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Original Article

Risk factors of infectious complications following flexible ureteroscope with a holmium laser: a retrospective study

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Abstract: Purpose: We aimed to evaluate the effectiveness of flexible ureteroscope for treating kidney stones and the risk factors for infectious complications following flexible ureteroscope (FURS) with a holmium laser. Methods: We retrospectively reviewed the data of 227 patients with kidney stones who underwent flexible ureteroscope with a holmium laser at our hospital from January 2012 to September 2014, including gender, age, comorbidity, urine analysis results, urine culture results, blood test results, stone size, operative duration, and residual stones. Patients with and without infectious complications were assigned to groups A and B, respectively. The dependent variables were postoperative infectious complications, and the risk factors for infectious complications following FURS were assessed using Chi-square tests and multivariate logistic regression analyses. Results: All the surgeries were successfully completed. The total stone-free rate was 81.9% (n = 186), and the incidence of infectious complications after FURS was 8.37% (n = 19). Fifteen patients (6.61%) developed fever postoperatively, 10 patients (4.41%) developed systemic inflammatory response syndrome (SIRS), 6 patients with fever were considered to have SIRS (2.64%), and 2 patients had sepsis (0.88%). Univariate analyses of groups A and B indicated that pyuria, stone size, operative duration, and infectious stones were risk factors for infectious complications after FURS ($P < 0.05$). Multivariate logistic regression analyses indicated that pyuria ($P = 0.017$), operative duration ($P = 0.026$), and infectious stones ($P = 0.030$) were independently related to infectious complications. Conclusion: Pyuria, operative duration, and infectious stones were risk factors for infectious complications following FURS. Hence, routine urinalysis findings should be carefully considered, particularly the finding of pyuria.

Keywords: Flexible ureteroscope, kidney stones, infectious complications, risk factors

Introduction

Flexible ureteroscope was first reported in 1964 by Marshall, who explored the ureter by using a 9F pediatric flexible cystoscope, without any working channel or active deflection [1]. Thereafter, Takayasu et al reported the successful use of a deflectable flexible ureteroscope for the management of upper urinary tract diseases [2], and the technology has rapidly developed over the last 10 years. At present, the flexible ureteroscopic procedure is the standard diagnostic and treatment method for upper urinary diseases. Furthermore, the use of a flexible ureteroscope, combined with a holmium laser, for the treatment of kidney stones has gradually become one of the main approaches in lithotripsy.

Nevertheless, postoperative infections are one of the most common complications of this procedure, and the preoperative use of prophylactic antibiotics is insufficient. To our knowledge, only a few clinical studies have reported on the infectious complications developing after FURS, and no studies have focused on the risk factors related to infectious complications. In the present study, we examined the risk factors that may potentially affect the development of infectious complications, including gender, age, comorbidity (diabetes, mellitus, hypertension, hydronephrosis, and renal insufficiency), rou-

tine urinalysis results, urine culture results, stone size, operative duration, residual stones, and stone composition.

Methods

Patients

We retrospectively analyzed the data of 227 patients who underwent FURS for kidney stones in our department from January 2012 to September 2014. The standard preoperative assessments to confirm the location and size of the stone included computer tomography (CT) and intravenous urography (IVP) of the kidney, ureters, and bladder (KUB). A 6-Fr D-J tube was inserted 7-10 days before the procedure, for dilation of the ureter, under local anesthesia. All patients received preoperative antibiotic administration 2-3 days before treatment, and a sterile urine culture was observed before the surgery in all the patients.

Patient demographic data, including age, sex, comorbidity, history of stone surgery, hydronephrosis, routine urinalysis results, urine culture results, stone size, operative duration, residual stones, and stone composition, were obtained. Cases wherein the FURS could not be completed, were excluded from the analysis.

Surgical technique

All the procedures were performed by 2 experienced urologists using a 8.0/9.8-Fr (Karl Storz Endoscope, Tuttlingen, Germany) or an 8.4-Fr (Olympus America Inc., Center Valley, PA, USA) flexible ureteroscope. The patients were placed in the lithotomy position under general anesthesia. Initially, we used foreign body forceps to remove the D-J tube that was placed 7-10 days prior to the operation through a semi-rigid ureteroscope; thereafter, a 0.035-inch Zebra Urologic Guidewire was placed into the renal pelvis under guidance with a rigid ureteroscope. After confirming the placement of the Zebra Urologic Guidewire in the renal pelvis, a Cook F14 Ureteral Access Sheath (UAS, Cook Medical Inc., USA) was placed to establish the working channel. The flexible ureteroscope was then pushed through the sheath, and the stone fragments were crushed by using a holmium laser (Coherent Power Suite, 60 Watts; Lumenis, Israel) with a 200-μm laser fiber. It is recommended that the lower kidney calyces or pyelogenic stones should be pushed back into the renal pelvis or the upper calyx for lithotripsy. Fragmentation was performed until the calculi pieces were reduced to a size of 2-3 mm, and the fragmented stones were extracted using a stone basket (1.7F, NGage, Cook Medical, Inc., USA). The laser energy and pulse frequency were varied on the basis of stone size.

During the procedure, visualization was improved by intermittent active irrigation that was performed by an assistant by using a 50-ml syringe connected to the perfusion line. High intra-kidney pressure was avoided by using a 14F UAS, which enhanced fluid outflow during the procedure. At the end of the procedure, a 4.7 Fr D-J tube (BARD, 4.7F, 28 cm, Germany) was routinely placed and was removed after 3-4 weeks. During the initial 2-3 days postoperatively, intravenous antibiotics were routinely administrated. Assessment of the KUB was performed to assess for the presence of residual stones and the location of the D-J tube at 2 days after FURS.

Definition of infectious complications

Infectious complications were considered to be present when patients exhibited a fever of > 38°C that persisted for 48 h, acute pyelonephritis, positive results in blood culture, and sepsis. The occurrence of fever postoperatively was defined as an increase in the body temperature to > 38°C, which persisted for 48 h [3]. Sepsis was defined as the presence of systemic inflammatory response syndrome (SIRS) that was caused by a suspected infection. According to the definition of SIRS by the American College of Chest Physicians and the Society of Critical Care Medicine in 2001, the patients should meet 2 or more of the following diagnostic criteria for SIRS: body temperature > 38°C or < 36°C; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg; and white blood cell count > 12,000 cells/μL or < 4,000 cells/μL [4].

Grouping of patients and statistical analysis

The patients with infectious complications were assigned to group A, whereas those without infectious complications were assigned to group B. The retrospectively collected data, including sex, age, comorbidity, history of stone surgery, urine culture results, pyuria, stone size, operative duration, and residual stones,

Table 1. Patients' data and univariate analysis of risk factors for postoperative infectious complications

Variables	Group A n = 19	Group B n = 208	*p* Value
Gender			
Male	7	111	0.168[b]
Female	12	97	
Mean age (years)	51.4 ± 15.2	48.2 ± 14.2	0.248[a]
Diabetes mellitus	2	14	0.630[c]
Hypertension	4	21	0.281[c]
Renal insufficiency	4	19	0.211[c]
Hydronephrosis	9	115	0.507[b]
History of stone surgery	10	89	0.408[b]
Urine culture			
Positive	6	33	0.082[b]
Negative	13	187	
Pyuria	15	83	0.001[b]
Stone size (cm)	2.06 ± 0.43	1.66 ± 0.52	0.000[a]
Operative duration (min)	99.42 ± 19.08	73.37 ± 19.37	0.000[a]
Residual stones	6	35	0.110[b]
Infectious stones	5	8	0.016[b]

Kidney insufficiency is defined as the presence of a preoperative serum creatinine level of ≥ 133 μmol/L. Pyuria is defined as the presence of ≥ 10 leukocytes/mL of urine on direct microscopy. [a]Mann-Whitney U test, [b]Chi-square, and [c]Fischer's exact test. Values are presented as mean ± standard deviation or number.

Table 2. Results of urine culture examinations

Bacterial species	Group A (n)	Group B (n)
Escherichia coli	2	12
Enterococcus faecalis	2	7
Proteus mirabilis	1	3
Enterobacter cloacae	0	3
Staphylococcus epidermidis	0	2
Klebsiella pneumoniae	0	2
Candida albicans	1	1
Pseudomonas aeruginosa	0	1
Hemolytic streptococcus	0	1
Burkholderia cepacia	0	1

were compared between the 2 groups by using univariate analyses (including the Mann-Whitney U test, Chi-square test, and Fischer's exact test) and multivariate logistic regression analysis with SPSS software. *P* values of < 0.05 were considered statistically significant.

Results

Flexible ureteroscope with a holmium laser was performed successfully in 227 patients, including 118 men (52%) and 109 women (48%). The mean age of the patients was 48.5 years (range, 16-79 years). Of these patients, 16 had diabetes mellitus, 25 had hypertension, and 124 had hydronephrosis. Moreover, 99 patients had a history of prior surgery, including percutaneous nephrolithotomy, ureteroscopic lithotripsy, and extracorporeal shock wave lithotripsy. Furthermore, 23 patients exhibited chronic renal insufficiency (creatinine, 133-335 mmol/L) and 39 patients had a positive urine culture. Routine urinalysis showed that the urinary leukocyte count ranged from 0 to 6531 cells/ml, and 98 patients had pyuria (**Table 1**).

Infectious complications were noted in 19 cases. Fifteen patients (6.61%) had fever postoperatively, including 8 patients with high fever (body temperature ≥ 39.5°C) and shivering. Ten patients were considered to have SIRS (4.41%), 6 patients with fever were considered to have SIRS (2.64%), and 2 patients developed sepsis (0.88%). All the patients underwent blood culture examinations and endotoxin level measurement. Four patients had bacteremia. Escherichia coli was found in 2 cases, Staphylococcus aureus was noted in 1 case, and Klebsiella pneumoniae was noted in 1 case. The endotoxin levels were increased in 16 patients (84.21%). However, all the patients recovered due to timely and effective treatment.

All the patients underwent urine culture examinations preoperatively, and 188 (83.70%) exhibited negative results, whereas 39 (17.18%) exhibited positive results. The results of urine culture are as follows: E. coli, 14 cases; Enterococcus faecalis, 9 cases; Proteus mirabilis, 4 cases; Enterobacter cloacae, 3 cases; S. aureus, 2 cases; K. pneumoniae, 2 cases; Candida albicans, 2 cases; Pseudomonas aeruginosa, 1 case; hemolytic streptococcus, 1 case; and Burkholderia cepacia, 1 case.

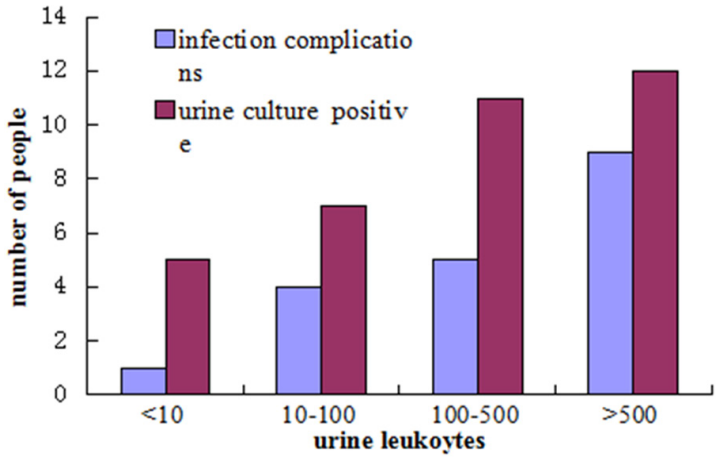

Figure 1. The relationship between urinary leukocyte count and infectious complications.

Infectious complications developed among 6 patients (15.38%; 6/39) with positive urine culture results and among 13 patients (6.91%; 13/188) with negative urine culture results (χ^2 = 3.021, P = 0.082) (**Table 2**).

Urinalysis indicated the presence of pyuria in 98 patients, including 15 patients (78.95%) in group A and 83 patients (39.90%) in group B (P < 0.05). Most of the patients who developed infectious complications had a urinary leukocyte count of > 10 cells/ml in routine urinalysis. After the routine urinalysis results of all patients were considered, we observed that the incidence of infection increased with an increase of the urinary leukocyte count (r = 0.977, P = 0.023) (**Figure 1**).

The overall stone-free rate was approximately 75.3% (171/227) after FURS with a holmium laser, which increased to 81.9% (186/227) at the 1-month follow-up assessment. The stone-free rates were lower in group A than in group B (63.16% vs. 83.17%; P = 0.110). The average operative duration was 75.2 min (range, 44-125 min). However, cases with larger stone burdens showed longer operative durations; the stones ranged from 0.8 cm to 2.5 cm in diameter, and included single and multiple stones. Compared with patients in group B, the patients in group A had significantly larger stone burdens (2.06 ± 0.43 vs. 1.66 ± 0.52, P < 0.05) and longer operative durations (99.42 ± 19.08 min vs. 73.37 ± 19.37 min; P < 0.05).

The stones were examined using an infrared spectrometric analyzer in all the cases. Urinary stones were most commonly composed of calcium oxalate (142 patients, 76.34%). Stone analysis indicated that 13 patients had infectious stones (including carbonate apatite and magnesium ammonium phosphate), 2 had uric acid stones (1.08%), and the remaining had stones with a mixed composition (30.84%). In addition, 5 patients with infectious struvite stones developed infectious complications; thus, the incidence of infectious complications among patients with infectious struvite stones was higher than that of patients with other stones (5/13, 38.46% vs. 14/214, 6.54%; P < 0.05).

Univariate analyses indicated that pyuria, stone size, operative duration, and infectious stones were significantly different between groups A and B (P < 0.05) (**Table 1**). Furthermore, multivariate logistic regression analyses of these risk factors indicated that pyuria, operative duration, and infectious stones were independently associated with infectious complications (odds ratio > 1, P < 0.05) (**Table 3**).

Discussion

The popularity of FURS in the management of kidney stones has increased given its low morbidity rates and high efficacy [5, 6]. Colic, fever, hematuria, pyelonephritis, and urosepsis are the most common postoperative complications following FURS. Many studies have assessed the use of prophylactic antibiotics in the management of upper urinary tract stones; although prophylactic antibiotics are commonly and conventionally used to prevent infectious complications, they appear to be insufficient [7-9]. O'Keeffe et al. reported that the incidence of septic shock was approximately 1.3% after endoscopic procedures for upper urinary tract stones, and the mortality rate was 66% in their series [10]. To our knowledge, only a few studies are performed on the risk factors for infectious complications after FURS. Without timely treatment, the patient may develop severe infectious complications. Therefore, the prevention of postoperative infections is very important.

Table 3. Multivariate logistic regression analyses of variables associated with infectious complications

	B	S.E.	Wals	*P* value	OR	OR (95% CI)	
						Lower	Upper
Pyuria	1.669	.697	5.731	.017	5.307	1.353	20.807
Stone size	1.212	.694	3.050	.081	3.360	.862	13.091
Operative duration	.037	.017	4.927	.026	1.038	1.004	1.072
Infectious stones	1.706	.787	4.701	.030	5.507	1.178	25.744

CI, confidence interval; OR, odds ratio.

Recent studies have indicated that SIRS is a simple and useful predictor for assessing the early stage of sepsis. As the incidence of severe infectious complications such as sepsis is very low, we used fever or/and SIRS as a clinical marker. These markers may be more reliable in the determination of risk factors for infectious complications following FURS. The incidence rate of postoperative infectious complications ranged from 1.7% to 18.8% in the studies in the literature (**Table 4**). However, the incidence of infectious complications was 8.37% in the present study.

Pyuria was an important risk factor for postoperative infections in the present study. Although urine culture is a standard method for diagnosing urinary tract infections, the incidence of a positive urine culture result was very low. Hence, a positive result of urine culture alone cannot be considered, and clinical evidence of pyuria should also be considered when managing upper urinary tract stones. In particular, the presence of ≥ 10 leukocytes/ml of urine on direct microscopy was closely correlated with symptomatic and culture-proven urinary tract infections [20]. Rao et al reported that bacteriuria and pyuria were risk factors for bacteremia, and that preoperative bacteriuria had a positive predictive value of 0.53 for the detection of preoperative endotoxemia (which was itself an important risk factor for urosepsis) [21]. Moreover, Matlaga et al considered that urinary tract infection may be a contraindication for FURS due to the potential for urosepsis [22].

The results of routine urinalysis should be carefully considered, particularly when a finding of pyuria is noted. Fifteen patients with pyuria developed infectious complications, whereas 6 patients with positive urine culture results and 13 patients with sterile urine had infectious complications. The Chi-square test indicated that the presence of a positive urine culture result may not be statistically significant, which may be due to preoperative antibiotic administration and the limited number of cases. Mariappan et al showed that a routine urine culture had a rather low predictive value for infectious complications and that a direct culture of the renal pelvis and a stone culture were better predictors for infection [23].

The European Association of Urology Guidelines recommend the use of cephalosporin or fluoroquinolone as prophylactic antibiotics prior to diagnostic ureteroscope and ureteroscopic lithotripsy [24]; however, no reports have recommended when the prophylactic antibiotics should be administered, Kumer and Mariappan reported that prophylactic antibiotic administration at 1 week before percutaneous nephrolithotomy (PCNL) could significantly reduce the risk of urosepsis [9, 25]. In the present study, all the patients received preoperative antibiotic administration for 2-3 days. The relatively lower incidence of infectious complication following FURS may be due to this routine administration of antibiotics. Although cases of infectious complication may be rarely encountered, any patient who experiences significant changes should be carefully examined and monitored.

The operative duration was another risk factor for infectious complications. In the 27 patients in the present study, the mean operative duration was 75.2 min (range, 44-125). Moreover, the patients with infectious complications had a significantly longer operative duration (mean time, 99.42 min). Furthermore, operative duration is one of the important factors associated with postoperative fever. In the present study, 14 patients (73.68%) developed infectious complications following FURS with an operative duration of > 90 min, whereas only 5 patients (26.32%) developed infectious complications following FURS with an operative duration of < 90 min. In addition, operative duration has been reported as an important risk factor for postoperative fever or sepsis during PCNL [10, 26]. Operative duration was found to be closely associated with the complexity of stone, difficult anatomy, and technical experience.

Univariate analysis indicated that the presence of larger-sized stones was another risk factor for postoperative infections. Twelve patients (15.58%) with a stone size of ≥ 2 cm had infectious complications, whereas only 7 patients

Table 4. A Review of the literature concerning infectious complication

Authors	Patients (n)	Stone size	Mean operative duration (min)	Infectious complications (n)
Hyams et al [11]	120	2-3 cm	74	Fever (1) Pyelonephritis (1)
Mariani [12]	16	41-97 mm	49	Fever (3)
Riley et al [13]	22	2.5-5 cm	72	Urosepsis (1)
El-Anany et al [14]	30	> 2 cm	85	Fever (2)
Akman et al [15]	34	2-4 cm	58.2	Fever (1) Urosepsis (1)
Zhang et al [16]	44	14.9 ± 2.3 mm	67.2	Fever (3)
Pan et al [17]	56	2-3 cm	NA	Fever (4) Urosepsis (3)
Breda et al [18]	15	2-2.5 cm	83.3	Fever (2)
Gu et al [19]	77	< 2 cm	42	Fever (3)

NA, Not analyzed.

(4.64%) with a stone size of < 2 cm had infectious complications. Takazawa et al reported that kidney stones with a size of ≥ 2 cm treated with flexible ureteroscope presented with a higher severity of fever and urosepsis [27]. In the management of a large stone burden, it is not necessary to fragment all the stones into small pieces, and it may be suitable only to reduce the stone size to 3-4 mm; otherwise, it would prolong the operative duration and increase the possibility of injuring the mucosa of renal pelvis with the holmium laser. At present, PCNL is the gold standard treatment modality for kidney stones larger than 2 cm in size, and FURS is considered as an alternative treatment to PCNL in specific cases with larger renal stones [15].

In the present study, 5 cases (38.46%) had infectious struvite stones, which indicated a higher possibility of infection as compared to other stone types. Mcaleer reported that infectious stones contain an average endotoxin level of 12223 ng/g, as compared to the 340.3 ng/g of endotoxin in normal stones; moreover, it is easier to identify the endotoxin in infectious stones [28]. The bacteria in the stones as well as the endotoxin may increase the risk of postoperative infection. Patients with infectious stones were reported to have a high risk of postoperative infectious complications [29], and residual infectious stone debris may act as a nidus for stone regrowth and future infections [30].

During the operation, the renal pelvis must be continuously irrigated to provide appropriate visibility for the surgeon. Although the indwelling UAS helped to reduce the renal pelvic pressure during FURS, the drainage effect deteriorated when the flexible ureteroscope was placed into the UAS. When perfusion fluid accumulates to a certain extent, the high pressure may cause pyelovenous backflow; consequently, bacteria and bacterial endotoxins can enter the bloodstream along with perfusion fluid absorption, and cause postoperative fever, bacteremia, or even sepsis However, we were unable to assess renal pelvic pressure in the present study, and were hence unable to assess these risk factors, However, it appears that the maintenance of low pressure in the renal pelvis may help reduce the intraoperative absorption of lavage fluid and the incidence of postoperative fever and bacteremia [31].

The present study indicated that the risk factors for infectious complications include pyuria, operative duration, and infectious stones. Based on our experience in the present study, we observed that urinary tract infection with pyuria should be controlled before FURS is performed, through the routine administration of antibiotics, based on the results of tests sensitive to the medication; FURS is a deliberate choice for managing cases with large stone burdens (> 2 cm); and the improvement of surgical skills and equipment is essential for achieving an appropriate operative duration. However, the limited number of cases, the retrospective study design, and the inclusion of only a single institution only enabled the assessment of a few risk factors. In future studies, the pressure of the renal pelvis will also be examined.

In the present retrospective study, we observed that pyuria and operative duration are indepen-

dently related to the development of infectious complications following FURS. Hence, the results of routine urinalysis should be carefully considered, particularly the presence of pyuria. We recommend that antibiotics should be routinely administered to patients 2-3 days before FURS is performed, particularly for patients with pyuria. Furthermore, the operative duration should be controlled to the extent possible. Thus, early recognition and treatment are effective for decreasing the occurrence of infectious complications.

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Disclosure of conflict of interest

None.

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