0.34) and MSHQ-EjD SF bother/satisfaction (p=0.551) in these two subsets. The lack of inclusion of the sexual function domain in USS-PROM is a shortcoming, which needs to be addressed because sexual function outcomes are a vital component of outcome evaluation following urethroplasty. Likewise, USS-PROM does not address the cause of treatment dissatisfaction due to "other problems".

Many studies have addressed the concerns regarding the effect of urethroplasty on sexual function (21,22). Patel et al. (23) did not find statistically significant differences in IIEF-5 scores before and after penile urethroplasty in 25 men. Similarly, in our study, there was no significant change in the mean IIEF-5 score between baseline and postoperative values in patients undergoing both anastomotic and augmentation urethroplasty.

MSHQ-EjD Short Form, was developed and validated for assessing ejaculatory dysfunction (EjD) in 2007 (11). Patel et al. (23) did not find a significant difference in MSHQ-EjD score in 20 men after penile urethroplasty. On the contrary, Sharma et al. (12) and Erickson et al. (22) found significant improvement in ejaculatory function after undergoing penile urethroplasty using the O'Leary Brief Male Sexual Function Inventory. In our study, there was significant improvement in MSHQ-EjD SF and MSHQ-EjD SF BOTHER scores in patients undergoing anastomotic urethroplasty as well as augmentation urethroplasty.

The technical success of urethroplasty is conventionally defined by the need for reintervention for recurrent urethral narrowing following urethroplasty. The recurrence of urethral stricture following urethroplasty ranges between 2% and 36.4%, with 75% treatment failures occurring within the first six months of surgery (14,24-26). Jackson et al. (20) reported that 15% patients in their study required surgical reintervention at a mean of 8 months after urethroplasty. In our study, four (7.8%)

Table 5. Distribution of various parameters in USS PROM treatment satisfaction groups

USS-PROM treatment satisfaction		Pre-surgery	Post-surgery	Mean Diff	95% CI Diff		p
					Lower	Upper	
Unsatisfied/very unsatisfied	Qmax	3.6	11.0	-7.3	-9.4	-5.3	0.001
	IPSS	21.4	9.8	11.6	5.2	18.0	0.007
	IPSS QoL	4.7	2.8	1.8	0.0	3.6	0.048
	USS PROM luts score	15.2	6.2	9.0	4.1	13.9	0.007
	Peeling's stream picture	3.6	2.4	1.2	0.2	2.2	0.033
	LUTS QOL	2.8	1.6	1.2	-0.2	2.6	0.07
	EQ-5D VAS	67.7	74.5	-6.8	-14.3	0.7	0.066
	EQ-5D TTO	0.8	0.8	0.0	-0.1	0.1	0.749
	IIEF-5	18.2	18.0	0.2	-0.9	1.2	0.695
	MSHQ-EjD SF	10.6	11.2	-0.6	-1.3	0.1	0.07
	MSHQ-EjD SF bother/satisfaction	1.4	0.8	0.6	-0.1	1.3	0.07
Very satisfied/satisfied	Qmax	4.6	19.4	-14.8	-15.9	-13.7	<0.001
	IPSS	20.9	2.7	18.2	17.1	19.3	<0.001
	IPSS QoL	4.5	0.5	4.1	3.8	4.3	<0.001
	USS PROM luts score	14.2	1.6	12.6	11.6	13.6	<0.001
	Peeling's stream picture	3.5	1.1	2.4	2.2	2.6	<0.001
	LUTS QOL	2.4	0.0	2.4	2.3	2.6	<0.001
	EQ-5D VAS	70.0	85.7	-15.8	-16.7	-14.8	<0.001
	EQ-5D TTO	0.8	1.0	-0.2	-0.2	-0.2	<0.001
	IIEF-5	21.1	21.3	-0.2	-0.8	0.3	0.408
	MSHQ-EjD SF	10.2	11.3	-1.1	-1.3	-0.8	<0.001
	MSHQ-EjD SF bother/satisfaction	1.8	0.8	1.0	0.8	1.3	<0.001

USS: Urethral stricture surgery, PROM: Patient-reported outcome measure, CI: Confidence interval, IPSS: International Prostate Symptom Score, MSHQ-EjD SF: Male Sexual Health Questionnaire Ejaculatory Dysfunction Short Form, LUTS: Lower urinary tract symptoms, IIEF-5: Abridged five-item International Index of Erectile Function, VAS: Visual analogue scale

patients required reintervention at a mean of 3.5 months after urethroplasty. One patient underwent EEA urethroplasty, while another required DVIU and two patients required urethral dilation. Thus, the overall technical success rate was 91.5% whereas 87.3% patients were satisfied as per the USS-PROM following urethroplasty. 4.2% of patients were unsatisfied with the surgery for reasons other than urinary complaints.

This study highlights that subjective changes in PROM complement objective measurement of urinary parameters in the evaluation of men undergoing urethroplasty for anterior urethral strictures.

Study Limitations

This study had certain limitations. The patient cohort was heterogeneous with varied stricture characteristics. Likewise, the types of urethral reconstruction procedures performed were heterogeneous, as is expected in this cohort of patients. The number of patients in the study was relatively small and the follow-up duration was limited to one year. Whether treatment satisfaction rates would be sustained in longer follow up is an issue that needs to be addressed. The lack of validation of the Hindi language translation of the questionnaires used in the study is another drawback of the study.

Conclusion

Patient-reported outcome measurements play an important role in evaluating the outcome of urethroplasty in men with urethral stricture disease and should be used concomitantly with objective measurements like Qmax and PVR. This helps in evaluating the outcomes of surgery in the form of patient satisfaction and quality of life.

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Ethics

Ethics Committee Approval: The Local Institutional Ethics Committee (no: 2018/EC/781, date: 31.01.2018) approved this study.

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.D., V.P., R.N., S.K., S.P., H.S., U.S.D., S.T., Concept: S.D., S.T., Design: S.D., S.T., Data Collection or Processing: S.D., V.P., R.N., S.K., S.P., H.S., U.S.D., S.T., Analysis or Interpretation: S.T., Literature Search: S.D., R.N., S.P., S.T., Writing: S.D., S.T.

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ORIGINAL RESEARCH
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Repeat Imaging to Avoid Surgery: An Initiative to Reduce-Negative Ureteroscopy in Patients with Ureteral Stones

Callum Lavoie, Max Levine, Timothy Wollin, Trevor Schuler, Shubha De

Division of Urology, Department of Surgery, University of Alberta, Edmonton, Alberta, Canada

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

Negative ureteroscopy is a clinical occurrence defined by ureteroscopy being performed for a ureteric or renal calculus identified on radiographic imaging pre-operatively, with no calculus ultimately being identified intra-operatively due to the calculus being passed prior to the procedure being performed. This occurrence has been reported in the existing literature with rates between 6.3 and 9.8% in cohorts consisting of patients with both ureteric and renal calculi. The rates of negative ureteroscopy can be reduced by having more timely operative intervention, and by utilizing repeat pre-operative imaging when indicated. Smaller and more distal calculi are more likely to pass prior to intervention and result in a negative ureteroscopy. This study provides further information regarding the rates of negative ureteroscopy in a specific cohort of patients with only ureteric calculi. These patients did have a higher rate of negative ureteroscopy than other populations in the literature. Additionally, patients who were more symptomatic from their stone undergoing more expedited intervention were actually more likely to have passed their stone prior to intervention when compared to patients undergoing delayed intervention. This highlights the need for repeat imaging when available prior to intervention.

Abstract

Objective: Negative ureteroscopy (nURS) describes the absence of ureteric stones during endoscopic visualization, despite imaging confirmation before surgery. This study aimed to identify the prevalence of, and factors predicting nURS in patients presenting with ureteral stones.

Materials and Methods: We performed a retrospective review of all uretersocopies for ureteral stones performed by three endourologists over a six-month periods. Only patients without previous intervention for the stone in question were considered for this study. nURS was investigated in relation to demographics, time from imaging to procedure, stone and procedure-specific characteristics, etc. Statistical analysis consisted of descriptive statistics and univariate and multivariate logistic regression analyses using SPSS statistical software.

Results: Eighty-two patients were reviewed, with 14.6% of those patients experiencing a nURS. The frequency of computed tomography imaging and time from imaging to procedure did not differ significantly between +URS and nURS. Stone size (7.74±3.09 vs 6.73±2.28 mm; p=0.298), and stone location (68.6% vs 75.0% distal; p=0.686) were also not significantly different. Significantly more nURS procedures were performed in the emergency (21.7% vs 50.0%; p=0.048). These emergency nURS patients also had a statistically significant shorter duration from imaging to URS (7.1 vs 20.7 days; p=0.001). nURS procedures were 3.60 times more likely to be performed as an emergency (odds ratio=3.60; 95% confidence interval=1.01-12.79; p=0.048).

Conclusion: We have identified 14% of patients undergoing ureteroscopy for ureteral stones at our center are being overtreated. Therefore, we believe that it is imperative that reimaging be considered in this patient population before surgery.

Keywords: Nephrolithiasis, ureteroscopy, negative ureteroscopy

Correspondence: Callum Lavoie MD, Division of Urology, Division of Urology, Department of Surgery, University of Alberta, Edmonton, Alberta, Canada
E-mail: callum1@ualberta.ca **ORCID-ID:** orcid.org/0000-0001-6671-520X
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Introduction

With an estimated 1 in 11 North Americans developing kidney stones, many will ultimately require surgery to remove obstructing ureteral stones (1). Most kidney stones will pass spontaneously, however endoscopic stone removal is now readily performed for all anatomic regions of the upper urinary tract. Technological advancements have made ureteroscopy increasingly common as first-line treatment (2), as well as secondary treatment for failed SWL (3-5).

Despite significant progress in endoscopic stone management, there are several well-established complications. This particular study is concerned with negative ureteroscopy (nURS), defined as a surgical procedure performed for a stone on imaging where no stone is ultimately found despite its presence on imaging. In these cases, it is believed that the patient passed the stone without awareness of this fact. This results in surgical intervention in patients in whom it is no longer required, exposing them to unnecessary risks. Additionally, it represents a source of wasted operative resources in our already strained Canadian public healthcare system. Given the need to be judicious with healthcare resources, while protecting the best interests of our patients, the objective of this study was to better understand the factors contributing to nURS in patients with ureteric stones. Patients with symptomatic ureteral stones are typically motivated to undergo expedited surgery due of ongoing symptoms, and to avoid the perceived ongoing pain until spontaneous passage (if it occurs at all).

Therefore, we sought to define the incidence and any predictors of nURS at our center to create strategies to minimize future occurrences.

Materials and Methods

We performed a retrospective evaluation of all patients who underwent ureteroscopy for ureteral stones at our center over six consecutive months. Only patients with untreated ureteral stones at the time of consultation were included in this analysis. Those with indwelling ureteral stents placed before surgery were excluded. A nURS was defined as failure to endoscopically locate the ureteral stone diagnosed on pre-operative imaging. Patients were reviewed with respect to demographics, presenting characteristics, and time from consultation to surgery. Pre-operative imaging was manually reviewed, and intraoperative reports were used to assess the specifics of each procedure. Flexible and/or semi-rigid ureteroscopy was performed at the discretion of the urologist performing these procedures. Surgical technique was not standardized, due to the retrospective nature of this analysis.

Statistical Analysis

Descriptive statistics were performed, comparing patients in which ureteroscopy identified stones (+URS) and nURS groups. Univariate, followed by multivariate regression analyses were performed to evaluate any associations with nURS.

Results

Of 245 ureteroscopies performed over a 6-month period, we identified 82 ureteroscopies matching our inclusion/exclusion criteria. There were no significant differences between age (50.9 +URS vs 47.1 y nURS, p=0.390), gender (52.9% vs 58.3% male, p=0.726), and body mass index (BMI) (30.1 vs 29.3, p=0.696) between +URS and nURS.

The overall incidence of nURS was 14.6%, (n=12). Stone size (7.74±3.09 vs 6.73±2.28 mm; p=0.298) and location were not a statistically significant different in nURS vs +URS. The majority of stones were distal (+URS 68.6% vs nURS 75%). Only 3 of 11 stones not found during ureteroscopy were proximally positioned (above the pelvic brim) on pre-operative imaging (p=0.656) (Table 1).

There was no difference in the rates of pre-op imaging modalities between +URS and nURS [computed tomography (CT) in 87.0% vs 83.3%; p=0.736], and the average time from the first imaging confirmation of ureteral stone to the date of ureteroscopy was not significantly different (18d±14 +URS vs 9d±6 -URS; p=0.08). Overall, there was no significant difference in historical stone procedures (20.0% +URS vs 25.0% nURS; p=0.694) (Table 1). There was also no difference in patients past medical history for pelvic surgery, or overall health as categorized by the American Society of Anesthesiologists Physical Status Classification (ASA score) (p>0.05).

Significantly more nURS procedures were performed as expedited cases that were performed on weekends or outside of elective operating room time (10% Routine vs 28.6% Expedited; p=0.048). Out of 81 total procedures, 25.9% (n=21) was expedited. Additionally, expedited cases had a shorter interval between imaging and ureteroscopy (7.10 days vs 20.66 days; p=0.001). Expedited vs routine cases also showed no significant differences in size (7.91 vs 6.80 mm), distal stone position (73.3% vs 61.9%), or pre-op imaging modality (CT 84.7% vs 90.5%) (p>0.05). No other differences were identified between age, gender, BMI, surgeon, or average ASA score. nURS procedures were 3.60 times more likely in those who were expedited (odds ratio=3.60; 95% confidence interval=1.01-12.79; p=0.048) (Table 2).

Table 1. Analysis of ureteral stones treated with ureteroscopy				
Variable	**+URS (n=70)**	**nURS (n=12)**	**p-value**	**OR (95% CI)**
Age (years)	50.8	47.1	0.390	1.020 (0.975-1.066)
Gender (male)	52.9%	58.3%	0.726	1.249 (0.361-4.314)
BMI	30.0	29.3	0.696	1.020 (0.923-1.128)
Avg ASA score	1.97	2.08	0.549	0.735 (0.268-2.013)
Emergency cases	21.7% (n=15)	50% (n=6)	0.048	0.278 (0.08-0.99)
Recur. stones	20.0%	25.0%	0.694	0.750 (0.179-3.140)
Stone size (mm)	7.74±3.09	6.73±2.28	0.298	1.149 (0.884-1.493)
Stone side (L)	58.6%	33.3%	0.115	2.828 (0.778-10.282)
Uteral stone location				
Distal	68.6%	75.0%	0.686	0.844 (0.156-4.570)
Middle	12.9%	16.7%		2.437 (0.283-21.029)
Proximal	18.6%	8.3%		
CT performed	87.0% (n=60)	83.3% (n=10)	0.736	1.333 (0.250-7.097)
Hydronephrosis	65.7% (n=46)	50.0% (n=6)	0.466	2.190 (0.632-7.598)
Time from first imaging to URS				
All patients	17.58	9.30	0.093	1.08 (0.99-1.18)
Emergency cases	7.57	6.00	0.469	1.09 (0.86-1.37)
Surgeon				
A (n=32)	37.1% (n=26)	50.0% (n=6)	0.264	5.53 (0.62-49.41)
B (n=25)	34.3% (n=24)	8.3% (n=1)		0.92 (0.25-3.46)
C (n=25)	28.6% (n=20)	41.7% (n=5)		

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, URS: Ureteroscopy, ASA: American Society of Anesthesiologists, CT: Computed tomography

Table 2. Analysis of emergency vs non-emergency ureteroscopies				
Variable	**ASA "E" (n=21) 25.9%**	**ASA Non-"E" (n=60) 74.1%**	**p-value**	**OR (95% CI)**
Age (years)	49	51	0.58	0.99 (0.995-1.026)
Gender (male)	52.4%	53.3%	0.94	1.04 (0.384-2.811)
BMI	28	30	0.17	0.94 (0.859-1.027)
Avg ASA score	1.90	2.02	0.46	0.73 (0.309-1.705)
Negative URS	**28.6%**	**10.0%**	**0.048**	**3.60 (1.013-12.793)**
Prev stone Tx	23.8%	20.0%	0.71	1.25 (0.381-4.096)
Stone size (mm)	6.80	7.91%	0.16	0.86 (0.705-1.060)
Stone side (L)	52.4%	55.0%	0.83	0.9 (0.332-2.437)
Ureteric location				
Distal	61.9%	73.3%	0.29	
Middle	9.5%	13.3%		0.85 (0.160-4.488)
Proximal	28.6%	13.3%		2.54 (0.745-8.651)
CT performed	90.5%	84.7%	0.52	1.71 (0.338-8.647)
Hydronephrosis	61.9%	65.0%	0.86	0.91 (0.310-2.638)
Img-URS time (days)	**7.10**	**20.66**	**0.001**	**0.822 (0.73-0.93)**
Surgeon				
A (31 cases)	28.6% (n=6)	41.7% (n=25)	0.16	
B (25 cases)	47.6% (n=10)	25.0% (n=15)	0.10	2.78 (0.839-9.200)
C (25 cases)	23.8% (n=5)	33.3% (n=20)	0.95	1.04 (0.277-3.917)

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, URS: Ureteroscopy, ASA: American Society of Anesthesiologists, CT: Computed tomography

Discussion

Our findings have illustrated a relatively high rate of negative ureteroscopies are being performed at our centre Knowing that 14% of endoscopic interventions for ureteral stones could be avoided, our goal should be to minimize nURS to enhance patient safety and the use of operative resources.

To date, this is the only series investigating negative ureteroscopies for patients undergoing ureteroscopy for ureteric stones. Several nURS reports have been published that combine renal and ureteral procedures. As our definition of nURS was the absence of the ureteric stones identified at the time of diagnosis, we sought to investigate this important sub-population of patients undergoing ureteroscopy. As they are usually symptomatic at the time of consultation, they are motivated to proceed with expedited surgery to avoid ongoing symptoms.

With this in mind, our experience is not significantly different then other reported rates. Kreshover et al. (6) reported 9.8% nURS rate from 2011 (over 256 renal+ureteric cases). Similarly, using California's administrative data, Lamberts et al. (7) found that of 19,000 ureteroscopies 6.3% were negative procedures. Again, a distinction was not made for stone presenting in the ureter. This is avoided in our analysis, as nURS was determined on the basis of intra-operative findings compared to a re-review of pre-operative imaging.

Somewhat counter-intuitively we have found that nURS disproportionately affects patients undergoing expedited ureteroscopy. Given that stone sizes and locations were similar, presumably these patients are being prioritized due to intractable pain and coping difficulties. When expedited surgery was performed within 7 days, 28.6% (6/21) of these patients presumably passed their stone before surgery compared to 10% (6/60) in those performed within 3 weeks. Why this population seems to pass stones more readily is unknown, however it does highlight the need for repeat imaging no matter how short the delay between evaluation and surgery, especially in those who are very symptomatic, as our review suggests they may be more likely to pass their stone. Parallel experiences have been reported in general surgery, where appendectomy has shown benefits of protocolized imaging and nomogram stratification. By using routine imaging to aid the clinical diagnosis of appendicitis, negative appendectomy rates decrease from 15% to 4.5% (8). The acceptable rate of negative procedures may be different for each procedure, but obviously our goal is to reduce it as much as feasibly possible.

At our center, reimaging for expedited surgery has not been used for several reasons. Firstly, before this analysis there was not a good understanding of the frequency of events. Additionally, these patients are not admitted at the time of consultation, and once in hospital for their surgery, limited accessibility to afterhours non-urgent imaging (namely ultrasonography). Difficulties also exist when arranging urgent outpatient imaging appointments with a few days notice, especially in rural communities where radiology services may not be readily available.

Therefore, with our new insight into this source of over-treatment, we have instituted a policy to reimage patients with a KUB X-ray the day before their surgery. If their stone was not visible on X-ray at the time of consultation, they be brought to our out-patient surgery center earlier in the day, and an ultrasound will be arranged with radiology. With these small steps, we hope to reduce the frequency of nURS, thereby avoiding unnecessary procedures and wasted surgical resources. Future analyses will then help to ascertain whether meaningful reductions in nURS rates can be achieved.

Conclusions

We have identified 14% of patients undergoing ureteroscopy for ureteral stones at our center are being overtreated. Therefore, we believe that it is imperative that reimaging be considered in this patient population before surgery.

Ethics

Ethics Committee Approval: This study was approved University of Alberta Research Ethics Board (approval number: Pro00057396).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.W., T.S., S.D., Concept: T.W., T.S., S.D., Design: C.L., T.W., T.S., S.D., Data Collection or Processing: C.L., M.L., Analysis or Interpretation: C.L., M.L., Literature Search: C.L., M.L., Writing: C.L., S.D.

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

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Are HoLEP Surgical Videos on YouTube Biased and Misleading or Are They Leading the Industry?

Ömer Koraş, Fatih Gökalp, Ekrem Yıldırak, Hakan Sigva, Nezih Tamkaç, Sefa Porgali, Bilal Kulak, Ferhat Uçurmak, Sadık Görür

Mustafa Kemal University Faculty of Medicine, Department of Urology, Hatay, Turkiye

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

Social media platforms are popular areas for sharing surgical skills and techniques, and presenting healthcare information. Additionally, the rate of patients receiving information about health by using search engines such as google and social media platforms increased due to the proliferation of mobile phones and the Internet. The studies emphasized that there is a spread of false information concerning urological conditions on these platforms. In addition, the published literature showed that the videos that did not contain accurate information were viewed more than informative videos. Video-sharing websites such as YouTube do not evaluate the misinformation in videos, especially in the field of health. There is no study evaluating the information sources of patients with benign prostatic hyperplasia. Our study showed that most of the videos related to holmium laser enucleation of the prostate surgery were uploaded by healthcare providers and the misinformation rate was significantly higher in videos uploaded by the industry. Our study suggests that the videos posted on presenting accurate and reliable information about disease videos should be allowed to be published after the approval of institutions such as healthcare associations and universities.

Abstract

Objective: In this study, we aimed to evaluate the content and quality of the most relevant YouTube videos related to holmium laser enucleation of the prostate (HoLEP) surgery.

Materials and Methods: The keywords "HOLEP", "laser enucleation" and "prostate enucleation" were used to perform a search on YouTube. Non-English language videos, videos with less than 4-minute duration, and repetitive videos were excluded. The reactions of the viewers to the videos were evaluated by recording the "total views", "views/month" and "likes and dislikes" parameters. The data were divided into two groups based on the source of upload: Group 1 consisted of healthcare providers and group 2 comprised of commercial companies and for-profit organizations.

Results: A total of 117 videos were included in the study. A significant portion of the videos (77.7%) had been uploaded by healthcare providers. There was no statistically significant difference between the uploading groups in terms of the DISCERN and the Global Quality score, scores (p=0.484 and p=0.108, respectively). However, Patient Education Materials Assessment Tool for Audiovisual Materials understandability and actionability scores were statistically significantly higher in group 2 (p=0.004 and p=0.022, respectively). In addition, when the misinformation scale was evaluated, there were significantly more videos with high-degree misinformation in group 2 (5.5% vs 33.3%, p=0.001).

Conclusion: On video sharing platforms, such as YouTube, the number of reliable videos with accurate and appropriate guidance about diseases and treatments should be increased, and these videos should be allowed to be posted after they have been approved by relevant institutions, including healthcare associations and universities.

Keywords: HoLEP, patient information, social media, YouTube

Correspondence: Ömer Koraş MD, Mustafa Kemal University Faculty of Medicine, Department of Urology, Hatay, Turkiye
Phone: +90 507 442 57 96 **E-mail:** korasdr@gmail.com **ORCID-ID:** orcid.org/0000-0001-9749-5254
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Introduction

Benign prostatic hyperplasia (BPH) begins to be seen after the age of 40 years, and its incidence increases with age, reaching 80-90% among the population aged 70 to 80 years (1). Surgical treatment is applied in symptomatic BPH cases that do not benefit from medical treatment and/or develop complications. There are many surgical alternatives to surgically treat symptomatic BPH [open prostatectomy, transurethral resection of the prostate, transurethral enucleation of the prostate, holmium laser enucleation of the prostate (HoLEP), etc.]. Among these surgical procedures, HoLEP has taken its place as a surgical treatment option of BPH due to its efficacy and safety in large prostates (2). It has been shown that full enucleation performed after HoLEP results in reduced possibility of repeat surgery, less bleeding, and decreased hospital stay due to the shorter duration of catheter use (3). For these reasons, HoLEP surgery has started to be preferred frequently, and its popularity is gradually increasing.

Video content providers allow patients to easily access information on various treatment methods, which can affect their treatment decisions. YouTube is one of the most popular video-sharing platforms, having more than 1 billion users who collectively watch more than 1 billion hours of videos every day (4,5). Unfortunately, information pollution caused by inaccurate information spreading through social media tools is a very important issue. Therefore, it is important to ensure the accuracy, reliability and understandability of online information obtained from patients concerning treatment methods. In previous studies, it has already been emphasized that there is a spread of false and/or biased information concerning urological conditions on YouTube (6,7). Besides, it can be difficult for patients to distinguish the accuracy of the content of existing from the marketing promises of the informing party.

To the best of our knowledge, there is no study in the literature evaluating HoLEP-specific surgical videos on YouTube. Therefore, we evaluated the content, reliability and quality of the most relevant YouTube videos related to HoLEP surgery.

Materials and Methods

Search Strategy and Video Inclusion Criteria

The keywords "HoLEP", "laser enucleation" and "prostate enucleation" were used to conduct a search on YouTube (http://www.youtube.com) on December 16, 2020, without using any search filter. To reduce bias, all researchers performed the search by clearing their browser's search history and disabling their location status. As the exclusion criteria for the study, videos shorter than 4 minutes, repetitive videos, those with irrelevant content (advertisements, patient references, slide-based presentations, and lectures) and non-English language videos were excluded from the study. A total of 1,416 videos were screened, and 1,156 videos were excluded from the study because they were non-English, irrelevant, or non-audio. Further 143 videos were excluded due to duplication. Thus, the number of videos that were eligible was 117 (Figure 1).

Video Parameters and Scoring System

The videos included in the study were watched by two independent surgeons, both specialized in endourology. In case of inconsistent evaluation between the two surgeons (non-matching results), a third physician evaluated the videos. In addition, the reactions of the viewers to the videos were assessed by recording the parameters of total views, views/month, and video likes and dislikes. The data were divided into two groups based on the source of upload: Group 1 consisted of healthcare providers (doctors, universities, academic journals, university or non-profit physicians, or professional organizations) and group 2 comprised commercial companies or for-profit organizations. The presence or absence of commercial bias was evaluated as described by Cornish and Leist (8). The degree of misinformation was assessed with reference to currently available evidence on surgical BPH treatment as reported using the EAU guidelines (9). In addition, we rated the extent of misinformation in the videos based on a Likert scale of 1 to 5 ("none", "low", "moderate", "high" and "extreme") (10). All videos were systematically evaluated using the Patient Education Materials Assessment Tool for Audiovisual Materials (PEMAT) and the validated DISCERN quality criteria (11-13).

PEMAT is a systematic method developed to select printable and audiovisual patient education materials, which are easier to understand and easier to act on. We used the version for audiovisual materials, which consists of 13 items measuring understandability and four items measuring actionability. The PEMAT provides two scores for each material-one for understandability and a separate score for actionability. Every item had a 1 point (agree) or 0 points (disagree) and N/A was not included in the calculation. Scores were multiplied by 100 to give a percentage score for understandability and actionability. There was no set cut-off value for the scores.

DISCERN is a standardized index of quality of consumer health information on treatment choices, which can be used by anyone without the need for specialist knowledge. The questionnaire consists of a total of 15 items plus an overall quality rating, with each item representing a separate quality criterion rated from 1 to 5 points (1-2 points: low; 3 points: moderate; and 4-5 points: high quality). Thus, a total score of 80 points is possible, with higher scores indicating higher quality. For the purposes of this study, we rated the videos using all relevant items and gave

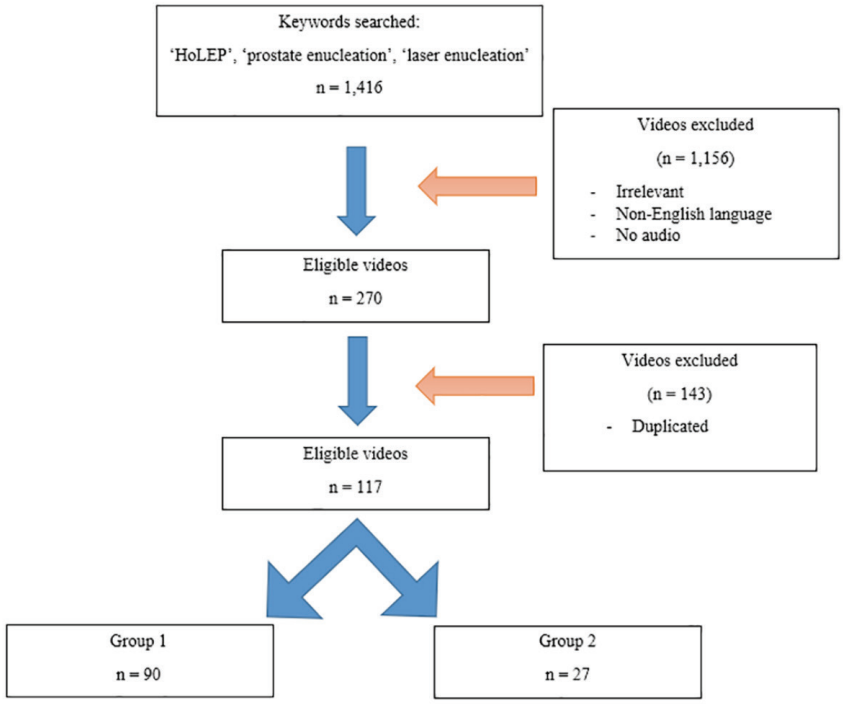

Figure 1. Selection of eligible YouTube videos for the study

them an overall quality rating although not all the videos were directly concerned with treatment choices.

To determine the overall quality of the videos, the Global Quality score (GQS), a five-point scale, was used (GQS: 1=poor quality; 5=excellent quality). This tool measures the accessibility quality and overall flow of the information contained within a video (14).

JAMA is a scoring system with a total of 4 points scored by evaluating whether the authors, institutions, references and sources are clearly stated in the video, whether there is information about copyright, whether there is any clear conflict of interest, and whether the dates of uploading and publication are clearly given (15).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) for Windows, version 23.0 was used for evaluating the data. The Shapiro-Wilk test was used to determine the normality of distribution. Continuous variables were expressed as median and ranges, and their statistical analysis was performed using the Mann-Whitney U test. Categorical variables were expressed as numbers and percentages and analyzed using the chi-square test. Differences were considered statistically significant when the p-value was <0.05.

Results

A total of 117 videos were included in the study. The median time since upload was 24.00 (range=8.00-53.00) months. The median length of the videos was 14.10 (range=6.59-30.03) minutes. The median number of views was 590.50 (range=144.00-2674.00). A significant portion of the videos (n=94, 77.7%) had been uploaded by healthcare providers. Although the videos generally focused on surgeons (number of videos=72, 61.5%), there were 45 (38.5%) videos targeting the general audience. Table 1 shows the characteristics of the videos. When the videos were evaluated according to the questionnaires, although the viewing rates differed according to the DISCERN groups, the increase was not linear. When GQS was evaluated, the median values for the number of views, views per day and likes increased in the videos with a GQS of >3 (p=0.019, p=0.019, and p=0.009, respectively). There was no significant change in the discern score by years (p=0.466).

When the data were divided into group 1 and group 2 according to the upload source, the median number of views was 643.50 (range=155.00-2331.00) and 520.00 (range=181.00-8547.00), respectively, indicating a slightly higher value for healthcare providers, albeit with no significant difference (p=0.916) (Table 2). There was no statistically significant difference between the upload source groups in terms of the median number of views (per day), median number of likes, reliability score, DISCERN

Table 1. Characteristics of the videos	
	Value
Duration (months)[a]	24.00 (8.00-53.00)
Video length (minutes)[a]	14.10 (6.59-30.03)
Total number of views[a]	590.50 (144.00-2674.00)
Number of views per day[a]	0.87 (0.18-3.43)
Number of comments[a]	0 (0.00-2.00)
Number of likes[a]	5.00 (1.00-16.00)
Number of dislikes[a]	0.00 (0.00-1.00)
Misinformation score[a]	3.00 (2.00-4.00)
LIKERT scale[a]	3.00 (2.00-4.00)
GQS score[a]	4.00 (3.00-4.00)
JAMA score[a]	2.00 (1.00-2.00)
PEMATa	
Understandability	80.00 (64.29-93.33)
Actionability	75.00 (50.00-100.00)
DISCERN group	
Low	11 (9.3%)
Moderate	29 (24.7%)
High	77 (65.7%)
GQS group	
GQS 1	1 (0.9%)
GQS 2	15 (12.8%)
GQS 3	28 (23.9%)
GQS 4	58 (49.6%)
GQS 5	15 (12.8%)
Misinformationb	
Severe	1 (0.8%)
High	14 (11.9%)
Moderate	39 (33.3%)
Low	38 (32.4%)
None	15 (12.8%)
Intended audience[b]	
Surgeon	72 (61.5%)
General	45 (38.5%)
Information presented by[b]	
Doctor	99 (85.3%)
Healthcare	5 (4.3%)
Industry	5 (4.3%)
Other	8 (6.1%)
Discussion of alternative treatment options[b]	
Absent	74 (63.2%)
Exist	43 (36.8)
Are side effects mentioned in the video?[b]	
Absent	64 (54.7%)
Exist	53 (45.3%)
Surgical benefits[b]	
Absent	5 (4.3%)
Exist	112 (95.7%)
Commercial bias[b]	
Absent	51 (43.6%)
Exist	66 (56.4%)
Depiction of real surgery[b]	
None	9 (7.7%)
Exist	108 (92.3%)

[a]Data expressed as median and range
[b]Data expressed as number and percentages
GQS: Global quality score, PEMAT: Patient Education Materials Assessment Tool for Printable Material

scores, and GQS of the videos (p=0.470, p=0.163, p=0.249, p=0.484, and p=0.108, respectively). However, when PEMAT was evaluated, the understandability scores [group 1=73.33 (range=60.00-92.86) and group 2=93.33 (range=80.00-100.00)] and actionability scores [group 1=75.00 (range=50.00-100.00) and group 2=100 (range=50.00-100.00)] were statistically significantly higher in group 2 (p=0.004 and p=0.022, respectively). Furthermore, according to the results of the misinformation scale, group 1 had uploaded more videos with low-degree misinformation [group 1=31 (34.4%)] and group 2=7 (25.9%)] while group 2 was the source of more videos with high-degree misinformation [group 1=5 (5.5%) and group 2=9 (33.3%)]. There was a statistically significant difference between the two groups in terms of misinformation evaluation (p=0.001).

Discussion

In this study, we evaluated the quality of YouTube videos on HoLEP that has gained popularity as a frequently preferred surgical method for BPH. The huge video archive on YouTube naturally consists of a large number of video content that examines each subject or topic from different perspectives. However, available evidence has shown that patients can be exposed to low-quality, biased, and/or commercial videos, which can lead to dangerous consequences (7,16). Therefore, it is important to evaluate the reliability and quality of YouTube videos that provide health information. Platforms such as YouTube allow patients to easily obtain information about the issues in which they are interested. However, based on the information presented here, patients can also make poor decisions or resort to expensive treatments. Nevertheless, the literature shows the increasing viewing of videos about the health field among patients or healthcare professionals (17).

Table 2. Comparison of the video data between the upload source groups			
	Group 1 (Healthcare) (n=90)	**Group 2 (Profit organizations) (n=27)**	**p-value**
Video length (minutes)[a]	14.38 (7.22-32.15)	13.22 (5.54-20.00)	0.517
Total number of views[a]	643.50 (155.00-2331.00)	520.00 (181.00-8547.00)	0.916
Number of views per day[a]	1.23 (0.33-3.54)	0.76 (0.15-2.81)	0.470
Number of comments[a]	1.00 (0.00-3.00)	0.00 (0.00-0.00)	**0.038**
Number of likes[a]	7.00 (2.00-18.00)	2.00 (0.00-18.00)	0.163
Number of dislikes[a]	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.891
Reliability score[a]	3.38 (2.75-3.88)	3.38 (2.75-3.75)	0.249
DISCERN score[a]	4.0 (3.0-4.0)	4.00 (3.00-4.00)	0.484
GQS[a]	4.0 (3.0-4.0)	3.00 (3.00-4.00)	0.108
JAMA score[a]	2.0 (1.0-3.0)	2.00 (1.00-2.00)	0.818
JAMA group[b]			
JAMA score <2	68 (75.5%)	20 (74.1%)	0.859
JAMA score >2	22 (24.5%)	7 (25.9%)	
PEMATa			
Understandability	73.33 (60.00-92.86)	93.33 (80.00-100.00)	**0.004**
Actionability	75.00 (50.00-100.00)	100 (50.00-100.00)	**0.022**
Misinformation degree[b]			
Extreme	1 (1.1%)	0 (0.0%)	**0.001**
High	5 (5.5%)	9 (33.3%)	
Moderate	32 (35.5%)	7 (25.9.0%)	
Low	31 (34.4%)	7(25.9%)	
None	11 (12.2%)	4 (14.8%)	

[a]Data expressed as median and range
[b]Data expressed as number and percentages
GQS: Global quality score, PEMAT: Patient Education Materials Assessment Tool for Printable Materials

Depending on the upload source of surgical videos on YouTube, the message conveyed to the viewer and its reliability may vary. In a study by Huang et al. (18), it was found that the videos that did not contain accurate information were viewed more and received more comments. In our study, regardless of the upload source, we observed that 16.2% had extreme- or high-degree misinformation while commercial bias was present in 55.7%. In addition, it was observed that complications and alternative treatments were not mentioned in most of the videos. In a review, it was emphasized that most of the health-related YouTube videos present inaccurate and unreliable information (19). The literature indicates that this misinformation is not necessarily caused by a source being inappropriate or having insufficient expertise, and it could actually be intentional (20). Therefore, we consider that surgical videos on YouTube may pose more of a threat than guidance for patients seeking information to make a treatment decision.

There is no study has evaluated the information sources of patients with BPH; therefore, it is not precisely known how the videos posted on video-sharing sites reflect on or affect patients. In previous studies, it was emphasized that the videos uploaded by universities or healthcare institutions provided more comprehensive information and had higher quality (21,22). In a study by Gul and Diri (23), the videos were classified as those containing reliable and unreliable information, and the GQS and reliability scores were found to be statistically higher in the former. In addition, the authors showed that the majority of videos containing reliable information had been uploaded by for-profit companies. In our study, 23.0% of the total videos had been uploaded by group 2. We attribute these differences to the variations in the subjects discussed in the videos. In our study, no significant difference was observed in the DISCERN, GQS and JAMA scores between the upload source groups. There was also no difference between the two groups in relation to the total number of views, likes and dislikes. A previous study-compared videos as useful and misleading, and in contrast to our findings, the authors reported the comprehensiveness score of GQS to be statistically significantly higher in useful videos (24). In the same study, when the data were compared according to the upload source, the GQS, misleading information and

comprehensiveness scores were found to be statistically higher for the videos uploaded by for-profit companies (24). In contrast, in our study, we also evaluated the videos using JAMA, PEMAT and Likert scales and found that the PEMAT and misinformation scores were higher in the videos uploaded by group 2. In a study by Fode et al. (25) to evaluate videos containing medical information, the median PEMAT understandability score was found to be 100% (range 50-100) and the median PEMAT actionability score was 100% (range 33-100). The results of multivariate regression analysis revealed that all parameters of videos uploaded by medical institutions had a statistically significant effect on the DISCERN rating (25). In our study, the PEMAT scores differed according to the upload source of the videos. The understandability and actionability scores of the videos uploaded by group 2 were statistically significantly higher compared to group 1. Furthermore, although there was misinformation in both groups, the number of videos with high-degree misinformation was significantly higher in group 2. We consider that the videos uploaded by group 2 aim to encourage or direct patients to undergo HoLEP surgery, which is a new and expensive treatment. In addition, in the study by Fode et al. (25), it was emphasized that there was no barrier and/or restriction when uploading content to websites, especially in the field of health (25). Our study shows that people watch these videos without distinguishing between poor and good content, or they may even not know how to make such a distinction. Thus, the videos they watch can direct them to a wrong treatment or misinformation. The PEMAT score also showed that these videos were easy to understand. Although the easy understandability of a video is a favorable characteristic, misinformation contained in some videos can have further negative effects on viewers. The subject of misinformation has been previously investigated and findings similar to our study have been presented by many studies.

Our findings highlight the importance of high-quality videos that objectively cover all spectrums of a treatment modality and can explain it in a way that patients can understand. High-quality information platforms are available (26). In addition, urology associations should be encouraged to upload high-quality and easy-to-understand videos to websites such as YouTube, where patients can research their diseases and treatment options.

Videos from a single video-sharing platform (YouTube) were viewed; however, since YouTube is an ever-evolving website, the evaluation of videos at a single time point may not accurately reflect what patients view after this initial search. By excluding non-English language videos, we may have further reduced the generalizability of our findings. Our study did not include videos available on other online video platforms such as Vimeo or those posted on academic department websites that may not be available on YouTube due to license agreements. Another limitation of the study can be considered the inability to obtain the demographic characteristics of video viewers. There is still no complete consensus on how to fully evaluate health-related online videos.

Conclusion

YouTube is one of the popular platforms for presenting healthcare information and developing skills. Considering these results, it is important to evaluate viewers' behavior according to video uploaders. Therefore, safe, unbiased, and high-quality HoLEP surgery videos should be uploaded cautiously and should take into consideration that patients and healthcare professionals who are viewing them. The number of videos posted on video-sharing websites such as YouTube presenting accurate and reliable information about diseases and treatments should be increased, and these videos should be allowed to be published after the approval of institutions such as healthcare associations and universities. We believe that further studies in urology and other medical fields will contribute to the quality and reliability of health-related video content.

Ethics

Ethics Committee Approval: Some studies that do not require ethical approval include those involving information freely available in the public domain.

Informed Consent: Not necessary.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.G., Design: Ö.K., S.G., Data Collection or Processing: E.Y., H.S., N.T., S.P., B.K., F.U., S.G., Analysis or Interpretation: Ö.K., F.G., S.G., Literature Search: Ö.K., F.G., E.Y., H.S., S.P., B.K., F.U., S.G., Writing: Ö.K., F.G., S.G.

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ORIGINAL RESEARCH
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Is Retrograde Intrarenal Surgery with Semi-rigid Ureterorenoscope Feasible for Isolated Renal Pelvic Stones?

Fatih Tarhan[1], Bilal Eryıldırım[1], Erdinç Dinçer[1], Burcu Hancı Sevinç[1], Kemal Sarıca[2]

[1]University of Health Sciences Turkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Urology, İstanbul, Turkiye
[2]Biruni University Faculty of Medicine, Department of Urology, İstanbul, Turkiye

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

Retrograde intrarenal surgery using with flexible ureterorenoscope and Holmium laser lithotripsy has become one of the standard treatments for patients with upper urinary tract stones. However, the small size of the working channels of flexible ureterorenoscope and the high cost are disadvantages. It has been suggested that semirigid urethroscope may be effective as an alternative to solve this problem. In this study, we found that semirigid urethroscope had a lower success rate and a higher complication rate compared to flexible ureterorenoscope. Therefore, we concluded that semirigid urethroscopy is unsafe and unsuccessful in the treatment of pelvic stones.

Abstract

Objective: We compared the success and complication rates of retrograde intrarenal surgery (RIRS) performed with semi-rigid ureterorenoscopy (srURS) or flexible ureterorenoscopy (fURS) for isolated renal pelvic stones.

Materials and Methods: A total of 247 patients who underwent RIRS with fURS (n=179; group 1) or srURS (n=68; group 2) were included in this study. Various factors related to patients, stones and surgical procedures were evaluated retrospectively.

Results: There was no difference between the patient groups according to mean age (49.12±1.10 years vs 49.59±1.60 years, p=0.745), gender distribution (p=0.152), mean hounsfield unit values (941±31.41 vs 1036±44.47 p=0.077), and mean hospitalization time (3.57±0.19 days vs 4.59±0.57, p=0.224). In group 1, the mean stone size (14.5±0.73 mm vs 15.5±0.62 mm, p=0.019) was statistically lower and the operative time (79.73±3.38 min vs 70.65±8.61, p=0.041) was statistically higher than those of group 2. The overall success rate in group 1 and group 2 was 93.9% and 63.6%, respectively (p<0.0001). The complication rate in group 2 (23.5%) was higher than that of the group 1 (12.3%) (p=0.047).

Conclusion: According to our results, the success rate of srURS was lower and the complication rate was higher than that of fURS. Therefore, we conclude that srURS was unsafe and unsuccessful for use in the treatment of pelvic stones. Prospective studies involving intrarenal pressure measurement and cost analysis must reach a conclusion in this respect.

Keywords: Urolithiasis, nephrolithiasis, ureteroscopy, retrograde intrarenal surgery

Introduction

The main goal in the treatment of renal stones is to attain the greatest stone-free status with minimal morbidity (1). Retrograde intrarenal surgery (RIRS) with holmium laser lithotripsy has become one of the standard treatments for patients with upper urinary tract stones (2,3). RIRS with a flexible ureteroscope (fURS) has been widely adopted and has become an effective, safe option in primary care for upper urinary tract stones smaller than 2 cm (4,5). The use of ureteral access sheaths (UAS) is also recommended during the treatment of kidney stones with fURS (4). On the other hand, it has been reported that the use of UAS may cause serious injuries to the ureter (6).

Although fURS is a safe and effective method for the treating of renal pelvic stones, it also has some disadvantages. The small size of the working channels of the fURS only allows the use of small stone baskets and laser fibers. High cost due to low

Correspondence: Fatih Tarhan MD, University of Health Sciences Turkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Urology, İstanbul, Turkiye
Phone: +90 532 722 34 35 **E-mail:** tarhanf@yahoo.com **ORCID-ID:** orcid.org/0000-0001-8168-0420
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physical durability remains a major disadvantage (7). Disposable devices developed to solve this problem, unfortunately, cannot eliminate the problem (8).

Semirigid ureteroscope (srURS) application is not preferred in the treatment of the renal stones due to its limited maneuverability and difficult access to the calyces. Furthermore, infectious complications and kidney damage directly related to increased intrarenal pressures may occur during srURS procedures (9). However, previous studies have reported that some patients with renal pelvis stones can be treated with srURS (10,11). The advantage of using srURS in these patients is that it allows for larger sized working equipment due to the wider working channel and a better visualization can be achieved with a high irrigation flow rate (10).

In this retrospective study, we performed RIRS with srURS or fURS for the treatment of isolated renal pelvic stones that were resistant or unsuitable for extracorporeal shock wave lithotripsy (ESWL). We evaluated the success and the complication rates of srURS and fURS.

Materials and Methods

A total of 335 patients with isolated renal pelvis stones who had undergone RIRS between January 2015 and December 2018 were assessed for participation in this study. Sixty-seven patients were excluded because they did not meet the inclusion criteria. A total of 267 patients who underwent RIRS with srURS or fURS were included in the study. RIRS was performed using fURS (group 1) in 179 patients and with srURS (group 2) in 88 patients. In 20 patients (22.7%) in group 2, the treatment was started with srURS and was proceeded to fURS since the stone or renal pelvis could not be accessed using srURS. Therefore, the data of these patients were not analyzed further. As a result, a total of 247 patients were included in the study.

Patients' data were analyzed retrospectively from hospital medical databases. Patients over the age of 18 with renal pelvis stones, either refractory or not suitable to ESWL, were included in the study. Patients with non-opaque stones, caliceal stones, solitary kidney, ureteropelvic junction obstruction, ureteral strictures, congenital anomalies, bilateral cases, neurogenic lower urinary dysfunction, and those who received immunosuppressive therapy and pregnant patients were excluded from the study. This study was achieved accordance to Helsinki Declaration (193/2013). The study was approved by our Institutional Review Board (22.07.2020-2020/514/182/8), and written informed consent was obtained from all patients before the treatment.

The diagnosis of urolithiasis was made by imaging methods such as kidney-ureter-bladder radiography (KUB), ultrasonography and low-dose, non-contrast computed tomography (CT). However, all patients were evaluated preoperatively by CT. The longest dimension of a stone was calculated as the stone size. Preoperative medical history, physical examination, comorbidities, the presence of DJ stents and results of complete blood count, plasma urea and creatinine values, clotting profiles, urinalysis and urine cultures were noted. Data of postoperative body temperature, blood pressure, heart rate and respiratory rate were recorded. The patients were evaluated comparatively in terms of demographic findings (age, gender), CT attenuation values of the stones [Hounsfield Unit (HU)], stone size, and procedures (duration, hospital stay, additional surgical interventions, stone-free rate, and complication rates).

Urine cultures of all patients were sterile before RIRS procedure. Patients with the positive urine cultures were treated with appropriate antibiotics and operated after control urine cultures were sterile. Anticoagulant drugs were discontinued 5-7 days before the procedure. A preoperative Double-J (DJ) stent was not placed to patients routinely, it was applied in the presence of kidney obstruction and infection.

All surgical procedures were performed under general anesthesia in the lithotomy position. Intravenous antibiotic prophylaxis (third generation intravenous cephalosporin) were administered one hour before general anesthesia induction and continued for 3 days postoperatively. The guidewire (0.035 inch, polytetrafluoroethylene coated flexible type guidewire, Boston Scientific, Marlborough, Massachusetts, USA) was placed in the upper urinary tract under fluoroscopic control using a 6/7.5 Fr srURS (Fiber-ureterorenoscope Richard Wolf, Germany).

In those who underwent RIRS with srURS, it was entered into the system with the guidance of the guidewire. The stones were fragmented with a holmium YAG laser (Sphinx Jr, LISA, Germany) using a 272 µm holmium laser fiber (Flexifib, LISA, Germany) with an energy 0.5-0.8 Joule and a frequency of 12-15 Hertz until it was considered small enough to pass spontaneously. A zero tip nitinol basket was used to remove the stone fragments. In patients undergoing RIRS with fURS, at first a 9.5/11 Fr UAS (Flexor Cook Medical, Bloomington, Indiana, USA) and then subsequently a 7.5-Fr fURS (Karl Storz Flex-X2, Tuttlingen, Germany) were placed in the system. An irrigation fluid (saline) bag was placed 80 cm above patient's level and a manual hand pump was used to increase the pressure of the irrigation fluid if necessary. The stones were fragmented using the same method as for srURS. At the end of the RIRS procedure, the ureter was checked and the fURS was removed under vision.

When srURS/fURS could not be introduced to the ureter because of ureteral orifice stenosis, the ureteral orifice was dilated with a balloon (UroMax Ultra, Boston Scientific, Marlborough, MA, USA). In cases where srURS/fURS could not reach the upper

urinary system, a DJ stent was placed into the ureter and procedure was repeated 2 or 3 weeks later.

The procedure was terminated after the stone-free status was confirmed by both ureterorenoscopy and fluoroscopy. At the end of the operation, DJ stent or ureter catheter was inserted in cases of ureteral trauma, residual fragments, bleeding, ureteral wall edema, a large stone burden (>1.5 cm), a longer operative time (>60 min), repeated access, impacted calculi, a recent history of urinary tract infection, and renal functional impairment. The operation time was calculated as the time from the ureteroscope entry into the ureteral orifice until the completion of the stent placement. The DJ stent was removed approximately 2-3 weeks after surgery in case of complete stone clearance.

Postoperative complications were scored according to the modified Clavien-Dindo classification (MCCS) (12). Complications such as postoperative fever, sepsis, and septic shock were categorized as infective complications. Postoperative fever was defined as an increase in body temperature to >38 °C, which continued for 48 hours. Sepsis was considered in the presence of a source of infection and systemic inflammatory response syndrome (having two or more of the following criteria: temperature <36 °C or >38 °C; heart rate >90/min; respiratory rate >12/min or $PaCO_2$<32 mmHg; white cell count >12.000 or <4.000/mm^3). Severe sepsis was described as sepsis with organ dysfunction. Septic shock was accepted as an acute circulatory failure condition characterized by permanent arterial hypotension. Definitions of temporary and permanent hematuria defined by Mandal et al. (13) were accepted.

A KUB was performed on the first postoperative day to assess the location of the DJ stent and to check for the presence of residual stone. The patients were evaluated with KUB and/or urinary ultrasound in the first postoperative month and with low-dose non-contrast CT in the third postoperative month. The success rate in the third month after surgery was evaluated. The results were classified as 'stone free (absence of any stone fragments)", "clinically insignificant residual fragments (CIRFs) (the ≤4 mm non-obstructed asymptomatic residual stones) (7)" or "residual stones" (the >4 mm or symptomatic stones). success has been determined as stone-free status or the presence of CIRF.

Statistical Analysis

The patients' data were presented as percentages, mean ± standard error. D'Agostino & Pearson test was performed to determine whether the data followed a Gaussian distribution or not. Fisher exact probability test was used to compare the categorical variables. Student's t-test or Mann-Whitney U test was used to compare the two groups. Point-biserial correlation analysis was used for nominal/quantitative scale data, and Phi correlation analysis was used for nominal/nominal scale data (https://www.socscistatistics.com/). A multivariate logistic regression analysis was performed to identify factors potentially affecting the success and complications. Receiver operating characteristic plots were used to define the detection cut-off. Statistical calculations, except point-biserial and Phi correlation, were made using MedCalc® Version 20.010-64-bit software (https://www.medcalc.org free trial). P<0.05 was considered statistically significant.

Results

The demographic data of the patients, characteristics of the stones and the procedures are given in Table 1. The mean stone size of the fURS group was statistically lower than that of the srURS group (p=0.019). The operative time of the fURS group was statistically longer than that of the srURS group (p=0.041). There were no differences between the groups in terms of other parameters (p<0.05) (Table 1).

The postoperative complications of the patients are shown in Table 2. There were no major ureteral injury in patients.

Table 1. Demographic data and stone properties

Parameters		Group 1 (fURS)	Group 2 (srURS)	p*
Age		49.12±1.10	49.59±1.60	0.745*
Gender	Female	108/179	34/68	0.152**
	Male	71/179	34/68	
Preoperative DJ stent		48/179 (26.80%)	14/68 (20.59%)	0.411**
Stone size		14.5±0.73	15.5±0.62	0.019*
Hounsfield unit		941±31.41	1036±44.47	0.077*
Operative time		79.73±3.38	70,65±8.61	0.041*
Hospitalization time		3.57±0.19	4.59±0.57	0.224*
Balloon dilatation		31/179 (17.3%)	10/68 (14.7%)	0.705**
Postoperative DJ stent/ureter catheter		148/179 (82.7%)	63/68 (96.6%)	0.067**

DJ: Double J, *Mann-Whitney-U, **: chi-square, fURS: Flexible ureterorenoscopy, srURS: Semi-rigid ureterorenoscopy

The overall complication rate in the srURS group (23.5%) was higher than that in the fURS group (12.3%) (p=0.047). The most common complications were ureteral stones requiring intervention in 14 patients (5.7%) and transient hematuria in 13 patients (5.3%). Emergency DJ stent or nephrostomy was applied to 12 patients, and endoscopic stone treatment was performed in 2 patients because to the ureteral stones. There were no statistically significant differences between the groups in terms of the rate of additional interventions (p=0.066). Infective complications were seen in 6 patients (3.4 %) in group 1 and 5 patients (7.4 %) in group 2 (p=0.181). A statistically significant difference was not found between the groups in terms of transient hematuria (p=0.757). Persistent hematuria was not observed in any patient. There was no grade 4 or 5 complications according to MCCS. (Table 2).

As seen in Table 3, the mean HU value was lower and the mean operative time was longer in patients with complications (p<0.05). No differences were observed in the development of complications in terms of gender (p=0.668) and the presence of preoperative DJ stents (p=0.621) (Table 3).

While there was a positive correlation between the development of complications and the type of operation (phi=0.165; p=0.009), and the operative time (r_{pb}=0.281; p=0.003), there was a negative correlation between the HU value and the development of complications (r_{pb}=-0.172; p=0.015). Logistic regression analysis revealed only the operative time as a statistically significant factor associated with complications [odds ratio 1.027, 95% confidence interval (CI) 1.0063-1.0473, p=0.010]. The optimal threshold of the operation time for complications was >85 min (sensitivity 87.50% and specificity 60.64%; 95% CI 50.0-70.6). The HU cut-off level for complications was calculated as ≤570 (sensitivity 46.15% and specificity 81.44%, 95% CI 74.7-87.0) (Table 4).

The stone-free, CIRFs, and the residual stone rates were 80.4% (n=144), 13.4% (n=24), 6.1% (n=11) in the fURS group. In the srURS group, the stones of 77.3% of the patients could be achieved and the treatment was successful in 82.4% of the patients. However, when patients whose stones could not be achieved with srURS were added to the srURS failure rate, the stone-free, CIRF, and residual stone rates were found to be 56.8% (n=50), 6.8% (n=6) and 36.4% (n=32) in the srURS group, respectively. In this case, the overall success rate was 93.9% (n=168) in the fURS group and 63.6% (n=56) in the srURS group. A statistically significant difference was observed between the two groups in terms of success rates (p<0.0001).

As shown in Table 5, the mean stone size was larger and the mean operative time was longer in patients with unsuccessful treatment than the patients with successful treatments (p<0.05). There was no difference in the success rate in terms of gender (p=0.335) and the presence of preoperative DJ stents (p=0.751). Negative correlations were found between the success of treatment with the stone size (r_{pb}=-0.277; p=0.00007) and with the operative time (r_{pb}=-0.249; p=0.016). Logistic regression analysis did not reveal any statistically significant factors associated with treatment success. The optimal threshold of the operation time was ≤80 min (sensitivity 68.33% and specificity 61.90%; 95% CI 55.0-

Table 2. The distribution of complications between groups according to the modified Clavien-Dindo classification

Degree	Complication	Overall (n=247) n (%)	fURS (n=179) n (%)	srURS (n=68) n (%)	p*
1	Temporary hematuria	13 (5.3)	9 (5.0)	4 (5.9)	0.757
1	Fever	1 (0.4)	0 (0)	1 (1.5)	0.181
2	UTI, pyelonephritis, SIRS, sepsis	10 (4.0)	6 (3.4)	4 (5.9)	
3a	DJ stent or nephrostomy	12 (4.9)	7 (3.9)	5 (7.4)	0.066
3b	Endoscopic stone treatment	2 (0.8)	0 (0)	2 (2.9)	
Total		38 (15.4)	22 (12.3)	16 (23.5)	0.047

UTI: Urinary tract infection, SIRS: Systemic inflammatory response syndrome, DJ: Double J. *chi-square

Table 3. Characteristics of patients with and without complications

	Patients with complications (n=36)	Patients without complications (n=211)	p*
Age	49.42±3.11	49.20±0.92	0.948
Hounsfield unit	771.2±81.90	986,8±25,72	**0.019**
Stone size	15.88±1.48	13.79±0.38	0.159
Operative time	111.3±10.76	76.00±3.10	**0.005**
Hospitalization time	7.25±1.56	3.45±0.15	**0.028**

*Mann-Whitney U

79.7) for success. The cut-off level of stone size for success was calculated as ≤12 mm (sensitivity 56.52% and specificity 69.41 %, 95% CI 58.5-79.0) (Table 5).

Discussion

There are few studies in the literature regarding the use of semirigid ureteroscopy in the treatment of renal stones. The first reported study was conducted by Nakayama (14) in 1998 using rigid ureterorenoscopy and ultrasonic lithotripter in 10 patients with renal pelvis stone. In this series, 70% success rates and urinary extravasation as a complication were reported. Subsequently, Ebert and Schafhauser (15) in 2008 treated kidney stones with srURS and laser by repositioning the stones into the renal pelvis in 12 patients. The overall success rate was 92%, and no complications were reported. Bryniarski et al. (16) treated 32 patients with renal stones larger than 2 cm with srURS and lasers in 2012. The success rate was determined as 75% and they did not report any serious complications. Mursi et al. (17) reported the results of RIRS with srURS in 15 patients with renal pelvis stones in 2013. The success rate was reported as 53%.

There are only two studies comparing the success of srURS and fURS. Atis et al. (11) reported the results of RIRS with srURS in 47 patients with isolated renal pelvic stones in 2012. Stone could be reached with srURS in 53% of the patients. The success rate was reported as 76% in the srURS group and 86.4% in the fURS group. There was no significant difference between the groups in terms of stone-free rates, complication rates, and length of hospital stay. In another study, Süer et al. (10) reported that 88 patients with isolated 1-2 cm diameter renal pelvis stones underwent RIRS by laser using rigid URS in 2015, and 55% of these patients could be treated without fURS. The success rate was reported as 83% in the srURS group and 87% in the fURS group. No major complications have been reported in this study (10).

It was reported that the predictors of reaching the stone during RIRS with srURS were the female gender (10,11), the patients' height (10), and the lower degree of hydronephrosis (10). However, the success rates in gender groups both in this study and in the Atis et al. (11) study were similar. Additionally, Atis et al. (11) reported that the degree of hydronephrosis did not affect stone-free rates in both groups.

The rate of access to renal pelvis stones (77%) in this study was higher than those of other studies (10,11). This might be due to the use of srURS with a small diameter. The success rate of RIRS with srURS in this study was lower than those of other studies previously conducted (10,11,14-16). A disadvantage of srURS is that it has a limited maneuvering capacity. When stone fragments migrated to the calyx, srURS could not access the stone. Thus, RIRS with srURS could lead to a lower stone-free rate than fURS. In the literature, comparable to our results, the operation time of the fURS group was reported to be longer than that of the srURS group (11). It was reported that there was a negative correlation between the success and

Table 4. Results of correlation analysis for success and complication of treatment

Factors	Complication		Success	
	r_{pb}/phi	p	r_{pb}/phi	p
Age	0.005*	0.943	0.087*	0.222
Gender	-0.033**	0.399	0.066**	0.350
Preoperative DJ stent	0.031**	0.629	0.009**	0.893
Method of RIRS	0.165**	**0.009**	-0.092**	0.807
Hounsfield unit	-0.172*	**0.015**	0.114*	0.147
Stone size	0.106*	0.099	-0.277*	**0.00007**
Operative time	0.281*	**0.003**	-0.249*	**0.016**

*Point-biserial correlation (rph), **Phi correlation (phi), DJ: Double J, RIRS: Retrograde intrarenal surgery

Table 5. Characteristics of patients with successful and non-successful treatment

	Patients with successful treatment (n=224)	Patients with unsuccessful treatment (n=23)	p*
Age	50.17±1.30	47.79±1.44	0.222
Hounsfield unit	989.9±36.35	912.3±38.41	0.153
Stone size	12.45±0.47	15.69±0.68	**0.0001**
Operative time	72.73±4.36	89.62±5.34	**<0.0001**
Hospitalization time	3.72±0.23	3.88±0.40	0.326

*Mann-Whitney U

the stone size in RIRS (18). In our study, it was found that there was a moderate negative correlation between the success of treatment and the stone size and the operative time. In our study, unlike other studies, complications were given according to MCCS.

Complication rates in the srURS group were higher than those in the fURS group ($p<0.047$). Our complication rates (15.4%) were consistent with the complication rates of RIRS in the literature (13,19,20). According to our findings, low HU value (≤570), long operation time (>85 min), and performing RIRS with srURS are associated with complications. Some studies found that the development of complications related to RIRS was affected by the stone size and the duration of the operation (19,21). In addition, the development of infective complications was associated with a long operative time (60 min) and high stone burden (22,23). Another disadvantage of srURS is the possibility of developing complications secondary to intrarenal reflux, which might develop due to increased intrarenal pressure during the procedure (9,24).

An interesting finding of our study was that a weak negative correlation was found between the HU value of the stone and the development of complications. The reason for developing more common complications in patients with low HU values might be that these were infection stones. Furthermore, this situation could be confirmed by performing a stone analysis.

Study Limitations

Despite these strengths, our study had some limitations. First, the study was retrospective nature. The second limitation was that there was no intrarenal pressure measurement was during RIRS. Lastly, the cost analysis has not been done.

Conclusion

In our study, srURS may be sufficient for the fragmentation of stones when stone can be achieved with srURS in 82% of patients. However, the overall success rate of srURS was lower and the complication rate was higher than that of fURS. Therefore, we conclude that srURS is unsafe and unsuccessful for use in the treatment of pelvic stones. Prospective studies involving intrarenal pressure measurement and cost analysis must reach a conclusion in this respect.

Ethics

Ethics Committee Approval: The study was approved by our Institutional Review Board (22.07.2020-2020/514/182/8).

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

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.T., B.E., K.S., Concept: F.T., B.E., K.S., Design: F.T., B.E., K.S., Data Collection or Processing: F.T., E.D., B.H.S., Analysis or Interpretation: F.T., B.E., E.D., B.H.S., K.S., Literature Search: F.T., E.D., B.H.S., Writing: F.T., B.E., E.D., B.H.S., K.S.

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

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Comparison of the Histological Response to Different Bulking Materials Used in Endoscopic Vesicoureteral Reflux Surgery

Ali Cansu Bozacı[1], Fazıl Tuncay Aki[1], Dilara Zeybek[2], Sevda Müftüoğlu[2], Serdar Tekgül[1]

[1]Hacettepe University Faculty of Medicine, Department of Urology, Ankara, Turkiye
[2]Hacettepe University Faculty of Medicine, Department of Histology and Embryology, Ankara, Turkiye

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

Subureteral injection of various bulking agents became the preferred treatment modality of vesicoureteral reflux. The ideal bulking agent should have a good mound effect at the tissue and preserve this effect for long term without any tissue reaction. This study aimed to compare the histologic effects of three bulking agents used in this era. We found that materials containing dextranomere hyaluronic acid can form satisfying degree of mound effect with adequate capsule duration as polyacrilate polyalcohol copolymer/glycerol materials without significantly less chronic inflammation around injection area. This information can help the clinician to make decision on material choosing during, especially about the possible further ureter obstruction after injection, and further secondary open surgery difficulties.

Abstract

Objective: To compare the histological responses of 3 bulking agents, which are used in the endoscopic treatment of vesicoureteral reflux, on rats' urinary bladder and subcutaneous tissue.

Materials and Methods: Thirty rats were divided into 3 groups according to the injection materials; Dextranomer Hyaluronic acid- Deflux® (DxHA-Df), Dextranomer Hyaluronic acid- Deal® (DxHA-Dx) and Polyacrilate Polialcohol Copolymer-Vantris® (PPC). In each group, material was injected both into the submucosa of the rats' urinary bladder dome and the subcutaneous tissue at their names. In each group, 5 rats were scarified at the 2nd and 6th months after injection. The histopathologic compartment was performed by scoring inflammation, neutrophil, eosinophil, macrophage, mast cell and giant cell reactions around the injected material.

Results: All materials maintained their bulky effect. Despite the large amount of degradation with dextranomer materials, there was minimal degradation with PPC. The materials had the same amount of capsule formation around the injection site, which was not related to the degradation properties of the material. There was no statistically significant result for bladder injections. For subcutaneous injections mast cell scores around the injection (DxHA-Df, DxHA-Dx, PPC: 1.4, 1.2, 0 respectively, p=0.024) were significantly different at 2nd month. Mast cell scores around the injection (DxHA-Df, DxHA-Dx, PPC: 1.0, 1.75, 0 respectively, p=0.007) were significantly different at 6th month also. The inflammation around PPC was higher at the 6th month (DxHA-Df, DxHA-Dx, PPC: 1, 1, 3.5 respectively, p<0.05).

Conclusion: Both dextranomer agents were degradable with good capsule formation and minimal inflammation in the adjacent tissue. PPC degraded minimally and caused significant inflammation at adjacent tissue.

Keywords: Vesicoureteral reflux, endoscopic treatment, injection materials

Correspondence: Ali Cansu Bozacı MD, Hacettepe University Faculty of Medicine, Department of Urology, Ankara, Turkiye
Phone: +90 533 232 03 02 **E-mail:** alicansu@doctor.com **ORCID-ID:** orcid.org/0000-0001-8726-8509
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Introduction

In the last two decades, subureteral injection of various bulking agents has become the preferred treatment modality of vesicoureteral reflux (VUR). This relatively easy, safe and efficient method increases the intravesical length of ureters, narrows the ureter lumen, and fixes the lower end of the ureter in the bladder wall by local fibrosis. The ideal bulking agent should have a good mound effect at the tissue and preserve this effect for a long term without any tissue reaction. The injection should be easy to apply and the material must be stable at its injection area without local or distant migration. The durability of the bulking agent and local tissue reaction are key elements, which also have significant impacts on the success of treatment.

The success of the endoscopic technique depends on many different factors such the reflux grade (1,2), voiding dysfunction (3), operator (2), and physicochemical properties of the injected material (4). Therefore, clinic studies do not seem suitable in terms of comparing only the injection materials' role in success. The purpose of this animal model is to compare the histological responses of 3 injection materials (2 different dextranomer materials, 1 polyacrylate material) on rat bladder and subcutaneous tissue and interpret the results with possible clinical situations.

Materials and Methods

Animals

The Institutional Care and Use Committee approved (Hacettepe University Animal Experimentations Local Ethics Board 2010/25-3) the study design, and researchers were accredited by Guidelines of Responsible Use and Human care. A total of 30 healthy male adult Sprague-Dawley rats grown to mean 352 grams (328-424 gr) and maintained at Hacettepe University Faculty of Medicine Experimental Animal Laboratory in temperature-controlled cages and a dark-light circle with free access to water and food.

Procedure

All injections and surgical interventions were performed out with sterile technique under general anesthesia with intraperitoneal xylazin 5 mg/kg and ketamine 15 mg/kg. Thirty rats were grouped into 3 for each material and sacrificed with carbon monoxide at 2nd and 6th months after the injections.

The three injection materials commercially available were compared in this study:

1. Dexell® (İstem Medikal, Ankara, Turkey (DxHA-Dx): Dextranomer microspheres 50 mg\1 cc, Hyaluronic acid 17 mg\1 cc, Sodium chloride 6.9 mg\1 cc

2. Deflux® (Q-Med AB, Uppsala, Sweden) (DxHA-Df): Dextranomer microspheres 50 mg\1cc, Hyaluronic acid 15 mg\1 cc, Sodium chloride 6.9 mg\1 cc

3. Vantris® (Promedon, Cordoba, Argentina) (PPC): Polyacrylate polyalcohol copolymer 60%, glycerol 40%.

The same researcher (A.C.B) performed all injections. PPD needles were adapted to commercial injectors containing study materials and scaled by 0.1 cc. The hair on the nape and abdomen was shaved. 0.1 cc of material was injected subcutaneously into the midline of the napes of the animals. Afterwards, bladder was exposed through 2 cm long vertical suprapubic incisions and emptied with palpation. Bladders were held with atraumatic forceps and traction was performed from the lateral walls. 0.1 cc of study material was injected into bladder wall at the dome. The abdomens were sutured and closed.

Outcomes

The experiments were terminated at 2nd and 6th month. After scarification, injection sites in the names were excised with 0.5 cm lateral margin. Abdomens were re-explored through the previous incision site, and bladders were removed by excising through the bladder neck. Excised tissues were kept in 10% formalin solution and prepared for inspection under a light microscope. 5 µm thick slides were stained with Hematoxylin-Eosin and Masson's trichrome.

Two histologists who were blinded to the groups examined and photographed the slides. Capsule thickness was measured using Leica Application Suite Programme®. Neutrophils, eosinophils, macrophages, mast cells, and giant cells around the injected material were counted and scored as described by Raut et al. (5) (Table 1).

Statistical Analysis

Statistical analyses were performed using SPSS 15.0 Program® and $p<0.05$ was considered as significant. Subgroups (classified according to time of sacrifice) were compared with Kruskal-Wallis tests. Conover's two-sample squared rank test for equality of variance was used to determine the subgroup leading to the difference.

Table 1. Scoring of inflammatory cells according to Raut et al scoring system (5). (Counted in 1 microscopic field under x40 magnification)

Score	Number of cells counted
0	None
1	1-5 cells
2	6-15 cells
3	16-25 cells
4	≥26 cells

Results

a. Histological Findings in Bladder Sections

During scarification, in some urinary bladders, there were no injection materials at the site of injection. Also, in their histological sections, no injection materials were seen. That is most probably the result of the thin bladder wall of rats and the leakage of material into the lumen or peritoneum after injection, which was an expected result after our pilot study. That is why we planned also to have injections into the subcutaneous tissue. The missing data was distributed equally into the groups and this error did not affect our statistical compartments. In specimens harboring the materials, biomaterials were concentrated within the lamina propria between the epithelial and muscular layers of the urinary bladder, which caused flattening of the overlying epithelium and protrusion into the lumen slightly. Microspheres could both be seen with full of material or empty at the injection area of each material. Capillaries and cellular infiltration, including active fibroblasts and infiltrative cells (especially lymphocytes) and rare multicellular giant cells, were observed within and around the microsphere groups (Figure 1). Lymphocytes and occasional mast cells were present outside the capsule, which was made of collagen fibrils and fibroblasts starting from the 2nd month groups. Degraded empty microspheres could have seen in 2nd and 6th month groups for each biomaterial.

Degradation of DxHA-DX and DxHA-DF was observed to get started earlier and to be completed at 6th month sections. However, the degradation of PPC was minimal with persisting full microspheres in 6th month sections.

For an objective comparison, infiltration and inflammatory cells were scored, and mean capsule thicknesses were calculated for each group (Table 2 and 3).

Both in 2nd and 6th month sections, all three groups were similar for all parameters (Table 3). Observationally, capsular and intracapsular collagen fibers were thicker, giant cell response was weaker and lymphocytic infiltration around the capsule was prominent in the PPC group, however there were no statistical differences among the groups (Table 2 and 3).

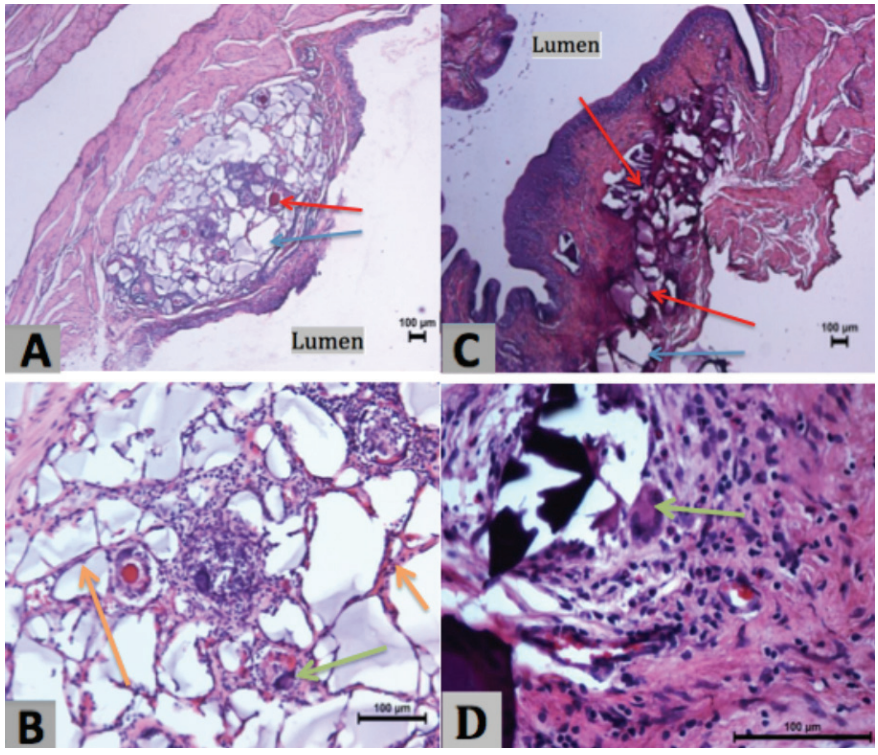

Figure 1. Bladder sections at 6th month. A. DxHA-Df (Deflux) injection site. Most of the microsphers are degraded (blue arrow), unique full microsphers are still exist rarely (red arrow). Bulking effect is seen, flattering of overlying epithelium and protrusion into the lumen slightly. (Hemotoxylin & eosin staining, x25). C. PPC (Vantris) injection site. Most of the microsphers are not degraded (red arrows), unique degraded microsphers are seen (blue arrow). Bulking effect is seen, flattering of overlying epithelium and protrusion into the lumen slightly. (Hemotoxylin & eosin staining, x25). B. Inside of the DxHA-Df (Deflux) injection site. Capillaries and cellular infiltration including active fibroblasts (orange arrows) and infiltrative cells (especially lymphocytes) and rare multicellular giant cells (green arrow) were observed within and around the microsphere groups (Hemotoxylin & eosin staining, x100). D. Inside of the PPC (Vantris) injection site. Capillaries and cellular infiltration including active fibroblasts and infiltrative cells (especially lymphocytes) and rare multicellular giant cells (green arrow) were observed within and around the microsphere groups (Hemotoxylin & eosin staining, x100)

PPC: Polyacrilate Polialcohol Copolymer-Vantris, DxHA-Df: Dextranomer Hyaluronic acid- Deflux®

b. Histological Findings in Subcutaneous Tissues

Majority of 2nd and 6th month sections in DxHA-DX and DxHA-DF groups showed complete degradation, whereas degradation was minimal in the PPC group (Figure 2).

Although collagen fibers between and around the PPC microspheres seemed thicker, mean capsule thicknesses of the three groups were found to be statistically similar (Table 2).

Mast cell infiltration around the capsule was higher in DxHA materials (p=0.024 in 2nd month and p=0.007 in 6th month sections). Overall, inflammatory infiltration around the injection site was prominent in 6th month sections of the PPC group (p<0.05). The rest of the histological parameters were statistically the same (Table 3).

Table 2. Median (min-mix) capsule thickness (µm) of the groups

		2nd month	6th month
Urinary bladder	DxHA-DX (n=2/3)	73.70 (69.20-78.20)	66.77 (64.34-69.20)
	DxHA-DF (n=3/5)	69.62 (65.48-73.76)	73.22 (68.94-77.33)
	PPC (n=3/5)	68.59 (66.28-70.90)	73.20 (68.91-75.83)
Subcutaneos tissue	DxHA-DX (n=5/4)	77.78 (73.60-85.80)	99.23 (95.70-102.47)
	DxHA-DF (n=5/4)	85.57 (79.59-89.02)	89.22 (86.47-107.81)
	PPC (n=3/4)	84.11 (80.70-84.52)	114.58 (88.64-131.10)

Number of rats at 2nd/6th months. (Kruskall-Wallis test, p>0.005)

Discussion

The majority of the materials used in endoscopic treatment of VUR were abandoned either due to their migration to distant tissues, rapid loss of mass effect, or granuloma formation (4,6). DxHA-Df is a biodegradable material containing cross-linked 80-120 µm dextranomer microspheres in a stabilized sodium hyaluronic acid carrier medium gel. The gel is absorbed the following injection, and microspheres induce a rapid fibroblast migration and collagen synthesis leading to the capsule formation. While high success rates for short-medium term ranging between 68 and 92% were reported (4,7-9); long-term recurrence rates necessitate to research on new materials. DxHA-DX is another biodegradable dextranomer gel with similar physical and chemical properties. PPC is a non-bio-degradable synthetic material as 320 µm microspheres in glycerol solution. Due to its large molecular size, its distant migration is unlikely, and the mass effect seems persistent for long term (10).

Microsphere sizes and counts were similar throughout the study period in both tissues and all groups. Degradation of DxHA-DX and DxHA-DF began and were completed earlier than PPC, as expected due to the synthetic non-biodegradable nature of the PPC molecule.

Ideally, the capsule formation should start early and persist for a long time. Dx-HA materials triggered capsule formation around 2nd month and persisted at the 6th month sections independent of degradation. PPC group, capsule formation and thickness were similar to other groups in 2nd and 6th month sections. Also, the capsule formation in the urinary bladder and

Table 3. Mean scores of histological parameters around enjection materials in urinary bladder and subcutaneous tissue sections

Infiltration		Urinary Bladder				Subcutaneous Tissue			
		Neutrophils	Eosinophil	Mast cells	İnfiltration	Neutrophils	Eosinophil	Mast cells	
2nd month	DxHA-DX (n=2/5)	0.5 (0-1)	0	0.5 (0-1)	0.5 (0-1)	1.6 (1-3)	0	0.2 (1)	1.2 (1-2)*
	DxHA-DF (n=3/5)	1.3 (1-4)	0	1 (0-2)	1 (0-2)	3 (3)	0	0.6 (0-1)	1.4 (1-2)*
	PPC (n=3/3)	3.3 (3-4)	0.33 (0-1)	0	0.33 (0-1)	3 (1-4)	0	0	0*
6th month	DxHA-DX (n=3/4)	2 (1-4)	0	0	0.33 (0-1)	1 (0-3)*	0	0	1.75 (1-2)*
	DxHA-DF (n=5/4)	1.6 (1-2)	0.2 (0-1)	0.6 (0-1)	1 (0-3)	1 (0-3)*	0	0	1 (1)*
	PPC (n=5/4)	2 (1-4)	0	1 (0-2)	0.6 (0-1)	3.5 (3-4)*	0	0	0*

n=Number of biomaterial found rats at urinary bladder/subcutaneus tissue groups, Kruskall-Wallis test *: p<0.05 and Conover's two-sample squared ranks test to find out the subgroup leading to the difference

subcutaneous tissue sections was similar in all groups (Table 2). Therefore, we can state that the quality and persistence of capsule seems unrelated to degradability of the materials and the tissue properties (Figure 3). Ormaechea et al. (10) reported fibrous capsule thickness reaching 70 µm around non-degraded PPC without significant inflammatory or pathologic infiltration 1 year after injection in dog ureters. Researchers attributed the low long-term recurrence rate after VUR treatment with PPC to non-biodegradable nature of the material in their clinical study (11). However, we think that such a conclusion can only be possible with prospective randomized trials on many control groups in which other (both biodegradable and non-biodegradable) biomaterials are also used, and clinical success rates or histological features are compared in longer time intervals. Unfortunately, in this study we do not have long-term (1 year or longer) data. Contrary to the findings of Ormaechea et al. (10), we saw prominent inflammation around PPC in 6th month sections (Table 3).

Although some giant cells could be seen inside the materials, we did not see any granuloma formation both inside and outside all material injections except one rat's bladder in the DxHA-Dx group. As Stenberg et al. (12) mention in their study, giant cells are expected within dextranomer injection

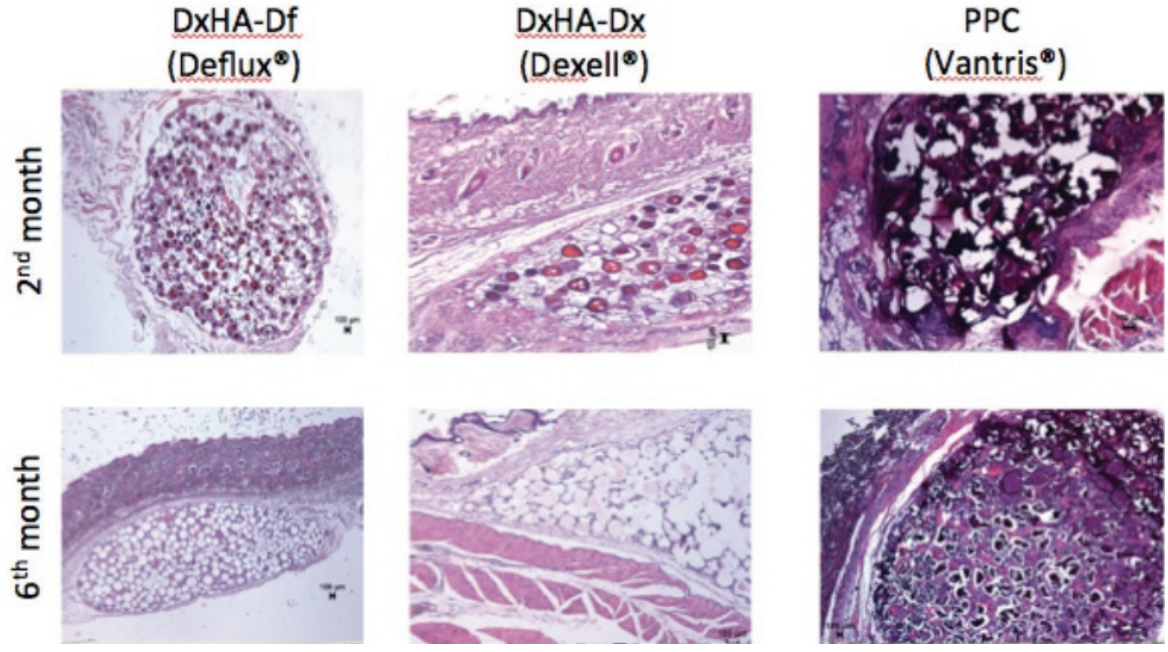

Figure 2. Amount of degradation in subcutaneous tissue of different materials at 2nd and 6th months. For DxHA materials degradation starts early and nearly completes in 6th month. But most of the injection material stays in PPC at 6th month. (Hematoxylin & Eosin, x25 magnification at light microscope, scale at the bottom: 100µm)

PPC: Polyacrilate Polialcohol Copolymer-Vantris, DxHA: Dextranomer Hyaluronic acid

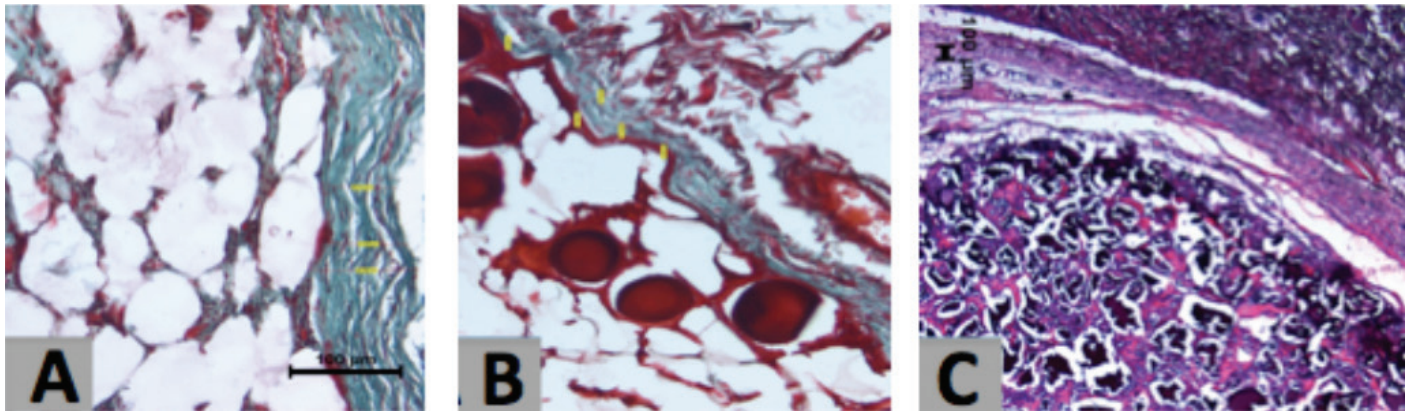

Figure 3. Capsule formations. (6th month, subcutanous tissue). All three materials have statistically equal amount of capsule formation. A. DxHA-Dx (Masson's trichrome x200), B. DxHA-Df (Masson's trichrome x200), C. PPC (Hematoxylene-Eosin x25)

PPC: Polyacrilate Polialcohol Copolymer-Vantris, DxHA-Df: Dextranomer Hyaluronic acid- Deflux®, DxHA-Dx: Dextranomer Hyaluronic acid- Deal®

area with collagen fibers as a result of the natural remodeling process. Giant cell reaction in the injection site is replaced by fibrosis and connective tissue formation during degradation progress. Mononuclear cell migration, mostly lymphocytes, was infiltrated full microspheres in early sections. As degradation proceeded, this infiltration was replaced by fibroblasts to start collagen formation and form a honeycomb appearance of empty microspheres. Previously, Broderick et al. (7) attributed failure of endoscopic VUR treatment in a 6-year-old child to phagocytosis of the injected material by giant cells shown in histological sections of distal ureters 5 months after the operation. Also, Alkan et al. (13) reported granuloma formation in 43.3% of the animals. However, we found a granuloma formation in only one histological section, which was obtained from the urinary bladder of one animal from the DxHA-Dx group. Therefore, we think that this pathological aggravation of the giant cell reaction is not a common feature and probably depends on host-specific factors rather than material properties.

Mast cell scores were higher for DxHA groups significantly for both 2nd and 6th months in subcutaneous tissue specimens (Table 3). As is known, tryptase secretion of these mast cells promotes the conversion of fibroblasts to myofibroblasts, which synthesis matrix elements of new connective tissue (14). It was just a slight difference in terms of cell number, which is not pathologic in a normal tissue reaction. Also, eosinophilic infiltration is nearly absent in specimens obtained from all groups in all periods. So, both findings suggest that mast cells are elements of a normal inflammatory process rather than an immunologic/allergic reaction, and biomaterials are similar in terms of allergic/immunogenic potential.

Kajbafzadeh et al. (15) compared the short- and long-term (1st and 6th months) local tissue reactions against PPC and DxHA-Df in bladders of eight rabbits. Inflammation markers (leucocyte common antibody and CD68) were significantly higher in the PPC group, both for short- and long-term specimens. While mild fibrosis of the DxHA-Df group in the short term subsided to non-noticeable levels in the long-term; severe fibrosis of the PPC group in the 1st month only decreased to a moderate level in 6th month. Our results overlap with this recent study. Also, we establish that a significantly persistent chronic inflammatory reaction continues around PPC material. This finding may indicate out continuous foreign body reaction and inflammation around non-biodegradable material, which may increase periureteral fibrosis causing an ureteral obstruction.

As we reviewed the literature, common conclusion of authors is to have a long term follow up endoscopically treated reflux patients, to detect reflux failure and upper urinary tract obstructions, for all kinds of injection materials. Data about the patients who needed urinary diversions (JJ stents/percutaneous nephrostomies) and open surgical repairs have been reported in many endoscopic treatment series (16-19). Although it is not objective to compare the role of the injection material in obstruction with these published papers, it can be realized that PPC has a higher potential risk of obstruction with less amount of material (20). These histological responses we detected might be a part of the puzzle for the explanation of the relatively higher postoperative obstruction (1.2-6.6%) reported in the PPC series (14,21,22). After our rat study, we believe that the sustaining inflammation around the PPC injection site can be a possible cause of obstructions. For an objective conclusion, we need long-term clinical results of case series, and meta-analysis to compare the results/complications of different materials.

Study Limitations

The small size of animals' urinary bladders led to difficulties in obtaining a standard injection volume and exact determination of material volumes. That's why we also injected all materials into the subcutaneous tissue of the napes of animals, to reach the nearly same injection volume for an objective outcome. Flattering the overlying bladder epithelium at the injection site is annotated as the maintenance of the mass effect.

Like other animal studies, this study also is far from making certain conclusions about the long-term results as maintaining bulking effect, the inflammation state, malignancy/immunologic complications. Long-term results of clinical case series, and meta-analysis comparing the results/complications of different materials can help us have more objective conclusions.

Conclusion

All used biomaterials in this study formed adequate capsule formation and maintained mass effect throughout the study period without toxic, immunologic, or neoplastic reactions. DxHA was seen to be degraded almost completely, whereas PPC was degraded only minimally at the end of the study. However, this finding cannot guarantee long-term effectiveness of PPC and randomized controlled studies conducted in longer periods on larger samples are needed. Long lasting and prominent inflammation around PPC may result in periureteral fibrosis and lack of pliability resulting in ureteral obstructions. Histological evaluations of the lower ends of ureters in cases that undergo ureteroneocystostomy after failed endoscopic treatments provide invaluable data.

Ethics

Ethics Committee Approval: The Institutional Care and Use Committee approved (Hacettepe University Animal Experimentations Local Ethics Board 2010/25-3) the study design, and researchers were accredited by Guidelines of Responsible Use and Human care.

Informed Consent: Not necessary.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.C.B., F.T.A., D.Z., S.M., Concept: A.C.B., F.T.A., D.Z., S.T., Design: A.C.B., F.T.A., D.Z., S.M., S.T., Data Collection or Processing: A.C.B., D.Z., S.M., Analysis or Interpretation: A.C.B., F.T.A., D.Z., Literature Search: A.C.B., F.T.A., D.Z., Writing: A.C.B., F.T.A., D.Z.

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ORIGINAL RESEARCH
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ICSI Cycles Using Motile Sperm from Fresh Ejaculate in Cryptozoospermic Patients and the Extremely Severe Oligospermia Patients Yield Similar Reproductive Outcome

Mustafa Albayrak[1], Mehmet Ali Akman[2]

[1]Florence Nightingale Hospital, Clinic of Obstetrics and Gynaecology and In Vitro Fertilization, İstanbul, Turkiye
[2]Private Office Practice, Specialist in Obstetrics and Gynecology, İstanbul, Turkiye

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

Literature is insufficient about the clinical and laboratory in vitro fertilization (IVF) outcome with intracytoplasmic sperm injection (ICSI) for men with crptozoospermia compared to men with extremely severe oligospermia (sperm count <1 mil/mL). Reproductive IVF-ICSI outcomes for men with crptozoospermia are comparable to those with extremely severe oligospermia provided that motile sperm are used in men with cryptozoospermia.

Abstract

Objective: In this retrospective study, we analyzed the in vitro fertilization (IVF) clinical and laboratory outcome of cryptozoospermia cases compared to the extremely severe oligospermia cases in a single IVF center.

Materials and Methods: All the IVF laboratory and clinical outcomes of cryptozoospermia and extremely severe oligospermia cases were analyzed and compared between January 2014 and December 2019 in Istanbul Florence Nightingale IVF Center. The same reproductive group treated all couples. Virtual azoospermia or cryptozoospermia were diagnosed once the mature sperm cells could be recognized after centrifugation (group 1). Patients without motile sperm were excluded. Extremely severe oligospermia was defined as a sperm count was less than <1 mil/mL (group 2). The study consisted of 33 virtual azoospermic patients with 40 cycles, whereas there were 40 severely oligospermic patients with 45 cycles. All patients underwent the intracytoplasmic sperm injection (ICSI) procedure and all the embryos were let to grow until the blastocyst stage on day 5. Groups were compared for clinical and laboratory reproductive outcome.

Results: Both the median maternal and paternal ages were similar. All outcomes including fertilization rates, blastulation rates, clinical pregnancy and delivery rates were comparable. The miscarriage rates did not also show any statistical difference.

Conclusion: Reproductive outcomes in cryptozoospermic IVF patients are comparable to those of extremely severe oligospermic patients provided that the ICSI is performed using motile spermatozoa. Our results favor using sperm from fresh ejaculate rather than surgical sperm retrieval when motile sperm is available in cryptozoospermic IVF patients.

Keywords: Cryptozoospermia, male infertility, oligospermia, IVF

Introduction

With recent technological advances in reproductive medicine, the success rates are steadily increasing in in vitro fertilization (IVF) practice. Despite these developments, there are still some controversial issues that have yet to be clarified. One of them is how to approach the cryptozoospermia patients.

According to World Health Organization (WHO) "cryptozoospermia" or "virtual azoospermia" refers to the situation when spermatozoa cannot be observed in a fresh sample, instead it could be found after an extended centrifugation followed by meticulous microscopic search (1). Since the number is so few, it is extremely difficult to find, and

Correspondence: Mustafa Albayrak MD, Florence Nightingale Hospital, Clinic of Obstetrics and Gynaecology and In Vitro Fertilization, İstanbul, Turkiye
Phone: +90 532 687 10 51 **E-mail:** mustafaalbayrak@icloud.com **ORCID-ID:** orcid.org/0000-0003-2941-7574
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in most laboratories, it is very easy to miss as well. That is why all the patients diagnosed to have azoospermia should be referred to a tertiary andrology center where a detailed semen analysis should be performed and used if any spermatozoa are recovered. This is extremely important to avoid unnecessary surgical interventions for the male partner, such as testicular sperm extraction (TESE) and to save the patients from unnecessary surgical expenses.

These oligospermia are usually classified into 3 classes; mild (10-15 mil/mL), moderate (5-10 mil/mL) and severe (<5 mil/mL) (2). Additionally, here in this study we referred to the oligospermia patients having less than <1 mil/mL on semen analysis as extremely severe oligospermia.

The aim of this retrospective study was to compare the outcome of the intracytoplasmic sperm injection (ICSI) cycles using motile spermatozoa recovered from fresh ejaculate of the cryptozoospermia patients to that of ICSI cycles with extremely severe oligospermia cases in the same IVF program.

Materials and Methods

In this retrospective study, we analyzed all the infertile couples with male factor IVF cycles managed at the Istanbul Florence Nightingale Hospital IVF Unit (including the andrology work-up) between January 2014 and December 2019. Couples were managed and ovum pickups were performed by a single IVF clinician (M.A.A.) and all andrology work-up was accomplished by the same andrology technician. Ethics approval was obtained from Demiroglu Bilim University Ethics Committee (ethics approval no: 2021-12-02).

According to the semen analysis on the day of oocyte pick up, we grouped the cycles into two: in the group 1 we included the cryptozoospermia cases, whereas in group 2 there were cycles in which sperm analysis showed less than 1 million/mL sperm (extremely severe oligospermia group). We excluded the cycles in which no motile sperm was detected and the ones where the ICSI was performed through the frozen sperm. None of the patients with the presence of motile spermatozoa on the day of oocyte pick up underwent surgery for sperm recovery. All sperm analyzes were performed at least twice.

Additionally, to decrease the possibility of female factor as the confounding factor as much as possible, the cycles where maternal age was more than 40 years and less than 5 mature oocytes (MII oocytes) aspirated were excluded from the study in which fertilization failure may have resulted from the female factor.

Briefly stimulation was done as follows: In all controlled ovarian hyperstimulation cycles the patients were stimulated with the use of the same gonadotropin, namely u-hMG (Merional® IBSA, Switzerland). The initial dose was 75-225 units daily s.c. which was adjusted based on the response to previous cycles and/or body mass index. When the leading follicle reached 14 mm in diameter one ampoule of GnRH antagonist Cetrorelix 0.25 mg daily s.c. (Cetrotide®, Merck, Germany) was added daily until the day of trigger. Once the follicles reached 18-20 mm in diameter, r-hcg 250 mcg sc (group 1) (Ovitrelle®, Merc Serono, Italy) was administered. Thirty-five hours later, oocytes were retrieved under general anesthesia. ICSI was used for all cycles and all the embryos were let to grow until the blastocyst stage on day 5. On the day of oocyte pick up, semen analysis was performed according to the WHO criteria (1).

Cryptozoospermia was only diagnosed when the mature sperm cells were reported after centrifugation at 1800 x g for at least five minutes in an azoospermic man at semen analysis.

The embryo transfer (ET) was performed by the same clinician with a full bladder under transabdominal guidance. Twelve days post ET, all the patients gave blood pregnancy test and test-positive ones were called for transvaginal ultrasonography 15 days later. We defined clinical pregnancy once we saw the gestational sac with fetal cardiac activity inside.

Power analysis was performed based on the study of Ben-Ami et al. (3). They found 15% (8/68) pregnancy rate for ejaculated sperm per cycle compared with 42% (17/48) in couples who underwent surgical sperm retrieval. Considering into account these results, with a power of 80% and alpha value 0.05 and beta value 0.2, the sample size calculated is 84 cycles (42+42) (https://clincalc.com/stats/samplesize.aspx).

Statistical Analysis

For data analysis, the Statistical Package for the Social Sciences (SPSS), version 21.0 (SPSS Inc., Chicago, IL) statistical computing software was used. Variables were given as medians (interquartil range). The quantitative data of the groups were compared with Mann-Whitney U test. Categorical data and relationships between the groups were analyzed using the chi-squared test. $P<0.05$ was considered statistically significant.

Results

In the group 1, there were 33 patients with 40 cycles and in group 2, there were 40 patients with 45 cycles (Table 1). Group 1 and group 2 did not differ in the mean age, the amount of hMG consumed, endometrial thickness on the day of hCG trigger, total and mature oocytes retrieved, fertilization rates and the number of embryos transferred. Additionally, the obstetric outcomes regarding clinical pregnancy, miscarriage and delivery rates did not reach statistically significant differences among the groups (Table 1).

Table 1. Patient and cycle characteristics with pregnancy outcome			
Variable	**Group 1 (Cryptozoo spermia) (n=40 cycles)**	**Group 2 (<1 mil/mL) (n=45 cycles)**	
Maternal age (year)*	31.50	28	NS
Range	(21-39)	(21-39)	
Consumed hMG medication (units)ǂ	2697.50±865.78	2419.44±773.77	NS
The end. thickness on hCG dayǂ	9.85±1.24	9.74±1.30	NS
Total oocytes retrieved*	9	12	NS
Range	(5-23)	(5-27)	
Number of M2 oocytes retrieved*	7	9	NS
Range	(5-17)	(5-20)	
Fertilization rate (%)*	80	80	NS
Range	(40-100)	(33.33-100)	
Number of transferred embryos*	2	2	NS
Clinical pregnancy rate (%)	67.50	64.44	
Miscarriage rate (%)	7.50	13.33	NS
Delivery rate (%)	60	51.11	NS
*values are in median, ǂ: values are in mean ± standard deviation			

Discussion

In this study, we found that the primary reproductive outcomes, including clinical pregnancy, miscarriage and delivery rates, were similar among the groups. Additionally, secondary outcomes, including the number of gonadotropins consumed, endometrial thickness on the day of hCG trigger, total and mature oocytes retrieved, fertilization rates and the number of embryos transferred did not differ between groups.

The cryptozoospermia is really a big challenge in IVF practice. If the ejaculate does not contain a suitable sperm sample due to inadequate motility or abnormal morphology, etc. the clinical decision is straightforward to proceed with performing surgical operation to recover the sperm. However, the ideal approach to cryptozoospermia in the presence of motile spermatozoa following centrifugation is still not clear. Some advocate the direct use of motile spermatozoon for ICSI from fresh ejaculate and others favor surgery to recover sperm (4-8). Hauser et al. (4) found that fresh TESE should be considered a treatment of choice in cryptozoospermia cycles showing superior fertility potential compared to use of motile sperm recovered after centrifugation. In another study, Miller et al. (5) compared the micro-TESE surgery with fresh ejaculate and found that they gave similar pregnancy rates. But the miscarriage rates were higher in the ejaculate group and they suggest doing fresh TESE in cryptozoospermic IVF patients. However, in our study, although the pregnancy and delivery rates were higher and miscarriage rate was lower in the group 1 compared to group 2, this difference did not reach statistical significance.

Even, several published meta-analyses showed some contradictory results. In their meta-analysis, Abhyankar et al. (6) concluded that the existing literature does not support a recommendation for men with cryptospermia to use TESE in preference over ejaculated sperm. Contrary to this, in another meta-analysis Ku et al. (7) found that the take home baby rates are higher in the TESE group and concluded that TESE has more advantages for ICSI patients with cryptozoospermia, especially in younger couples. Similarly, in another meta-analysis Kang et al. (8) found that TESE yields better embryo quality, higher pregnancy and implantation rates and recommend that TESE should be the treatment of choice in cryptozoospermic IVF patients.

In our current practice, we do not proceed to surgery if fresh ejaculate yields motile spermatozoa in the cryptozoospermic IVF patients. We think the presence of motile spermatozoa on the day of oocyte pick up is the most essential factor in proceeding with surgery or not. It is a very critical decision to perform surgery in these patients with very limited numbers of spermatozoa. It is well known that spermatogenesis is a focal and periodic process. This means one can miss the sperm producing region during surgery and deceptively present the case as complete azoospermia. Additionally, one can find the focus and may harm that solely sperm producing region and unfortunately, if the IVF treatment fails, these patients may never father a child. Therefore, considering these potential disadvantages of surgery and the absence of solid-state evidence of superiority, we think balance tips toward non-surgical approach. Therefore, considering our results, since performing ICSI with motile

spermatozoa derived from fresh ejaculates in cryptozoospermia cases yields comparable results to those cases with extremely severely low sperm counts (<1 mil/mL), we can comment that the use of motile spermatozoa derived from fresh ejaculates is at least as good as (maybe even better) surgical sperm recovery in cryptozoospermia cases and should be the method of choice.

Study Limitations

To note, this study was limited by its retrospective nature. However, we do not think that this limitation decreases its scientific quality to much extent because our criteria in defining the groups were strict such as the female age (<40) and at least more than 5 oocytes were picked up at OPU procedure. The single and same clinical and laboratory technician may also be considered among the study strengths.

Conclusion

In conclusion, we found that the outcome of using spermatozoa derived from fresh ejaculate in cryptozoospermic IVF patients is comparable to that of extremely severe oligospermic patients provided that the ICSI is performed using motile spermatozoa. Thus, we think that the preferred approach should be to use motile spermatozoa obtained from fresh ejaculate for ICSI and avoid surgical operation in crptozoospermia.

Ethics

Ethics Committee Approval: Ethics approval was obtained from Demiroglu Bilim University Ethics Committee (ethics approval no: 2021-12-02).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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ORIGINAL RESEARCH
Urooncology

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Do Hipnotic Anesthetic Agents Used in Patients Undergoing Radical Prostatectomy Have An Effect on the Neutrophil/Lymphocyte Ratio? Retrospective Study

Meryem Onay[1], Dilek Çetinkaya[1], Adem Özer[1], Ata Özen[2], Cavit Can[2], Birgül Yelken[1]

[1]*Eskişehir Osmangazi University Faculty of Medicine, Department of Anesthesiology and Reanimation, Eskişehir, Turkiye*
[2]*Eskişehir Osmangazi University Faculty of Medicine, Department of Urology, Eskişehir, Turkiye*

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

Anesthetic agents and applications affect tumor pathophysiology and immunosuppression in the postoperative period. It was observed that anesthetic agents used in patients with cancers such as prostate cancer where there is increased inflammatory response in the early postoperative period. The probability of complications was higher in patients who received propofol with high preoperative neutrophil/lymphocyte ratio (NLR). In prostate cancer, preoperative high NLR (>1.7) may have a predictive value for bleeding, blood transfusion, and postoperative respiratory distress.

Abstract

Objective: Anesthetic agents and applications affect tumor pathophysiology and immunosuppression in the postoperative period. We evaluated the changes made by hypnotic anesthetic agents used during anesthesia on neutrophil/lymphocyte ratio (NLR) in patients undergoing radical prostate surgery and its relationship with short-term morbidity.

Materials and Methods: Age of patients who had radical prostatectomy, physical classification of the American Society of Anesthesiology, perioperative blood transfusion, drugs used during general anesthesia (intravenous, opioid, volatile anesthetic), duration of anesthesia, analgesics used in postoperative pain was examined. Preoperative, postoperative day-0 and day-2 NLR results were recorded.

Results: The data of 159 patients who underwent radical prostatectomy were assessed. The patients were divided into 2 groups; Group pentotal-sevoflurane/desflurane (PSD) (n=101) and Group propofol-sevoflurane/desflurane (PrSD) (n=58). There was no difference in terms of preoperative and postoperative 2 day NLR value, but the highest NLR values in the postoperative day 0 was found to be in Group PrSD. Postoperative complications were higher in Group PSD. However, preoperative NLR values of these complications were higher in Group PrSD. Erythrocyte (red blood cell) replacement patients were divided into 2 groups; between 0 and 2 units (n=147) and more than >2 units (n=12), their preoperative NLR ratios were 2.54 (0.7-16.3) and 3.3 (1.8-8.8) respectively. The cut value of NLR for bleeding was set at 1.77.

Conclusion: Increased NLR result is associated with immunosuppression and tumorigenesis, and is an easy and inexpensive technique. In prostate cancer, preoperative high NLR (>1.7) may have a predictive value for bleeding, blood transfusion, and postoperative respiratory distress.

Keywords: Radical prostatectomy, neutrophil/lymphocyte ratio, anesthetic agents

Introduction

Prostate cancer is the most commonly diagnosed malignant tumor in men across the world, but it is the second most common cause of cancer-related mortality and radical prostatectomy is the first choice in the treatment of localized prostate cancer (1). However, prostate cancer is a type of cancer with a frequency of relapses and metastases. The reasons for this include excessively aggressive behavior of the tumor, as well as perioperative factors that cause cancer cell dissemination due to tissue manipulation during surgery and immunosuppression (2). These perioperative factors include blood transfusion, postoperative pain, severe

Correspondence: Meryem Onay MD, Eskişehir Osmangazi University Faculty of Medicine, Department of Anesthesiology and Reanimation, Eskişehir, Turkiye
Phone: +90 222 239 29 79 **E-mail:** dr.meryemonay@hotmail.com **ORCID-ID:** orcid.org/0000-0002-5028-9135
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hypothermia, psychological stress, type of surgery, type of anesthesia (general, regional or combined), and cell-mediated immunity depression during surgery (2,3).

It is known that the anesthetic agent and method affect the pathophysiology of the tumor in the postoperative period. In particular, intravenous anesthetics (except propofol), opioids and volatile anesthetics have been reported to be involved in immunosuppression and angiogenesis (4). In addition, regional anesthesia is superior to general anesthesia in preventing cancer recurrence (5).

Inflammation is blamed for potentially causing prostate carcinogenesis and progression and the importance of the strategies aimed at the inflammatory process to prevent prostate cancer is emphasized (6). Recommended as an indicator of the inflammatory state of the host and the general immune response to various stress stimuli, neutrophil/lymphocyte ratio (NLR) is the ratio of the neutrophil count to the lymphocyte count in a peripheral blood sample (1,7). In addition, it has been specified that high NLR ratios before treatment are associated with poor prognosis in various types of cancer and high NLR (>2) ratios can be independent positive predictors of biochemical recurrence (7).

Based on the information that NLR is a marker of postoperative poor prognosis in patients undergoing radical prostate surgery, and that anesthesia practices worsen the prognosis in these patients due to immunosuppression, this study is intended to compare the changes caused by the hypnotic anesthetic agents used during anesthesia on NLR ratios and their relation with short-term morbidity.

Materials and Methods

Upon the approval no: 2020-29 from the hospital ethical committee, this study was conducted studied the retrospective records of the data pertaining to patients who performed radical prostatectomy with general anesthesia between January 2015 and January 2020. The blood transfusion in the past 12 weeks, those with antibiotic use due to acute infection or with steroid use due to an inflammatory disease, those administered neoadjuvant therapy for prostate cancer (hormone or radiotherapy) areas, those performed simultaneous biopsy or surgery on other organs were excluded from the study. Because NLR analysis in prostate cancer, transrectal prostate biopsy used during diagnosis may be sensitive to subclinical prostate inflammation and even systemic infection. Results may be affected by subclinical inflammations if adequate time has not elapsed between blood measurements and biopsy.

Age, body mass index, American Society of Anesthesiologists (ASA) physical status classification, perioperative blood transfusion, drugs used during general anesthesia (intravenous, opioid, and volatile anesthetic), duration of anesthesia, analgesics used for postoperative pain were also obtained from the patient records. The preoperative, postoperative day-0 and day-2 NLR ratios were calculated as the ratio of the number of neutrophils to the number of lymphocytes collected in a peripheral blood test. According to the NLR cut-off value, the presentcohort was divided into two groups: a high-NLR and a low-NLR group.

The patients underwent a routine general anesthesia protocol after routine non-invasive monitorization (electrocardiogram, non-invasive blood pressure, peripheral oxygen saturation, and esophageal temperature probe). In the induction of anesthesia, intravenous anesthetics (thiopental or propofol), muscle relaxants (rocuronium), and opioid (remifentanyl or fentanyl) were administered and then maintained using a volatile anesthetic (sevoflurane, desflurane). All patients underwent radical prostatectomy with laparotomy technique accompanied by retropubic incision in the supine position. At the end of the operation, the patients were administered paracetamol-tramadol for analgesic purposes.

Postoperative hospital stays in the intensive care unit and in hospital, as well as postoperative complications/problems were included in the records.

Statistical Analysis

Continuous data are given as mean ± standard deviation. Categorical data are given in percentages (%). Shapiro Wilk's test was used to investigate whether the data are normally distributed. Two way repeated measures ANOVA (one factor repetition) test was used for repeated measurements. The Pearson Exact chi-square was used to analysis for the categorical data. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY:IBM Corp.) was used to perform the analyses. $P<0.05$ was considered the criterion for statistical significance. To determine the optimal cut value for NLR, the receiver operating characteristic of NLR for bleeding was analyzed.

Results

The data of 159 of 172 patients who underwent radical prostatectomy were assessed. Thirteen patients with missing data could not be included in the study. The mean age of the patients was 62.4±5.84 and according to the ASA 28% (n=46) of the patients were ASA I, 58% (n=93) ASA II, 12% (n=20) ASA III. The duration of anesthesia was 245±46.8/min and the discharge time was 9.84±6.15/day. 28% (n=45) of the patients needed intensive care in the postoperative period (Table 1). There was no statistically significant relation between NLR and

anesthesia duration (p=0.07), need for intensive care (p=0.414), and discharge time (p=0.922). 33.3% of the patients were at pT3a pathological stage and 30.2% of them were at the pT2 pathological stage.

The patients were divided into 2 groups according to the anesthetic agent administered during general anesthesia: thiopental-sevoflurane, thiopental-desflurane peritoneal-sevoflurane/desflurane (PSD) (n=101), pentotal-sevoflurane/desflurane (PrSD) (n=58). In the intergroup comparison, there was no difference in terms of preoperative NLR value [group PSD: 2.24 minimum-maximum (min-max): 0.44-16.3], group PrSD: 2.25 (min-max: 0.48-8.8), while the highest NLR values in the postoperative day 0 was found to be group PrSD (p<0.05) (Figure 1). NLR values on the 2nd postoperative day were similar in both groups [group PSD: 6.77 (min-max: 0.8-20), group PrSD:6.61 (min-max: 2.14-13.3)].

In the postoperative period, 69% of patients had no complications. Postoperative complications included fever (0.6%), arrhythmia (1.9%), electrolyte disorder (0.6%), hypertension (2.5%), bleeding (10.7%), coronary vasospasm (2.5%), respiratory distress (8,1%), perforation of the rectum (1.9%), wound site opening (0.6%) and edema of the legs (0.6%). In Table 2, the distribution of complications by anesthetic agents and preoperative NLR values are presented. The most common complication was bleeding, although it was seen more in group PSD, preoperative NLR value in the group was statistically significantly higher (2.55 versus 4.06). Other complications were higher in the group. However, preoperative NLR values of these complications were higher in group PrSD (Table 2). In addition, these complications postoperative day 0 NLR values were higher in group PrSD.

The cut value of NLR for bleeding was set at 1.77. The preoperative value was >1.77 in 61% of the patients with bleeding in the PSD group and 80% in the PrSD group (Figure 2).

During the perioperative period, patients were evaluated in two groups for red blood cell transfusion. These patients were evaluated as those with red blood cell transfusion between 0 and 2 units (n=147) and others with red blood cell transfusion of more than >2 units (n=12), and their preoperative NLR ratios were 2.54 (0.7-16.3) and 3.3 (1.8-8.8), respectively. This difference was statistically significant (p<0.05). Red blood cell transfusion was performed in 47 patients during the perioperative period. While 33 (70.3%) of these patients were in group PSD, 14 (29.7%) were in group PrSD. 35 of the patients in need of intensive care were in group PSD, while 11 patients were in group PrSD.

Table 1. Demographic data

	Mean	Standard deviation
Age	62.4	±5.84
BMI (kg/m²)	22.53	±6.21
Gleason score	6.89	±1.02
Duration of anesthesia (minutes)	245	±46.8
Time of discharge (days)	9.84	±6.15

BMI: Body mass index

Discussion

In this study, we evaluated not only the long-term outcomes of preoperative, postoperative day-0 and day-2 NLR but also the association of prostate cancer patients with perioperative NLR and outcomes of hypnotic anesthetic agents in an analysis of 159 patients who underwent radical prostatectomy under general anesthesia. NLR values were higher on days 0 with PrSD administration. The most common complications in the postoperative period were bleeding and respiratory distress. The preoperative NLR values of these patients were found to be >1.77.

It has been found that a high NLR rate is correlated with poor prognosis in various organ cancers such as lung, stomach, colon and pancreas in many studies (8). The decreased lymphocyte ratio is associated with an immunosuppressive state, resulting in reduced efficacy in malignant tumor formation, progression and elimination. In prostate cancer NLR rate has been associated with early biochemical recurrence, clinicopathological features [pathological stage, Gleason score, preoperative prostate specific antigen (ng/mL), pathological lymph node, prostate capsule invasion, seminal vesicle invasion, surgical margin, nerve invasion] and poor prognosis in some studies (1,8).

Although many studies have been conducted to assess anesthesia techniques and oncological outcomes, the relationship between the surgery- or anesthesia-induced immunosuppression and the cancer recurrence has yet to be clarified (9). Wuethrich et al. (2)

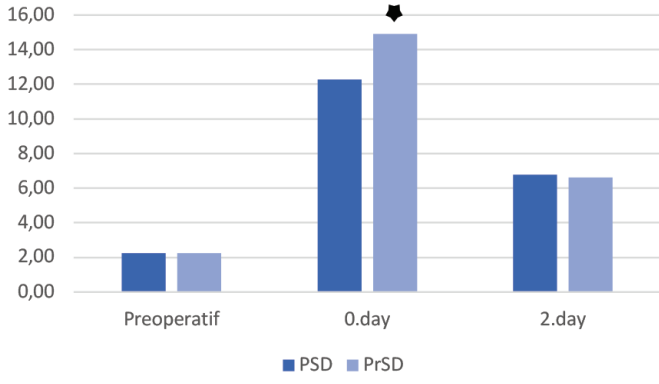

Figure 1. Perioperative NLR (median) values between groups

NLR: Neutrophil/lymphocyte ratio, PSD: Pentotal-sevoflurane/desflurane, PrSD: Propofol-sevoflurane/desflurane, *p<0.05

studied patients with advanced prostate cancer (stage pT3/4) who underwent retropubic radical prostatectomy surgery under perioperative epidural+general anesthesia or general anesthesia. The study reported no reduction in cancer progression or improvement in survival after radical prostatectomy in the epidural+general anesthesia group compared with the other general anesthesia group (postoperative opioid) in terms of recurrence during 14 years of observation. However, the study by Biki et al. (10) reported significantly less biochemical recurrence in the epidural+general anesthesia group compared to the general anesthesia group that was administered postoperative opioid. In their study, Lusty et al. (4) emphasized the role of regional anesthesia in reducing mortality in prostate cancer surgery, as the reason for this decrease in the use of opioid and volatile anesthetics in regional anesthesia applications, the reduction of surgical stress response and improvement of oncoimmunological responses directly through the anti-inflammatory effect of local anesthetics.

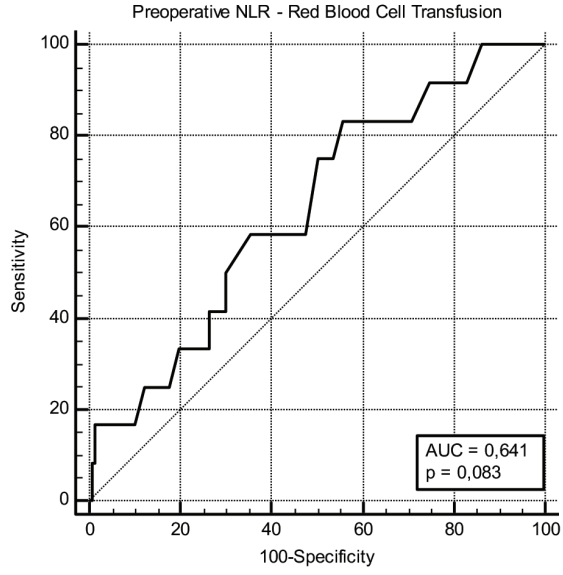

Figure 2. Preoperative NLR for the postoperative bleeding

NLR: Neutrophil/lymphocyte ratio, AUC: Area under the curve

The intravenous anesthetics of thiopental and ketamine suppress natural killer cell activity (9). Thiopental inhibits neutrophils function and suppresses activation of T-lymphocyte activation, as well as nuclear factor kappa B (NF-κB). Propofol increases the cytotoxic T lymphocyte activity, reduces pro-inflammatory cytokines and inhibits COX-2 and Prostaglandin E2 functions. In this case, reducing neuroendocrine responses due to surgery through hypothalamic-pituitary-adrenal axis and sympathetic nervous system suppression, propofol and regional anesthesia might cause less immunosuppression and relapse of certain types of cancer compared to volatile anesthetics and opioids (9). Opioids (especially morphine) reduce natural killer cell activity against cancer cells and increase tumor growth and angiogenesis upon activation of vascular endothelial growth factor (VEGF) (4). Inhalation agents suppress cell-mediated immunity, stimulate T-lymphocyte apoptosis and can contribute to tumor relapse by increasing angiogenesis with hypoxia-induced factor-1a activity (11). Looney et al. (12) observed that the group receiving sevoflurane-opioid anesthesia for breast cancer had an increased level of VEGF associated with angiogenesis compared with the group administered propofol-paravertebral anesthesia.

In this study, we classified the anesthetic agents administered into 2 groups. We did not add them to the assessment, as all patients received opioids and the effects of inhalation agents were similar. In all groups, the preoperative NLR value was above 2. The group with the highest postoperative NLR value was the PrSD group, which was statistically significant. Studies reported that propofol had no effect on immunosuppression, however, in our study, the values were higher in the propofol group. However, this height was only in the early postoperative period. Day 2 values were similar in both groups. This may be attributed to a single dose administration of propofol only in the induction of anesthesia. It may be more accurate to evaluate NLR values in longer-term infusion applications.

In patients with stomach cancer, short-term postoperative complications, intraoperative bleeding and blood

Table 2. Distribution of complications according to the anesthetic agents used

	PSD	PrSD	PSD Preoperative NLR (mean)	PrSD Preoperative NLR (mean)	p
Bleeding (n=18)	13	5	2.55	4.06	0.032
Respiratory distress (n=13)	9	5	2.75	2.10	0.13
Arhythmia (n=3)	2	1	2.65	4	0.028
Electrolyte disorder (n=1)	1	-	3.62	-	
Elevated blood pressure (n=4)	3	1	1.78	2.2	0.074
Swelling of the legs (n=1)	1	-	1.53	-	
Coronary spasm (n=4)	3	1	1.50	2.26	0.081

PSD: Pentotal-sevoflurane/desflurane, PrSD: Propofol-sevoflurane/desflurane

transfusion rates were reported to be higher in those with NLR >2 (13). The most common complications in this study were bleeding and respiratory distress. The complication incidence rate was higher in group PSD, but patients in group PrSD had higher preoperative NLR than those in group PSD. It was also seen that the NLR values of the patients who had blood transfusion were above 1.7, and the preoperative NLR was even higher in the patients who had more than 2 transfusions. Similarly, the number of patients staying in the intensive care unit and the number of transfused patients were higher in group PSD.

Study Limitations

The study had its limitations in itself. First, the data were collected from a single center and retrospectively, and the distribution among the groups was uneven. Although we excluded the factors that affect the NLR ratio, it is necessary to keep in mind that neutrophils and lymphocytes counts may also be affected by the agents used and their doses, as well as by comorbidity.

Conclusion

To conclude, was observed that anesthetic agents were used in patients with cancers such as prostate cancer, where there is an increased inflammatory response in the early postoperative period. Although this increase in propofol seems to be more, it would not be correct to link this increase only to propofol. In addition, the probability of complications was higher in patients who received propofol with high preoperative NLR. It seems rational to avoid the use of propofol in general anesthesia for patients with a high preoperative NLR value.

Additionally, preoperative high NLR (>1.7) may have a predictive value for bleeding, blood transfusion, and postoperative respiratory distress. However, there is a need for further prospective randomized controlled studies to clarify the effects of anesthesia on immunity, tumor recurrence, and survival.

Ethics

Ethics Committee Approval: Upon the approval no: 2020-29 from the hospital ethical committee, this the present study was conducted studied studying the retrospective records of the data pertaining to patients who performed radical prostatectomy with general anesthesia between January 2015 and January 2020 (Eskisehir Osmangazi University Ethics Committee).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.O., A.Ö., C.C., Concept: B.Y., Design: M.O., D.Ç., Data Collection or Processing: M.O., Ad.Ö., Analysis or Interpretation: M.O., D.Ç., Literature Search: M.O., Writing: M.O., D.Ç., B.Y.

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

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

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ORIGINAL RESEARCH
General Urology

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Publication Rates and Publication Times of Studies Presented at the First Four Meetings of the Society of Urological Surgery in Turkey (MSUST)

Mesut Altan[1], Alp Kısıklı[1], Kadir Emre Baltacı[1], Perviz Shahsuvarlı[1], Ali Cansu Bozacı[1,2], Hasan Serkan Doğan[1,2], Serdar Tekgül[1,2]

[1]Hacettepe University Faculty of Medicine, Department of Urology, Ankara, Turkiye
[2]Hacettepe University Faculty of Medicine, Department of Urology, Division of Pediatric Urology, Ankara, Turkiye

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

Most of urological associations published their publication rates, following their own meetings. The present study investigates the publication rate of abstracts presented at the four national meetings of the Society of Urological Surgery in Turkey. The present study aims to determine a valid time period for the announcement of publication rates following a meeting, as a means of standardization.

Abstract

Objective: This study determines the publication rates and publication times of studies presented at the first four Meetings of the Society of Urological Surgery in Turkey (MSUST).

Materials and Methods: The first four books of abstracts published by MSUST were examined, and an analysis of the abstracts of authors published between January 1, 2012 and January 1, 2021 identified from the PubMed, Web of Science, Scopus and Google Scholar databases were analyzed. The publication time refers to the interval between the date of the congress and the date on which the publication was made available on a journal website.

Results: A total of 1,436 abstracts were reviewed, and the publication rates for the first four MSUST were 50.7%, 33.4%, 28.2%, and 26.9%, respectively, with a mean publication rate of 33.4%. In an assessment of the publications made within 2 years of a meeting, the publication rates were found to be 27.6%, 25.8%, 24.2% and 26.9%, respectively. The mean publication rate within a 2-year period was determined to be 26%. The median time of publication when calculated prospectively, was 22 (-2-88), 12 (-2-60), 10 (-2-39) and 7 (-2-24) months. The ratios of articles from the first three MSUST, published within 2 years to total publication were found to be 54.3%, 77.3%, and 85.5%, prospectively.

Conclusion: The ratio of studies presented at MSUST congresses that are subsequently published is increasing, and more than half of these publications occur within the first 2 years following the congress, which can serve as an indicator of the legitimacy of a scientific meeting.

Keywords: Publication rate, urology, scientific meeting

Introduction

The publication rate is considered an important criterion of success by societies and congress organizers, and such prestigious organizations as the European Association of Urology, the American Urological Association and the British Urological Association publish publication rates following their own events (1-3). These rates, and the impact factors of the journals that feature these publications are viewed as vital indicators of reputation (4). Studies focusing on publication rates can be categorized based on their evaluation of such factors as time period or the types of presentation (oral, poster) (5).

This study investigates the publication rate of abstracts presented at the four national meetings of the Society of Urological

Correspondence: Mesut Altan MD, Hacettepe University Faculty of Medicine, Department of Urology, Ankara, Turkiye
Phone: +90 555 865 81 93 **E-mail:** altan_mesut@hotmail.com **ORCID-ID:** orcid.org/0000-0001-8884-9954
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Surgery in Turkey (MSUST), with an additional aim being to determine a valid time period for announcing the publication rates following a meeting as a means of standardization.

Materials and Methods

The abstract books of four MSUST (held in 2012, 2014, 2016, and 2018) were reviewed, and searches of the PubMed, Web of Science, Scopus and Google Scholar databases for publications of the presented abstracts were made. A total of 1,485 abstracts (oral presentations, poster presentations and posters) were reviewed from January 1, 2012 to January 1, 2021.

The search of the databases first used the name of the first author of the abstract, and if no results were found, the subsequent authors were searched. Published papers with identical abstracts in terms of hypothesis, study design and conclusion were included as a match. Abstracts published more than 3 months before the meeting were excluded from the study.

The abstracts were subdivided into subspecialties as urooncology, andrology, pediatric urology, endourology, female urology and transplantation, while abstracts related to more than one subspecialty were included in both. The presentation type (oral, poster presentation and poster), study types (prospective, retrospective, laboratory and case report) and origin of the study (multicenter, university, training and research hospital, public hospital and private hospital) were all found to influence the publication rate. The publications were subdivided into three groups, as indexed (SCI, SCI-expanded), international (PubMed indexed but SCI, SCI- expanded) and national journals.

Results

Of the 1,485 abstracts, 49 were excluded as they were published more than three months before the congress, and as a consequence, 1,436 abstracts were studied. The overall publication rate of studies presented at MSUSTs and the overall publication of MSUSTs over a 2-year period were 33.4% and 26%, respectively. The overall publication rates from the first, the second, third and fourth MSUSTs were 50.7%, 33.4%, 28.2%, and 26.9%, respectively, and the publication rates in indexed journals were 32%, 19.9%, 14.1%, and 13.9%, respectively. The publication rates of studies presented at MSUSTs are presented in Table 1 and Figure 1. The publication rates within two years of the first, second, third and fourth the MSUST were 27.6, 25.8, 24.2, and 26.9 percent, respectively, as presented in Table 2 and Figure 2.

The median publication times following the first, second, third and fourth the MSUST were 22 (-2-88), 12 (-2-60), 10 (-2-39) and 7 (-2-24) months. A survival analysis of the abstracts published within 24 months of the first, second, third and fourth the MSUST were 54.3%, 77.3%, 85.5%, and 100%, respectively. The overall publication curve is presented in Figure 3. The median publication rates within two years of the first, second, third and fourth the MSUST were 11 (-2-24) months, 10 (-2-24) months, 8 (-2-24) and 7 (-2-24) months, respectively (p=0.192).

Oral presentations, laboratory studies and multicenter studies recorded the highest publication rates in their categories (37%, 67.6%, and 46.5%, respectively). Publication rates by presentation type, study type and study center are given in Table 3. More than half of the abstract topics were in the fields of urooncology and endourology. Abstracts related to andrology, pediatric urology and transplantation had a higher ratio in overall publications than in overall abstracts. The abstract and publication rates by subspecialty are presented in Table 4.

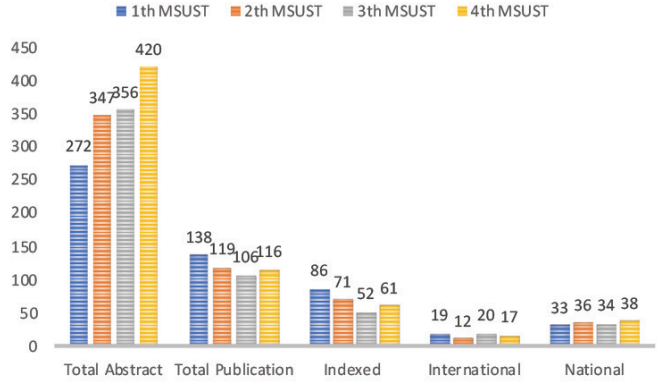

Figure 1. Total abstracts and publications

MSUST: Meetings of the Society of Urological Surgery in Turkey

Table 1. Publication rates

Parameters	1st MSUST	2nd MSUST	3rd MSUST	4th MSUST
Overall publication	138 (50.7%)	119 (33.4%)	106 (28.2%)	116 (26.9%)
Follow up, month	96	72	48	24
Indexed publication	86 (31.6%)	71 (19.9%)	52 (13.8%)	61 (14.1%)
International publication	19 (7%)	12 (3.4%)	20 (5.3%)	17 (3.9%)
Turkish publication	33 (12.1%)	36 (10.1%)	34 (9%)	38 (8.8%)

MSUST: Meetings of the Society of Urological Surgery in Turkey

Discussion

Meeting of Urological Surgery in Turkey (MSUST) is a biannual scientific meeting held with national and international participation since 2012. The congress keeps attendees up-to-date with the most recent scientific developments, and also serves as a platform for the debate of the key topics in the field. The event facilitates discussion of the received abstracts and the follow-up of new publications, serving as an environment for scientific nourishment, and researchers and other participants compile and submit their abstract papers accordingly. Over the last few years, the publication rates of abstracts sent to such meetings have gained increasing value (5), while studies in this field have sought to clarify the reasons for rejecting abstracts that fail to get published. It is generally accepted that a high publication rate of the studies presented at such congresses would be a point of significant prestige for such meetings and the organizing institutions. A number of noteworthy urological institutions, such as the European Association of Urology and the American Urology Association, like societies that focus on other specializations, share the publication rates of the studies presented at their meetings (1,2).

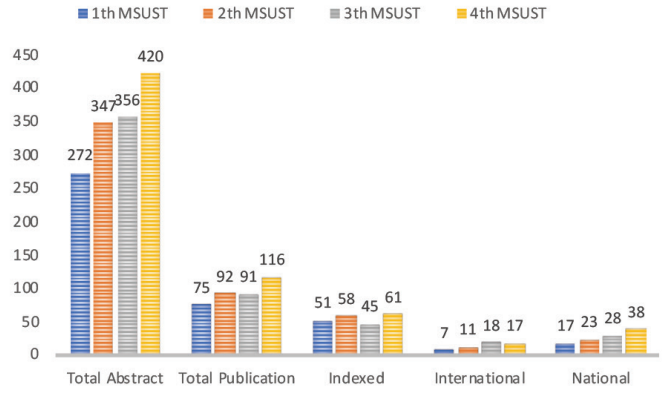

Figure 2. Total abstracts and publications within two years

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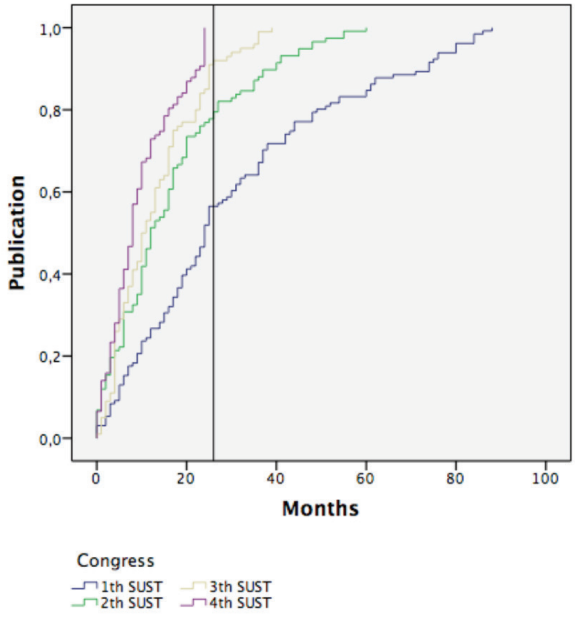

Figure 3. Publication curves for the four MSUSTs

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The publication rate from the 2000 European Association of Urology meeting was 55 percent with a mean time of 17 months (6). For the meetings of the European Society for Pediatric Urology (ESPU) (2003-2010) the publication rate was 47 percent, 65 percent within the first two years (7). Autorino et al. (8) reported a 20.5 percent publication rate for the 2001 and 2002 World Congress of Endourology (WCE), with a mean publication time of 14.6 months (maximum 48 months), although 80 percent of the publications were within 24 months. The authors' investigation of randomized controlled studies following the 2004, 2005, and 2006 WCE revealed a publication rate of 47.3 percent (45/94), with 16.4 months being the mean publication time (9). The publication rate was 22.1 percent within a mean of 13 months (1-45 months) following the annual 2002 and 2004 Societè Internationale d'Urologie meetings (10). The same ratio was 61.6 percent for podium or oral presentations with an 11-month median publication time for the 2003 International Continence Society (ICS) Meeting (11).

Publication rates were also investigated at several Turkish scientific meetings. The authors revealed a publication rate of 10.8 percent within an average of 11.77 months (1-33 months) for one a well-known Turkish urology meeting - the Turkish National Urology Congress - based on a search of the PubMed, Google Scholar and Scopus databases (12). The publication rates were 28, 21.9, and 34.5 percent for the Turkish National

Table 2. Publication rates in two years

Parameters	1st MSUST	2nd MSUST	3rd MSUST	4th MSUST
Overall publication	75 (27.6%)	92 (25.8%)	91 (24.2%)	116 (26.9%)
Indexed publication	51 (18.8%)	58 (16.3%)	45 (12%)	61 (14.1%)
International publication	7 (2.6%)	11 (3.1%)	18 (4.8%)	17 (3.9%)
Turkish publication	17 (6.2%)	23 (6.5%)	28 (7.4%)	38 (8.8%)
Median time to publication	11 (-2-24)	10 (-2-24)	8 (-2-24)	7 (-2-24)

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Rhinology Congress, the Turkish National Otorhinolaryngology and Head & Neck Surgery and the National Congress of Gynecology and Obstetrics, respectively (13-15). A search of the abstracts was made from the PubMed, Turkmedline and Ulakbim National databases, and the median times until publication were less than 24 months in all studies. The publication rate for the first MSUST congress was reported in a previous study involving a search of the PubMed and SCI-E databases to be 28.3 percent, with a mean time of 21.1 months (16), although the authors did not specify the time periods and level of compatibility between the paper and abstract. In the present study, the overall publication rate was found to be 33.4% and the same rate in two years was 26 percent. While examining the publication rates within the first two-year period, the publication rates in Turkish journals followed annual upwards trend (from 6.2% to 8.8%), some of which may be submissions of studies to Turkish journals after being rejected by indexed journals, but may also be attributed to the criteria set forth by the Turkish Council of Higher Education.

In this study, oral presentations were found to have better publication rates than poster presentations, while the most publications by study type, from high to low, were laboratory, prospective and case report studies. Multicenter studies recorded higher publication rates than the other forms, and studies linked to private hospitals had a higher rate of publication than those of university hospitals. It was interesting to note that the number of abstracts received from private hospitals was very low. As Scherer et al. (5) suggested in their systematic review, studies with positive results and larger sample sizes, those dealing with basic sciences, and oral presentations, randomized clinical trials, multicenter studies and authors from academic settings had significant effects on publication rates.

Table 3. Publication rates according to presentation type, study type and study center

Parameters		Total abstracts	Publications
Presentation type	Oral presentation	494	183 (37%)
	Poster presentation	794	276 (34.8%)
	Poster	148	20 (13.5%)
Study type	Prospective	212	101 (47.6%)
	Retrospective	912	280 (30.7%)
	Laboratory	74	50 (67.6%)
	Case report	238	48 (20.2%)
Center of study	University	765	233 (30.5%)
	Multicenter	228	106 (46.5%)
	Training and research hospital	334	116 (23.3%)
	Public hospital	69	10 (14.5%)
	Private hospital	40	14 (35%)

Table 4. Abstract and publication rates by subspecialty

Subspecialty	In abstract	In publication	Rate of publication/ abstract
Andrology	12%	16%	45.7% (85/186)
Pediatric urology	11%	12%	37.6% (62/165)
Transplantation	2%	3%	35.9% (14/39)
Continence	17%	16%	32.1% (85/265)
Urooncology	35%	32%	31.1% (171/549)
Endourology	23%	21%	31.8% (113/355)

As mentioned earlier, many institutions and congress organizers report their own publication rates, but when it comes to the comparison of such statistics, science is still taking its baby steps, and there may be many reasons for this, such as the differences in the time period, the differences in different studies, the search criteria, the databases in which the abstracts are scanned, and the level of compatibility between the papers and abstracts. Despite these setbacks, although a comparison is prevented, publication rates can still provide us with a gross estimation of the significance of a meeting. This is at the heart of the need to standardize such criteria as the databases scanned and the various publication qualifications, and a fixed time period must be established. In this study, the four different meetings, although recording different median times, were assessed with a time period shorter than two years, and the publication rates within these two years were found to be similar. Even for the first meeting, which had the longest follow-up time, more than half the publications were made within the first two years. Taking this into consideration, we believe that any given meeting should announce their publication rates for a fixed time frame, and that this should be set at 2 years. This might be attributed to the fact that corresponding authors started to lose motivation to publish their studies after 2 years of attempts.

Another important criterion that needs to be included could be the acceptance rate of submitted abstracts. The lower the acceptance rate the publication rate would be expected to be higher. Generally, studies that are rejected by a congress are not submitted for publication, which may be due to the reluctance of the author to resubmit the study for further assessment in fear or further rejection (17). Interestingly, the authors claimed that this pessimism was not associated with the study quality, originality, sample size, design or results (17). Studies published before scientific meetings are also not submitted to journals for several reasons. Studies rejected by congresses would likely be declined by journals due to the more rigorous peer-review process associated with indexed journals than scientific meetings. Following the rejection by a journal, some authors choose not to submit their studies to other journals (18). Another factor is that authors may not have sufficient time to

prepare a manuscript for publication (18), and some abstracts are prepared specifically for scientific meetings rather than not for journals. The most important reason for this situation is that training programs often pay for the travel costs for national congresses (1).

Study Limitations

The main limitation of this study is its lack of inclusion of rejected studies and its subsequent failure to offer insight into why they remained unpublished. In contrast, the most significant aspect of this study is the information it provides regarding the context of studies and their publication rates following a scientific meeting.

Conclusion

MSUST congresses have a comparable publication rate compared with many other prestigious international meetings, and this rate continues to increase. There is a need to define a threshold for the comparison of the publication rates of such events, and 2 years should be considered appropriate in this regard.

Ethics

Ethics Committee Approval: Some studies that do not require ethical approval include those involving information freely available in the public domain.

Informed Consent: Not necessary.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.A., H.S.D., Design: M.A., H.S.D., S.T., Data Collection or Processing: M.A., A.K., K.E.B., P.S., A.C.B., Analysis or Interpretation: M.A., H.S.D., Literature Search: M.A., H.S.D., Writing: M.A., H.S.D., S.T.

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

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ORIGINAL RESEARCH
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Correlation of Acute Flank Pain with the Number of Pregnancies and Hydronephroses; An Observational Study

Abubekir Böyük[1], Latif Mustafa Özbek[2], Raşit İlhan[3], Samed Verep[4], Meryem Merve Ören[5], Selçuk Erdem[6], Tzevat Tefik[6]

[1]Beylikdüzü Kolan Hospital, Clinic of Urology, İstanbul, Turkiye
[2]Private Atasam Hospital Samsun, Clinic of Urology, Samsun, Turkiye
[3]Iğdır State Hospital, Clinic of Gynecology and Obstetrics, Iğdır, Turkiye
[4]Özalp State Hospital, Clinic of Urology, Van, Turkiye
[5]İstanbul University-İstanbul Faculty of Medicine, Department of Public Health, İstanbul, Turkiye
[6]İstanbul University-İstanbul Faculty of Medicine, Department of Urology, İstanbul, Turkiye

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

Hydronephrosis may occur frequently in pregnancy and may cause no symptoms or signs. However, it may present as acute flank pain or pyelonephritis in nullipara patients. Our study showed that pregnancy-related hydronephrosis symptoms are mostly seen in the late second or third trimester. Whenever the degree of hydronephrosis increases, the severity of accompanying symptoms also increases. Ureteral JJ stent placement is a safe method for patients who do not respond to conservative therapy.

Abstract

Objective: We investigated the correlation of acute flank pain incidence with the number of pregnancies and hydronephrosis.

Materials and Methods: Forty-eight patients were included in the study. Patients with urinary tract infection, abnormal urinalysis and urinary stone have been excluded. Twenty-four patients were nulliparous, and the remainder multiparous. All patients underwent urinary ultrasound by the same radiologist. The visual analog scale (VAS) was completed at the time of admission. Intravenous fluid, paracetamol and oral nitrofurantoin were administered to all patients. Patients who did not benefit from conservative treatment underwent ureteral JJ stent placement.

Results: Nulliparous pregnant were younger and had earlier gestational weeks (25.1±3.7 - 28.7±3.8 p=0.004 and 22.9±3.7 - 26.3±4.0 p=0.005), as well as higher VAS scores. In nulliparous pregnant women, a significant, medium level-positive correlation was found between the degree of hydronephrosis (DoH) and the VAS scores. We observed that the higher DoH was related to higher VAS scores. However, in multiparous pregnant women, no correlation was observed between DoH and VAS scores. In the comparison of two groups, there were no significant differences in body mass index, DoH, hydronephrosis side, serum creatinine levels, type and side of pain. Forty-two percent of the patients described colic pain. Forty-four patients benefitted from conservative treatment, whereas only 4 patients underwent JJ stent insertion.

Conclusion: This study demonstrates the correlation between acute flank pain and hydronephrosis. The DoH increases as the pain intensifies, especially in the nulliparous, where the correlation is stronger.

Keywords: Pregnancy, hydronephrosis, acute flank pain, nulliparous, multiparous

Correspondence: Abubekir Böyük MD, Beylikdüzü Kolan Hospital, Clinic of Urology, İstanbul, Turkiye
E-mail: dr_bekirr@hotmail.com **ORCID-ID:** orcid.org/0000-0002-0746-2377
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Introduction

Flank pain is a condition that commonly leads to emergency department visits and not infrequently observed in pregnant women. In pregnant women, flank pain is mostly due to hydronephrosis. Mild hydronephrosis is reported in 90% of pregnant women during pregnancy, with most being nulliparous (1-3).

It has been claimed that the mechanism of hydronephrosis formation in pregnancy, in addition to uterine compression, is progesterone hormone's relaxing effect on the smooth muscle (4,5). Hydronephrosis in pregnancy may cause pyelonephritis and urosepsis. It is frequently seen on the right side, probably due to uterine dextrorotation and protection of the left ureter by the sigmoid colon (6,7).

Although hydronephrosis may be seen in 90% of pregnant women, in most cases they are followed up without any symptoms. But certain patients may present with severe flank pain, recurrent urinary tract infections, and even renal dysfunction (6,8). Most the patients benefit from the conservative approach and medical treatment. However, invasive procedures such as ureteral stent or renal nephrostomy may be required in 6% of patients (6,9).

In this study, we investigated the relationship between nulliparity and multiparity with hydronephrosis and pain, as well as the relationship between the degree of hydronephrosis and pain. Factors other than pregnancy, such as ureteral or renal stones and urinary tract infection that may lead to hydronephrosis and pain were excluded.

Materials and Methods

This study was conducted in Iğdır State Hospital between the dates of October 2018 and February 2019. During this time, 237 pregnant women had outpatient visits to the hospital. Among these patients, there were 93 pregnant women accompanied by acute flank pain. Among these 93 pregnant women, 48 patients who met the criteria were included in the study. The study consisted of 2 groups and a total of 48 patients comprising of group 1 nulliparous (n=24) and group 2 multiparous (n=24) pregnant women who were admitted to ER, gynecology, or urology wards.

Written informed consent was obtained from patients' and their spouses before the study. The consent explained that no additional intervention was performed other than routine protocols and treatments, and only the requisite findings would be used in the study. Urinalysis, urine culture, serum creatinine values were obtained from all patients and the described character of pain and demographic data were recorded. All patients had urinary ultrasound (US) by the same radiologist. To assess the degree of hydronephrosis (DoH), maximal anterior-posterior diameter of the renal pelvis was measured by US. A visual analog scale (VAS) with a numerical evaluation was obtained from all patients. Patients who had hematuria or pyuria on urinalysis, had signs of urinary calculi, pyelonephritis, or pyelonephrosis on urinary US and had positive urine culture result were excluded from the study. Every patient had an obstetric consultation, and the fetus and pregnancy status were evaluated. All patients were hospitalized, administered intravenous fluid therapy, paracetamol as analgesic, oral nitrofurantoin as antibiotherapy and were recommended to bed rest. Antibiotic treatment was initiated as a prophylaxis and was administered for 5 days. The specific antibiotic treatment was not based on any guideline recommendations. Ureteral JJ stents were placed in patients who did not respond to conservative treatment.

Statistical Analysis

In the statistical analyses, compliance with normal distribution was evaluated with Kolmogorov-Smirnov analysis. Mann-Whitney U test was employed for continuous data and chi-square test for categorical data. The covariance of the Dog and the VAS score values were evaluated with Spearman Correlation analysis (In the interpretation of the correlation coefficient, values were categorized as follows: 0.0-0.24 weak, 0.25-0.49 medium, 0.50-0.74 strong, 0.75-1.00 compelling). For statistical significance, in the 95% confidence interval, p-value below 0.05 was considered significant. SPSS v 21.0 program was used for statistical analysis.

Results

Of the patients included in the study, 56.25% (n=27) were in the second and 43.75% (n=21) were in the third trimesters. Of the second trimester patients, 66.6% were nulliparous (n=18) and 33.4% multiparous (n=9). No first trimester or the early second trimester patient existed. Most were through the late second trimester or in the third trimester. The number of births given by the multiparous was 2.9±0.9 (2-5).

Hydronephrosis was observed in 66.7% of patients and 62% of the pain was observed on the right side. Of the patients presenting with acute flank pain, 50% (n=12) of the nulliparas and 33.3% (n=8) of the multiparas described colic-like pain, while the rest described suppressive, blunt, or aching pain. There were no statistically significant differences between the two groups.

In this study, age and gestational age values were found to be significantly lower in nulliparous pregnant women compared with multiparous (age 25.1±3.7 - 28.7±3.8 p=0.004 and gestational week 22.9±3.7 - 26.3±4.0 p=0.005 respectively), however VAS score values turned out to be higher in nulliparous (7.2±1.2

and 5.8±1.9 p=0.004, respectively) (Table 1). In the total cohort, a significant, medium level, positive correlation was spotted between DoH and VAS score values. VAS score values increased as the DoH increased in the total cohort (r=0.349, p=0.015) (Table 2). When the two groups were evaluated separately, a medium level, same-direction, significant correlation is found between DoH and VAS scores in the nulliparous (Table 3). As the hydronephrosis increased in the nulliparous, VAS score values also increased (r=0.494 p=0.014). Whereas in multiparas, there was no correlation between the degree of hydronephrosis and VAS score (r=0.178 p=0.405) (Table 3). To our knowledge, this is one of the first studies comparing nulliparous and multiparous pregnant women.

Comparing the two groups, no statistically significant difference existed in terms of body mass index, hydronephrosis grade, hydronephrosis side, creatinine value, type and side of pain (Table 1). In both groups, 91.7% of the patients (n=20) benefited from conservative treatment and 8.7% (n=4) were placed with ureteral JJ stent. Two of the pregnant women who had ureteral stents were nulliparous, and two were multiparous. One patient with ureteral stent had grade II and the other 3 had grade III hydronephrosis. Ureteral JJ stent was placed on the left side in one patient and on the right side in 3 patients. All patients with ureteral JJ stenting described colic pain and had VAS scores of 9 (n=2) and 10 (n=2). Ureteral JJ stent placement significantly decreased the hydronephrosis and pain. Control US was performed 2 weeks following JJ stent placement. The patients included in the study were followed until 36th-38th gestational weeks on average. However, obstetric data were not obtained after giving birth.

Discussion

This prospectively evaluated study demonstrated that DoH and the number of pregnancies correlated with the severity of pain in pregnant women. While our findings are similar to the literature at some points, they seem to support the opposite

Table 1. Patient demographic and clinical data

	Nullipara					Multipara					
	Mean	Standard deviation	Median	Minimum	Maximum	Mean	Standard deviation	Median	Minimum	Maximum	p
Age	25.1	3.7	25.0	18.0	33.0	28.7	3.8	28.0	20.0	37.0	**0.004**
Gestational age (week)	22.9	3.7	22.0	18.0	30.0	26.3	4.0	28.0	19.0	34.0	**0.005**
Number of births						2.9	0.9	3.0	2.0	37.0	
BMI	23.7	3.4	23.8	16.2	31.6	25.6	3.6	26.1	19.2	35.0	0.081
Creatinine mmol/L	0.6	0.1	0.6	0.4	0.8	0.6	0.1	0.6	0.4	0.8	0.983
VAS score	7.2	1.2	7.0	5.0	10.0	5.8	1.9	5.5	2.0	10.0	**0.004**

BMI: Body mass index, VAS: Visual analog scale

Table 2. Correlation of hydronephrosis grade with VAS score in total cohort

		Hydronephrosis grade - VAS score
Spearman's rho	r	0.349
	p	**0.015**
	n	48

*Correlation is significant at the 0.05 level (2-tailed), VAS: Visual analog scale

Table 3. Correlation of hydronephrosis grade with VAS score

Nulliparous-Multiparous		
Nullipar	r	0.494
	p	**0.014**
	n	24
Multipar	r	0.178
	p	0.405
	n	24

*Correlation is significant at the 0.05 level (2-tailed), VAS: Visual analog scale

view at others. The incidence of acute flank pain and higher hydronephrosis on the right side is consistent with the literature (6,7,10). Some studies have reported that hydronephrosis is more common, especially in primigravidae (1,6). In our study, especially in the nulliparous, hydronephrosis and pain were found to have medium level, positive correlation. In the literature, there are studies which state that hydronephrosis is common in pregnant women; that there is no relationship between hydronephrosis and acute flank pain and that most cases develop asymptomatically (6,8). Farr et al. (11) reported that hydronephrosis was not observed in some patients with flank pain. In the same study, Farr et al. (11) stated that there was no correlation between hydronephrosis and pain intensity. Many studies in literature have investigated hydronephrosis and its prevalence, as well as the relationship between hydronephrosis and pain. The main difference in our study is that all patients were admitted with acute flank pain. The detection of hydronephrosis in the pregnant women admitted caused us to consider hydronephrosis to be associated with acute flank pain. It is also possible that anatomic factors and gestational anxiety might have been effective in the positive correlation between the pain and the DoH and in higher VAS scores of the nulliparous than the multiparous (12). In the lack of concrete evidence such as psychiatric examination results, we think that this may be subject of another study.

In the literature, cases of complicated urinary tract infection such as pyelonephritis that developed during and after the second trimester causing serious complications have been reported (13). No patients with urinary tract infection were included in our study and none of the patients included in the study developed pyelonephritis on follow-up. The majority of patients (91.7%) benefited from conservative treatment. Only 4 patients (8.3%) underwent ureteral JJ stent placement. This ratio is consistent with the literature, yet the small number of patients is a limiting factor for a strong interpretation (6).

The most important difference that distinguishes our study from other studies is the comparison between multiparous and nulliparous patients together with assessing the relationship between flank pain and DoH. In some studies, patients with symptoms like fever and signs of white blood cell and C-reactive protein elevation were included (14). In contrast to these studies, patients who had only flank pain and normal biochemical tests but had no symptoms like fever were included in our study. We think that our study also enables a stronger evaluation of the relationship between hydronephrosis and flank pain without different symptoms and signs. In some studies, it has been reported that hydronephrosis is common during pregnancy and is asymptomatic (6,8). However, patients with mild hydronephrosis were also included in these studies, and pregnant women with mild hydronephrosis constitute the vast majority. In our study, there are patients in the late periods of the second trimester and in the third trimester. As a result, we think that hydronephrosis increases with the progression of pregnancy and pain associated with it is observed.

As we were the only urology center in the city, all patients were followed up by the same team. Ureteral JJ stent placed in a patient was removed before delivery and the other three stents were removed in 3-4 weeks following delivery. The removal of a stent before delivery was done upon the demand of the patient due to hematuria and irritative stent symptoms. This patient had weekly US follow-up until birth, reported minor pain on the side of stent removal resolved with conservative treatment without the need to re-intervene. No major complication developed in the patients with ureteral JJ stents. Although we cannot make a strong interpretation due to the small number of patients, this result is consistent with the literature (15). The degree of hydronephrosis in the patients who were placed stents were grade 2 and grade 3 (n=1, n=3, respectively) and their VAS scores were 9 and 10 (n=2, n=2, respectively). In concurrence with the study of Tsai et al. (15) we think that JJ stents are more effective than conservative treatment in pregnant women with advanced hydronephrosis. JJ stents may safely be inserted in these patients. The most important limiting factor in our study was the number of patients. A stronger result might be obtained with a higher number of patients. It should also merit to mention that birth and postnatal data of the patients included in our study are not available.

Conclusion

This study demonstrates that there is a relationship between acute flank pain and hydronephrosis as well as the severity of pain increases with the DoH. Especially in nulliparas, this relationship is stronger. Ureteral JJ stent is a safe and effective treatment method for pregnant women who do not respond to conservative treatment.

Main Points

- There is a relationship between acute flank pain and hydronephrosis as well as the severity of pain increases with the DoH,

- In the total cohort, a significant, medium level, a positive correlation was observed between hydronephrosis grade and VAS score values.

- In nulliparas, this relationship is stronger,

- Ureteral JJ stent is a safe and effective treatment method in pregnant women who do not respond to conservative treatment.

Ethics

Ethics Committee Approval: Not approved.

Informed Consent: Written informed consent was obtained from patients' and their spouses before the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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CASE REPORT
General Urology

Doi: 10.4274/jus.galenos.2021.2021.0089
J Urol Surg, 2022;9(2):143-145

Iatrogenic Renal Rupture in Conduitoscopy - A Diagnostic Trauma

James Kovacic[1,2], Edward Latif[1,2]

[1]Gosford Hospital Ringgold Standard Institution, Department of Urology, Gosford, Australia
[2]Central Coast Local Health District Ringgold Standard Institution, Department of Urology, Gosford, Australia

Abstract

This unique case is the first published renal rupture with hematoma as a result of conduitoscopy. Whilst cases of renal hematoma following ureteropyeloscopy are a recognized entity, published complications following conduitoscopy are absent from the literature. This case serves as a warning that even simple conduitoscopy can result in life threatening bleeding and demonstrates the need for caution and risk management with diagnostic procedures. It is hoped that by individual patient assessment for specific risk factors, and by harm reduction methods, such complications may be avoided in the future.

Keywords: Renal rupture, conduitoscopy, endourology

Introduction

Here we present a novel case of a severe iatrogenic renal rupture and perinephric hematoma following a conduitoscopy to investigate recurrent macroscopic hematuria following commencement of apixaban for atrial fibrillation. The patient had previously undergone cystectomy and ileal conduit formation 15-years prior for high-grade non-muscle invasive bladder cancer with carcinoma *in situ*. Recurrence of urothelial cell carcinoma post-cystectomy is a well-known risk, typically identified within the remaining urothelial tissue (1). As a result, the assessment of a patient's urological tract in the instance of hematuria must exclude disease recurrence. Whilst upper tract investigation is typically performed using delayed computed tomography (CT), our patient was affected by chronic kidney disease (with GFR 18), hence a flexible conduitoscopy and conduitogram was undertaken.

Case Report

A 77-year-old female with a background of cystectomy and ileal conduit formation 15-years prior presented to a district hospital for conduitoscopy and conduitogram. The case was complicated by a significant renal rupture causing a right renal interpolar artery pseudoaneurysm, and resulted in a prolonged hospital stay with multiple post-operative complications.

The patient had previously undergone cystectomy for high-grade non-muscle invasive urothelial carcinoma and carcinoma *in situ* of the bladder. Over the past 12 months, she had recurrent macroscopic hematuria in the context of newly started anticoagulation, recurrent urinary tract infections, bilateral severe hydronephrosis with a non-functional, atrophic left kidney, and chronic kidney disease. Pre-operative non-contrast CT demonstrated no clear cause and urine cytology was atypical. The bilateral hydronephrosis was presumed to be a result of ureteric reflux secondary to the ileal conduit. Our patient also had a significant medical history including cervical cancer with prior radiotherapy, recurrent small bowel obstruction, colostomy, hypertension, and being a current smoker. She lived alone and was independent in her activities of daily living. Flexible conduitoscopy was performed under general anesthesia in the supine position with an antibiotic cover. Apixaban had been withheld for 72-hours. An 18Fr Olympus flexible cystoscope was inserted into the ileal conduit with gravity fed normal saline irrigation. The procedure was challenging because of a tortuous distal conduit. The intraoperative conduitogram demonstrated a dilated right-sided collecting system without mucosal abnormalities; the anastomosis could not be visualized endoscopically and visual inspection of the upper tracts was not undertaken (Figure 1). Within the conduit, two polyps were identified and biopsied using a piranha forcep. Second opinion from the on-call colorectal surgeon was gained given the lesions did not appear to be urothelial in nature. A repeat

Correspondence: James Kovacic MD, Gosford Hospital Ringgold Standard Institution, Department of Urology, Gosford, Australia
Phone: +61 411 359 053 **E-mail:** james.kovacic@health.nsw.gov.au **ORCID-ID:** orcid.org/0000-0002-8615-4371
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conduitogram was completed following biopsy, which did not demonstrate any contrast extravasation. The procedure took approximately 60 minutes and the patient's haemodynamics were stable throughout with systolic blood pressure between 120-140 mmHg. Whilst in recovery, the patient required inotropic support and developed worsening right flank pain. Serial venous blood gas demonstrated a falling hemoglobin 104g/L to 68g/L. A triple phase CT identified a 9.7x9.8x7.4 cm right-sided perinephric renal hematoma with multifocal areas of cortical disruption and contrast extravasation consistent with arterial injury (Figure 2). The patient was resuscitated and stabilized before being transferred to the nearest tertiary facility for interventional radiology management selective embolization. She underwent digital subtraction angiography, which identified an active blush of contrast on the right-side emanating from a 1.5 cm pseudoaneurysm of an interpolar artery (Figure 3). The vessel was successfully mobilised using a 2x5 mm coil.

In the subsequent days, her renal function deteriorated, with peak creatinine reaching 476 before the commencement of hemodialysis. She also developed systemic inflammatory response syndrome (SIRS) with fevers, C-reactive peptide (CRP) 392 and a white cell count (WCC) 16.7. IV ceftriaxone was started to cover the chest, urinary, and infected hematoma source. A chest tube was placed to drain a large, reactionary right-sided pleural effusion. One month following her initial procedure, she remained on dialysis with ongoing low-grade temperatures. Repeat imaging demonstrated an interval increase in the perinephric hematoma size with stable hemoglobin, so a drain was inserted under radiological guidance. Subsequent draining cultures were positive for *Bacteroides fragilis*. A second drain was placed weeks later due to slow interval size reduction in follow-up imaging, with repeat drain cultures positive for a resistant *Escherichia coli* and *Enterococcus faecalis*. Antibiotics were then changed to IV tazocin and ciprofloxacin. The drains were removed with a daily output under 50 mls of serious fluid.

One month later the patient developed fevers and flank pain again with imaging demonstrating a reaccummulation of her perinephric collection. A new drain was inserted and remained for a further 6-weeks with repeat imaging demonstrating

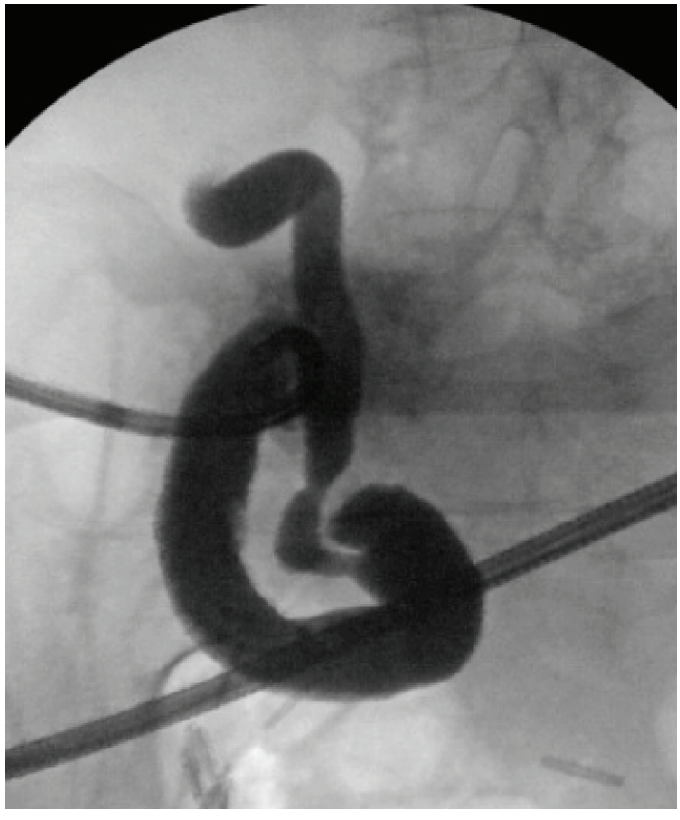

Figure 1. Conduitogram with right-sided reflux

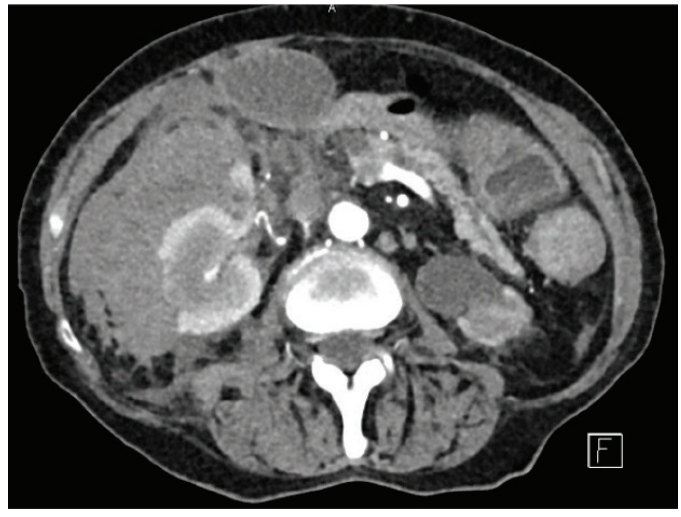

Figure 2. Axial CT with arterial extravasation

CT: Computed tomography

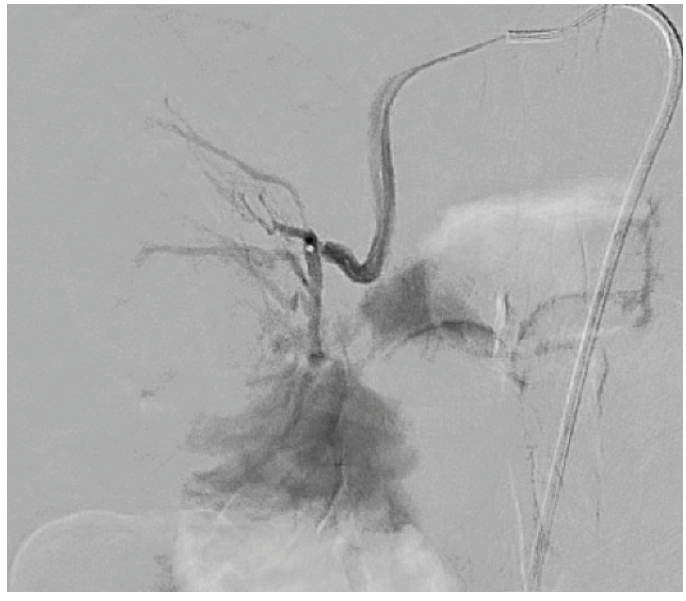

Figure 3. Embolisation of right interpolar artery

almost complete resolution of her collection. At this stage, hemodialysis continues with normalizing interval renal function and reasonable residual cortex of her right kidney. The outpatient follow-up has been arranged with serial imaging. Histology of the large ileal conduit lesions has returned as benign inflammatory tissue.

Discussion

Conduitoscopy is a procedure with limited indications, and as a result of small case numbers, evidence regarding its complications is not well published in the literature. This is the first reported case of renal rupture following conduitoscopy, a life threatening complication from a fairly innocuous procedure. We believe the tight stoma combined with a longer than anticipated operation and poor pre-existing renal parenchyma resulted in significant reflux, renal rupture akin to an AAST Grade 4 injury, and a renal segmental artery pseudoaneurysm.

A recent systematic review found that ureteropyeloscopy for the management of renal and ureteric stones had a peri-renal hematoma rate of 0.45% (2). Studies within this demographic have identified several risk factors for hematoma development, which include moderate to severe hydronephrosis, large stone burden, renal cortex thinning, prolonged operative durations, low body mass index, hypertension, and high pressure irrigation (2-8). Several of these factors were present in this study and may explain why a reasonably non-invasive procedure was complicated by such significant pathology. However, risk reduction was also undertaken by way of using low-pressure irrigation and the procedural outcome was an unwelcome surprise.

The rationale behind conducting a conduitogram was based on the need for upper tract assessment for urothelial lesions. The non-contrast CT imaging had demonstrated bilateral hydroureteronephrosis but no cause for hematuria was identified. Several factors limit the utility of non-contrast imaging in this setting, including inability to identify small urothelial lesions or arteriovenous pathology. Although CT IVP is the standard form of imaging with a sensitivity of 88-100% in the identification of upper tract urothelial lesions, our patient's renal failure prevented this (9). A study by Razavi et al. (9) demonstrated 69% sensitivity of MR urography for upper tract malignancy, and as a result, this was not undertaken in favor of conduitogram that would allow for radiographic and histopathological assessment (10).

Despite using gravity fed irrigation no more than 60 cm H_20 and a small French flexible scope, a renal rupture occurred. The message is to use an abundance of caution, avoid high pressure irrigation particularly in open refluxing anastomosis, and recognize the deteriorating patient early despite them having a minor procedure. In terms of avoiding similar events in the future, we suggest care when investigating, if possible use of CT IVP rather than conduitogram, and ideally perform the procedure under local anesthetic so the patient can provide feedback during the operation.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

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CASE REPORT
Urooncology

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A Large Bladder Tumor During Pregnancy: Twin Challenge

Gagandeep Singh[1], Sunil Chawla[2], Priyaranjan Nandy[1], Meenakshi Rajput[2]

[1]Command Hospital, Clinic of Urology, Udhampur, India
[2]Command Hospital, Clinic of Obstetrics and Gynaecology, Udhampur, India

Abstract

Urological malignancies during pregnancy are extremely rare, affecting about 13 in 1,000,000 pregnancies. Common signs of urological malignancies especially bladder tumors such as hematuria, urgency, lower abdominal pain, may be attributed to the pregnancy. Combined with the hesitancy to undergo imaging, these overlapping symptoms may result in delayed diagnosis. We report the case of a young female who was incidentally detected to have a large bladder tumor during the second trimester of her pregnancy. She underwent a transurethral resection of the bladder tumour during 26th week of pregnancy and histopathology was suggestive of a high-grade lamina invasive urothelial carcinoma. Her pregnancy continued till 34 weeks, when she delivered a 2.14 kg healthy female child. Restaging transurethral resection of the bladder tumour done four days after delivery was negative for malignancy. She is presently on intravesical Bacillus Calmette-Guérin therapy. Although a rare occurrence, treatment of bladder malignancies during pregnancy requires a multidisciplinary approach while taking into consideration the mother's health, neonatal outcome and the perspective of both parents.

Keywords: Bladder tumour, pregnancy, intravesical therapy

Introduction

Malignant tumors during pregnancy are a rarity with the overall incidence being approximately 2.35/10,000 (1) and the commonest are malignant melanomas (2.8/1,000), cervix (1/2,200), breast (1/3,000) and lymphomas (1/6,000) (2,3). Urological malignancies during pregnancy are extremely rare, affecting about 13 in 1,000,000 pregnancies (4). Common signs of urological malignancies especially bladder tumors such as hematuria, urgency, lower abdominal pain, may be attributed to the pregnancy. Combined with the hesitancy to undergo imaging, these overlapping symptoms may result in delayed diagnosis.

The first reported case of bladder carcinoma in pregnancy was by Waser (5) in 1927. Since then, less than 50 cases have been reported in literature (6). Due to the rarity of the presentation, there are no standard guidelines for the subject. The treatment hence needs to be tailored in consultation with the Obstetrician and family.

Case Report

32-yr-old lady, an antenatal case, G3P1A1L1, presented at 26 weeks period gestation with c/o intermittent, gross, total, painless hematuria for 3 months. There was no history of tobacco consumption in any form with no other significant past medical or surgical history. Ultrasound revealed a single live intrauterine fetus of 24 weeks with mild dilatation of the pelvicalyceal system on the right side. There was a 4.3x4.7x5.2 cm echogenic mass lesion noted along the right posterolateral wall of urinary bladder with significant vascularity within. Contrast-enhanced magnetic resonance imaging of pelvis confirmed a 4.3x4.5x4.7 cm sized mass lesion seen arising from the right posterolateral wall of urinary bladder. The lesion was isointense on T1WI, mildly hyperintense on T2WI, STIR (Figure 1) and showed intense post contrast enhancement (Figure 2). There appeared to be focal disruption of the hypointense line on T2WI in the bladder underneath the lesion - likely representing invasion into the deep muscle. A prominent vessel was seen to enter the lesion from its base. No extension of the lesion beyond the bladder wall was noted. The right ureterovesical junction did not appear to be involved. Perivesical fat was normal. A single live intrauterine fetus was seen corresponding to 25 weeks period of gestation.

After discussing the case with both parents and the obstetrician and counseling about the risk to the fetus, the patient gave informed, written consent and underwent bipolar transurethral resection of the bladder tumour (TURBT) under regional

Correspondence: Gagandeep Singh MD, Command Hospital, Clinic of Urology, Udhampur, India
Phone: +91 9764610900 **E-mail:** gagan150582@gmail.com **ORCID-ID:** orcid.org/0000-0002-3567-5353
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anaesthesia. Intraoperative finding - large 5x5 cm frondy growth with broad base and foci of calcification over the right lateral wall away from the right ureteric orifice. Histopathology revealed high grade papillary urothelial neoplasm with evidence of invasion of underlying lamina propria; single focus of deep muscle seen in the TURBT specimen did not show definite evidence of invasion. Extensive pleomorphism and calcification were seen, however these cells were negative for Vimentin on immunohistochemistry. The case was discussed with the couple and it was decided to defer Restaging TURBT till delivery.

Pregnancy was continued until 34 weeks in view of intrauterine growth retardation. She underwent spontaneous normal delivery and delivered a 2.14 kg healthy female child. She then underwent restaging TURBT under regional anesthesia 4 days after the delivery. Intraop finding - no recurrence, deep muscle biopsies were taken from the scar site. Histopathology the biopsy result was negative for malignancy. Thereafter, in view of high-risk bladder cancer, the patient was started on intravesical therapy - 80 mg intravesical Bacillus Calmette-Guérin (BCG) as per the SWOG regime 4 weeks after the surgery. She has been on regular therapy and follow-up as per National Comprehensive Cancer Network (NCCN) guidelines and is recurrence free at 1 yr follow-up (7).

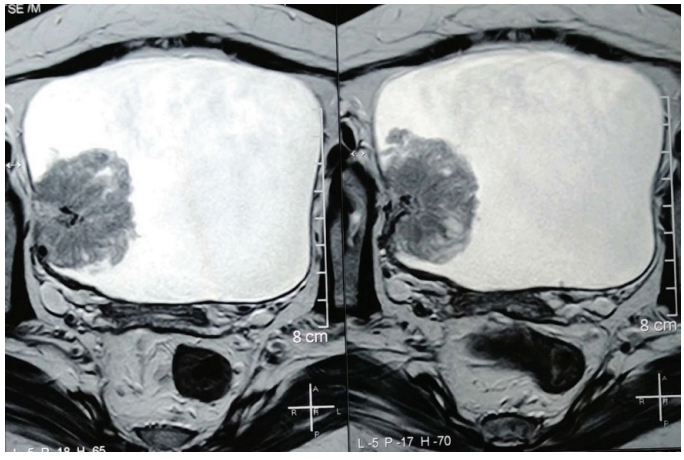

Figure 1. T1 and T2 WI of bladder tumour

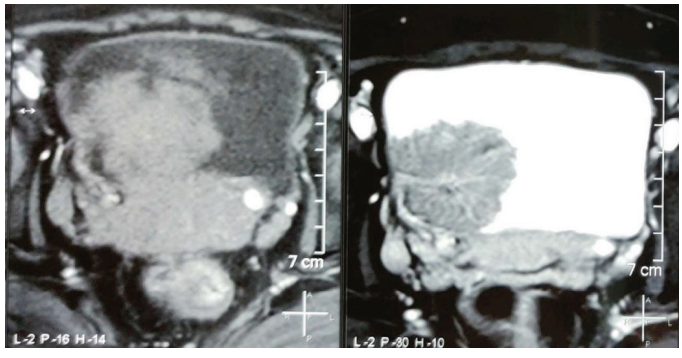

Figure 2. Intense post contrast enhancement

Discussion

Urological malignancies in pregnancy are a rarity, with an approximate incidence of 0.0013%. The commonest tumors are renal tumors, followed by bladder tumors and finally pheochromocytomas. Bladder tumors during pregnancy have been described since 1927, with transitional cell carcinoma (TCC) being the most common (70%) (6). The objective of this case report is to highlight the multidisciplinary care and selective approach involved in the management of bladder cancers, which present during pregnancy.

It has long been debated in the literature whether pregnancy plays a potential "protective" or "increased risk" role in the occurrence and spread of cancer. The antigens of the fetus are tolerated by the immune system of the mother. The point to be considered is whether this state of tolerance of the immune system of the mother "protects or potentiates" the development of cancer. Some theories state that pregnancy is a state of immunosuppression to tolerate the antigens of the fetus, however, this state of immunosuppression is specific only to fetal antigens as pregnant ladies mount an adequate immune response to all other antigens: Viral, bacterial, helminthic or neoplastic.

In the general population, TCC account for more than 90% of bladder cancers and superficial cancers account for more than 70% of newly diagnosed bladder TCCs. Painless hematuria is the commonest presentation in bladder tumors (80-90%). In pregnant women, however, the presentation is often delayed as urinary symptoms in pregnancy are often ignored and hematuria mistaken for vaginal bleeding. Thus, unwarranted obstetric examination is often carried out in these patients to rule out causes such as placenta praevia and abruptio placenta (8). When correctly identified as hematuria, complete evaluation should be conducted and bladder cancer should be considered in the differential diagnosis. Cystitis is the most common cause of hematuria in pregnancy (9), but hematuria not responding to antibiotic warrants complete detailed evaluation. Ultrasonography of the bladder is useful, but in no way diagnostic, as half of the cases were identified on ultrasonography. Flexible cystoscopy under local anesthesia is an extremely useful option in evaluating hematuria in pregnancy.

Imaging during pregnancy is also a dilemma. Computed tomography scan is contraindicated due to the well-known factor of radiation exposure. Hence, magnetic resonance imaging is the imaging modality of choice for the evaluation of bladder tumors during pregnancy.

The factors, which decide the treatment are the trimester of pregnancy at which the patient has presented and the stage of malignancy (10). Patients are stratified into low,

intermediate and high-risk groups based on the AUA Risk Stratification criteria for non-muscle invasive bladder cancer (NMIBC). Thereafter, they may be managed as per the NCCN Guidelines Version 3.2021 for NMIBC (7). Options for intravesical therapy include gemcitabine, mitomycin and BCG. There is a high risk of local vesical irritative symptoms, which however is mild and transient. Systemic side effects though rare may range from mild symptoms to severe illness (e.g. sepsis, arthritis). There are only two case reports of intravesical therapy during pregnancy (11,12) with normal fetal outcomes reported in both. Due to the known embryotoxicity of live vaccines like BCG and systemic chemotherapy like mitomycin, great caution needs to be exercised in the use of these agents during pregnancy (13). A more pragmatic approach would be to continue the patient on 3 monthly follow-up cystoscopy and defer the use of intravesical therapy till termination of pregnancy. In patients with muscle-invasive bladder carcinoma, with or without lymph node involvement, neoadjuvant platinum-based chemotherapy followed by radical cystectomy is the treatment of choice (7). The deciding factor whether to proceed with the termination of pregnancy and further treatment or to initiate chemotherapy during pregnancy or after completion of pregnancy would be the trimester of pregnancy. Complications of chemotherapy during pregnancy, such as intrauterine ototoxicity (14), intra-uterine growth retardation and pre-term contractions, should be discussed with the patient. It is advisable to perform the radical cystectomy 3-4 weeks after delivery to minimize the increased risk of blood loss due to pregnancy induced pelvic congestion. In patients with metastatic bladder cancer, palliative chemotherapy is the only treatment option.

Except for the early first trimester, when there is a high risk of miscarriage, TURBT can be performed at any time during the surgery. Spinal anesthesia is considered a safer alternative than general anesthesia. A bipolar technique with a lesser incidence of bladder perforation and electrolyte imbalance is a better option than the monopolar technique. The decision for normal vaginal delivery or cesarean section should be based on obstetric and fetal factors. Theoretical risks of obstructed labor due to large bladder tumour, the dissemination of the tumor during the passage of the fetus through the birth canal, injury to the bladder during cesarean section should also be taken into consideration. Treatment goals should include postponement of delivery beyond 35-37 weeks of gestation, whenever possible, to safeguard neonatal outcome (14).

Conclusion

Although a rare occurrence, bladder malignancy should be considered a possible diagnosis when pregnant women present with symptoms such as gross hematuria. The trimester at which the lady presents and the stage of the tumor are the two most important determinants of treatment. Surgery can be offered safely in all three trimesters. Due to limited experience and high risk of adverse fetal outcomes, intravesical therapy should be postponed until after delivery and patients should be managed with regular cystoscopy follow up after the TURBT. To summarize, the treatment of bladder malignancies during pregnancy requires a multidisciplinary approach while taking into consideration the mother's health, neonatal outcome and the perspective of both parents.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.S., S.C., M.R., Concept: G.S., S.C., M.R., Design: S.C., Data Collection or Processing: P.N., Analysis or Interpretation: P.N., Literature Search: G.S., P.N., Writing: G.S.

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

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

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CASE REPORT
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Percutaneous Biopsy in Adult Wilms Tumor and A Review of the Literature

Emre Emekli[1], Elif Gündoğdu[2]

[1]Etimesgut Şehit Sait Ertürk State Hospital, Clinic of Radiology, Ankara, Turkiye
[2]Eskişehir Osmangazi University Faculty of Medicine, Department of Radiology, Eskişehir, Turkiye

Abstract

Wilms tumor is rare in adults, constituting only 0.5% of all renal masses. Tumors in adults are diagnosed later than those in children, and survival after treatment is still low. Some reasons for this are considered as patients not receiving neoadjuvant chemotherapy before surgery and late initiation of treatment due to delays in receiving pathology results. In this paper, we present a 38-year-old male patient diagnosed with Wilms tumor after percutaneous biopsy and review the related literature.

Keywords: Renal mass, adult Wilms tumor, percutaneous biopsy

Introduction

Wilms tumor constitutes 5-6% of all pediatric tumors. It is the most common renal tumor seen in childhood, with most being diagnosed within the first five years of life (1). In adults, Wilms tumor is rare, accounting for only 0.5% of all renal masses (2) and having an incidence of 0.2 per million (3). Current treatment approaches have increased survival in children up to 90%; however, tumors in adults are diagnosed later than those in children and remain have a lower survival rate. The main reasons for this situation are delays in diagnosis due to the rarity of the disease and lack of complete treatment protocols for adults. Other reasons are considered as patients not receiving neoadjuvant chemotherapy before surgery and late initiation of treatment due to delays in receiving pathology results (4). However, there are publications in the literature that recommend percutaneous biopsy (PCB) before surgical treatment in young adult patients with renal masses suspected to be Wilms tumors (3).

In this paper, we present a 38-year-old male patient who was suspected to have lymphoma and Wilms tumor in the preliminary diagnosis based on imaging characteristics and was diagnosed with Wilms tumor as a result of PCB performed for differentiation.

Case Report

A 38-year-old male patient presented to an external healthcare center with the complaint of left flank pain and was referred to our tertiary hospital with a preliminary diagnosis of a renal mass. Dynamic renal computed tomography (CT) was examined on the patient. CT revealed a mass lesion originating from the left kidney, occupying a large area in the left retroperitoneal area, measuring approximately 20 cm at its largest dimension, partially extending into the bony pelvis, extending from the midline to the right, and containing necrotic areas in the central part (Figure 1A, 1B). In the dynamic examination, the mass showed progressive enhancement in the solid parts, except for the necrotic parts. The mass was observed to significantly compress the renal vein, but thrombosis was not present. Pathological lymph nodes with the largest having a 2-cm short axis, were detected in the right and left paraaortic areas. Magnetic resonance imaging was performed with a preliminary diagnosis of lymphoma and demonstrated mass originating from the left kidney containing cystic necrotic areas with hypointensity in T1-weighted images and hyperintensity in T2-weighted images, and contrast enhancement of solid parts (Figure 2A, 2B). Since a differentiation between lymphoma-Wilms tumor and mesenchymal lesion could not be made, percutaneous tru-cut biopsy was performed from the mass. As a result, the mass was diagnosed as a Wilms tumor. In positron emission tomography

Correspondence: Emre Emekli MD, Etimesgut Şehit Sait Ertürk State Hospital, Clinic of Radiology, Ankara, Turkiye
Phone: +90 505 687 62 32 **E-mail:** emreemekli90@gmail.com **ORCID-ID:** orcid.org/0000-0001-5989-1897
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CT performed for staging purposes, mass lesions with high standardized uptake value:12 values were observed in the mass and aortic lymph nodes. No distant metastasis was detected. Based on the diagnosis of Wilms tumor, the patient was started on neoadjuvant chemotherapy that consisted of ifosfamide, etoposide. After observing a reduction in mass size and tumor regression in control imaging, left radical nephrectomy was performed (Figure 3A, 3B). The operative specimen consisted of left kidney with a portion of the ureter and on gross examination the tumor was 13x9.5x11.5 cm large, white- grayish, solid. The renal capsule, the renal sinus, renal vein were infiltrated by the tumor and the tumor involved lymphovascular spaces. Pathology showed blastemal predominant WT, with a minor epithelioid component. No features of anaplasia were found. The radical nephrectomy pathology result of the patient was evaluated as Stage 3 Wilms tumor. The patient was followed up and no recurrence or metastasis was detected in imaging during the first two years. The patient was followed up with thorax, abdomen and pelvic CT for a 3-month period.

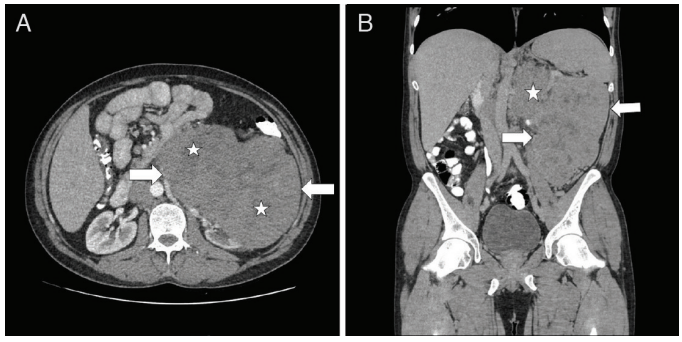

Figure 1. CT examination of the patient before chemotherapy at the time of diagnosis A. Axial and B. Coronal plane CT shows a mass lesion originating from the left kidney (arrow) and containing necrotic areas in the central part (star)

CT: Computed tomography

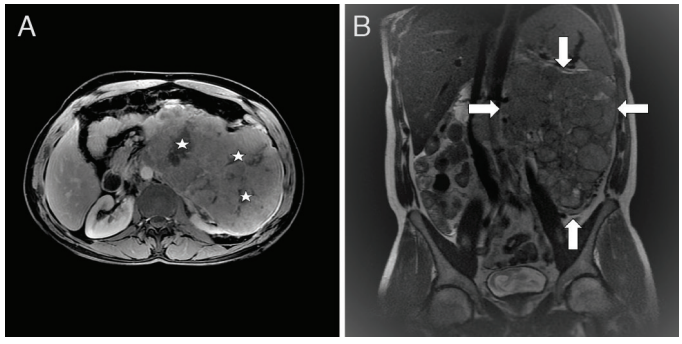

Figure 2. MRI examination of the patient at the time of diagnosis A. Axial T1-weightened MRI shows a mass originating from the left kidney containing cystic necrotic areas with hypointensity (star) and contrast enhancement of solid parts and B. Coronal T2-weightened T2 MRI plane shows mass lesion extending into the bony pelvis, extending from the midline to the right (arrows)

MRI: Magnetic resonance imaging

Liver metastasis emerged in imaging performed at the end of the second year. Abdominal CT examination revealed a newly developed mass in the right lobe of the liver, which was primarily evaluated as a metastasis. The patient underwent right hepatectomy. The pathology metastectomy result of the patient was evaluated as a Wilms tumor metastasis. No recurrence was detected in the next 3 months follow-up abdomen CT. Written and informed consent from the patient was obtained for publishing.

Discussion

Wilm tumor has a poorer prognosis in adults than in children. However, recently, there has been an increase in relative survival. The combination of radiotherapy, chemotherapy and surgery is recommended for treatment. Some studies have reported that the five-year survival rate has increased to 82.6% in the group with favorable histological characteristics (5).

However, despite many developments, the lack of protocols for adults makes the diagnosis, treatment and follow-up of Wilms tumor difficult. Similar to children, treatments vary according to tumor stage and histological type in adults. Due to its lower incidence, no phase 3 studies or treatment guidelines are available for adult Wilms' tumors, and in most isolated cases, the management is extrapolated from pediatric guidelines. The standard pediatric treatment has been proposed by two groups; the International Society of Paediatric Oncology (SIOP) and the National Wilms Tumor Study (NWTS) (6). One of the main differences between the two protocols is that the NWTS approach advocates up-front nephrectomy, whereas the SIOP protocols emphasize neoadjuvant chemotherapy (7). The most effective chemotherapeutics in treatment of nephroblastoma are vincristine, actinomycin D, ifosfamide, carboplatin, cyclophosphamide, etoposide and doxorubicin. According to SIOP, neoadjuvant chemotherapy reduces the risk of tumor rupture and reduces the probability of recurrence (8). This

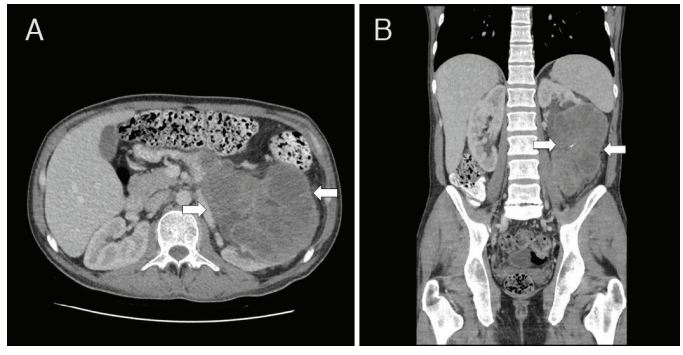

Figure 3. CT examination of the patient after neoadjuvant chemotherapy A. Axial and B. Coronal plane CT shows a reduction in mass size and tumor regression (arrow)

CT: Computed tomography

makes it necessary to make a diagnosis before the operation and accurately stage the tumor (9). But the use of PCB in patients with renal masses is a method that is not widely preferred due to the possibility of tumor seeding and frequent complications, such as bleeding. After imaging in patients with renal masses, the diagnosis is usually made by performing total or partial nephrectomy (10).

Another critical point in adult Wilms tumors is the lack of guidelines on how to follow-up patients after surgery. The current protocol of SIOP surveillance for Wilms' tumor recommends that abdominal imaging and chest X-ray should be performed every 3 months for the first 2 years. imaging is repeated every 4-6 months in the third and fourth years and annually in the fifth year (11). The same recommendation is advised for adults in studies since most of the relapses occur within 2 years of completion of therapy (9).

It has been reported that there may be inadequacies in the differential diagnosis of renal cell carcinoma (RCC) from benign masses, such as lipid-poor angiomyolipoma and renal oncocytoma and malignant masses (12). There are publications showing that clear cell RCC can be distinguished from other masses to a large extent, but the differential diagnosis of other subtypes is mostly impossible (13). In addition, rare mass lesions, such as Wilms tumors are often not considered in differential diagnosis. Mostly, PCB is used only when primary diagnoses, such as lymphoma and urethral carcinoma, are considered based on imaging characteristics or in cases where a differential diagnosis of infection or non-renal mass cannot be made (10).

In PCB studies conducted early in the 21st century, the rate of non-diagnostic PCB was reported as 31%, and the false negativity rate was as high as 25%. Based on these and similar results, PCB was not included in most localized renal mass algorithms (14,15). However, in a more recent study, the diagnosis rate of PCB was reported as 72% for fine-needle biopsy, 87% for core biopsy, and 92% for both (16). In addition, Ozambela et al. (17) determined the rate of PCB-related complications as 5.18% for hematuria and 1.75% for pneumothorax. The rate of others, including perirenal hematoma, pseudoaneurysm, and arteriovenous fistula, was reported to be 0.1%. Despite all these recent developments, when the same authors examined the rate of percutaneous renal mass biopsies (RMB) performed in the USA between 2006 and 2017, they observed that although the number of RMB procedures had increased over the years, this was not sufficient. They also stated that less than 15% of patients with renal masses underwent PCB (17). The American Association of Urology and the American Society of Clinical Oncologists report that the PCB technique is reliable and has high diagnostic value. PCB is indicated in small-sized renal masses that are probably benign, in patients who will be actively monitored due to low life expectancy, and in these cases scheduled for thermal ablation, and when the mass is considered to be of hematological, inflammatory, or infectious origin. In addition, PCB is recommended in cases with Wilms tumor, in which a pathological diagnosis would change the treatment protocol of the patient and impact survival (18,19).

It is known that the earlier chemotherapy is started in adult patients with Wilms tumor, the better survival is, and chemotherapy is recommended before surgery in this patient group. In a previous study, patients who started treatment in the first 30 days after surgery and those who received delayed treatment were compared. The five-year survival rate was 80% in patients who received early treatment, while it was 28.6% in the other group (20). Based on this information, the diagnosis of Wilms tumor based on PCB may start treatment at the earliest stage in these patients. In this study, because of the preliminary diagnosis of lymphoma and Wilms tumor, PCB was performed, which allowed for the early diagnosis of Wilms tumor. Thus, chemotherapy was applied before surgery, and because of the reduction in the size of the mass, the operation was safer. With this case report, we wanted to emphasize the current position and importance of the PCB method in patients with Wilms tumors and renal masses in general.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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