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Original Article

Administering antibiotic-loaded irrigation fluid as an alternative for prophylactic intravenous antibiotics in transurethral ureterolithotripsy (TUL): a randomized controlled trial

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Abstract: Prophylactic antibiotics are commonly used to prevent infections and complications during surgeries. In this study inflammatory responses and infectious complications after utilizing antibiotic-loaded irrigation compared with intravenous (IV) prophylactic antibiotics. Eighty-eight participants with ureteral stones enrolled in this prospective randomized controlled trial. Participants were allocated into two groups, namely "standard" with 45 participants, and "antibiotic-loaded" with 43 participants. The "standard" group received standard normal saline irrigation with 1 gram of IV ceftriaxone 30 minutes before in transurethral ureterolithotripsy (TUL), while the "antibiotic-loaded" group received ceftriaxone-added irrigation fluid and did not receive any IV antibiotics. The laboratory tests, including Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), venous blood gas (VBG), IL-6, creatinine, sodium, potassium, SIRS score, and urine culture were recorded. The continuous variables are described using either mean (standard deviation (SD)) or median (interquartile range (IQR)) and the t-test and Mann-Whitney test are used to infer them. The discrete variables are reported as numbers (percentages) and the Chi-squared test is applied to them. Statistical analyses were performed by the SPSS software (V.26, IBM) with a considering significance criterion of 0.05. Statistically differences were not found in postoperative inflammatory and infectious complications among the two groups (P>0.05) including SIRS score (P=0.385), WBC (P=0.589), IL-6 (P=0.365), ESR (P=0.171), CRP (P=0.279), Platelet (P=0.501), positive urine culture (P=0.922), and post-operative fever (P=0.162). Administering antibiotic-loaded irrigation fluid was as safe and effective as IV ceftriaxone in TUL and could be a reasonable alternative for IV antibiotics.

Keywords: Urolithiasis, transurethral ureterolithotripsy (TUL), infection, prophylactic antibiotic

Introduction

Urolithiasis is a significant cause of morbidity, affecting between 10% and 15% of the world population [1]. The prevalence of urolithiasis has increased because of the effects of obesity, diabetes mellitus, and alternation in eating patterns on the development of urinary stones [2]. The treatment aim for urolithiasis is complete stone clearance. The lack of effective medical therapy makes surgical management the main approach for patients with symptomatic stones. Stone composition, location, size, and patient characteristics should be considered for stone treatment [3, 4]. The development of endoscopic lithotripsy and other techniques has replaced traditional open surgery with endoscopic procedures. Multiple non-invasive or minimally invasive options are available to treat a stone, such as transurethral ureterolithotripsy (TUL), extracorporeal shock wave lithotripsy (SWL), and percutaneous nephrolithotomy (PCNL) [5].

Among these therapeutic modalities for ureteral stones, TUL has a better stone-free rate (SFR)

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with a single procedure. However, regardless of the size, there was a trend for TUL to achieve a better SFR compared to SWL in the patients with <1 cm stone. TUL also was attributed to a lower retreatment rate than SWL. Although TUL has reasonable symptomatic relief and stone-free rates, symptomatic UTI and urosepsis are some of the postoperative complications [6-8].

Following TUL, one of the most common complications leading to hospitalizations is systemic inflammatory response syndrome (SIRS) [9]. SIRS represents an exaggerated physiological response to various harmful stimuli, such as infection, trauma, surgical procedures, acute inflammation, ischemia/reperfusion, and malignancies. This response aims to localize and eliminate the sources of the insult. Despite its defensive intent, the dysregulated release of cytokines can precipitate a significant inflammatory cascade, potentially resulting in vital organ failure and, in severe cases, mortality [10]. Excessive innate immune responses or failure of adaptive immune responses can lead to SIRS, infection, and sepsis [7, 11, 12]. On the other hand, the urinary tract can be exposed to bacteria by instruments inserted into the urinary tract, and by broken stones which lead to infection and inflammation [13]. Cytokines, such as interleukin-6 (IL-6), can be used as an invasive marker to diagnose ureteral damage and infection [14]. Pyelonephritis, prostatitis, epididymitis, and urosepsis can also occur after TUL [15]. These infectious complications can cause morbidity and potential mortality. Efforts must be taken to minimize these complications, especially in high-risk patients, including administration of prophylactic antibiotics, limiting stenting and operation time, and careful therapeutic management for patients suffering large stones and concomitant comorbidities [16].

Prophylactic antibiotics are commonly used to prevent infections and complications during various surgical procedures in urology. The most important purposes of prophylactic antibiotics are to prevent wound infection and decrease febrile infectious complications such as pyelonephritis, prostatitis, epididymitis, and urosepsis [15]. Based on the American Urological Association (AUA) guideline, a single dose of antibiotic prophylaxis is recommended for stone intervention in TUL an hour before the surgery [17].

Administering string local antibiotics is not a new idea. For the first time, carbolic acid was used by Joseph Lister as a local antiseptic on surgical wounds to prevent infection in the mid-1800s [18]. Local antibiotics allow the delivery of high concentrations of antibiotics to the surgery site while having no significant risk of systemic toxicity. The other reason behind using local antibiotics is to deliver high concentrations of antibiotics to eradicate remaining planktonic organisms and sessile organisms in biofilms. High concentrations of antibiotics are effective against biofilms, so local antibiotics may have a remarkable role in diminishing infectious complications [19-21].

During TUL, irrigation is the continuous delivery of saline solution to clear stone fragments. Destruction of stones during TUL may lead to the growth of microorganisms that are integrated into the biofilms, and the migration of bacteria and their toxins in the blood flow due to the hydrostatic pressure generated by the irrigation fluid [22, 23].

Our study objective was to compare the inflammatory responses and infectious complications after utilizing antibiotic-loaded irrigation with systemic antibiotics. The secondary outcome was to evaluate the infectious complications between the two groups.

Materials and methods

Study design

This prospective randomized controlled trial was conducted between October 2023 and March 2024 after signing the written informed consent from the Persian Registry for Stones of Urinary System (PERSUS). The study protocol was approved by the ethics committee of the Tehran University of Medical Sciences on 15 January 2023 (IR.TUMS.SINAHOSPITAL.REC.1402.020). The study was performed following the Helsinki Declaration. This study was also registered and approved by the Iranian Registry of Clinical Trials on 25 September 2023 (IRCT20190624043991N20). All patients signed a written informed consent form before the study initiation. It should also declare that our trial adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement [24].

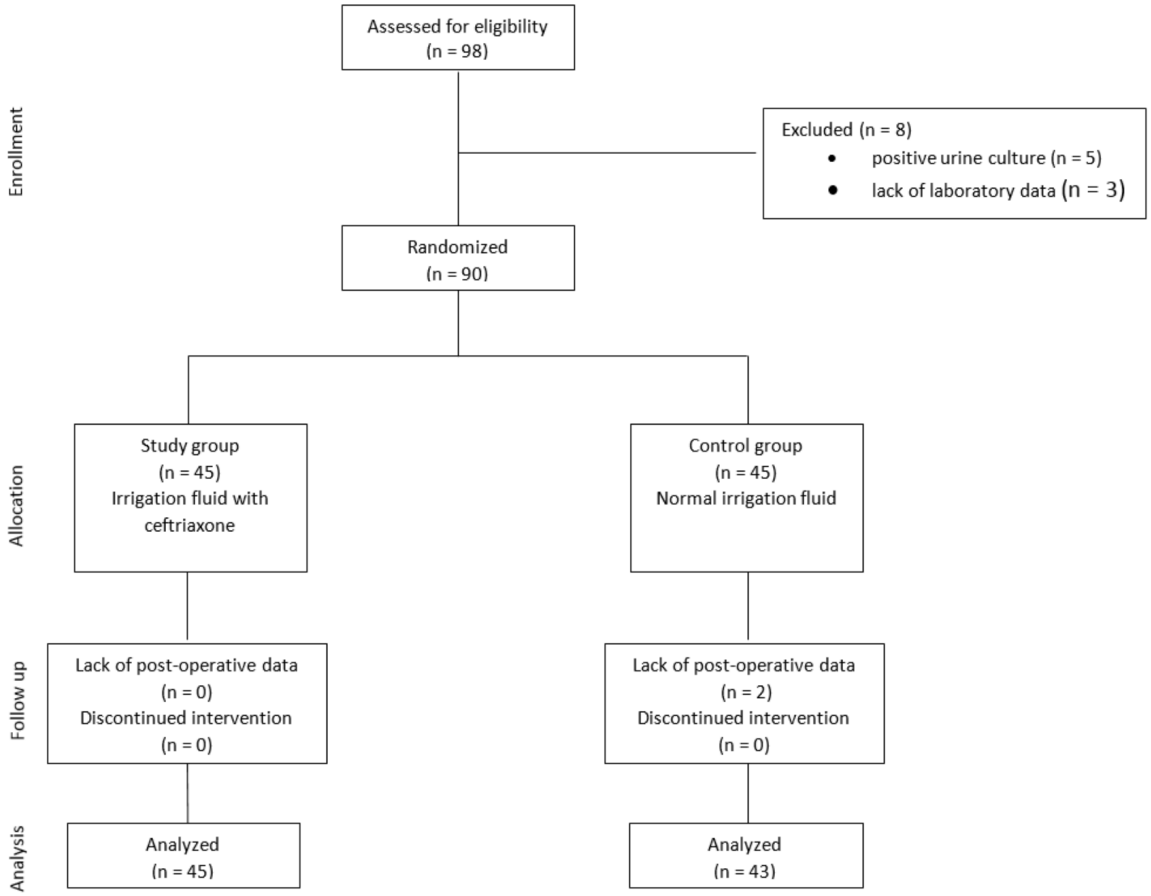

Figure 1. CONSORT flow diagram of the present trial.

Patients

Ninety-eight patients who presented at the urology clinic with ureteral stones were enrolled for the trial (**Figure 1**). The inclusion criteria were: age more than 18, patients with ureteral stones confirmed by non-contrast-enhanced computed scan (CT), stone size less than 2 cm, and willingness to take part in the research. The exclusion criteria were: history of genitourinary surgery, simultaneous renal stone, bilateral ureteral stone, changing therapeutic plan to open surgery, presence of Double J stent, anatomical or functional disorders of the genitourinary system, positive urine culture before surgery, receiving antibiotics within the past three months, severe hydronephrosis, using immunosuppresses drugs before surgery, urinary tract infection (UTI) in past three months, diabetes mellitus, and pregnancy. The consecutive method was used for sampling based on the study by Wollin et al. [22]. The prevalence of complications reported was 9.4%, a=5% ($Z_{1-\frac{\alpha}{2}}$ = 1.96), and e=0.04. The sample size was calculated to be 80.

$$n = \frac{Z^2 \times P \times (1 - P)}{e^2}$$

Data collection

Eighty patients were eligible and randomly allocated to either the “standard” or “antibiotic-loaded” groups. Permuted balanced block randomization was used for randomization and the block size of four was considered four, via web-based block randomization. The laboratory tests, including Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), venous blood gas (VBG), IL-6, creatinine, sodium, potassium, and urine culture, were recorded one hour before the surgery and daily after the procedure for one week. SIRS score was also evaluated for each individual before and after the surgery. To identify

Table 1. A description of variables, compared between two groups

		Antibiotic-loaded	standard	*p*-value
Age, mean (SD)		48.9 (12.8)	46.3 (17.0)	0.417[a]
BMI, mean (SD)		25.8 (2.1)	25.8 (2.8)	0.999[a]
Sex, no. (%)	Male	33 (73.3)	33 (76.7)	0.712[b]
	Female	12 (26.7)	10 (23.3)	
Stone location, no. (%)	Upper ureter	14 (31.1)	7 (16.3)	0.235[b]
	Middle ureter	18 (40)	23 (53.5)	
	Lower ureter	13 (28.9)	13 (30.2)	
Stone size, median (IQR)		9 (7-11)	9 (7-14)	0.584[c]

SD: standard deviation; IQR: interquartile range; BMI: body mass index; a: t-test; b: Chi-squared test; c: Mann-Whitney test.

SIRS criteria, the American College of Chest Physicians in 2001 was used, which requires the presence of ≥2 of the following: temperature greater than 38°C or less than 36°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute or arterial carbon dioxide tension (PaCO2) less than 32 mmHg, and white blood cell count greater than 12,000 cells/μL or less than 4,000 cells/μL.

Our primary objective was to compare the inflammatory responses between two groups including SIRS, WBC, Platelet Interleukin 6, ESR, and CRP. The secondary objective was to evaluate the infectious complications such as post-operative urine culture and post-operative fever.

Surgical procedure

General anesthesia was used for all participants. All patients underwent Transurethral Lithotripsy (TUL) with a semi-rigid 8 Fr ureteroscope (Karl Storz SE, Germany) and pneumatic lithotripter. All surgeries were carried out by 2 expert urologists. Demographic data, including age, sex, body mass index (BMI), and previous urolithiasis were obtained during the first visit. Stone characteristics, including stone size and location, were documented. Complications according to the Clavien-Dindo classification were recorded within one month, other reported items such as any reaction to antibiotics, surgery time, length of hospital stay, re-admission due to Urinary Tract Infection (UTI) or pain, and further need for auxiliary treatment such as Shock Wave Lithotripsy (SW) were evaluated for all patients.

Patients were assigned into two groups - "standard" and "antibiotic-loaded". The "standard" group received normal saline irrigation fluid and 1 gram of intravenous (IV) ceftriaxone 30 minutes before surgery, while the "antibiotic-loaded" group received ceftriaxone-added irrigation fluid and did not receive any IV antibiotics. According to the Clinical & Laboratory Standards Institute (CLSI), the minimum inhibitory concentration (MIC) of ceftriaxone is 7 mg/L, to achieve this concentration in antibiotic-loaded irrigation fluid, 500 mg of ceftriaxone dissolved in 3 L normal saline. All patients were hospitalized for at least 24 hours.

Statistical analysis

The continuous variables are described using either mean (standard deviation (SD)) or median (interquartile range (IQR)) and the t-test and Mann-Whitney test are used to infer them. The discrete variables are reported as numbers (percentages) and the Chi-squared test is applied to them. Statistical analyses were performed by the SPSS software (V.26, IBM) with a considering significance criterion of 0.05. **Figure 1** depicts the flow chart of the study.

Results

Baseline characteristics

We conducted a trial on 88 participants, out of which 22 were female and 66 were male. The sample comprised two groups: antibiotic-loaded and standard (conventional perioperative IV antibiotic), with 45 and 43 patients respectively. The ages of the patients in both groups ranged from 20 to 80 years. Details of the demographics of the patients are given in **Table 1**. The mean age (SD) of the local group was 48.9 (12.8) years, and that of the control group was 46.3 (17.0) years (*p*-value =0.417). The two

Table 2. A description of variables of interest, compared between two groups

		Antibiotic-loaded	Standard	*p*-value
Urine culture (Positive), no. (%)		2 (4.6)	2 (5.0)	0.922[a]
Post-operative fever (T>38°C), no. (%)		2 (4.4)	0 (0)	0.162[a]
Hospital stay (>1), no. (%)		5 (11.4)	4 (9.5)	0.781[a]
Re-admission, no. (%)		1 (2.2)	2 (4.6)	0.612[a]
Need for auxilary treatment, no. (%)		8 (17.7)	10 (23.2)	0.602[a]
GFR (post-operative), mean (SD)		48.66 (12.16)	45.13 (9.78)	0.139[b]
Surgery time		32 (11)	31.5 (17.1)	0.309[c]
SIRS (Yes), no. (%)	Before TUL	6 (13.3)	8 (18.6)	0.499[a]
	After TUL	9 (20.0)	5 (11.6)	0.385[a]
WBC, mean (SD)	Before TUL	8.4 (2.4)	8.2 (2.5)	0.701[b]
	After TUL	7.8 (2.2)	8.0 (2.4)	0.589[b]
Interleukin 6, median (IQR)	Before TUL	16.0 (14.6-16.8)	16.5 (14.8-22.8)	0.093[c]
	After TUL	15.6 (13.6-18.8)	15.5 (14.8-24.8)	0.365[c]
ESR, median (IQR)	Before TUL	15 (12-27)	12 (11-20)	0.164[c]
	After TUL	14 (11-21)	12 (10-19)	0.171[c]
CRP, median (IQR)	Before TUL	12 (9-19)	10.8 (9-12)	0.214[c]
	After TUL	9.2(5.8-13)	10.5 (9-14)	0.279[c]
Platelet, median (IQR)	Before TUL	260 (213-311)	250 (218-302)	0.470[c]
	After TUL	228 (191-282)	223 (191-263)	0.501[c]

SD: standard deviation; IQR: interquartile range; GFR: glomerular filtration rate; SIRS: Systemic inflammatory response syndrome; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TUL: transurethral ureterolithotripsy; a: Chi-squared test; b: t-test; c: Mann-Whitney test.

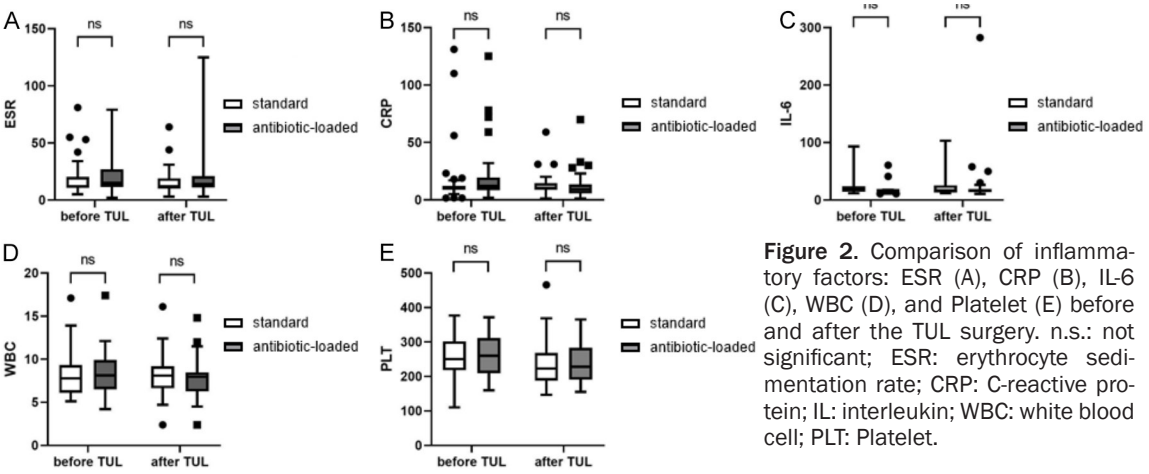

Figure 2. Comparison of inflammatory factors: ESR (A), CRP (B), IL-6 (C), WBC (D), and Platelet (E) before and after the TUL surgery. n.s.: not significant; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IL: interleukin; WBC: white blood cell; PLT: Platelet.

groups had 33 (73.3%) and 33 (76.4%) men respectively (*p*-value =0.712). There were no statistical differences in comorbidities among the groups (*p*-values >0.05). A comparison of other characteristics is presented in **Table 1**, indicating no significant differences. Regarding postoperative complications, no significant differences were found between the two groups. Most of them were Clavien-Dindo grade 1 or 2. Fortunately, none of the patients had allergic reactions to ceftriaxone (in both groups).

Inflammatory responses

The variables of interest were compared in **Table 2**. The SIRS score was evaluated among the patients and there were no differences observed between the two groups (*p*-value =0.385). The inflammatory factors, including WBC (*p*-value =0.589), IL-6 (*p*-value =0.365), ESR (*p*-value =0.171), CRP (*p*-value =0.279), and Platelet (*p*-value =0.501), also showed no differences after the procedure when compar-

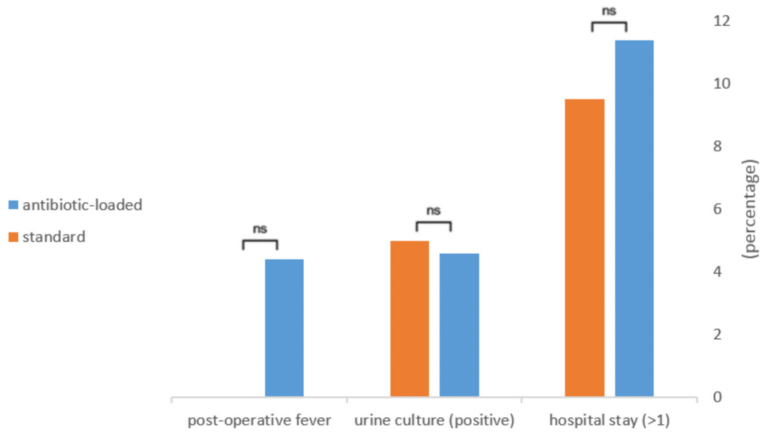

Figure 3. Comparison of post-operative fever, urine culture, and hospital stay after TUL between two groups.

ing the two groups (**Figure 2**). Inflammatory factors were also measured preoperatively and showed no differences between our study groups (**Table 2**).

Infectious complications and surgical outcomes

As shown in **Figure 3** infectious complications such as positive urine culture and post-operative fever were also compared, revealing no significant differences (p-value =0.922 and p-value =0.162, respectively). Comparing GFR (p-value =0.139), hospital stay (p-value =0.781), and surgery time (p-value =0.309) between the two groups, no statistical differences were shown. Re-admission was statistically similar between the two groups with p-value =0.612 (all 3 patients re-admitted due to UTI). 8 (17.7%) patients in the Antibiotic-loaded group and 10 (23.2%) patients in the standard group needed auxiliary treatment, but the difference was insignificant.

Discussion

Antibiotic prophylaxis is recommended in TUL. However, the diagnostic ureteroscopy doesn't require antimicrobial prophylaxis. According to the European Association of Urology (EAU) guideline, there is a lack of high-quality evidence that antibiotic prophylaxis should be given for ureteroscopy stone removal. AUA guideline suggested a single dose of antibiotic prophylaxis for stone intervention in TUL and laparoscopic/robotic stone surgery an hour before the surgery. It is also mentioned that in the case of UTI, the appropriate antibiotic should be initiated. Antibiotic prophylaxis is not recommended in simple, healthy, and asymptomatic outpatient cystoscopy or urodynamic studies. Nevertheless, for asymptomatic bacteriuria that may impact the integrity of urethral mucosa, antimicrobial prophylaxis should be performed [25]. In a meta-analysis by Deng et al., 11 studies with a total of 4,591 patients participated, post-operative febrile UTI risk was evaluated and no significant difference was seen in a single dose of preoperative antibiotic and no antibiotic prophylaxis. However, patients receiving preoperative prophylaxis had a significantly lower risk of pyuria and bacteriuria. In this study, only IV and oral routes were investigated, and no significant difference was seen between two groups [13]. Similarly, another meta-analysis by Lo et al., assessed the efficacy of prophylactic antibiotics against post-TUL infections. Four trials enrolling 500 patients were subjected to their meta-analysis. Findings showed a significant reduction in pyuria with prophylactic antibiotics (risk ratios =0.65) and bacteriuria (risk ratios =0.26). Patients who received prophylactic antibiotics tended to have lower rates of febrile UTI, although the difference was not statistically significant [26]. In a randomized clinical trial by Hsieh et al., 206 patients with preoperative sterile urine undergoing TUL were divided into four groups to receive prophylactic antibiotics with single-dose i.v. cefazolin (1 g), ceftriaxone (1 g), oral levofloxacin (500 mg), or no treatment (control group). Postoperative pyuria was significantly lower with prophylactic antibiotics, especially with levofloxacin and ceftriaxone. Bacteriuria and febrile UTI have shown no significant difference between the four groups [27]. As the literature review showed, prophylactic antibiotics are necessary before TUL to prevent post-operative complications. Our study sought to evaluate the effect of adding ceftriaxone to irrigation fluid as an alternative method for IV ceftriaxone with the hypothesis that antibiotic-loaded irrigation fluid could have the same effect on post-operative inflammatory and infectious complications as IV antibiotics.

In this study, we divided patients into 2 groups of IV antibiotics, as standard group, and Antibiotic-loaded, which received ceftriaxone-added irrigation fluid without IV antibiotics. Our findings revealed that there was no significant difference between the local delivery of ceftriaxone and systemic ceftriaxone administration in the perioperative period. Inflammatory responses including ESR (p-value =0.171), CRP (p-value =0.279), IL-6 (p-value =0.365), WBC (p-value =0.589), Platelet (p-value =0.501), and SIRS (p-value =0.385) score were not statistically different between our study groups. These results showed that ceftriaxone-added irrigation fluid had the same efficacy and potency compared to IV ceftriaxone. Based on these findings, it seems that adding antibiotics to the irrigation fluid is just as effective as using preoperative IV antibiotics as prophylaxis. Intraoperative irrigation with antibiotics or bactericidal agents was previously investigated in general surgery, nevertheless, has not been studied extensively in urology. In a study by Mangold et al., they used intraoperative irrigation with 0.05% chlorhexidine gluconate in cesarean delivery to reduce surgical site infection. Even though the surgical site infection (SSI) was reduced in the study group, the changes were not significant [28]. In another study by Slopnick et al., 216 patients who underwent elective cystoscopy were evaluated. They used polymyxin and neomycin in normal saline for the study group and regular normal saline for the other group as irrigation fluid. In the sixth week of follow-up, they found no significant difference between the groups in terms of post-operative UTI. Findings revealed that antibiotic-loaded irrigation fluid did not impact postoperative infectious complications [29]. On the other hand, in the study by Yildiz et al., gentamicin was added to the irrigation fluid for sterilization of the renal collecting system in RIRS surgery. Postoperative fever, SIRS, and hospital length of stay were significantly lower in the group that received gentamicin-added irrigation fluid. This study showed that antibiotic-loaded irrigation fluid could decrease postoperative infectious complications [30]. In an interesting study by Huen et al. on pediatric patients with neurogenic bladder who perform clean intermittent catheterization, they used a mixture of neomycin and polymyxin instillation to reduce UTI episodes. They concluded that antibiotic bladder instillations decrease the frequency of symptomatic UTIs, emergency department visits for UTIs, inpatient hospitalization, and the need for oral antibiotic prophylaxis. They also found that there was no increase in multidrug resistance (MDR) in UTI organisms with the use of intravesical antibiotic instillation [31].

The presence of stones in the ureter is associated with the presence of bacteria. One of the main complications of ureteroscopic procedures is urosepsis, which occurs in 5% of patients undergoing ureteroscopy for stone disease, according to a meta-analysis performed by Bohjani et al. This can happen due to the release of bacteria after stone breakage. Using irrigation techniques can cause the bacteria to wash back into the renal pelvis and bloodstream [32]. Fragmentation of the stones and using irrigation fluid simultaneously could spread the bacterial population into the calyceal system and cause invasion of the blood vessels. In a study by Croghan et al., the relationship between intrarenal pressure (IRP) and urosepsis was investigated. Among 120 patients 6 developed urosepsis, and the analysis revealed that IRP was significantly higher in those patients. This study showed that irrigation fluid characteristics, such as IRP, can affect post-operative infectious complications, so theoretically, changing other irrigation fluid characteristics like adding antibiotics to the irrigation fluid may help prevent infectious complications [33]. Our result showed no significant differences between the two groups in terms of post-operative fever (p-value =0.162) and post-operative positive urine culture (p-value =0.922). We observed that adding antibiotics to the irrigation fluid was effective in preventing infectious complications.

Previous studies were mostly focused on determining the efficacy of prophylaxis. However, our study seeks to find an alternative prophylaxis method with the same efficacy and potency compared to the standard method. Our study was limited by some factors. Even though it was carried out in a tertiary urological center, it was still a single-center study. Since this was a single-blind RCT it was susceptible to outcome assessment bias and performance bias. Also, single-blind studies cannot effectively control the placebo effect. Further studies should be carried out utilizing different antibiotics to make a better conclusion. Lastly, this was the first study investigating the effect of antibiotics in washing fluid in preventing post-TUL compli-

cations so we did not have other studies with the same condition to compare our results. More research is needed to assess the effect of administrating antibiotics in washing fluid in the future.

Conclusion

In conclusion, using ceftriaxone-added irrigation fluid could be an alternative to administering a single dose of IV antibiotics, which is just as effective in preventing infectious and inflammatory complications in TUL.

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Disclosure of conflict of interest

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