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Are prophylactic antibiotics necessary in patients with preoperative sterile urine undergoing ureterorenoscopic lithotripsy?

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Objective

- To compare the efficacy of prophylactic antibiotics in reducing post-surgical infections in patients undergoing ureterorenoscopic lithotripsy (URSL).

Patients and Methods

- The study was a double-blind, prospective, randomized controlled trial.
- Between 2009 and 2012, 212 patients with preoperative sterile urine undergoing URSL were randomly allocated, in a ratio of 1:1:1:1, to receive prophylactic antibiotics with single-dose i.v. cefazolin (1 g), ceftriaxone (1 g) or oral levofloxacin (500 mg), or no treatment (control group), respectively.
- Urine analysis and urine cultures were obtained between postoperative days 5 and 7.
- Pyuria was defined as ≥10 white blood cells/high power field. Significant bacteriuria was defined as ≥100,000 colony-forming units uropathogens/mL. Febrile urinary tract infection (fUTI) was defined as a body temperature of 38.5 °C with pyuria or significant bacteriuria ≤7 days after surgery.

Results

- In total, 206 patients were eligible for analysis.
- The rates of postoperative pyuria were significantly lower in patients with prophylaxis than in the control group (48.4 vs 64.7%, $P = 0.04$).
- Patients receiving prophylaxis with levofloxacin and ceftriaxone had a significantly lower risk of pyuria compared with the control group (52.0 and 36.5 vs 64.7%, respectively; $P < 0.05$).
- The rates of bacteriuria and fUTI tended to be lower in patients with prophylaxis, although the difference was not significant (4.5 vs 11.8%, $P = 0.09$, 1.3 vs 5.9%, $P = 0.09$).
- There was no significant difference in rates of bacteriuria and fUTI between the four groups. Patients with proximal stones had a higher risk of developing postoperative fUTI (odds ratio 9.35; $P = 0.03$).

Conclusion

- Antibiotic prophylaxis significantly reduces the incidence of pyuria after URSL and tends to diminish the risk of bacteriuria and fUTI.

Keywords

antibiotics, infection, prophylaxis, stones, ureteroscopy

Introduction

Ureterorenoscopic lithotripsy (URSL) is a common urological treatment for ureteric stones. This procedure poses a risk of postoperative UTIs of up to 25% in patients without prophylactic antibiotics [1,2]. Preoperative prophylactic antibiotics play an important role in reducing postoperative surgical site infections; however, only a few randomized controlled trials have compared the efficacy of different regimens of prophylactic antibiotics in preventing surgical site infections after URSL [1,3,4]. These studies showed that preoperative prophylactic antibiotics could significantly reduce bacteriuria after URSL and a variety of prophylactic antibiotic regimens have been suggested by different guidelines [5–7]. The aforementioned studies, however, were conducted mostly a decade ago and, recently, with the development of smaller-calibre semirigid ureteroscopes and the introduction of the holmium:YAG laser, URSL has evolved into a safer and more efficacious method to treat stones. Nonetheless, there is also a growing resistance of antibiotics that may lead to antibiotics failure [8] so the possibility of surgical site infection after URSL may be different from that a decade ago. With these considerations in mind, we conducted a prospective, randomized, double-blind, controlled trial to evaluate the efficacy of prophylactic antibiotics in preventing postoperative infections in patients undergoing ureteroscopic removal of ureteric stones in a single institution.

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Material and Methods

Study Design

All procedures were performed in compliance with the guidelines for good clinical practice and the Declaration of Helsinki. The study was approved by our institutional review board. All patients provided written informed consent before enrolment. The design was a prospective, randomized, double-blinded controlled study.

Participants

From January 2010 to June 2012, patients with ureteric stones and sterile urine scheduled to receive URSL in our institution were invited to participate in the study. To allocate the participants, a computer-generated list of random numbers was used by a study nurse. The patients were randomly allocated, using a randomization ratio of 1:1:1:1, to receive a single dose of i.v. cefazolin (1 g), ceftriaxone (1 g) or oral levofloxacin (500 mg) or no prophylactic antibiotics. The inclusion criteria were patients aged 18–65 years undergoing primary URSL for single ureteric stone without pre-existing ureteric stents. Exclusion criteria were: pyruria (>10 white blood cells per high-power field), positive leukocyte esterase, positive nitrite or bacteruira on preoperative urine analysis; known allergy to quinolone or cephalosporin; having received antibiotics for treatment of UTIs or other infections over the 4-week period before the procedure; and being immunocompromised, such as those patients with liver cirrhosis. The preoperative patient evaluation included a thorough history taking, physical examinations, blood chemistry tests, urine analysis and urine culture. The patients in the experimental groups received a single dose of oral levofloxacin (500 mg) 1–2 h preoperatively, or i.v. cefazolin (1 g) or ceftriaxone (1 g) 30–60 min preoperatively.

Intervention

All the endourological procedures in the present study were performed in a standard suite and a sterile technique was strictly practised and maintained in all cases. We used a 6-F semirigid ureteroscope and a Holmium:YAG laser lithotriptor to break down the stone. Postoperative ureteric stenting was performed with the placement of a 6-F ureteric stent on the relevant side at the surgeon's discretion. Urethral catheters were removed <6 h postoperatively.

Outcomes and Follow-Up

After URSL, patients underwent plain abdominal film of kidney, ureter and bladder assessment on postoperative day 1 for confirmation of stone clearance and urine analysis + urine culture on postoperative days 5–7. Pyuria was defined as ≥10 white blood cells per high-power field. Significant bacteriuria was defined as ≥100,000 colony-forming units uropathogens/mL. Postoperative febrile UTI (fUTI) was defined as a body temperature of ≥38 °C with pyuria or significant bacteriuria over the period of 7 days after the operation. Patients with ureteric stents had these removed on postoperative day 10 to 14 via cystoscopy at clinics.

Sample Size Calculations

The study sample size was calculated in accordance with the 3:1 allocation rule. An α value of 0.05 and a β value of 0.2 were assumed to detect a 16.5% difference in rates of postoperative bacteriuria (25% for the control group and 8.5% for the antibiotics group). The minimum sample sizes to detect statistically significant differences were 53 and 159 patients in the control and the antibiotics group, respectively. We further divided the patients with prophylactic antibiotics, using a randomization ratio of 1:1:1, into three groups, one of which received cefazolin, another ceftriaxone and the other levofloxacin.

Statistical Methods

We used MedCalc® version 12.3.0.0 to analyse the data. Comparisons of variables between patients with and without prophylaxis were performed using the independent *t*-test (continuous data), the chi-squared test or Fisher's exact test (categorical data) and the Mann–Whitney *U*-test (ordinal data). Comparisons of variables among the four groups were performed using ANOVA (continuous data) and the chi-squared test (categorical data) and Kruskal–Wallis (ordinal data). *Post-hoc* analysis with multivariate logistic regression was used to assess the risk factors for postoperative fUTI, i.e. the use of antibiotics or not, location of the ureteric stone (proximal vs middle and distal), operation time (min) and stone size (mm^2).

Results

Participants

Over the period of the study, 730 patients underwent URSL at our institution. After excluding those with UTIs or recent antibiotics use, those aged >65 or <18 years old, those who were immunocompromised, and after exclusion for administrative reasons, 233 patients were invited to participate in the study and a total of 212 patients agreed to join the study. These patients were randomly allocated into four groups. One patient without ureteric stenting was lost to follow-up and five patients did not receive postoperative check-ups of urine analysis and urine culture. Finally, 206 patients were eligible for analysis (Fig. 1).

Baseline Data

Table 1 shows the baseline characteristics and surgical outcomes of the four groups of patients. Age, gender, body

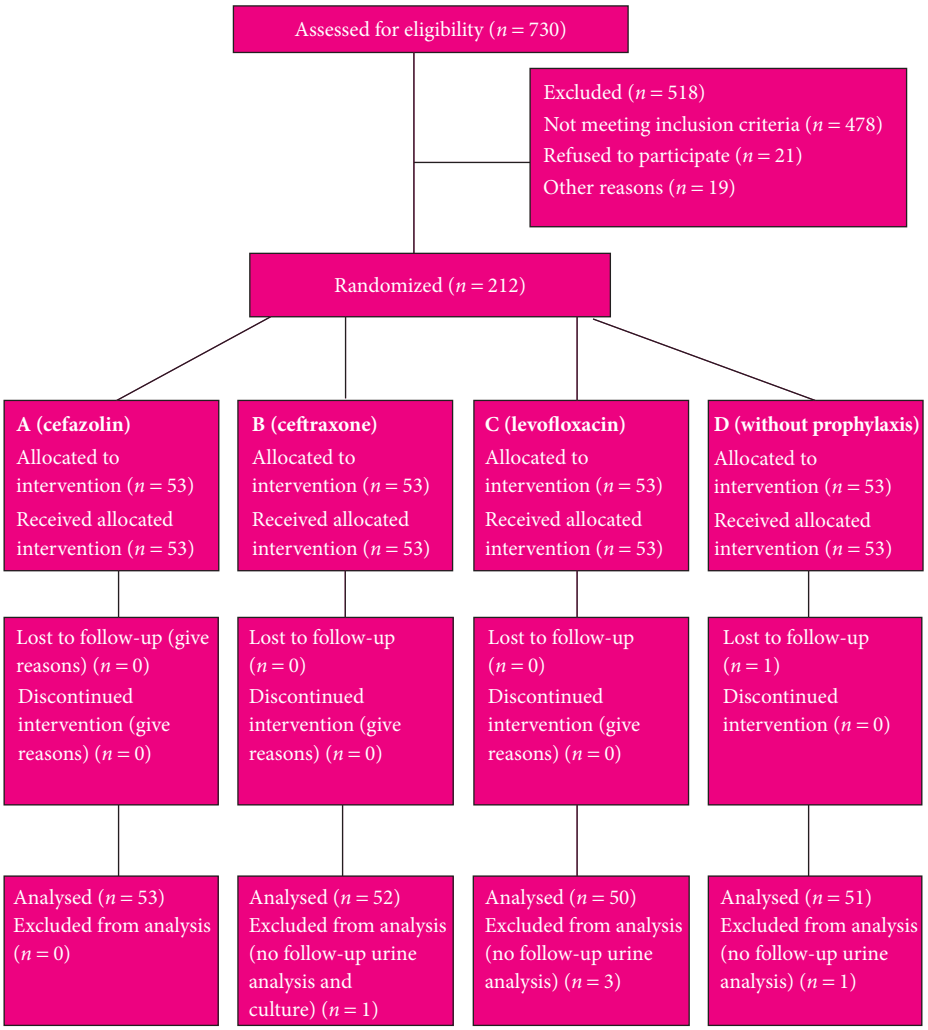

Fig. 1 Flow diagram showing the randomization process for patients who underwent URSL.

Table 1 Demographics and surgical outcomes of the study participants.

	Cefazolin 1000 mg	Ceftriaxone 1000 mg	Levofloxacin 500 mg	Control group: without prophylaxis	*P*
Number of patients	53	52	50	51	N/A
Mean (SD) age, years	46.8 (9.4)	46.3 (9.6)	46.6 (10.8)	47.8 (12.1)	0.89
Gender: male/female	41/12	41/11	41/9	40/11	0.86
Mean (SD) body mass index, kg/m^2	26.1 (3.8)	26.1 (4.7)	25.9 (3.6)	27.5 (4.9)	0.22
Laterality: right/left	26/27	25/27	24/26	26/25	0.97
Location					0.30
Proximal	17	15	14	16	
Middle	8	7	5	7	
Distal	28	30	31	28	
Mean (SD) stone size, mm^2	31.4 (40.5)	31.3 (31.7)	29.4 (24.3)	29.7 (25.6)	0.86
Mean (SD) operation time (min)	29.0 (15.4)	32.3 (25.0)	31.1 (19.7)	33.0 (19.4)	0.76
Ureteric stenting, *n* (%)	51 (96.2)	51 (98.1)	48 (96.0)	50 (98.0)	0.93
Postoperative pyuria, *n* (%)	30 (56.6)	19 (36.5)*	26 (52.0)*	33 (64.7)	0.04
Postoperative fUTI, *n* (%)	1 (1.9)	0 (0)	1 (2)	3 (5.7)	0.27
Stone-free rate, *n* (%)	52 (98.1)	50 (96.1)	47 (94.0)	50 (98.0)	0.93

$P < 0.05$ when compared with patients without prophylactic antibiotics (control group).

Table 2 Bacteria growth in the four groups.

	Cefazolin 1000 mg	Ceftriaxone 1000 mg	Levofloxacin 500 mg	Control group: without prophylaxis	*P*
Number of patients	53	52	50	51	N/A
Bacteriuria*, *n* (%)	3 (5.7)	3 (5.8)	1 (2.0)	6 (11.8)	**0.24**
Urine culture, *n* (%)					
Enterococcus faecalis	1 (1.9)	2 (3.8)	0 (0)	2 (3.8)	
Escherichia coli	2 (3.8)	1 (1.9)	0 (0)	2 (3.8)	
Staphylococcus aureus	0 (0)	0 (0)	0 (0)	1 (1.9)	
Klebsiella pneurnoniae	0 (0)	0 (0)	0 (0)	1 (1.9)	
Staphylococcus haemolyticus	0 (0)	0 (0)	1 (2.0%)	0 (0)	

*There were no significant differences in bacteriuria rates among the four groups of patients. *Growth ≥10^5 colony-forming units per mL.*

Table 3 Baseline data and peri-operative characteristics of the five patients with postoperative fUTI.

Patient	Age, gender	Group	Stone location	Urine culture
A	46 years, male	Cefazolin	Left middle	*E. coli* (ESBL)
B	51 years, male	Control group (without prophylaxis)	Right upper	*E. coli*
C	59 years, male	Levofloxacin	Left upper	No growth
D	60 years, female	Control group (without prophylaxis)	Right upper	Gram(+) cocci <10^5 CFU/mL
E	39 years, male	Control group (without prophylaxis)	Right upper	Enterococcus faecalis

CFU, colony-forming units; ESBL, extended-spectrum β-lactamases.

mass index, stone location and stone size were comparable among the four groups of patients. No significant differences were observed among the groups in the peri-operative variables, including operating times and duration of ureteric stenting.

Outcomes and Estimation

Patients who received prophylactic antibiotics had lower rates of postoperative pyuria than those in the control group (48.4 vs 64.7%, $P = 0.04$). The rates of bacteriuria and fUTI tended to be lower in the patients with prophylactic antibiotics (4.5 vs 11.8%, $P = 0.09$, 1.3 vs 5.9%, $P = 0.09$ [Table 2]).

The postoperative pyuria rates were significantly lower in patients who received prophylaxis with levofloxacin and ceftriaxone. Patients with levofloxacin prophylaxis had relatively lower bacteriuria rates than patients in the control group (11.8 vs 2%, $P = 0.053$). The difference in bacteriuria was not significant between the control and the ceftraixone or the cefazolin group. Similarly, the rates of postoperative fUTI were not significantly different among the four groups because of the relatively small sample size.

The baseline characteristics of the five patients with fever after URSL are shown in Table 3. We found that patients with proximal stones were at a higher risk of developing postoperative fUTI than those with middle and distal ureteric stones (6.5 vs 0.7%, odds ratio [OR] 9.35, 95% CI 1.07–82.0; $P = 0.03$); however, the risk of proximal ureteric stones giving rise to postoperative fUTIs was only close to statistical significance (OR 8.33, 95% CI 1.02–85.3; $P = 0.06$) in multivariate logistic regression after adjusting for the effects of antibiotics prophylaxis (OR 0.25, 95% CI 0.04–1.61, $P = 0.15$). Only six patients did not receive ureteric stenting after URSL, and similar rates of postoperative pyruria and bacteriuria were observed in patients with vs without postoperative ureteric stenting (53 vs 33.3%, $P = 0.34$ and 6.5 vs 0%, $P = 1.0$).

Discussion

The URSL procedure is widely used to treat patients with ureteric stones. Patients with preoperative bacteriuria or UTIs should receive treatment with antibiotics despite the controversy over whether patients with sterile urine should receive prophylactic antibiotics [2]. As there is still no consensus on which kinds of antibiotics should be given, one of the objectives of the present study was to evaluate the efficacy of prophylactic antibiotics in reducing bacteruria after URSL when compared with patients without prophylaxis. Our results showed that patients with prophylactic antibiotics had significantly lower postoperative pyuria rates (48.4 vs 64.7%, $P = 0.04$). The postoperative bacteriuria and fUTI rates tended to be lower in patients with prophylactic antibiotics vs those without (4.5 vs 11.8%, $P = 0.09$ and 1.3 vs 5.9%, $P = 0.09$), although the difference was nonsignificant. The results of sample size calculations showed that the estimated bacteriuria rates were 25% in the control group and 8.5% in the antibiotics group [1]; however, the actual bacteruira rates were relatively lower in patients with and without prophylaxis, which may be attributable to advances in technique and

instrumentation in URSL. As for the comparisons of the four groups of patients, the patients using levofloxacin and ceftriaxone prophylaxis had the lowest rates of pyuria. The rates of bacteriuria tended to be lower in the levofloxacin group than in the control group, though not significantly so. The rates of fUTI were not significantly different among the four groups of patients because of the small sample size.

To date, only four randomized placebo controlled trials have evaluated the efficacy of antibiotics prophylaxis in reducing the infections after URSL. When compared with the control group, the results of the cefotaxime group showed that cefotaxime can reduce the postoperative bacteriuria rates from 25 to 8.5% [1]. Another randomized controlled trial showed that levofloxacin can reduce bacteriuria rates from to 12.5 to 1.8%, while no difference in fUTI was observed [4]. In a recent study, Aghamir et al. [9] enrolled 114 patients undergoing URSL and showed there was no difference in postoperative bacteriuria and fUTI between patients with or without prophylactic (1 gm cefazolin). Chistiano et al. [3] did not show any difference in bacteriuria or fUTI after URSL between patients undergoing prophylaxis with cefazolin and those receiving ciprofloxacin. Based on the aforementioned studies and the present results, we can conclude that preoperative antibiotics can reduce bacteriuria after URSL; however, bacteriuria and pyuria after URSL could only serve as surrogate endpoints for infection complications of URSL. Since the rate of fUTI after URSL is low, the efficacy in reducing post-URSL fever needs more studies or meta-analysis for validation.

The AUA best practice guidelines suggest that all patients undergoing URSL require prophylactic antibiotics with fluoroquinolone or trimethoprim-sulfamethoxazole [7]; but European Association of Urology (EAU) guidelines suggests that patients with proximal ureteric stones should have prophylaxis with third-generation cephalosporin, while distal ureteric stones do not require any prophylactic antibiotics [6]. Japanese urological guidelines recommend the use of first- or second-generation cephalosporin or fluroquinolone for patients undergoing URSL for the duration of 24 to 72 h [5]. Based on the findings of the present study, we cannot conclude which kind of prophylactic antibiotics is more appropriate, but a trend towards less pyuria and less bacteriuria was observed in patients with antibiotics prophylaxis.

The high absorption rate of oral fluoroquinolone and the high concentration of fluoroquinolone in the urine makes oral fluoroquinolone a good candidate for prophylactic antibiotics in the urological field [10]. For patients who undergoTRUS-guided biopsy, single-dose levofloxacin can effectively reduce postoperative infections [11]. In addition, the costs of oral form antibiotics were lower in the levofloxacin groups owing to the simpler use of oral rather than i.v. administration.

Although a trend towards resistance in *Escherichia coli* to levofloxacin has been reported [8], the present data showed that the rates of pyuria and bacteriuria were lower in the levofloxacin group. Patients with levofloxacin prophylaxis had lower bacteriuria rates when compared with the control group (11.8 vs 2%, $P = 0.053$), which was consistent with the findings of Knop et al. [4] that levofloxacin reduced the postoperative bacteriuria rate. These data suggest that use of oral levofloxacin for prophylaxis in patients who underwent URSL may be advocated; however, care should be taken if the area is endemic for quinolone-resistant *E. coli*.

In addition to prophylactic antibiotics, the possible risk factors for postoperative infections include stone sizes, locations, operating time, and the surgeon's experience [12]. EAU guidelines suggest that the risk of developing postoperative infections in patients with a proximal ureteric stone is similar to that in patients with renal stones, and third-generation cephalosporin should be given [6,13]. Similarly, we found that patients with proximal stones were at higher risk of developing postoperative fUTI (4/62 vs 1/144, OR = 9.35, 95 CI = 1.07–82.0; $P = 0.03$) in univariate anaylsis. We suggest, therefore, that all patients with proximal ureteric stones undergo prophylaxis with antibiotics despite having preoperative sterile urine because of the higher risk of developing postoperative fUTI.

Whether ureteric stenting is necessary after uncomplicated URSL is still under debate [14]. A recent meta-analysis showed that ureteric stenting is associated with higher rate of bothersome LUTS [15]. The risk of pyruia or pyelonephritis in non-stented patients tended to be lower but not significantly so (risk ratio = 0.55, 95% CI 0.29–1.07; $P = 0.08$). In the present study, a large proportion of patients (97.1%) underwent ureteric stenting after URSL; therefore, there was no significant difference in postoperative pyruria and bacteriuria between patients with and without postoperative ureteric stenting. As a result, we did not perform multivariate analysis with regard to the effects of ureteric stenting on pyruia, bacteriuria and fUTI after URSL. Whether ureteric stenting is associated with more infectious complications remain unanswered and warrants further studies.

Although the present study was a prospective, double-blind, randomized controlled trial, it was conducted in a single centre. To generalize the results globally, multicentre prospective randomized trials through the auspices of different urological organizations, e.g. the European Society for Infection in Urology of the EAU, will be required to resolve the question of which is the optimum regimen for prevention of UTI in URSL with both good efficacy and lower cost.

Based on the findings of the present study, we also need to know if sterile distal ureteric stone need antibiotics prophylaxis. We did not routinely check the stone analysis and

therefore we did not know the exact effects of the stone components on the postoperative infection rates. Ureteric stones in Taiwan are mostly calcium oxalate and calcium phosphate, which may differ from other areas. In addition, the results of the present study did not answer whether a single dose of antibiotics should be modified to a longer period based on intra-operative findings, i.e. polyps or turbid urine. Lastly, we did not use symptom scores to evaluate the associated symptoms, such as dysuria, urinary frequency and urgency.

In conclusion, although there was no significant difference in postoperative fever between different antibiotics regimens, our results showed that levofloxacin and ceftriaxone were associated with a lower incidence of postoperative pyuria. Proximal ureteric stones were associated with higher rates of postoperative fever, which was consistent with the EAU guidelines that preoperative antibiotics should be given to all patients undergoing ureterorenoscopy for proximal stones.

Conflict of Interest

The study was supported by the Taipei Tzu Chi Hospital, The Buddhist Tzu Chi Medical foundation: TCRD-TPE-99-C1-2, IRB: 98-IRB-019-XD. Nothing to declare for authors.

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Abbreviations: URSL, ureterorenoscopic lithotripsy; fUTI, febrile UTI; OR, odds ratio; EAU, European Association of Urology.