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UROLITHIASIS

Early ureteroscopic treatment in patients with urosepsis associated with ureteral calculi is a safe approach. A pilot study

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Introduction Emergency drainage of the urinary tract is the first necessary approach in patients with urosepsis secondary to obstructive ureteral calculi. The appropriate waiting time before definitive treatment has not been determined. We hypothesized that early ureteroscopic treatment after the patient has been stabilized is as safe as deferred treatment.

Material and methods A pilot study was developed between November 2013 and September 2017. Patients with urosepsis associated with ureteral calculi were included. All the patients were initially decompressed with a ureteral stent. Patients were randomized to early ureteroscopic treatment (EUT), who received definitive treatment during the initial hospitalization, or deferred ureteroscopic treatment (DUT), that received definitive treatment in a second hospitalization. The stone location and size, sex distribution, age, APACHE II score, length of hospital stay, days with ureteral catheter and complications were registered. Statistical analysis was performed using Stata 12.0.

Results A total of 13 patients were included in the EUT group and 13 in the DUT group. No differences in sex distribution, stone location, APACHE II score, age, stone size and time between admission and urinary drainage were found. Total length of hospital stay and complications were also similar between both groups. A statistically significant difference was found in terms of duration of antibiotic treatment ($p = 0.04$) and total days with double J catheter ($p = 0.0009$).

Conclusions EUT for ureteral stone is as safe as DUT in patients admitted with urosepsis secondary to ureterolithiasis. EUT is associated with a shorter period of ureteral stent and it is not associated with an increase in complications.

Key Words: sepsis ‹› ureterolithiasis ‹› ureteroscopy

INTRODUCTION

Urosepsis is an infectious process that is defined as inflammation of the upper urinary tract that causes bacteremia, leading to local and distant tissue destruction [1]. Within the population diagnosed with sepsis, 20 to 30% present with the focus of their infection in the genitourinary tract [2]. Obstructive uropathy is responsible for 78% of urosepsis, while urolithiasis causes 43% of obstructive uropathy in urosepsis [3].

Currently, urosepsis secondary to obstructive urolithiasis is considered to be a life-threatening emergency and it must be treated using dual therapy including broad-spectrum antibiotics and urgent surgical decompression [4]. It is associated with a high mortality rate, up to 19%, if decompression is not performed [5]. The European Urological

Association guidelines recommend antibiotic treatment for several days before stone removal [6]. However, the appropriate waiting time before performing an active treatment such as endoscopic ureterolithotomy (URS) has not been established [5, 6].
We hypothesized that early ureteroscopic treatment during the initial hospitalization after stabilization is a safe treatment in patients with urosepsis secondary to ureterolithiasis.

MATERIAL AND METHODS

Patient demographics

Once approved by the local ethics committee, a pilot study was performed at our institution between November 2013 and September 2017. Patients admitted with urosepsis associated with ureteral calculi were asked to participate in this study. All the patients who volunteered to participate were randomized into two different groups: early ureteroscopic treatment (EUT), who received definitive treatment after 48 to 72 hours of stabilization (defined as no fever, tachypnea, or tachycardia) during the initial hospitalization; or deferred ureteroscopic treatment (DUT), who received definitive treatment during a second hospitalization at least 7 days after discharge. Urosepsis was defined as a positive urine or blood culture plus meeting two or more of the systemic inflammatory response syndrome (SIRS) criteria, as follows: body temperature higher than 38°C or lower than 36°C, heart rate higher than 90/min, hyperventilation as evidenced by respiratory rate higher than 20/min or $PaCO_2$ lower than 32 mmHg, or a white blood cell count higher than 12,000 cells/μL or lower than 4,000/μL [7]. Urine and blood culture results were obtained for all patients at admission.
All the patients underwent decompression using a ureteral stent during the first 12 hours after admission. The APACHE II score was calculated at admission. Stone characteristics (side, location, and diameter), sex distribution, age, and time between admission and urinary drainage were recorded. Endoscopic treatment was performed using a semi-rigid ureteroscope. If there was retropulsion to the kidney, a flexible ureteroscope (Wolf Cobra) was utilized. No pressure system was used in any of these patients. Operating time and complications after the URS were recorded (e.g. fever, sepsis, ureteral injury) and using the Clavien-Dindo classification [8]. Total duration of hospitalization, antibiotic treatment, length of the ureteral stent, and complication rate were also compared. In the DHT group, we considered the initial hospitalization plus the readmission for definitive treatment as the total duration of hospitalization. Association between sepsis severity according to APACHE II score and complications was assessed.

Statistical analysis

Statistical analysis was performed using Stata 12.0v. Categorical variables were compared using Fisher's exact test. Normal distribution was analyzed in continuous variables using the Schapiro-Wilk test. In normally distributed variables, we analyzed the homogeneity of the variance and the correspondence t-test was performed. The Kruskal-Wallis test was used for non-normally distributed variables. P values of <0.05 were considered to be significant.

RESULTS

During the study period, 81 patients were hospitalized for suspicion of sepsis secondary to ureteral calculi. Among them, 53 patients met the selection criteria, and 27 of these patients volunteered to participate in the study (Figure 1). One patient

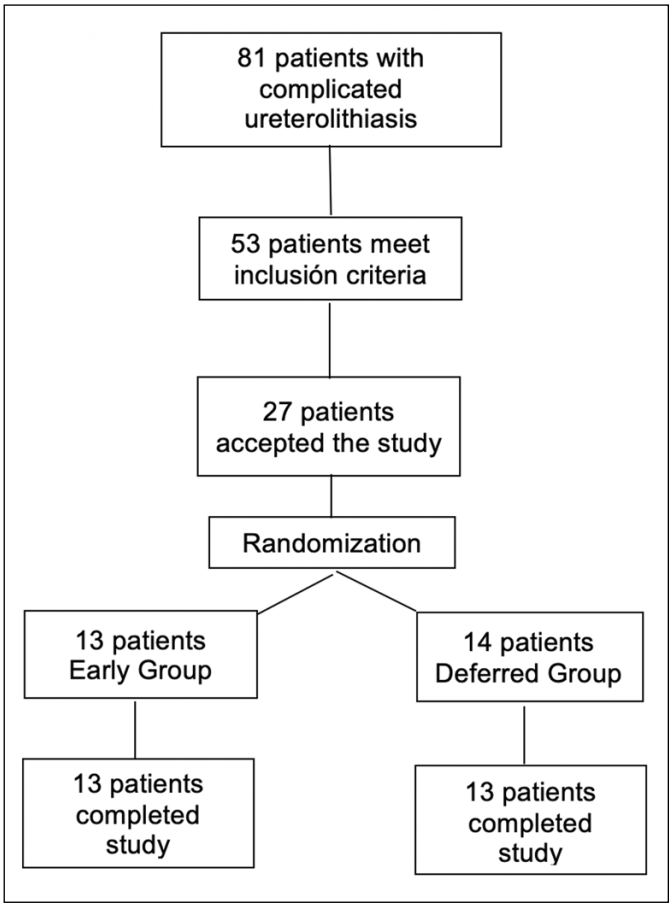

Figure 1. *Flow chart of patients.*

rejected the protocol after the randomization process and withdrew from the study. Thus, there were 13 patients in the EUT group and 13 patients in the DUT group. Mean age was 43 years (standard deviation [SD], 14.9 years) in the DUT group and 49 years (SD, 20.4 years) in the EUT group. Mean stone size was 6 mm (SD, 3 mm) in and 7 mm (SD, 4 mm) in the DUT and EUT groups, respectively. There were no differences in gender distribution, side of ureteral calculi, stone location, or APACHE II score. General characteristics of the population are described in Table 1. Age, stone size, and time between admission and urinary drainage were also similar in both groups. At admission, seven patients (53.8%) from the EUT group and eight patients (61.5%) from the DUT group were managed in the intensive care unit. Ten patients (77%) in the EUT group and 11 patients (85%) in the DUT group had a positive blood culture at the admission (Table 2). Table 3 describes the specific characteristic of every single patient in each group (APACHE II score, initial scheme of antibiotics and complications).

Four patients (15.4%) passed their stone before undergoing endoscopic treatment (three in the DUT group and one in the EUT group). Among the patients who required surgery, 81.8% were treated with a semi-rigid ureteroscope only (ten patients in the EUT group and eight patients in the DUT group). Four patients were treated with a flexible ureteroscope (two patients in each group). All flexible procedures were performed with a 12/14 Fr ureteral access sheath.

Total duration of hospitalization and complications were similar between both groups (Table 4). Among the 26 patients, three had complications. Two of them were in the DUT group, as follows: one ureteral injury that was managed with a postopera-

Table 1. *General characteristics of the population*

	SHT group	DHT group	P value
Female	8 (61.5%)	10 (76.9%)	
Male	5 (38.5%)	3 (23.1%)	0.673
Mean age	49.15	43.15	0.3993
Mean APACHE II	9.3	7.07	0.246
Side of lithiasis			
Right side	8 (61.54%)	5 (38.46%)	
Left side	5 (38.46%)	8 (61.54%)	0.434
Location of lithiasis			
Proximal ureter	6 (46.15%)	4 (30.77%)	
Medium ureter	1 (7.69%)	2 (15.38%)	
Distal ureter	6 (46.15%)	7 (53.85%)	0.751
Mean stone size	7.38 mm	6.07 mm	0.5342

Table 2. *Results of blood and urine cultures*

	Blood culture				Urine culture			
	SHT	%	DHT	%	SHT	%	DHT	%
E. coli	4	40	5	45.45	8	72.7	9	69.23
S. agalactiae	–	0	–	0	2	18.2	–	0
S. epidermidis	1	10	–	0	–	0	–	0
P. mirabilis	1	10	1	9.1	–	0	1	7.69
E. faecium	–	0	–	0	–	0	1	7.69
E. fecaelis	–	0	–	0	–	0	1	7.69
K. pneumoniae	–	0	–	0	–	0	1	7.69
C. albicans	–	0	–	0	1	0	–	0
Negative culture	4	40	5	45.45	–	9.1	–	0
TOTAL	10		11		11		13	

Table 3. *Specific characteristics of all patients*

Patient ID	Study Group	Gender	Age	Stone size	Stone location	APACHE II Score	Days between surgeries	Initial scheme of antibiotics	Operative time	Complications
1	EUT	F	20	3	Distal	5	Passed the stone	Ceftriaxone	–	No
2	EUT	M	47	4	Distal	5	5	Ceftriaxone	45	No
3	EUT	F	64	8	Distal	25	7	Ceftriaxone + Amikacin	30	No
4	EUT	F	43	6	Proximal	2	4	Ceftriaxone	45	No
5	EUT	F	47	4	Proximal	4	4	Ceftriaxone	45	No
6	EUT	M	17	4	Proximal	5	4	Ceftriaxone	45	No
7	EUT	M	55	17	Proximal	9	5	Ceftriaxone	80	No
8	EUT	M	86	10	Proximal	11	7	Ceftriaxone	30	No
9	EUT	F	27	5	Distal	6	9	Imipenem	15	No
10	EUT	F	70	14	Medial	12	4	Ceftriaxone	50	Fever
11	EUT	F	41	6	Distal	7	8	Ceftriaxone	15	No
12	EUT	M	52	11	Proximal	9	7	Ceftriaxone	70	No
13	EUT	F	70	4	Distal	21	3	Piperacillin + Tazobactam	30	No
14	DUT	F	53	10	Distal	7	17	Ceftriaxone + Amikacin	40	No
15	DUT	F	41	7	Proximal	1	28	Ceftriaxone	50	No
16	DUT	M	33	3	Distal	5	Passed the stone	Piperacillin + Tazobactam	30	No
17	DUT	F	41	6	Proximal	10	15	Ceftriaxone + Amikacin	60	Ureteral injury
18	DUT	F	18	4	Medial	2	13	Ceftriaxone	40	No
19	DUT	F	32	3	Distal	3	17	Ceftriaxone + Amikacin	35	No
20	DUT	F	44	9	Medial	2	11	Ceftriaxone + Amikacin	60	No
21	DUT	F	32	4	Proximal	7	9	Ceftriaxone	40	Pain post URS
22	DUT	M	51	7	Distal	15	12	Piperacillin + Tazobactam	30	No
23	DUT	F	40	6	Distal	3	Passed the stone	Ceftriaxone	–	No
24	DUT	F	40	5	Distal	1	13	Ceftriaxone	30	No
25	DUT	F	79	12	Proximal	15	19	Piperacillin + Tazobactam	60	No
26	DUT	M	57	3	Distal	21	Passed the stone	Ceftriaxone + Amikacin	–	No

tive JJ stent (Clavien-Dindo III) and one patient with post-operative uncomplicated renal colic (Clavien-Dindo I). One patient in the EUT group developed post-URS fever (Clavien-Dindo I). No patients died during this study. There was no association between highest APACHE II score (equal or more than 10) and complications ($p = 0.21$).

A statistically significant difference was found in the duration of antibiotics ($p = 0.04$) and total days with a double J catheter ($p = 0.0009$; Table 4). Only one patient in the DUT group received a stent after ureteroscopic treatment while five patients in the EUT group received a stent after URS. These catheters were removed on an outpatient basis and the indwelling time of the catheter was factored into the analysis. No patient received a urethral catheter in any group.

DISCUSSION

Urosepsis is a detrimental systemic response in the host, which develops from a complicated urinary

Table 4. *Outcomes between both groups*

	SHT group	DHT group	P value
Total length of stay (mean)	8	7	0.326
Mean days with JJ stent	8.5	18.38	0.0009
Total length of antibiotic treatment (days)	17.2	19.92	0.04
Postoperative fever	1	0	0.308
Clavien I complications	1	2	1.0

tract infection (UTI), and it is associated with significant morbidity and mortality [9]. A complicated UTI is one that occurs in a patient with a structural or functional abnormality that prevents the flow of urine, and in this study, it was lithiasis [10]. Emergency drainage is a priority treatment in these patients, and the definitive treatment for lithiasis is performed thereafter. However, the length of wait time before definitive treatment is performed has not been defined [11].

For our study, we considered urosepsis to be all patients who had a positive urine or blood culture and who met two or more of the SIRS criteria. We did not exclude patients with a negative urine culture because a negative urine test does not rule out a UTI in the setting of complete obstruction where infected urine may not drain to the bladder [12]. Also, we did not exclude patients with a negative blood culture because sometimes blood cultures may not be positive in septic patients for several reasons such as infection by fastidious organisms, previous antimicrobial therapy, growth inhibitory factors in the blood, and sampling error [13]. Most of our patients in both groups (77% in EUT and 85% in DUT) had a positive blood culture result that was associated with bacteremia. Additionally, the use of two or more SIRS criteria to identify sepsis does not necessarily indicate a dysregulated and potentially life-threatening infection, but the new Sepsis-3 definitions are still not universally accepted and they are becoming controversial [14, 15]. We believe that the combination of the present criteria are a good selection tool to select populations within the scope of this study.

Yousef et al. previously compared the outcomes after ureteroscopic lithotripsy in patients who initially presented with urosepsis using a match-pair analysis. In their study, patients who initially presented with urosepsis were treated definitively after a median duration of 32 days [16]. In our study, the group of patients who received early treatment had a mean of 5.38 days since the initial drainage. Multiple studies have reported a reduced quality of life in patients with a ureteral catheter, with approximately 80% of patients reporting bothersome symptoms and side effects. The use of a ureteral catheter affects several aspects of daily life, and some of the symptoms reported by the patients include symptoms of the lower urinary tract, hematuria, sleep disorders, sexual function and desire, loss of work days, and anxiety [17, 18]. Performing early treatment of the lithiasis and achieving a significant reduction in the time with a catheter should be associated with a considerable reduction of the symptoms that are associated with its use, without an increase in associated complications. Thus, we consider that patients should be treated as soon as possible because a ureteral catheter is associated with a decrease in quality of life and bothersome symptoms such as frequency, urgency, dysuria, or flank pain [19].

Wang et al. recently showed that an immediate ureteroscopic treatment would be safe when performed by experienced surgeons. They did not find an increase in complications between immediate ureteroscopic management or percutaneous nephrostomy, although they described that emergent retrograde ureteroscopic management may lead to increased bacteremia because of the increase in body temperature [20]. In our study, we did not find statistically significant differences in morbidity or total length of hospitalization in patients who underwent early definitive treatment for lithiasis. Fever was not an important complication. In this scenario, we consider that early endoscopic treatment would be a safety option and it was not associated with an increased risk of bacteremia for the patient.

There are several limitations of our study. Half of the patients that met the selection criteria declined to participate in the study. This was a personal decision and it was not related to exclusion of severely ill patients that would lead to a selection bias in the study. It may be because of the patients' fear of participating in clinical studies. We decided to perform the surgery using only the clinical criteria and with no blood test or other information related to the decision process. We believe that this is an easy and efficient way to determine the right time to perform the surgery. Since this is a pilot study

there is a small number of patients included on it. With our results a larger, multi-center study is required to confirm our results.
To the best of our knowledge, there were no published studies that established a definite time for the definitive treatment that is used for ureteral calculus in septic patients who underwent previous drainage. We believe that it is important to develop more prospective studies with a larger number of patients, which can confirm our findings and perhaps establish other benefits or risks for early disease resolution.

CONCLUSIONS

Early ureteroscopic management of ureteral stones is as safe as deferred treatment of patients admitted with urosepsis secondary to ureterolithiasis. Early ureteroscopic treatment is associated with a shorter period with a ureteral stent, which can potentially improve the patients' quality of life and it is not associated to an increase in terms of complications.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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