Flexible ureteroscopy lithotripsy combined with metallic ureteral stents for the treatment of patients with upper urinary tract calculi

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Abstract. Flexible ureteroscopy lithotripsy (FURS) is the most common treatment for patients with upper urinary tract calculi (diameter, <2 cm). The purpose of this prospective study was to assess the efficacy of FURS combined with metallic ureteral stents (MUS) for the treatment of upper urinary tract calculi. A total of 38 patients with upper urinary tract calculi were recruited in the present study, to compare the efficacy between FURS and FURS combined with MUS (FURS-MUS). The results demonstrated that FURS-MUS shortened operative time compared with FURS (35.2±1.2 vs. 57.4±1.7 min, respectively; P<0.01). Data also indicated that the clearance rate in FURS-MUS and FURS was decreased from 94.5 and 87.8%, respectively (P<0.05). FURS-MUS treatment decreased the duration of postoperative hospital stay compared with FURS (4.5±0.5 vs. 7.5±1.5 days, respectively; P<0.05). These data demonstrated that FURS-MUS significantly increased postoperative inflammation score compared with FURS (6.2±0.8 vs. 4.2±1.0, respectively; P<0.05). The complication rate and blood loss exhibited no significant difference between FURS-MUS and FURS (complication rate, 6.5% vs. 5.9%, respectively; blood loss, 4.2% vs. 4.6%, respectively). FURS-MUS significantly decreased inflammatory cytokines and risk of sepsis, and improved readmission rate, stone recurrence and progression-free survival compared with patients treated with FURS. In conclusion, these data suggested that FURS-MUS may be an efficient, minimally invasive and reproducible operation for patients with upper urinary tract calculi.

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Introduction

Urinary calculus is one of the most common urinary system diseases worldwide (1). A previous study indicated an association between chronic kidney disease and urinary calculus, regardless of stone location, and demonstrated that urinary calculus leads to inflammation during urinary tract infection (2). Currently, extracorporeal shock wave lithotripsy is used as an efficient technique for the treatment of urinary calculus (3-5). A clinical investigation indicated that young patients with urinary calculi were treated successfully, in a single procedure, using pneumatic lithotripsy under ureteroscopy (6). A previous study evaluated the efficacy of ureteroscopy and pneumatic lithotripsy in pregnant women with urethral calculi, and this study also identified that lithotripsy can be regarded as a safe and effective treatment for the mother and the fetus (7).

Metallic ureteral stents (MUS) have been widely used in the surgical treatment of ureteral obstruction and upper urinary tract calculi (8). Chow *et al* (9) demonstrated that MUS are effective and safe to use in the treatment of non-urological malignancies, abdominal ureteral obstruction and lymphatic metastasis. Additionally, ureteral stent exchange is usually performed under fluoroscopic and cystoscopic guidance, which is a good option to use as an alternative to the cystoscopic procedure or percutaneous procedure through percutaneous nephrostomy tract for its plasticity and probability (9). Furthermore, MUS combined with endoureterotomy has also been used as a therapeutic approach for experimental ureteral stricture; however, this technique is not a reliable therapeutic option for ureteral disorders due to failure of these devices (10). Further research is required to establish the application of MUS as a treatment for urinary calculus.

In the present study, the efficacy of flexible ureteroscopy lithotripsy combined (FURS) with MUS was assessed for the treatment of upper urinary tract calculi. The present study also analyzed the benefits between FURS-MUS and FURS in a total of 38 patients with upper urinary tract calculi.

Materials and methods

Patients. The present study was performed in The Fifth Affiliated Hospital of Guangzhou Medical University

(Guangzhou, China) between August 2013 and December 2016. The mean age of patients included in the current study was 42.4 years old (range, 28.6-56.4). A total of 38 patients with upper urinary tract calculi were recruited and 24 male patients and 14 female patients were included. All patients were not receiving any previous/ongoing treatment at the time of enrollment. A total of 18 patients received FURS and 20 patients received FURS-MUS. All patient characteristics are summarized in Table I. Patients with chronic renal failure and diabetes mellitus were excluded from the current study. All patients were required to exhibit calculi with diameters of <2 cm. The inclusion criteria were as follows: i) Age >18 years old; ii) diagnosed upper urinary tract calculi. The exclusion criteria were as follows: i) Glomerular filtration rate <45; ii) a diagnosis of bladder or prostate cancer; iii) claustrophobia; and iv) contraindications to urological imaging. The clinical design of the present study was approved by the ethics committee of the First Branch of the Fifth Affiliated Hospital of Guangzhou Medical University (approval no. 20120418R). All patients provided informed consent.

Surgical procedure. The methods of FURS and FURS-MUS were performed under local anesthesia by urologists. The FURS protocol was standardized to a previous study (11). The stone was positioned in the excretory phase. The FURS procedures were performed using a 7.5-F flexible ureterorenoscope (Karl Storz SE & Co.) through the cystoscope under fluoroscopy. A Flexi-Tip Dual Lumen Ureteral Access Catheter (Cook Medical) was used for insertion of a second 0.038-inch guidewire. A ureteral access sheath (9/11F or 12/14F; Rapidia Tech Inc.) was subsequently used to insert the ureteroscope into the ureter and disintegration was performed using a 200-micron holmium laser fiber at an energy level of 0.5-0.8 J and at a rate of 10-20 Hz. Stones located in the ureteropelvic junction were pushed into the renal pelvis softly for disintegration. The perfusion pressure of the irrigating fluid was <40 cm H_2O, and the irrigating fluid volume was <2,000 ml for all patients during surgery. For FURS-MUS, MUS of 7.5 mm in diameter, and 10.0-15.0 cm in length, were used to advance the stent proximally in the bladder prior to FURS, as described previously (12). A representative FURS-MUS computed tomography (CT) scan image of one patient is presented in Fig. 1 (13).

Cytokine analysis. Blood samples (10 ml) were collected from each patient, and serum was isolated via centrifugation at 8,000 x g for 10 min at 4˚C. Serum levels of interleukin (IL)-1β (cat. no. RLB00), tumor necrosis factor-α (TNF-α; cat. no. RTA00), IL-6 (cat. no. R6000B), IL-8 (cat. no. D8000C) and interferon-γ (IFN-γ; cat. no. DIF50) were evaluated using commercial ELISA kits (all, R&D Systems China Co., Ltd.), according to the manufacturer's protocols.

Inflammation scoring system. Criteria for the evaluation of inflammation were determined using an inflammation scoring system (14). Mean inflammation severity scores were evaluated using the percentage of white blood cells, according to a previous report (15). Inflammation severity scores were evaluated as follows: Mild, 0-3; moderate, 4-7; severe, 8-10.

Measurement of parameters. The stone clearance rate was determined using the number of residual stones/total number in each patients with upper urinary tract calculi, as described previously (16). The occurrence of sepsis was determined as organ dysfunction in the presence of proven or suspected infection based on the Sepsis-3 guidelines (17). Blood loss was calculated during the intraoperative period for patients who received FURS or FURS-MUS. Readmission rate indicated by the amount of patients in need of further treatment.

Complication rate analysis. A CT scan was performed for every patient prior to surgery, and 24-48 h following surgery, to assess stone free status. Stone opacity was classified based on preoperative plain Kidney-Ureter-Bladder CT scan (18). Stone recurrence was also assessed using a CT scan. The nephrostomy tube was removed on postoperative day 3-4 when the drainage was clear. The Double-J stent was extracted 1-2 weeks following surgery.

Operative time and blood volume. The operative time was calculated from the time of first incision to the placement of the nephrostomy tube. The blood volume was calculated in a blood collection tube (TYK09; Chongqing New World Trading Co., Ltd.).

Statistical analysis. All data are presented as the mean ± SEM. All experiments were conducted in triplicate. Statistical analysis was performed using Stata/SE software version 12.1 (StataCorp LP). A Student's t-test was used to evaluate the differences between two groups. Progression-free survival was analyzed using the Kaplan-Meier method and the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Efficacy of FURS-MUS for operative time in upper urinary tract calculi patients. The operative time between FURS-MUS and FURS in patients with upper urinary tract calculi was assessed. The results demonstrated that FURS-MUS shorted the mean operative time compared with FURS in all 38 patients (35.2±1.2 vs. 57.4±1.7 min, respectively; $P<0.01$: Table II). This observation indicated that FURS-MUS is an efficient method for the treatment of patients with upper urinary tract calculi.

Efficacy of FURS-MUS for clearance rate in patients with upper urinary tract calculi. Clearance rate is an important indicator that is used to evaluate the efficacy of lithotripsy treatment in patients with urinary tract calculi (19). In the current study, the clearance rate of FURS-MUS and FURS treatment was analyzed in patients with upper urinary tract calculi. An increased clearance rate was observed in the FURS-MUS group compared with FURS (94.5 and 87.8%, respectively; $P<0.05$; Table II). This result indicated that FURS-MUS is more efficient in treating upper urinary tract calculi.

Efficacy of FURS-MUS for postoperative inflammation in patients with upper urinary tract calculi. Inflammation was analyzed in patients with upper urinary tract calculi following FURS-MUS or FURS treatment. The results indicated that

Table I. Characteristics of patients with upper urinary tract calculi.

Characteristics	FURS	FURS-MUS	P-value
Sex			
Male	10	13	0.035
Female	8	7	
Mean patient age, years	40.5	41.2	0.78
Body mass index, kg/m^2	20.6±3.2	19.8±3.5	0.064
Mean ureteral stone diameter, mm	0.153	0.162	0.65
Stone opacity			
Radio-opaque	12 (66.67%)	14 (70%)	0.58
Radiolucent	6 (33.33%)	6 (30%)	0.76

FURS, flexible ureteroscopy lithotripsy; MUS, metallic ureteral stents.

Figure 1. A representative FURS-MUS computed tomography scan of a patient with urinary tract calculi. Black arrow, MUS in a patient with urinary tract calculi. FURS, flexible ureteroscopy lithotripsy; MUS, metallic ureteral stents.

FURS-MUS significantly increased postoperative inflammation compared with FURS (Table II; 6.2±0.8 vs. 4.2±1.0 min, respectively; P<0.05). However, blood loss exhibited no significant difference between FURS-MUS and FURS (4.2±1.8 ml vs. 4.6±1.2 ml) in patients with upper urinary tract calculi (Table II). These results indicated that FURS-MUS increased inflammation and decreased blood loss in patients with upper urinary tract calculi.

Efficacy of FURS-MUS for hospital stays in patients with upper urinary tract calculi. In the present study, the duration of hospital stay and complication rate were investigated in patients with upper urinary tract calculi. Data indicated that FURS-MUS treatment decreased postoperative hospital stay duration compared with FURS (4.5±0.5 vs. 7.5±1.5 day, respectively; P<0.05) for patients with upper urinary tract calculi (Table II). No significant difference was observed between the complication rates of FURS-MUS and FURS (6.5% vs. 5.9%, respectively) for patients with upper urinary tract calculi. These data indicated that FURS-MUS decreased hospital stay duration, and did increase complication rates in patients with upper urinary tract calculi.

Table II. Efficacy of FURS and FURS-MUS for the treatment of patients with upper urinary tract calculi.

Parameters	FURS	FURS-MUS	P-value
Operative time, min	57.4±1.7	35.2±1.2	0.0047
Clearance rate, %	87.8	94.5	0.0360
Postoperative inflammation	4.2±1.0	6.2±0.8	0.0326
Blood loss, ml	4.6±1.2	4.2±1.8	0.762
Hospital stay, days	7.5±1.5	4.5±0.5	0.0378
Complication rate, %	6.5	5.9	0.0826

FURS, flexible ureteroscopy lithotripsy; MUS, metallic ureteral stents.

Efficacy of FURS-MUS for inflammatory cytokines in patients with upper urinary tract calculi. Changes in inflammatory cytokines were recorded in patients with upper urinary tract calculi. The results demonstrated that FURS-MUS significantly decreased inflammatory cytokine expression, including IL-1β, IL-6, IL-8 and IFN-γ expression, compared with FURS in patients with upper urinary tract calculi (Table III; IL-1β, IL-6, IL-8 and IFN-γ, P<0.01). FURS-MUS also decreased TNF-α expression (P<0.0203). These data suggested that FURS-MUS could decrease inflammatory cytokine expression in patients with upper urinary tract calculi.

Readmission rate between FURS-MUS and FURS groups. The differences in readmission rate were investigated between the FURS-MUS and FURS-treated patient groups. The unplanned readmission rate in FURS-MUS and FURS groups during a period of 420 days are presented in Fig. 2. The readmission rate was 22.2% (n=4) and 10% (n=2) in the FURS and FURS-MUS groups, respectively (P<0.01). The mean interval between discharge from hospital and readmission was 15 and 24 days in the FURS and FURS-MUS group, respectively (Fig. 3; P<0.01). A total of three (16.7%) patients exhibited sepsis in the FURS group, while only one patient (5%) exhibited sepsis in the FURS-MUS group (Fig. 4; P<0.01). These data suggested that FURS-MUS decreased readmission rate and the risk of sepsis in patients with upper urinary tract calculi.

Stone recurrence between the FURS-MUS and FURS groups. The stone recurrence was analyzed between the FURS-MUS and FURS groups. The results demonstrated that stone recurrence was 16.7% (n=3) and 5% (n=1) after 420 days in the FURS and FURS-MUS groups, respectively (Fig. 5; P<0.01). The results also demonstrated that FURS-MUS

Table III. Efficacy of FURS-MUS in inflammatory cytokine expression in patients with upper urinary tract calculi.

Cytokine	FURS	FURS-MUS	P-value
TNF-α, ng/l	17.43±5.56	11.52±3.42	0.0203
IL-1β, mg/l	15.62±4.25	10.28±2.17	0.0048
IL-6, mg/l	18.42±5.46	11.30±2.75	0.0037
IL-8, mg/l	32.28±8.56	15.20±3.60	0.0010
IFN-γ, mg/l	42.36±8.82	26.17±5.07	0.0008

FURS, flexible ureteroscopy lithotripsy; MUS, metallic ureteral stents; TNF-α, tumor necrosis factor-α; IL, interleukin; IFN, interferon.

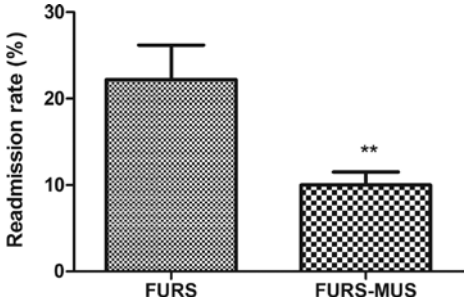

Figure 2. Readmission rate between the FURS-MUS and FURS groups in patients with urinary tract calculi. **P<0.01 vs. FURS. FURS, flexible ureteroscopy lithotripsy; MUS, metallic ureteral stents.

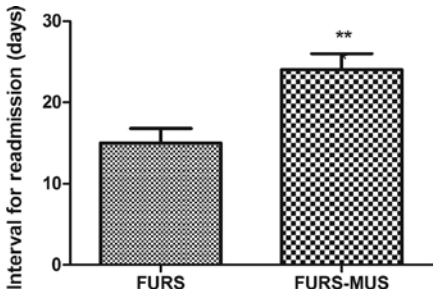

Figure 3. Mean interval between discharge from hospital and readmission between the FURS-MUS and FURS groups for patients with urinary tract calculi. **P<0.01 vs. FURS. FURS, flexible ureteroscopy lithotripsy; MUS, metallic ureteral stents.

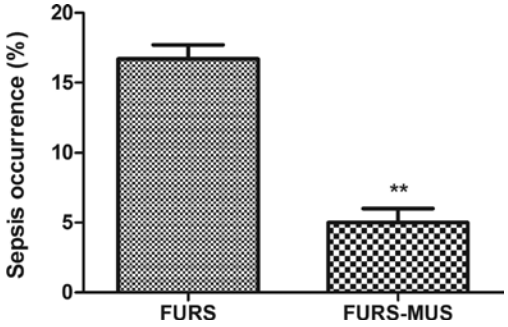

Figure 4. Occurrence of sepsis between the FURS-MUS and FURS groups for patients with urinary tract calculi. **P<0.01 vs. FURS. FURS, flexible ureteroscopy lithotripsy; MUS, metallic ureteral stents.

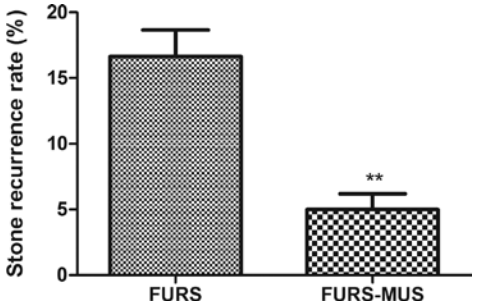

Figure 5. Stone recurrence between the FURS-MUS and FURS group for urinary tract calculi patients. **P<0.01 vs. FURS. FURS, flexible ureteroscopy lithotripsy; MUS, metallic ureteral stents.

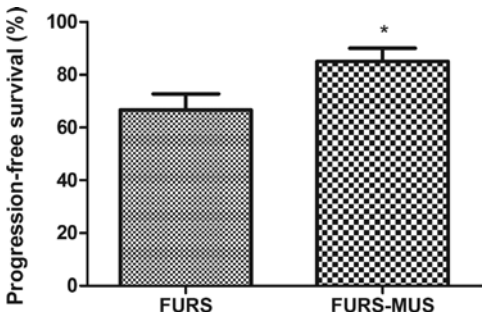

Figure 6. Progression-free survival between the FURS-MUS and FURS group for patients with urinary tract calculi. *P<0.05 vs. FURS. FURS, flexible ureteroscopy lithotripsy; MUS, metallic ureteral stents.

exhibited significantly higher progression-free survival rates than patients who underwent FURS (66.67% vs. 85%, respectively; P<0.05; Fig. 6). These data indicated that FURS-MUS improved stone recurrence and progression-free survival in patients with upper urinary tract calculi.

Discussion

Currently, FURS is most commonly used in the treatment of patients with proximal ureteral and renal calculi (20). A previous study indicated that ureteroscopic laser lithotripsy can be used as an effective treatment modality for patients with spinal cord injury and with upper urinary tract calculi (21). Additionally, MUS can be used in the treatment of malignant ureteral obstruction (22). In the current study, the therapeutic effects of FURS-MUS in patients with upper urinary tract calculi were investigated. The results indicated that FURS-MUS is an efficient method for the treatment of patients with upper urinary tract calculi.

FURS is a safe, highly efficient, minimally invasive and reproducible operation for the removal of upper urinary tract calculi in infants (23). The current study indicated that auxiliary MUS contributed to the treatment with FURS for patients with upper urinary tract calculi. Data in the current study indicated that the FURS-MUS technique can be used as a novel method for the treatment of upper urinary tract calculi, and to aid in the rapid recovery of patients with upper urinary tract calculi. The results demonstrated that FURS-MUS decreased hospital stay duration and operative

time, and increased stone clearance rate. The current study also demonstrated that FURS-MUS increased the stone clearance rate in patients with upper urinary tract calculi compared with patients treated using FURS. The FURS-MUS technique can be performed easily in all patient cases. As compared with the FURS technique, FURS-MUS presents the advantages of low postoperative inflammation and readmission rates.

Postoperative inflammation is the most common characteristic in patients with upper urinary tract calculi (24). In the present study, it was indicated that FURS-MUS increased postoperative inflammation compared with FURS. This discrepancy in postoperative inflammation rates between FURS and FURS-MUS was caused by MUS. A previous study demonstrated that chronic inflammation is associated with the volume of the prostate and storage symptoms, which may also be one of the causes of lower urinary tract symptoms (25). The results of the current study reported that FURS-MUS did not increase the complication rate for patients with upper urinary tract calculi. The use of FURS-MUS decreased complications and drawbacks compared with single FURS due to the shortened operative time. Additionally, the blood loss was not significantly different between the FURS-MUS and FURS techniques. The results of the current study indicated that FURS-MUS significantly decreased the inflammatory cytokines TNF-α, IL-1β, IL-6, IL-8 and IFN-γ in patients with upper urinary tract calculi, which may contribute to a shorter hospital stay duration when compared with FURS. In all cases, FURS-MUS allowed for easy access to the stone through a ureteral access sheath with minimal tract dilation. Fewer perioperative complications were observed in cases receiving FURS-MUS than in those receiving only FURS, and this result provided new evidence of the efficacy of FURS-MUS use in the treatment of upper urinary tract calculi.

A previous study revealed that patients with upper urinary tract calculi are associated with an increased risk of sepsis and mortality (26). Therefore, decreasing the occurrence of postoperative sepsis is beneficial for patients with urinary tract calculi. The results of the current study indicated that FURS-MUS decreased the occurrence of sepsis, which further led to the lower readmission rate than that for FURS alone in patients with urinary tract calculi. Additionally, FURS-MUS increased the mean interval between discharge from hospital and readmission. A previous report indicated that stone recurrence is a risk factor for patients with urinary tract calculi and new stones can occur following surgery (27). In the present study, the results demonstrated that FURS-MUS significantly decreased stone recurrence compared with FURS during a 420-day period, which resulted in a higher progression-free survival rate compared with patients who underwent FURS. However, other risk factors in patients between the FURS-MUS and FURS groups need to be assessed in future studies. Additionally, the present study used a small number of cases. Therefore, in future studies, the efficacy of the FURS-MUS technique should be identified in additional populations of patients with upper urinary tract calculi.

In conclusion, the data in the current study indicated that FURS-MUS represents a notable improvement for the treatment of upper urinary tract calculi. FURS-MUS technique increased postoperative inflammation and improved the operative time, hospital stay duration, readmission rate, stone recurrence and clearance rate for patients with upper urinary tract calculi. These data provided evidence that FURS-MUS may have a specific role in the range of urological treatments for patients with upper urinary tract calculi, suggesting that FURS-MUS is reliable method for the treatment of upper urinary tract calculi.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TL designed experiments and wrote manuscript. XZS, XL and YZH performed the experiments.

Ethics approval and consent to participate

The Ethical Committee of the he Fifth Affiliated Hospital of Guangzhou Medical University approved this study. Written informed consent was provided by all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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