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Original Article

Clinical efficacy of flexible ureteroscopic lithotripsy with holmium laser and microchannel percutaneous nephrolithotripsy for upper ureteral calculi and their effects on oxidative stress and inflammatory factors

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Abstract: Objective: This study set out to determine the clinical efficacy of flexible ureteroscopic lithotripsy (FURL) with holmium laser and microchannel percutaneous nephrolithotripsy (mPCNL) for upper ureteral calculi and their effects on oxidative stress and inflammatory factors. Methods: This study recruited 128 patients with upper ureteral calculi, including 64 patients in the observation group treated with FURL with holmium laser, and the other 64 patients in the control group were treated with mPCNL. The two cohorts of patients were compared with respect to operation time, intraoperative blood loss and stone-free rate (SFR), postoperative hospital stay, and preoperative and postoperative renal function indexes, as well as levels of inflammatory factors and oxidative stress factors. Results: No significant differences were observed in the operation time and SFR between the two groups (P>0.05). Intraoperative blood loss and postoperative hospital stay were lower in the observation group than in the control group (P<0.05). Serum creatinine (Scr) increased while estimated glomerular filtration rate (eGFR) reduced in both groups 3 days after operation (P<0.05). On day 3 and day 7 after operation, the levels of malonaldehyde (MDA) and C-reactive protein (CRP) increased in both groups, and increased first and then decreased (P<0.01); while the levels of superoxide dismutase (SOD) decreased, and showed a reduction at first and an increase afterwards (P<0.001). In comparison with the control group, MDA was lower while SOD was higher in the observation group 3 and 7 days after operation (P<0.001). Conclusion: Compared with mPCNL, FURL with holmium laser is effective in treating upper ureteral calculi, with less damage to the body, less impact on renal function, and more effective reduction of inflammation and oxidative factors in the body.

Keywords: Flexible ureteroscopy, microchannel percutaneous nephrolithotripsy, upper ureteral calculi, clinical efficacy, oxidative stress, inflammatory factors

Introduction

Upper ureteral calculi, a common and frequently occurring disease in urology has an incidence rate of 1-5% and a recurrence rate as high as 50%, it also shows an increasing annual trend [1]. The formation of stones is related to the decrease of daily urination, which causes the precipitation of calcium oxalate, calcium carbonate and other substances with low solubility in urine to form tiny calculi [2, 3]. Its primary clinical manifestations are hematuria and lumbago, and can be complicated with secondary infections of ureteral obstructions. In case of severe obstruction, it can lead to severe hydronephrosis, which may further affect renal function and lead to obstructive nephropathy [4, 5]. As to the treatment, surgery is available for patients who fail to respond to conservative treatment [6]. Currently, microchannel percutaneous nephrolithotripsy (mPCNL) is widely used in clinic because of its high stone-free rate (SFR) and minimally invasive surgery [7, 8]. Meanwhile, the development and application of holmium laser technology has driven the gradual popularization of ureteroscopic holmium laser lithotripsy in clinical treatment of upper ureteral calculi [9]. Studies have shown that flexible ureteroscopic lithotripsy (FURL) with holmium laser is more effective than rigid ureteroscopy in treating this disease [10, 11]. Clinical studies indicate that mPCNL has a

higher SFR than FURL with holmium laser. Another study revealed that for the treatment of upper ureteral calculi, the treatment efficacy of FURL with holmium laser is equivalent to that of mPCNL; however, the former causes less damage to the body, so the clinical efficacy of the two approaches remains controversial [12, 13]. In light of this, this study compared the treatment efficacy of FURL with holmium laser and mPCNL for upper ureteral calculi, aiming to provide more evidence for clinical research.

Materials and methods

Patient clinical data

With the approval of the hospital Ethics Committee, 128 patients (age: 18-65 years, average age: 37.5±9.7 years) with upper ureteral calculi treated in the Department of Urology of our hospital from May 2019 to August 2020 were enrolled and randomized into the observation group (n=64) for FURL with holmium laser and the control group (n=64) for mPCNL. All the enrolled patients signed the informed consent form.

Inclusion criteria

Patients: (1) Conformed to the diagnostic criteria of upper ureteral calculi [14]. (2) Aged ≥18 years; (3) With stone size between 1 and 4 cm (including 1 cm and 4 cm), and the stone location was above the fourth lumbar vertebra; (4) With American Society of Anesthesiologist (ASA) grade I-III; (5) With normal coagulation and bone marrow function; (6) With complete clinical data.

Exclusion criteria

Patients (1) with stone >4 cm or stone position lower than the fourth lumbar vertebra; (2) with abnormal coagulation or bone marrow function; (3) with hepatorenal insufficiency; (4) with surgical contraindications.

Surgical methods

Patients with pre-operative urinary tract infection were given anti-infection treatment, while those without were given routine antibiotics to prevent infection.

Control group: the patient was placed in the lithotomy position after general anesthesia, and the ureteral catheter F5 (Cook Medical, USA) was inserted retrogradely with a cystoscope and fixed. Then the renal area of the patient in a prone position was elevated with a back cushion, and 0.9% normal saline was injected into the ureteral catheter to cause kidney hydronephrosis. The best puncture point was selected according to the location of hydrops, and a successful puncture was indicated when urine or purulent fluid was discharged during the puncture. After that, the Zebra Urological Guidewire was inserted through the puncture needle sheath, and the fascial dilator was used to expand to the size of F18. Thereafter, the Peelway sheath was indwelt in the dilated passage and the ureteroscope was inserted to locate the calculi. Holmium laser lithotripsy was then performed, and saline was used for irrigation and washing. After lithotripsy, the residual stones and bleeding were observed carefully, the ureteroscope and ureteral catheter were removed, while the F5 double J tubes and nephrostomy tube were retained.

Observation group: after general anesthesia, the ureteral lumen of the patient in a lithotomy position was checked by rigid ureteroscope, and the guide wire was placed in the ureteral lumen. Then, the soft ureteroscope sheath was inserted along the guide wire, and the ureteroscope was placed along the guide wire to locate the stone. The stones were then demolished by holmium laser and rinsed with normal saline. For larger stones, they were removed by ureteroscopic basket extraction. After lithotripsy, the residual stones and bleeding were observed carefully, the ureteroscope was removed, while the F5 double J tubes were retained.

Routine anti-infection treatment was given after the operation. The nephrostomy tube was removed 4-5 days after operation in the control group, while double J tubes 4 weeks after operation in both groups.

Outcome measures

Primary outcome measures: (1) Operation related indexes: operation time and postoperative hospital stay, as well as intraoperative blood loss and SFR were recorded in the two groups. The SFR standard was based on the 2014 Chinese Guidelines for the Diagnosis and Treatment of urological diseases [15]. (2) Renal function indexes: Venous blood (5 mL) was collected from patients before and 3 days after operation for the determination of serum creatinine (Scr) and estimated glomerular filtra-

Table 1. The CKD-EPI equation

Gender	Age (years)	GFR (CKD-EPI) ($mL \cdot min^{-1}(1.73\ m^2)^{-1}$)
Female	≤62	$144 \times (Scr/62)^{-0.329} \times (0.993)^{age}$
	>62	$144 \times (Scr/62)^{-1.209} \times (0.993)^{age}$
Male	≤80	$141 \times (Scr/80)^{-0.411} \times (0.993)^{age}$
	>80	$141 \times (Scr/80)^{-1.209} \times (0.993)^{age}$

Note: CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; Scr: serum creatinine.

tion rate (eGFR) that calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (**Table 1**). (3) Inflammatory factors and oxidative stress indicators: two tubes of venous blood (5 mL each) were drawn from patients before operation and 3 days and 7 days after operation for the detection of C-reactive protein (CRP), malonaldehyde (MDA) and superoxide dismutase (SOD) in serum by means of serum enzyme-linked immunosorbent assay (ELISA). All the kits were purchased from Nanjing Jiancheng Bioengineering Institute, China.

Secondary outcome measures: Postoperative complications: postoperative complications such as fever and bleeding were observed and recorded in the two groups.

Statistical methods

The collected data were analyzed by SPSS 17.0 statistical software. Recorded as mean ± standard deviation ($\bar{x} \pm sd$), the continuous variables conforming to a normal distribution and homogeneity of variance were analyzed by the independent sample t test and expressed as t. Inter-group comparison was performed using the independent sample t-test, while intra-group comparison before and after treatment was conducted by the paired sample t-test. Data at multiple time points were analyzed using repeated measures analysis of variance combined with post-event Bonferroni test. The counting data were analyzed by Pearson Chi-square test and expressed as χ^2. The level of significance was taken as $P<0.05$.

Results

Comparison of general data between the two groups

The two groups showed no significant difference in general data ($P>0.05$; **Table 2**).

Comparison of intraoperative indicators between the two groups

Operation time and SFR did not reveal any significant difference between the observation group and the control group ($P>0.05$), while less intraoperative blood loss and shorter postoperative hospital stay were observed in the observation group ($P<0.001$; **Table 3**).

Comparison of renal function indexes between the two groups before and after operation

The pre-treatment Scr and eGFR levels showed no evident difference between the two groups ($P>0.05$). On the 3rd day after operation, however, Scr increased and eGFR decreased in both groups ($P<0.001$), with lower Scr and higher eGFR in the observation group ($P<0.001$; **Table 4** and **Figures 1**, **2**).

Comparison of oxidative stress factors between the two groups before and after operation

Significant differences were absent in MDA and SOD levels between the two groups before operation ($P>0.05$). At 3 and 7 days after operation, however, MDA was found to be increased in the two groups, and it increased first and decreased afterwards ($P<0.001$); while SOD decreased, and showed a reduction at first and an increase afterwards ($P<0.001$). In comparison with the control group, MDA was lower while SOD was higher in the observation group 3 and 7 days after operation ($P<0.001$; **Table 5**).

Comparison of inflammatory factors between the two groups before and after operation

The pre-treatment CRP levels showed no statistical difference between the two groups ($P>0.05$). However, CRP levels were increased in both groups after operation, and they increased first and decreased afterwards ($P<0.01$). The levels of CRP in the observation group were lower than those in the control group 3 and 7 days after operation ($P<0.001$; **Table 6**).

Comparison of postoperative complications between the two groups

There were 5 cases of fever and 2 cases of bleeding in the observation group after opera-

Table 2. Comparison of general information ($\bar{x}$ ± sd, n)

	Observation group (n=64)	Control group (n=64)	χ^2/t	P
Gender (male/female)	39/25	36/28	0.290	0.590
Age (years)	37.4±9.6	37.9±9.8	0.292	0.771
Body mass index (kg/m^2)	23.69±2.85	23.19±3.06	0.957	0.341
Stone size (cm)	2.18±0.71	2.21±0.75	0.232	0.817
Stone number	2.7±1.0	2.7±1.1	0.378	0.706
Type of stone (n)			0.325	0.850
Ipsilateral ureteral calculi with renal pelvis and calyceal calculi	29	27		
Multiple renal pelvis and calyceal calculi	30	33		
Staghorn calculi	5	4		
Associated diseases				
Type 2 diabetes mellitus	14	10	0.821	0.365
Coronary heart disease	17	19	0.155	0.694
Obesity	13	16	0.401	0.526
hyperuricemia	21	26	0.841	0.359
X-ray examination			2.032	0.154
Displayable	62	64		
Not displayable	2	0		
Stone composition			0.586	0.994
Calcium carbonate	21	18		
Calcium oxalate	12	13		
Phosphate	18	20		
Uric acid	2	3		
Cystine	1	1		
Dihydroxyadenine	1	1		
Others	9	8		

Table 3. Comparison of intraoperative indicators ($\bar{x}$ ± sd, n)

	Observation group (n=64)	Control group (n=64)	χ^2/t	P
Operation time (min)	73.59±18.46	68.79±14.89	1.169	0.108
Intraoperative blood loss (mL)	15.69±6.47	37.92±16.75	9.904	<0.001
Postoperative hospital stay (d)	4.1±1.5	7.7±1.4	13.732	<0.001
Stone-free rate (n, %)	56 (87.50)	59 (92.19)	0.771	0.380

Table 4. Comparison of renal function indexes before operation and after operation ($\bar{x}$ ± sd)

	Before operation		3 day after operation	
	Observation group (n=64)	Control group (n=64)	Observation group (n=64)	Control group (n=64)
Scr (μmol/L)	58.67±7.32	59.14±7.67	68.24±5.79$^{***,\#\#\#}$	76.28±6.84***
eGFR (mL/min·1.73 m^2)	96.29±5.78	96.94±6.15	91.25±4.26$^{***,\#\#\#}$	88.54±4.47***

Note: Compared within group before operation, ***P<0.001; compared with control group after operation, $^{\#\#\#}$P<0.001. Scr: serum creatinine; CysC: Cystatin C; eGFR: estimated glomerular filtration rate.

tion, and the incidence of postoperative complications was 10.94% (7/64). In the control group, fever was observed in 7 patients and bleeding in 4, and the incidence of postoperative complications was 17.19% (11/64). The results determined no significant differ-

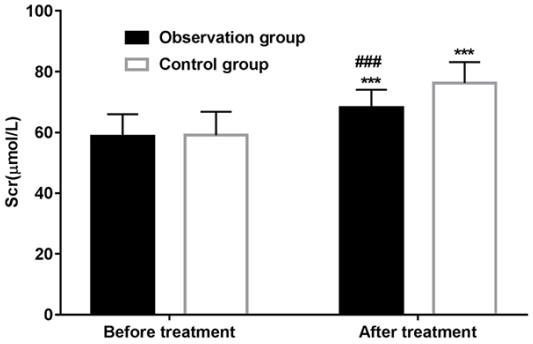

Figure 1. Comparison of Scr level before operation and after operation. Compared within group before operation, ***P<0.001; compared with control group after operation, ###P<0.001. Scr: serum creatinine.

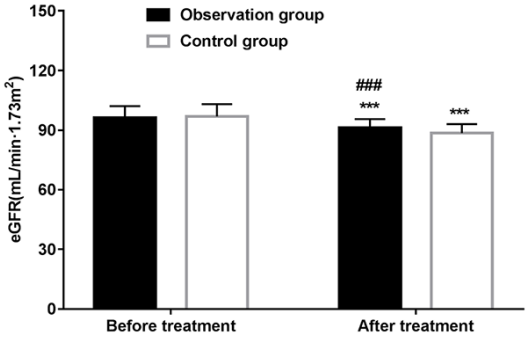

Figure 2. Comparison of eGFR level before operation and after operation. Compared within group before operation, ***P<0.001; compared with control group after operation, ###P<0.001. eGFR: estimated glomerular filtration rate.

ence in the incidence of postoperative complications between the two groups (χ^2=1.034, P=0.309).

Discussion

Previously, open surgery was widely used for upper ureteral calculi due to its high SFR and clinical efficacy, but it causes great harm to the human body, so the physicians are actively looking for alternative methods [16]. With the development of minimally invasive technology, mPCNL and flexible ureteroscopy techniques are increasingly applied in clinical practice [17, 18]. Some studies have found that mPCNL will still cause body damage, while comparatively, flexible ureteroscopy techniques cause less damage by using the natural passage of the human body. However, some studies have argued that the effect of mPCNL is better than that of flexible ureteroscopy in stone removal [19, 20]. In this study, it was found that patients treated with FURL with holmium laser had less bleeding and shorter hospital stay, which may be related to reduced injury and better postoperative recovery. Whereas, no significant difference was observed with respect to stone clearance; so further studies with larger samples are needed to analyze the SFR by the two approaches.

Upper ureteral calculi are always accompanied by hydronephrosis, which in severe cases can lead to the decline of renal function and obstructive nephropathy. Scr and eGFR, which were considered in previous studies to be able to better evaluate renal function, were used as renal function indexes in this study. When renal function is impaired, Scr will increase while eGFR will decrease [21, 22]. Studies have shown that the efficacy of flexible ureteroscopy for renal calculi is comparable to that of PCNL, but the former does less harm to the renal function of patients, and has less effect on blood coagulation and oxidative stress reaction, so it has certain advantages over PCNL [23]. In this study, it was found that FURL with holmium laser for upper ureteral calculi led to little damage on renal function. The reason may be that mPCNL has greater trauma and causes different degrees of oxidative stress. At the same time, in the process of mPCNL, clear vision can be obtained only by perfusion flushing. When the perfusion pressure is greater than the physiological pressure of the renal pelvis, it can cause renal pelvis fluid reflux, resulting in renal interstitial edema, and subsequently increasing the hydrostatic pressure. Once the hydrostatic pressure exceeds the pressure of renal arteriole, it will cause blood flow stagnation, trigger coagulation dysfunction, and further develop into renal parenchymal ischemia and hypoxic lesions, affecting the renal function of patients.

The secretion of inflammatory factors and oxidative stress factors increases under the condition of body injury. Although both methods applied in this study belong to minimally invasive surgery, they will still cause body injuries, which inevitably lead to inflammation and oxidative stress reactions in the body [24]. Evidence has shown that postoperative inflammatory states and the degree of oxidative stress are correlated with the prognosis of

Table 5. Comparison of oxidative stress factors before operation and after operation ($\bar{x} \pm sd$)

	MDA (mg/L)	SOD (ng/L)
Before operation		
Observation group (n=64)	22.24±2.79	122.19±12.18
Control group (n=64)	22.49±2.96	124.41±12.51
3 day after operation		
Observation group (n=64)	41.63±5.63***,###	86.28±8.62***,###
Control group (n=64)	57.35±6.24***	75.63±9.79***
7 day after operation		
Observation group (n=64)	31.57±3.89***,@@@,###	116.39±10.58***,@@@,###
Control group (n=64)	44.26±4.27***,@@@	98.36±10.36***,@@@

Note: Compared within group before operation, ***P<0.001; compared within group 3 days after operation, @@@P<0.001; compared with control group after operation, ###P<0.001. MDA: malondialdehyde; SOD: superoxide dismutase.

Table 6. Comparison of inflammatory factors before operation and after operation ($\bar{x} \pm sd$)

	CRP (mg/L)
Before operation	
Observation group (n=64)	6.79±1.91
Control group (n=64)	6.82±1.75
3 day after operation	
Observation group (n=64)	11.79±2.98***,###
Control group (n=64)	15.78±3.75***
7 day after operation	
Observation group (n=64)	8.23±1.93**,@@@,###
Control group (n=64)	11.74±2.79***,@@@

Note: Compared within group before operation, **P<0.01, ***P<0.001; compared within group 3 days after operation, @@@P<0.001; compared with control group after operation, ###P<0.001. CRP: C-reactive protein.

patients [25]. Ureteroscopic holmium laser lithotripsy is indicated to be safe and effective for upper ureteral calculi with less damage to human body, which can promote postoperative recovery of patients, effectively reduce oxidative stress and inflammatory stress of the body, and reduce the incidence of complications [26]. In the present study, we detected the inflammatory factors and oxidative stress factors before and after operation. It was observed that compared with patients treated with mPCNL, the postoperative inflammatory and oxidative stress reaction of patients treated with flexible ureteroscopy were lower, and the postoperative inflammatory and oxidative stress indicators were better. This may be due to the fact that the flexible ureteroscopy does not require the establishment of surgical channels but uses the natural channels of the human body, and the holmium laser is used for accurate dissolving of calculi with less damage to the surrounding tissues, thus reducing postoperative inflammation and oxidative stress [27, 28].

Given the limited sample size and the absence of postoperative follow-up in the present study, multi-center research with an expanded sample size and postoperative follow-up on patients' renal function will conducted, so as to further explore the advantages and disadvantages of the two surgical methods.

To sum up, given that FURL with holmium laser is effective for upper ureteral calculi, with little damage to the body, with little influence on renal function and better reduction in inflammation and oxidation factors in the body, it is worthy of clinical application.

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Disclosure of conflict of interest

None.

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