

Effects of flexible ureteroscopy on kidney: A prospective clinical trial

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ABSTRACT

Objective: To investigate the effects of flexible ureteroscopy (F-URS) on the operated side of a kidney by assessing the renal damage markers, urine neutrophil gelatinase-related lipocalin (NGAL) and serum cystatin-C (Cys-C), and overall kidney function with the measurements of standard serum creatinine and urine albumin and protein levels.

Material and methods: A total of 30 patients who underwent F-URS for treatment of upper urinary stone disease were prospectively evaluated. Preoperative serum urea, creatinine, and Cys-C levels were noted. Levels of urine albumin, protein, creatinine, and NGAL in spot urine samples from the operated side of a kidney obtained through the access sheath preoperatively and through the ureteral catheter 1 and 24 hours postoperatively were also measured. Preoperative and postoperative parameter levels were statistically compared.

Results: The patients' mean age was 46.6 ± 15.9 years. The mean operative and fluoroscopy times were 90.67 ± 32.5 and 3.15 ± 1.43 minutes, respectively. The urine creatinine, albumin, protein, albumin/creatinine, and protein/creatinine levels were similar in preoperative and postoperative periods. Postoperative serum urea, creatinine, and Cys-C levels and urine NGAL and NGAL/creatinine levels were not also found with remarkable changes from the baseline levels.

Conclusion: F-URS is a safe therapeutic intervention in the treatment of urolithiasis, especially regarding renal damage, and functional outcomes.

Keywords: Biomarkers; kidney, kidney function tests; ureteroscopy.

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Introduction

In urological practice, development of surgical instruments with advanced technology consolidated the use of flexible ureteroscopy (F-URS), and the treatment of upper urinary tract stones with the combination of F-URS and holmium: yttrium aluminum garnet (Ho:YAG) laser lithotripsy has become a widely preferred method worldwide.^[1,2] In F-URS, optimal visualization with a clear operative field, which requires fluid irrigation, is vital. Fluid irrigation provides adequate working space and scope maneuverability that improve the procedure's efficacy.^[3,4] Nevertheless, there is a potential risk of high hydrostatic pressure in the kidneys with irrigation. Increased hydrostatic pressure may cause harmful effects at the tubular level, mainly on tubular transport at the level of the tubular collecting system with reduced net driving force

for filtration and glomerular filtration rate (GFR).^[5] To date, with a small number of studies, there is limited knowledge about the effect of F-URS on renal function.^[1,6-8] These limited studies also commonly assessed renal function on the basis of the serum creatinine characteristics or nuclear medicine tests. Moreover, they investigated the functional effects of F-URS in patients with healthy and functionally deteriorated kidneys. Therefore, we think that the use of current accepted biomarkers for acute renal damage in healthy kidneys may be more suggestive.

In this study, we aimed to investigate the effects of F-URS on the operated side of a healthy kidney by assessing the currently accepted renal damage markers, such as urinary neutrophil gelatinase-related lipocalin (NGAL) and serum cystatin-C (Cys-C). Changes in the overall

kidney function were also investigated using the standard serum creatinine and urine albumin and protein assessments.

Material and methods

This study was approved by the clinical studies ethics committee of Bagcilar Training and Research Hospital (ID: 03.2014.219) and conducted in accordance with the ethical principles described by the Declaration of Helsinki. All the patients signed an informed consent form for the study. Between April 2014 and January 2015, a total of 52 patients who underwent treatment of upper urinary tract stones with F-URS were enrolled to this prospective study. After the exclusion of pediatric and complicated cases and patients with impaired renal/hepatic functions, anatomical or functional solitary kidney, recurrent urinary tract infections, urinary tract anomalies, grade 3 and above hydronephrosis, previous SWL treatment history, and failed F-URS history, a total of 30 patients were finally included in the study. All the patients were evaluated with low-dose non-contrast abdominal computer tomography (CT) before the procedure, and the stone characteristics were determined. Preoperative serum urea, creatinine, and Cys-C levels were noted with patient characteristics and comorbidities.

All the patients had sterile urine culture, and all procedures were performed with standard steps of F-URS under general anesthesia with Fiberoptic Flex-X2™ (Karl Storz GmbH & Co, Tuttlingen, Germany) or Cobra-Vision™ Flexible Dual-Channel Ureteroscopes (Richard Wolf GmbH, Knittlingen, Germany) and Ho:YAG laser (Sphinx Jr.®, Lisa Laser, Katlenburg, Germany) lithotripsy.^[2,9] Fluid irrigation was maintained with gravity-based technique with the fluid bag located at 100 cm above the patient level. In addition, a handheld system was used to enhance fluid irrigation when necessary. A 9.5F or 12F access sheath (Flexor®, Cook Medical Inc., Bloomington, IN, USA)

Main Points:

- Treatment of upper urinary tract stones with the combination of F-URS and Ho:YAG laser lithotripsy has become a widely preferred method worldwide.
- Nevertheless, there is a potential risk of high hydrostatic pressure in the kidneys with irrigation during F-URS.
- To date, with a small number of studies, there is limited knowledge about the effect of F-URS on renal function.
- We investigated the effects of F-URS on the operated side of a healthy kidney by assessing the currently accepted renal damage markers, such as NGAL and serum cystatin-C.
- Our study revealed that F-URS with a ureteral access sheath is a safe procedure in the treatment of renal or upper ureteral stone disease in terms of renal damage and functional outcomes.

was placed to the ureter in all cases, and laser lithotripsy with pulse energy ranging from 2.5 to 3 J and pulse rate ranging from 10 to 30 Hz using a 272 micron core laser fiber was performed (FlexiFib®, Lisa Laser Katlenburg, Germany). Low pulse energy and high frequency settings for dusting technique were used during laser lithotripsy. Nevertheless, the fragmentation method with higher pulse energy and lower frequency in larger stones was preferred. The fragments were retrieved with an endoscopic basket catheter (N-Gage Nitinol Stone Extractor, Cook Medical Inc., Bloomington, IN, USA). After performing all the procedures, routine ureteral catheter was inserted into the operated side.

The spot urine samples from the operated side were collected through the access sheath right after its placement and after 1 hour from the procedure for measurement of urine albumin, protein, creatinine, and NGAL levels. The spot urine samples at postoperative 24 hours were also collected from the ureteral catheters. The blood samples were collected 1 hour after the procedure for measurement of serum Cys-C levels and at postoperative 24 hours for measurement of serum urea, creatinine, and Cys-C levels. Urine creatinine, albumin, and protein levels were determined using Cobas® 6000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Urine NGAL level was measured using enzyme-linked immunosorbent assay method (Sunred Biological Technology Co. Ltd, Shanghai, China). Serum urea and creatinine levels were measured enzymatically using Cobas® 6000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Serum Cys-C level was measured using particle-enhanced immunonephelometry with Behring BN II Nephelometer (Siemens Healthcare GmbH, Erlangen, Germany). Assessment of stone-free status was determined using non-contrast abdominal CT 6 weeks postoperatively.

Statistical analysis

Statistical analysis was performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA). Data distributions were evaluated with Kolmogorov Smirnov test. Descriptive statistic methods (mean, standard deviation, frequency) were used to evaluate data. Friedman test and Wilcoxon test were used for the comparison of the parameters between preoperative and postoperative periods. Differences were considered significant at $p<0.05$ and 95% confidence interval.

Results

The patients' mean age was 46.6 ± 15.9 years, and the mean body mass index was 27.94 ± 4.98 kg/m². A total of 14 patients (46.6%) had comorbid diseases (Table 1). The mean stone size was $24.6.6\pm15.3$ mm, and all the stones were opaque with the mean stone Hounsfield Unit of 932.7 ± 431.24 . None of the patients had coralliform stones. Five patients (16.7%) had previ-

ously replaced double-J (DJ) ureteral catheter. A total of 21 and 9 patients underwent the procedure for the left and the right kidney stone, respectively. The characteristics of stone localizations are found in Table 1.

The mean duration of operation and fluoroscopy was 90.67 ± 32.5 and 3.15 ± 1.43 minutes, respectively. In 14 cases (46.7%), a 9.5F access sheath was used, and in the remaining 16 patients, a 12F access sheath was used. In 2 cases, ureteral balloon dilatation was applied. No intraoperative complications were found in any patient. Prolonged fever treated by parenteral antibiotics and additional analgesic requirement were observed in 4 and 3 patients, respectively. There were no any other postoperative complications found, and mean hospital stay was 3.1 days. Stone-free status was detected in 23 (76.7%) patients.

The levels of creatinine, albumin, protein, and albumin/creatinine and protein/creatinine ratios were similar in the preoperative, postoperative early, and postoperative first day spot urine samples (Table 2). Urine NGAL and NGAL/creatinine ratio levels increased 1 hour after the procedure and at postoperative

first day, but these differences were not significant ($p=0.164$ and $p=0.134$, respectively) (Table 2). Similarly, we did not find significant differences in preoperative and postoperative first day serum urea and creatinine levels ($p=0.601$ and $p=0.213$, respectively) (Table 2). Although mean serum Cys-C level increased at early postoperative period, it returned to baseline level 24 hours after the procedure, and the increase was not significant ($p=0.49$) (Table 2).

Discussion

Effective F-URS procedure requires optimal visualization of the urinary tract, as in all endoscopic surgical procedures. Although the most important part of adequate visualization is lighting the surgical area, in whatever type, irrigation is another essential entity in endoscopic urinary tract procedures. Irrigation provides a clear field of vision by dilatating the tracts, stone debris drainage, and blood clots during F-URS.^[10,11] In urological practice, normal saline solution at body temperature is the preferred irrigating fluid to minimize the side effects of potential fluid absorption from mucosal injury or pyelolymphatic or pyelovenous backflow. Indeed, other irrigation solutions are commonly associated with adverse effects. For instance, sterile water has a lytic effect on erythrocytes whereas electrolyte-free solutions have a risk of functional impairment in cardiovascular and nervous systems.^[4,11] Regardless of the solution type, the other adverse effect of the use of irrigation solutions is increasing the intrarenal collecting system pressure. The physiological baseline of human intrarenal pressure is determined at 10 mmHg (13.59 cmH₂O), but it was found to substantially increase during ureteroscopy.^[11] Increasing the fluid pressure to improve the irrigant flow (forced irrigation) in an attempt of providing successful therapy may result in higher intrarenal pressures.^[12] Auge et al.^[13] investigated baseline and perioperative intrarenal pressure profiles of five patients with previously inserted nephrostomy

Table 1. Characteristics of stone localizations and patient comorbidities

Stone localization, n	Comorbid diseases, n
Upper ureter 6 (20%)	None 16 (53.3%)
Renal pelvis 6 (20%)	DM 2 (6.6%)
Upper calyx 4 (13.3%)	DM+HT 1 (3.3%)
Middle calyx 5 (16.7%)	HT 4 (13.3%)
Lower calyx 9 (30%)	CAD 1 (3.3%)
	Others 6 (20%)

DM: diabetes mellitus; HT: hypertension; CAD: coronary artery diseases; others: chronic obstructive pulmonary disease and hypothyroidism

Table 2. The levels of urine and serum kidney function test parameters and biomarkers at preoperative and postoperative periods

	Preoperative	Postoperative first hour	Postoperative 24 hours	p
Serum urea (mg/dL)	32.86 ± 16.1		31.9 ± 19.16	0.601*
Serum creatinine (mg/dL)	0.97 ± 0.58		1.0 ± 0.61	0.213*
Urine albumin (mg/dL)	19.13 ± 20.04	23.12 ± 25.93	26.9 ± 26.36	0.361 [#]
Urine albumin/creatinine	49.02 ± 50.45	61.28 ± 55.49	73.53 ± 55.13	0.07 [#]
Urine protein (mg/dL)	33.04 ± 35.49	45.31 ± 57.94	47.53 ± 50.37	0.367 [#]
Urine protein/creatinine	85.83 ± 92.58	116.76 ± 121.6	120.13 ± 80.96	0.116 [#]
Urine NGAL (ng/mL)	871.57 ± 127.36	886.83 ± 129.23	923.9 ± 118.46	0.164 [#]
Urine NGAL/creatinine	0.29 ± 0.18	0.35 ± 0.23	0.4 ± 0.33	0.134 [#]
Serum Cys-C (mg/L)	0.95 ± 0.47	1.04 ± 0.5	0.95 ± 0.53	0.49 [#]

NGAL: neutrophil gelatinase-related lipocalin, Cys-C: cystatin-C. *Wilcoxon test, [#]Friedman test.

tube. They determined the baseline intrarenal pressure as 13.6 mmHg (18.4 cmH₂O); however, it increases to 60 mmHg (81.5 cmH₂O), 79.2 mmHg (107.6 cmH₂O), and 94.4 mmHg (128.3 cmH₂O), when a flexible ureteroscope was inserted in the distal ureter, proximal ureter, and renal pelvis, respectively. Recently, Jung et al.^[11] investigated the intrarenal pressure profiles during F-URS. They reported that during the active use of ureteroscopy for stone fragmentation with Ho:YAG laser or during use of stone basket and forced irrigation, the pelvic pressure reached up to 328 mmHg (445.9 cmH₂O). Increased fluid pressure in the urinary tract may lead to harmful consequences in the kidney tissue owing to pyelolymphatic and/or pyelovenous backflow.^[13] Previously, it was well documented that tubular hydrostatic pressure has inhibitory effects on tubular transport at the distal convoluted tubule and collecting ducts. It was also found that it reduces GFR by distorting the net driving force for filtration.^[5] Increased hydrostatic pressure in the intrarenal collecting system is also associated with postoperative pain, renal colic, and sepsis. The other potential source of kidney damage during F-URS is laser energy next to or directly onto the renal tissue.^[1] Considering these harmful effects and adverse events of intrarenal pressure and laser energy, F-URS may be associated with renal function deterioration. Nevertheless, to date, there are limited data about the renal functional effects of F-URS. Moreover, existing relevant limited studies commonly investigated the renal effects using radiological examinations combined with conventional blood tests and urinalysis, but they did not provide information on separate renal function.^[1,14] Consequently, it is hard to say that these previous reports make clear statements on renal effects of F-URS. Separate renal function may be determined directly with renal scintigraphy examinations. It can also be determined by the implication of molecular renal damage markers.^[15,16] To our knowledge, only one study used the evaluation of separate renal function with renal scintigraphy after F-URS. In that study, Piao et al.^[7] determined the separate renal function in patients who underwent mini percutaneous nephrolithotomy (mini PCNL) and F-URS for renal stones >10 mm. They used diethylenetriamine pentaacetic acid (99mTc-DTPA) and technetium-99m dimercaptosuccinic acid (99mTcDMSA) scintigraphy and found improved scintigraphic renal functions. They reported that postoperative mean separate renal function increased to 47.9% from the preoperative level at 45.6%. Even if the separate renal function was determined by renal scintigraphy, we think that this may not reveal the potential renal impairment after F-URS. Most of the renal damages may get better and recover after the ending up of the main harmful factor. Roberts et al.^[17] reported that renal impairment was found with renal scintigraphy 5 hours postoperatively in mice kidney with 30-minute ischemia-reperfusion injury. Nevertheless, 99mTc-mercaptoacetyltriglycine (MAG3) scintigraphy did not reveal any renal impairment in ischemic mice kidney 24 and 48 hours after I/R injury, and accumulation of 99mTc-MAG3 in the kidney

did not differ from that of sham-treated kidney. Similarly, Herrler et al.^[18] found that unilateral kidney ischemia leads to decreased renal fractional radionuclide uptake 8 days postoperatively. The uptake rate remained decreased as time goes on, but it improved 14 days after the injury. These results may suggest the inefficacy of late scintigraphic evaluation of renal function after any potential harmful factor. Furthermore, postoperative early renal scintigraphic evaluation seems impossible in routine clinical practice. Thus, we preferred to use the accepted molecular renal damage markers in the investigation of potential renal injury in the operated side after F-URS. Previous reports about the effects of F-URS on kidney utilized both healthy and functionally deteriorated kidneys. Hoarau et al.^[1] investigated the renal function after F-URS in 163 patients and concluded that F-URS have favorable outcomes on kidney function. Patients with chronic kidney disease were also included to the study. Indeed, 27 patients (16.6%) had lower than 60 mL/min/1.73 m² GFR levels. Similarly, Piao et al.^[7] included patients with altered kidney functions to their study. In their study cohort, the mean estimated GFR was 78.3±26.2 mL/min/1.73 m² and the mean separate scintigraphic kidney function was 45.6%. With appropriate preoperative planning and patient selection, successful stone removal and optimal results with minimal morbidity may be achieved by patients with solitary kidney through F-URS.^[19] In the literature, there are however some interesting studies investigating the effects of F-URS on solitary kidney which reported on eradication of separate renal function evaluation. In one of them, Atis et al.^[20] reported a difference in preoperative and 2-week postoperative creatinine levels after removal of the stent periods with stone-free rates at 83.3% and 95.8% after the first and second the procedures, respectively, in patients with solitary kidney. Nevertheless, the mean serum creatinine level preoperatively was 1.54±0.55 mg/dL (range, 0.7–2.8). In another study, Giusti et al.^[6] prospectively investigated 29 patients with solitary kidney with a mean preoperative serum creatinine level at 1.5±0.6 mg/dL. They reported that F-URS is a safe and effective treatment modality for renal stones in patients with solitary kidney. The higher preoperative serum creatinine levels of the study cohorts of Atis et al.^[20] and Giusti et al.^[6] indicate that some of the patients might have had borderline renal functions. In this study, we only investigated the patients with healthy kidney. Although we did not perform preoperative scintigraphic renal function evaluation, we excluded patients with higher serum creatinine levels. The mean preoperative serum creatinine level of our cohort was 0.97±0.58 mg/dL.

To identify the kidney injury early, several biomarkers, including NGAL, Cys-C, kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18), liver-type fatty acid-binding protein (L-FABP), N-acetyl-β-D-glucosaminidase (NAG), and urine microRNAs, in urine or plasma have been described.^[20-23] Separate kidney injury and function can be determined by the implication of these

molecular markers.^[15,24] The diagnostic and prognostic values of urine NGAL for acute kidney injury were documented with a meta-analysis in 19 studies.^[25] It has also been found that measurement of serum and urine Cys-C levels predicted the decrease in GFR before the increase of serum creatinine level.^[26] Thus, we preferred to use NGAL and Cys-C in investigating the potential kidney tissue injury in the operated side after F-URS. In the literature, there are limited studies investigating these markers to clarify the effects of URS on kidney with controversial results. Benli et al.^[27] investigated urine NGAL, Cys-C, KIM-1, and L-FABP levels in 30 patients who underwent semi-rigid URS and concluded that URS affects the kidney with remarkably increased urine NGAL levels. Zhao et al.^[28] also used NGAL, Cys-C, and KIM-1 to explore the effects of F-URS and revealed that the marker concentrations are remarkably increased after the treatment indicating kidney injury. In another study, Fahmy et al.^[29] investigated urine NAG and KIM-1 levels in 60 patients who underwent F-URS or SWL and in healthy controls. KIM-1 and NAG levels remarkably increased after SWL treatment but not after F-URS. Dede et al.^[23] evaluated kidney damage after F-URS measuring urine NGAL, KIM-1, L-FABP, and NAG levels in 30 patients with kidney stone and reported that F-URS is a safe method. All these studies measured the urinary markers in voided urine samples instead of that obtained from the affected kidney. We thought that using the voided urine sample may not provide a clear evidence about the kidney damage induced by URS. Although the operated side of the kidney expresses the urinary damage markers, this may be masked by the urine produced on the other side of the kidney in voided urine sample. The main strength of our study was the investigation of the basic separate renal changes associated with kidney damage before the functional alterations using urine molecular markers in the operated side of the kidney. Normal serum Cys-C levels range between 0.53 and 0.95 mg/L in healthy population.^[24] The mean preoperative serum Cys-C level was also 0.95 ± 0.47 mg/L in our cohort. The cut-off value of urine NGAL varied in the literature from 89 to 213 ng/mL.^[24] In our cohort, mean preoperative urine NGAL level was 871.57 ± 127.36 ng/mL. Although it increased at postoperative early period (886.83 ± 129.23 ng/mL) and at postoperative first day (923.9 ± 118.46 ng/mL), the changes were not remarkable. Several studies reported that use of urine biomarkers with urine creatinine was more useful regarding diagnostic efficacy and that it reduced intraindividual variations.^[30] For that purpose, we also used the normalization of urine NGAL to creatinine. Nevertheless, changes in the urine NGAL/creatinine ratios were not remarkably different. As a result, our findings revealed that F-URS had no adverse effects in kidney tissue or function.

This study has some limitations. First, the patient number could have been larger and long-term renal function changes after the procedure were not considered. Detailed subgroup analysis (parameters that affect postoperative renal functions, such as opera-

tion times, stone size, laser pulse number, and stone location) could also have been more helpful in interpreting the results. Owing to our relatively small sample size, we could not determine subgroups. Second, the use of ureteral access sheath may have led to negative results by maintaining lower pressures in the kidney. Lastly, treatment of patients with prolonged fever and renal colic with drugs might have affected our marker outcomes. Whether the ureteral catheter or the drainage influences the marker outcomes is a questionable point. Nevertheless, we think that this cannot be accepted as a limitation. In contrary, the use of a ureteral catheter is the strength of this study, which provided direct determination of the urinary parameters from the operated side of the kidney.

In conclusion, our findings revealed that F-URS with a ureteral access sheath is a safe therapeutic intervention in the treatment of renal or upper ureteral stone disease, especially regarding renal damage and functional outcomes.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bagcilar Training and Research Hospital (ID: 03.2014.219).

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