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Original Article

Retrospectively analysis of risk factors for systemic inflammatory response syndrome following retrograde intrarenal stone surgery

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Abstract: Purpose: This study aimed to analyze the risk factors that affect the development of postoperative systemic inflammatory response syndrome (SIRS) following retrograde intrarenal stone surgery (RIRS). Patients and methods: We retrospectively analyzed the data of RIRS in the treatment of renal stones between August 2010 and January 2014. The patients were divided into two groups as patients developing SIRS and not developing SIRS. Univariate and multivariate statistical analyses were performed to determine factors affecting the development of SIRS. Results: The study included 320 patients (185 males and 135 females), among whom 12.5% (40/320) developed SIRS. In the univariate analysis, there was significant difference between the two groups in mean stone size (P=0.001), access (P=0.001), operative time (P=0.02), Urine culture (P=0.001), renal pelvis urine culture (P=0.001), stone culture (P=0.001), and rate of irrigation (P=0.001). While age, gender, history of stone surgery, hydronephrosis, stone composition were not related to the development of SIRS. Multivariate analysis further confirmed that access (P=0.021), stone size (P=0.03), operative duration (P=0.026), renal pelvis urine culture (P<0.001) and stone culture (P<0.001) were the risk factors of RIRS-associated SIRS. Conclusions: Access, stone size, operative duration, RPUC and SC are significant predictors of SIRS following RIRS.

Keywords: Renal stone, systemic inflammatory response syndrome, retrograde intrarenal stone surgery, risk factors

Introduction

In recent years, the application of flexible ureteroscopy, combined with holmium laser for treatment Kidney stone have been expanded, flexible ureteroscopy lithotripsy often appear infectious complications after surgery [1]. Many researches focus on complications after Percutaneous nephrolithotomy (PCNL), although PCNL was an effective surgical method, much researches indicated these patients with complicated stones who underwent PCNL may develop postoperative systemic inflammatory response syndrome (SIRS), with a small percent even lead to multiple organ dysfunction syndrome (MODS) [2], patients with SIRS require more therapy, unplanned increase in level of care and prolonged hospitalization, and higher costs [3]. So far, the major causes for SIRS following RIRS are not studied. No one can explain it exactly, therefore, an investigative basis needed be established for prevention of SIRS.

In order to investigate risk factors, we add more factors as possible causes in our research, we examined the risk factors that may potentially affect the development of SIRS, including gender, age, hydronephrosis, stone size, operative duration, stone composition, access, rate of irrigation, preoperative UC, renal pelvis urine culture (RPUC), stone culture (SC). We retrospectively assessed the relationship between these risk factors and post-RIRS SIRS.

Patients and methods

Patients

Between August 2010 and January 2014, a total of 320 patients with the complete data admitted for RIRS were included in our department, this study was approved by ethical committee of Renmin Hospital of Wuhan University and all patients need to sign informed consent at preoperation. Patients were recruited from Department of Urology, The exclusion criteria

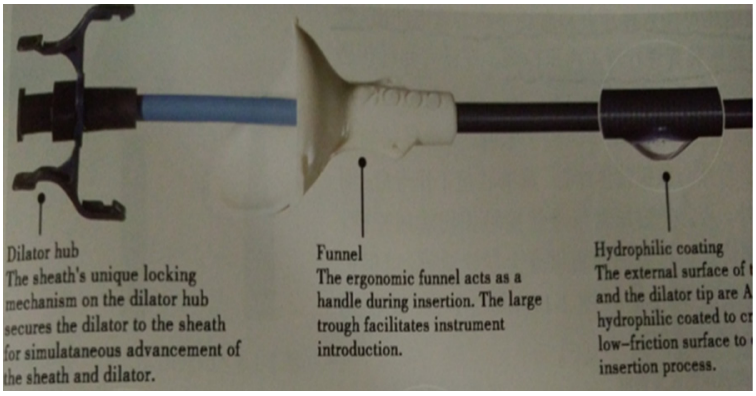

Figure 1. Single ureteral access sheath (single-UAS, COOK).

Figure 2. Dual-lumen ureteral access sheath (Dual-lumen UAS, COOK).

was designed: patients with tumors, diabetes mellitus, hematopathy, those who taking immunosuppressants, patients with a horseshoe kidney, polycystic kidney or ureteropelvic junction stricture, having a heart rate higher than 90 beats/min before surgery, those with heart or kidney failure, preoperative fever treated by antibiotics, or a RIRS in combination with PCNL in same patient.

Preoperative examination including, a medical history, the middle urine culture (UC, a week before operation), an ultrasound, a complete blood count, Preoperative assessments to confirm the location and size of the stone included computer tomography (CT) and intravenous urography (IVU) of the kidney, ureters, and bladder (KUB), all patients received ceftriaxone 2.0 g intravenously if they were not allergic to penicillin 3 days before RIRS. Then, ceftriaxone intravenously was provided for three days after RIRS to control a general infection.

Methods

All procedures were performed by the same experienced urologist with a standard technique, after induction of general anesthesia was completed, patients were placed in the lithotomy position, then, under the help of cystoscopy, a guide wire (Sensor®, Boston Scientific, Natick, USA) was placed into the renal pelvis, a 4-F ureteral catheter was insered into the renal pelvis for collecting renal pelvis urine culture (RPUC), using a F14 ureteral access sheath (UAS) to established the working channel, there were two kinds of UAS-single UAS (**Figure 1**) and dual-lumen UAS (**Figure 2**). A standard Storz Flex-X™ flexible ureteroscope, 7.5F, was passed along the access sheath into the renal pelvis, we used isotonic saline as the irrigation fluid. Flexible ureteroscope was conducted and all stones were broken up by holmium laser (Coherent Power Suite, 60 Watts; Lumenis, Israel). The small fragments were removed by forceps and irrigation fluid. A sample of the extracted stones was washed by 0.9% normal saline, then crushed to powder form, Packed in sterile tubes and sent to laboratory for stone culture (SC). After operation, a 5 Fr D-J tube (BARD, Germany) was placed and was removed after 4 weeks.

SIRS was diagnosed in patients who met two or more of the following four criteria [4]: (i) body temperature lower than 36°C or higher than 38°C; (ii) heart rate greater than 90 beats/min; (iii) respiratory rate greater than 20 breaths/min or $PaCO_2$ less than 4.3 kPa; and (iv) white blood cell count (WBC) greater than 12×10^9/L or less than 4×10^9/L.

In our study, 320 patients were treated with RIRS, no one need to blood transfusion, 40 (12.5%) of which developed SIRS (SIRS group) and 280 (87.5%) did not developed (Non-SIRS group). For these two groups, general factors of patients include: gender, age, history of stone surgery, hydronephrosis, mean stone size;

Table 1. The clinical characteristics and data of the patients treated with RIRS

	Non-SIRS 280 (87.5%)	SIRS 40 (12.5%)	*P*
Gender Male:Female	160:120	25:15	0.203
Age, year (rang)	45.3±9.2 (20-75)	48.2±11.5 (21-79)	0.157
History of stone surgery			
No	232 (82.9%)	26 (65.0%)	0.426
Yes	48 (17.1%)	14 (35%)	
Hydroneprosis			
Yes	130 (46.4%)	30 (75.0%)	0.811
No	150 (53.6%)	10 (25.0%)	
Mean stone size (cm)	1.5±0.8	1.8±0.9	0.001
Stone composition			
Pelvis	213 (76.1%)	31 (77.5%)	0.347
Pelvis + calyx	67 (23.9%)	9 (22.5%)	
Access			
Single-UAS	31 (11.1%)	35 (87.5%)	0.001
Dual-lumen UAS	249 (88.9%)	5 (12.5%)	
Rate of Irrigation (ml/min)	39.2±2.3	75.6±11.3	0.001
Operative time (min)	70.6±23.5	98.1±11.6	0.02

Table 2. Results of Urine and stone culture

	SIRS 40 (12.5%)	Non-SIRS 280 (87.5%)	*P*
UC			
Pos	13 (32.5%)	29 (10.4%)	0.001
Neg	27 (67.5%)	251 (89.6%)	
RPUC			
Pos	10 (25.0%)	12 (4.3%)	0.001
Neg	30 (75.0%)	268 (95.7%)	
SC			
Pos	19 (47.5%)	13 (4.6%)	0.001
Neg	21 (52.5%)	267 (95.4%)	

operative factors (access, rate of irrigation fluid and mean operative time), preoperative UC, intraoperative renal pelvic urine culture (RPUC), and SC were compared. All patients' important signs were exactly recorded for 24 hours and blood cell analysis was examined to help with the diagnosis of SIRS the next day.

Statistical analysis

In the statistical analysis, all data were conducted by the statistical package of the social sciences (SPSS) for Windows version 20.0. All data are recorded as the mean ± SD. Univariate analysis was used (Student's t test for parametric variables and Kruskall-Wallis test for nonparametric variables) to find the major risk factors for the development of SIRS after RIRS SIRS. Chi square test and Fisher's exact test were used for the comparison of ratios. Multivariate logistic regression analysis with SPSS software we defined $P<0.05$ was considered statistically significant.

Results

A total of 320 patients who underwent RIRS were retrospectively analyzed, **Table 1** lists the clinical characteristics and data of the patients treated with RIRS. In this study, the average age was 46.7±3.2 years (range 20-79 years). Among them there were 185 (57.8%) men and 135 (42.2%) women, after operation, 40 (12.5%) of which developed SIRS (SIRS group) and 280 (87.5%) did not developed (Non-SIRS group), in two groups, no one developed septic shock, All patients recovered satisfactorily.

Relevant risk factors of SIRS we listed in **Tables 1** and **2**, we used univariate test analysis, gender ($P=0.203$), average age ($P=0.157$), history of stone surgery ($P=0.426$), hydronephrosis ($P=0.811$), stone composition ($P=0.347$) were not remarkable difference between the two groups ($P>0.05$), similarly on univariate analysis, the incidence of SIRS correlation with mean stone size ($P=0.001$), access ($P=0.001$), operative time ($P=0.02$), UC ($P=0.001$), RPUC ($P=0.001$), SC ($P=0.001$). Rate of Irrigation ($P=0.001$) remained important predictors of a postoperative systemic response.

In **Table 2** listed results of Urine and stone culture, including preoperative UC, intraoperative RPUG, and stone culture (SC). 42 patients (13.1%) preoperative UC were positive, these patients were treated by antibiotics before operation, 22 cases (7.9%) were positive in RPUC, SC was positive in 32 cases. In this reserach, we found that the most common source of infection was Escherichia coli, followed by

Table 3. Bacterial characterization detected in cultures

	UC		RPUC		SC	
	SIRS 13 (32.5%)	Non-SIRS 29 (10.4%)	SIRS 10 (25.0%)	Non-SIRS 12 (4.3%)	SIRS 19 (47.5%)	Non-SIRS 13 (4.6%)
E.coli	11	21	5	8	9	7
Staphylococcus	1	4	2	-	5	2
Enterococcus	1	2	-	2	2	4
Klebsiella	-	2	2	1	2	-
Pseudomonas	-	-	1	1	1	-

Table 4. Multivariate logistic regression analyses of variables associated with SIRS

	OR (95% CI)	*P*
Access	3.090 (1.186, 8.049)	0.021
Stone size	5.507 (1.178, 25.744)	0.03
Operative time	1.041 (1.004, 1.072)	0.026
RPUC	0.091 (0.036, 0.208)	<0.001
SC	0.159 (0.058, 0.422)	<0.001

Staphylococcus, Enterococcus, Klebsiella, Pseudomonas (**Table 3**).

Multivariate logistic regression analyses of these risk factors indicated that access, stone size, operative duration, RPUCs and SCs were independently associated with SIRS (**Table 4**, $P<0.05$).

We observed a post-procedural systemic inflammatory response in 40 patients (12.5%), 2 of them with Post-RIRS SIRS needed particular care treatment (high fever with body temperayure >39.6°C), Blood cultures no bacterial growth. 278 (86.9%) patients exhibited negative results preoperative UC, only 42 (13.1%) exhibited positive results.

Discussion

The widespread popularity of RIRS in the management of renal stones has increased given its low morbidity rates and high efficacy [5]. Postoperative fever after RIRS was the most common complication, it can be progressed to urosepsis and septic shock in some cases [6]. Probably most SIRS patients recovered without severe sequelae; some surgeons may ignore the risk of SIRS. Although prophylactic antibiotics are commonly and conventionally used to prevent infectious complications, they appear to be insufficient, several studies reported the incidence of SIRS after PCNL of 11.2-37% [7-10]. O'Keeffe 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 [11]. We found a 12.5% incidence rate in our study. So far, few studies focus on risk factors for systemic inflammatory response syndrome following retrograde intrarenal stone surgery. Untreated can lead to serious complications.

In this study, we used SIRS as an important marker to determinate risk factors following RIRS. At present, it has remained a challenge to predict which patients will develop SIRS after RIRS. Previous researches showed that gender, age, history of stone surgery, hydroneprosis [12], stone composition, stone type [13] were factors associated with post-PCNL SIRS. We established that these parameters did not correlate with the occurrence of post-RIRS SIRS. Univariate analyses indicated that stone size, access, operative duration, rate of Irrigation, and UCs, SCs, RPUCs were significantly different in both group ($P<0.05$) (**Tables 1** and **2**). Furthermore, multivariate logistic regression analyses of these risk factors indicated that access, stone size, operative duration, RPUCs and SCs were independently associated with SIRS (**Table 4**, $P<0.05$).

Stone size was a important risk factors for Post-RIRS SIRS, 33 patients with a stone size >2 cm had SIRS, whereas only 7 patients with a stone size <2 cm had SIRS, it may due to increase the possibility of injuring the mucosa of renal pelvis with the holmium laser and prolong the operative duration in management of large stone size. Researches indicated that stone size of >2 cm treated by flexible ureteroscope presented with a higher severity of fever and urosepsis [14]. RIRS should be considered as an alternative treatment to PCNL in specific cases with larger renal stones [15].

The operative time was another risk factor for SIRS. In our study, mean operation time was 78 min (range, 53-121), 32 patients developed SIRS following RIRS with an operative time of >90 min, whereas only 8 patients developed SIRS with an operative duration of <90 min, Operative time has been reported as an important risk factor for postoperative fever or sepsis during PCNL [16]. Multivariate logistic regression analyses indicated that operative duration was independently associated with SIRS (P<0.05).

Continuously irrigated fluid needed to provide appropriate visibility for the surgeon during the operation, it can increase renal pelvic pressure, the high pressure (>40 cm H_2O) may cause pyelovenous backflow and servere injury of renal [17]. Besides, bacteria and bacterial endotoxins can enter into the bloodstream along with perfusion fluid absorption, then caused fever or SIRS. The indwelling UAS helped to reduce the renal pelvic pressure during operation. Laboratory data reported by Rehman [18] have shown that the simultaneous use of the UAS with pressurized irrigation through the flexible ureteroscope enhances visualization of the upper tract while maintaining low (<40 cm H_2O) intrapelvic pressures because of the rapid outflow through the UAS. However, we were unable to assess renal pelvic pressure in this study. In Non-SIRS group, 249 (88.9%) patients underwent by dual-lumen UAS, 5 (12.5%) patients in SIRS group underwent by Single-UAS, two groups showed significant difference (P=0.001). Many researches indicated that keep a Low pressure of the renal pelvis may help decrease the incidence of post-RIRS SIRS or fever [19].

The results of urine culture should be carefully considered, a reliable and easy metric such as UCs, RPUCs, or SCs would prove useful to predict post-RIRS SIRS. At most facilities, it is common practice to culture bladder urine preoperatively to identify potentially offending bacteria in the upper tract. However, preoperative UCs does not always correlate with SCs and RPUC, Mariappan [20] studied the correlation of midstream urine, pelvic urine, and fragmented SCs. UCs was positive in 11.1% of patients, while SCs and RPUCs were positive in 35.2 and 20.4%, respectively. Only three patients (5.6%) had positive UC with positive SC and/or RPUC. In a large retrospective study of 338 patients who underwent PCNL 82 (24.2%) had postoperative fever, which progressed to sepsis in 5 (1.5%) [21]. Of the 82 patients with SIRS 54 (66%) had negative urine cultures and the remaining 34% with positive cultures were treated with culture specific antibiotics until urine cultures yielded no bacterial growth. Eswara [22] reported 274 patients underwent FURS and 54 patients underwent PCNL, 3% of the patients occurred sepsis, these patients preoperative middle urine cultures were negative, but 70% of the patients SCs culture were positive. Our results indicated that UCs was not a independently associated with SIRS (P>0.05). Mariappan demonstrated that a positive stone and pelvic UCs increases the risk of developing SIRS following the procedure by fourfold, Our study supports these findings by showing that patients with postoperative SIRS had a significantly higher prevalence of positive RPUCs and SCs. Unfortunately, SC and RPUC did not provide immediate results which are usually available only 48 h after surgery, but these results are helpful if fever persists for more than 48 h after surgery.

Our study indicated that the risk factors include access, stone size, operative duration, RPUCs and SCs. Based on our experience in this study, RIRS is a deliberate choice for managing cases with large stone size (*>2 cm*); Use dual-lumen UAS if possible; urinary tract infection should be controlled before RIRS; Postoperative use sensitive antimicrobial agents according to the result of SCs and RPUCs; and the improvement of surgical skills is essential to reduce operative duration as possible. However, the retrospective study design, the limited number of cases in our study, and the inclusion of only a single institution only enabled the assessment of a few risk factors. In future studies, we will measure the pressure of the renal pelvis via other ways to assess the relation with post-RIRS SIRS.

Conclusions

In this study, we observed that access, stone size, operative duration, RPUCs and SCs were independently associated with the development of Post-RIRS SIRS. We recommend collecting RPUCs and SCs to identify the offending organism and guide treatment because intraoperative cultures may be essential in directing the antibiotic regimen postoperatively and

should be routinely used to prevent the progression to clinical septic shock in patients with post-RIRS SIRS.

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Disclosure of conflict of interest

None.

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