Same session bilateral ureteroscopy for multiple stones: Results from the CROES URS Global Study.

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Abstract

Introduction and Objective:

This study presents a comparison of the international experience with ipsilateral ureteroscopy (I-URS) and bilateral ureteroscopy (B-URS) for multiple, bilateral ureteric and renal stones vs. single stone treatment. Patient and treatment characteristics and outcomes were compared.

Methods:

The CROES Ureteroscopy Global Study includes 114 centers in 32 countries. Patients undergoing B-URS, I-URS, and URS for a single stone were examined from January, 2010 to October, 2012. Intra-operative characteristics and post-operative outcomes were identified for each patient. Inverse-probability weighted regression adjustment (IPWRA) analyses were used to compare outcomes independent from differences between centers and patient characteristics.

Results:

The CROES URS Global Study consists of 11885 patients. A total of 2153 (18.7%) patients were treated for multiple stones with 1880 (87.3%) and 273 (12.7%) patients undergoing I-URS and B-URS respectively. The IPWRA models for B-URS versus I-URS and multiple versus single stone treatments show that patients with B-URS and multiple stone treatments have lower stone free rates (SFR), higher re-treatment rates, and longer operating times compared to patients whom underwent I-URS and single stone treatment. There was no difference in complication rates between B-URS, I-URS, and single stone ureteroscopy.

Conclusion:

This study presents a large series of patients undergoing B-URS and I-URS treated patients . Our findings suggest a decrease in SFR, increased re-treatment rates, increased operating time and a longer hospital admission in patients treated for multiple stones.

The treatment of multiple stones and B-URS is safe when compared to single stone and I-URS.

Introduction

Over the past two decades advances in flexibility, size, and optics of both digital and fiberoptic ureteroscopes along with the development of novel grasping devices, ureteral access sheaths, and laser fibres has enabled the urologist to efficiently and safely access and treat stones in virtually all parts of the urinary tract.¹⁻³ As a result, guidelines from both the European Association of Urology (EAU) and the American Urological Association/Endourological Society (AUA/ES) now recommend ureteroscopy as a first-line therapeutic option for both ureteric and renal calculi.^{2,3} Approximately 25% of patients present with multiple stones. Since 30% of asymptomatic stones eventually become symptomatic⁴, many urologists routinely treat patients with multiple ipsilateral stones under a single anesthetic.⁵⁻¹⁰ As ureteroscopy is generally well tolerated and associated with a low complication rate many advocate a single session for treating bilateral stones as well.¹¹⁻¹⁶

Recent studies examining ureteroscopy for multiple ipsilateral stones (I-URS) suggest this approach to be associated with longer procedure times, higher ureteric stent placement rates, and a longer stent dwell time.^{5,6,16} I-URS does not increase hospital length of stay (LOS) and when compared to URS for a single stone, similar success rates are seen with no difference in complication rates.^{5,16} By treating asymptomatic renal stones during the treatment of symptomatic ureteric stones, the need for auxillary treatments may decrease along with potentially preventing future episodes of renal colic.¹⁴ Some studies examining I-URS suggest safety and efficacy only with smaller stones.^{7,9,12}

Bilateral ureteroscopy for multiple stones (B-URS) is more controversial than I-URS due to potential increased risk for bilateral complications.¹⁴ Recent studies examining B-URS show that it is safe and efficient for smaller stones¹¹⁻¹⁶ although

associated with longer operating room times¹⁴. In addition, patients undergoing B-URS are more likely to have a ureteric stent placed post-operatively and have the stent left in situ for a longer period of time^{13,15}. Complication rates may also be higher with B-URS when compared with unilateral procedures^{12,15}.

As with any endourologic treatment, the success rates of both I-URS and B-URS are affected by stone-, clinical-, anatomic- and technical factors. Although percutaneous nephrolithotomy (PCNL) remains the gold standard for treating large volume upper tract stones, I-URS and B-URS are reasonable treatment options, for patients with multiple, bilateral and a stone burden less than 20mm. We present an international experience with I-URS and B-URS for urolithiasis using data collected from the Clinical Research Office of the Endourological Society (CROES) Ureteroscopy Global Study. We compare I-URS and B-URS treatment characteristics and outcomes as well as the outcomes of multiple stone treatment (I-URS and B-URS) with single stone treatment.

Methods

The CROES URS Global Study includes 114 centres in 32 countries. All centres used the CROES website (www.croesoffice.org) to enter data in an online available data management system [between Januari 2010 and October 2012](#). The data is encrypted and stored at a central database at the CROES office. All participating centres treated patients according to their local protocols for urolithiasis URS treatment. Institutional Research Board (IRB), or Institutional Ethics Committee approval was obtained by all participating centres prior to the study. Details on content of data collection are described elsewhere¹⁷.

Study population

The CROES URS Global study includes data from 11885 patients. Of the 11885 patients, 11500 (96.8%) had information on the number of stones and 2153 (18.7%) patients were identified as undergoing either B-URS or I-URS. Various patient characteristics were collected and included: age, gender, American Society of Anesthesiologists (ASA) score, body mass index (BMI), and urological history regarding congenital abnormalities, previous stone treatment and cardiovascular disease. Data on stone side and location was used to categorize patients as having multiple ipsilateral or bilateral stones (Figure 1). Multiple ipsilateral stones are defined as more than one stone in the ipsilateral collecting system and bilateral stones are defined as stones in both sides of the urinary tract (renal and/or ureteral).

Intra-operative characteristics

Operative data including operation time (defined as the time from the insertion of the endoscope until the insertion of a bladder catheter), access sheath use (yes/no), type of URS used (flexible/semi-rigid), post-operative stent placement (yes/no) and intraoperative complications were recorded. Intra-operative complications were captured by treating urologist in predefined categories^{18,19}: uneventful, bleeding, perforation, failed, converted and avulsion. If a complication did not meet any of these categories, then the complication could be described in an open textbox. Complication severity was not captured.

Post-operative outcomes

Postoperative assessment of stone free rates (SFR) varied and was left to the discretion of the urologist at each centre. SFR was defined as the absence of stone or fragments > 1mm based on any imaging modality. Retreatment rates, which included

readmission, and hospital admission longer than one day were recorded. Postoperative complications were categorized according to the Clavien-Dindo grading system^{20,21}. A composite outcome of any intra- or post-operative complications (yes/no) was created.

Statistical analyses

Descriptive information is presented as mean with standard deviation (SD) for normally distributed variables, and median with inter-quartile ranges (IQR) for skewed continuous variables. Categorical variables are presented as frequencies and percentages. Percentages exclude missing values from denominators.

Univariate regression analyses testing the univariate prediction of outcomes by single versus multiple stones and ipsilateral versus bilateral stones was performed. For dichotomous outcomes, logistic regression analysis was used. For the continuous variable of operating room (OR) time, linear regression analysis was performed using the natural logarithm of OR time, since the variable did not meet the assumption of normal distribution assumption.

As patients with multiple stones are likely to differ from those with a single stone, and patients with bilateral stones are likely to differ from those with ipsilateral stones, inverse-probability-weighted regression adjustment (IPWRA) analyses was used. IPWRA is a regression analysis in which inverse probability weights of baseline characteristics are used in a regression model describing the relationship of interest. Generally, in an observational study, the weighting adjustment removes sampling bias²². IPWRA analyses are performed in three steps. In the first step, pre-operative best fit prediction of having multiple stones over single stones, or having bilateral over ipsilateral stones, by age, gender, ASA score, BMI, and medical history regarding congenital abnormalities, previous stone treatment, cardiovascular disease, and pre-

operative stent placement are computed. In the second step of the IPWRA analyses, best prediction models of actual treatment outcomes (SFR, retreatment, long hospital stay, complications, and operation time) are computed using the following intra-operative characteristics and possible confounders: pre-operative stent placement, type of URS, post-operative stent placement, stone impaction, the use of an access sheath, case volume, and OR time. The final step of the IPWRA analysis consists of combining the pre-operative and intra-operative best prediction model with the analyses of the adjusted relationship between both B-URS versus I-URS and multiple versus single stone treatment with outcomes.

All analyses were performed using STATA version 13, StataCorp LP, College Station, USA (www.stata.com).

Results

The CROES URS Global study consists of 11885 patients with stone data available for 11500 patients. A total of 2153 (18.7%) patients were treated for multiple stones. The majority of these patients underwent I-URS (87.3%) with 1033 (48.0%) on the left side and 847 (39.3%) on the right side. The remaining 273 (12.7%) patients underwent B-URS (see **Figure 1**). **Figure 2** outlines stone location schematically.

Clinical characteristics of patients treated with I-URS and B-URS are presented in **Table 1**. B-URS was more likely to be performed at high-volume centres, in patients with fewer previous treatments, lower rates of cardiovascular disease, in males, and longer operating times than I-URS patients. Post-operative hospital admission was no longer in B-URS patients and SFR was similar. The B-URS group is likely a selected and healthier population, with fewer co-morbidities and previous treatments. Overall, patients being treated for multiple stones were more likely to have a pre-operative ureteric stent ($p <$

0.05) and more likely to have a post-operative ureteric stent ($p < 0.05$) than patients treated for a single stone.

Univariate analyses of B-URS versus I-URS (A) and multiple versus single stone treatments(B) are presented in **Table 2**. The univariate models for B-URS versus I-URS show that patients with B-URS have lower SFR, higher retreatment rates, longer operating times and longer post-operative hospital admission compared to patients whom underwent I-URS. The univariate models for multiple versus single stone treatment show that patients with multiple stone treatment have lower SFR, higher retreatment and complication rates, longer OR times and longer post-operative hospital admission.

Pre-operative models to predict either B-URS versus I-URS and single versus multiple stone treatments are computed using backward selection procedure. For single versus multiple stone treatment, ASA-score, case volume, OR time and previous stone treatment are significant predictors. For B-URS versus I-URS, presence of congenital abnormalities, stone location, case volume and previous treatment are significant predictor variables. The intra-operative prediction model is the same for single versus multiple stone treatments and B-URS versus I-URS and includes: stone impaction, type of URS, use of access sheath, and post-operative stent placement.

Table 3 shows the final multivariate prediction models of the IPWRA analyses comparing B-URS with I-URS (A) and multiple with single stone treatment (B). The IPWRA models for B-URS compared to I-URS show that operation time is significantly longer in the B-URS group. When comparing B-URS to I-URS, B-URS is associated with 5% lower SFR, 6% higher retreatment rates, 4% shorter hospital admission and 3% more complications. These findings are, however, not significant. These relationships are independent from baseline differences in ASA-score, local case volume, OR time,

previous stone treatment and intra-operative stone impaction, type of URS, access sheath use, and post-operative stent placement for single versus multiple stone treatment. When B-URS versus I-URS variables are examined, there is no difference in presence of congenital abnormalities, stone location, local case volume, previous treatment and intra-operative stone impaction, type of URS, access sheath use, and post-operative stent placement comparing B-URS with I-URS. The significant difference between B-URS and I-URS, represent the average treatment effect, or the effect attributed to having B-URS. The final IPWRA models for multiple stones compared to single stones (B) shows that procedures for multiple stone treatments are significantly longer. These models also show 7% lower SFR, 5% higher retreatment rates and 3% longer hospital admissions. No difference in complication rates was seen when ureteroscopy for multiple stones was compared to treatment for a single stone.

Discussion

This study represents the largest series of patients undergoing URS for multiple bilateral and ipsilateral stones. Previous studies examining ipsilateral^{5-11,16}, and bilateral single session treatment¹²⁻¹⁵ were smaller, included selected patients and were generally from a single centre or surgeon **(Table 4)**. Only two studies examined the use of both I-URS and B-URS^{11,23}. Current results indicate lower SFR, higher retreatment rates, longer OR times, and longer post-operative hospital admission in patients treated for multiple stones compared to patients treated for a single stone. Moreover, B-URS patients have lower SFR, higher retreatment rates, longer OR times, and longer post-operative hospital admission compared to I-URS patients. There was no difference in complication rate between B-URS, I-URS, and single stone ureteroscopy rates.

Stone Free rates

Both multiple versus single and B-URS versus I-URS are associated with lower SFR in the treated area. A possible explanation may lie in the different types of stone composition¹².

As a limitation, it is possible that urologists contributing to the CROES database may listed all stones in the database, but only targeted and treated ureteric stones, with no intention to treat the renal calculi, but then indicating failure of treatment due to the remaining renal stones. Also, stone free status was defined as the absence of fragments greater than 1mm based on any imaging modality. However, the ability to identify stone fragments of 1mm largely depends on type of imaging .

Retreatment and readmission

Both multiple versus single and B-URS versus I-URS more often require retreatment. This finding suggests that patients with multiple stones are a different kind of stone former and could possibly be explained by other lithogenic factors such as environment or genetics²⁴.

A limitation of the CROES URS database is that it is difficult to distinguish between retreatment and readmission. A patient may be readmitted and undergo retreatment or vice versa. In order to definitively determine if treatment for bilateral stones and multiple ipsilateral stones during a single session compared to staged procedures in fact increases long term SFR and symptom free period, still remains to be determined.

Operation time

The finding that procedure time is longer in multiple versus single, and B-URS versus I-URS stone treatments is not unexpected. A larger stone burden will require more time to treat. Further insight could be attained by examining a patient's cumulative lifetime stone operation time. While treating bilateral stones in one setting can increase OR time, the total number of access sheath insertions and ureteric stents placements it can decrease potential complications and morbidity as well as potentially shortening a patient's cumulative lifetime operating room time. Undergoing two shorter separate general anesthetics might have a fractionally higher anesthetic risk to patients. As a disadvantage of multiple stone treatment unnecessary treatment for stones that might have passed spontaneously, may be performed.

Length of hospital stay

Both multiple versus single and B-URS versus I-URS require longer post-operative hospital admissions. This finding may be due to the nature of the treatment. B-URS versus I-URS remains controversial and is currently not supported by guidelines. Most urologists may decide to observe patients with asymptomatic calculi.

A major advantage of the CROES URS Global study is the ability to give a global perspective of URS for urolithiasis. The inclusion of multiple international centres also has a disadvantage. In some countries, predominantly the United States and Canada, the vast majority of URS cases are performed in an outpatient setting. Patients undergoing URS in other countries such as the Netherlands are typically admitted for 24 hours. We currently used 2 or more nights, to define longer stay. In this variable, patients with a prolonged stay with a total of one night, are underestimated. Future studies should aim at collecting deviation from usual local practice more than length of stay.

Complications

Current retrospective data suggests that even though there is a perceived increased risk of damage to the urinary tract with B-URS, it is in fact not associated with a higher complication rate when compared to I-URS, which matches prior published studies^{5,16}.

Statistical methods

Methods as currently used, are proposed to cover the heterogeneity between two populations that are compared. By using all the patients compared to a subset of patients when using a match-case analyses, the currently presented method has more power for estimations and population wide conclusions as none of the cases is dropped. One could wonder what 'mainstream' multivariate logistic and linear regression would have given as a result. We have performed the analyses with this approach as well (data not shown), in which we corrected for the same possible confounders. Although numbers were slightly different, the results lead to the same conclusions.

Conclusion

The treatment of multiple stones and B-URS is safe when compared to single stone and I-URS respectively. However, the efficacy of multiple stone treatment remains debatable. Our findings suggest a decrease in SFR, increased retreatment rates, increased operating time and a longer hospital admission in patients treated for multiple stones.

References

1. Bader, M. J., Eisner, B., Porpiglia, F., Preminger, G. M. & Tiselius, H.-G. Contemporary management of ureteral stones. *Eur. Urol.* **61**, 764–72 (2012).
2. Türk, C. *et al.* EAU Guidelines on Interventional Treatment for Urolithiasis. *Eur. Urol.* (2015). doi:10.1016/j.eururo.2015.07.041
3. Assimos, D. *et al.* *Surgical Management of Stones: American Urological Association/Endourological Society Guideline, PART I. The Journal of Urology* **196**, (2016).
4. Glowacki, L. S., Beecroft, M. L., Cook, R. J., Pahl, D. & Churchill, D. N. The natural history of asymptomatic urolithiasis. *J. Urol.* **147**, 319–321
5. Alkan, E. *et al.* Combined ureterorenoscopy for ureteral and renal calculi is not associated with adverse outcomes. *Cent. Eur. J. Urol.* **68**, 187–192 (2015).
6. Bilgasem, S., Pace, K. T., Dyer, S. & Honey, R. J. D. Removal of Asymptomatic Ipsilateral Renal Stones Following Rigid Ureteroscopy for Ureteral Stones. *J. Endourol.* **17**, 397–400 (2003).
7. Cocuzza, M. *et al.* Combined Retrograde Flexible Ureteroscopic Lithotripsy with Holmium YAG Laser for Renal Calculi Associated with Ipsilateral Ureteral Stones. *J. Endourol.* **23**, 253–258 (2009).
8. Lai, D., Chen, M., He, Y. & Li, X. Simultaneous retrograde intrarenal surgery for ipsilateral asymptomatic renal stones in patients with ureteroscopic symptomatic ureteral stone removal. *BMC Urol.* **15**, 22 (2015).
9. Lee, S. H. *et al.* Effectiveness of Flexible Ureteroscopic Stone Removal for Treating Ureteral and Ipsilateral Renal Stones: A Single-Center Experience. *Korean J. Urol.* **54**, 377–382 (2013).
10. Sun, L. & Peng, F.-L. Treatment of Ipsilateral Renal Ureteral Calculi by Combining

Retroperitoneal Laparoscopic Surgery with Tubeless Mini-Percutaneous Nephrolithotomy. *Urol. Int.* **90**, 139–143 (2013).

11. Takazawa, R., Kitayama, S. & Tsujii, T. Single-session ureteroscopy with holmium laser lithotripsy for multiple stones. *Int. J. Urol.* **19**, 1118–1121 (2012).
12. Huang, Z. *et al.* Flexible ureteroscopy and laser lithotripsy for bilateral multiple intrarenal stones: is this a valuable choice? *Urology* **80**, 800–4 (2012).
13. Gunlusoy, B. *et al.* Is Bilateral Ureterorenoscopy the First Choice for the Treatment of Bilateral Ureteral Stones? An Updated Study. *Urol. Int.* **89**, 412–417 (2012).
14. Drake, T., Ali, A. & Somani, B. K. Feasibility and safety of bilateral same-session flexible ureteroscopy (FURS) for renal and ureteral stone disease. *Cent. Eur. J. Urol.* **68**, 193–196 (2015).
15. Watson, J. M., Chang, C., Pattaras, J. G. & Ogan, K. Same session bilateral ureteroscopy is safe and efficacious. *J. Urol.* **185**, 170–4 (2011).
16. Goldberg, H. *et al.* The Impact of Retrograde Intrarenal Surgery for Asymptomatic Renal Stones in Patients Undergoing Ureteroscopy for a Symptomatic Ureteral Stone. *J. Endourol.* **27**, 970–973 (2013).
17. de la Rosette, J. *et al.* The Clinical Research Office of the Endourological Society Ureteroscopy Global Study: Indications, Complications, and Outcomes in 11,885 Patients. *J. Endourol.* **28**, 131–139 (2013).
18. Tepeler, A. *et al.* Categorization of intraoperative ureteroscopy complications using modified Satava classification system. *World J. Urol.* **32**, 131–6 (2014).
19. Schoenthaler, M. *et al.* Postureteroscopic Lesion Scale: A New Management Modified Organ Injury Scale—Evaluation in 435 Ureteroscopic Patients. *J. Endourol.* **26**, 1425–1430 (2012).
20. Clavien, P., Sanabria, J. & Strasberg, S. Proposed classification of complications of

- surgery with examples of utility in cholecystectomy. *Surgery* **111**, 518 (1992).
21. Dindo, D., Demartines, N. & Clavien, P. Classification of Surgical Complications. *Ann. Surg.* **240**, 205–213 (2004).
 22. Xie, J. & Liu, C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat. Med.* **24**, 3089–110 (2005).
 23. Schatloff, O. Editorial Comment to Single-session ureteroscopy with holmium laser lithotripsy for multiple stones. *Int. J. Urol.* **19**, 1121–1122 (2012).
 24. Monico, C. G. & Milliner, D. S. Genetic determinants of urolithiasis. *Nat Rev Nephrol* **8**, 151–162 (2012).

Figure 1. Percentage of type of stones treated.

Figure 2. Type of stones.

Table 1. Descriptive information on study population of the CROES URS Global Study.

	Single stones (n=8626)	Multiple ipsilateral stones (n=1880)	Multiple bilateral stones (n=273)
Baseline characteristics			
Age	49.9(15.8)	48.8(13.6)	49.8(15.6)
Gender, n(%)			
Male	5648 (65.5)	1215 (64.7)	198 (72.5)
Female	2972 (34.5)	663 (35.3)	75 (27.5)
BMI, n(%)			
Underweight	183 (2.5)	43 (2.6)	3 (1.4)
Normal weight	2534 (35.1)	576 (34.5)	80 (37.6)
Overweight	3157 (43.8)	673 (40.3)	88 (41.3)
Obese	1208 (16.7)	338 (20.2)	39 (18.3)
Super obese	134 (1.9)	40 (2.4)	3 (1.4)
ASA score, n(%)			
I	4668 (57.7)	825 (47.0)	159 (60.9)
II	2748 (34.0)	703 (40.0)	83 (31.8)
III	642 (7.9)	213 (12.1)	19 (7.3)
IV	36 (0.4)	16 (0.9)	-
Congenital abnormalities, n(%)			
Yes	421 (4.9)	105 (5.6)	3(1.1)
Cardio Vascular Disease, n(%)			
Yes	2423 (28.1)	658(35.0)	78(28.6)
Previous stone treatment, n(%)			
Yes	3089 (35.8)	1055(56.1)	109(39.9)
Stone location			
Ureter	7540 (87.4)	8399 (89.2)	231 (84.6)
Kidney	1085 (60.0)	1 (0.01)	-
Both	-	1019(10.8)	42 (15.4)
Pre-operative stent, n(%)			
Yes	1366 (15.9)	431 (23.0)	37 (13.6)

Procedure characteristics			
	Single stones	Multiple ipsilateral stones	Multiple bilateral stones
Impacted stones, n(%)			
Yes	2363 (27.8)	653 (35.0)	79 (29.3)
Acces Sheath, n(%)			
Yes	1149 (13.3)	433 (23.0)	27 (9.9)

Post-operative stent, n(%) Yes	6894 (80.1)	1608 (85.5)	240 (87.9)
Type of URS, n(%) Flexible	7060 (82.1)	1240(66.2)	221 (81.0)
Semirigid	975 (11.3)	203 (10.8)	16 (5.9)
Both	566 (6.6)	430 (23.0)	36 (13.2)

Procedure outcomes			
	Single stones	Multiple ipsilateral stones	Multiple bilateral stones
Stone free rate, n(%) Yes	7701 (90.3)	1515 (82.1)	223 (83.8)
Retreatment and readmission, n(%) Yes	1998 (13.9)	399(21.2)	57(20.9)
Long stay, n(%) Yes	2896 (33.7)	794(42.5)	118(43.5)
Complications, n(%) Yes	572 (6.6)	151 (8.0)	21 (7.7)
Operation time	50 (30-70)	60(40-85)	50(32-70)

Data are n (%) of patients for whom data were available. Percentages exclude missing values from denominators.

Table 2. Univariate IPWRA analyses.**A. Univariate regression analyses Ipsi- or bilateral**

	Stone Free Rate	Retreatment	Long hospital stay	Complications	Operation time
IpsiBi	-0.051* (0.048)	0.056** (0.006)	0.044** (0.005)	0.028 (0.425)	1.542*** (0.000)
Observations	2092	2134	2113	2125	9500

B. Univariate regression analyses single versus multiple stone treatment

	Stone Free Rate	Retreatment	Long hospital stay	Complications	Operation time
SingleMultiple	0.522*** (0.000)	1.642*** (0.000)	1.311*** (0.000)	1.459*** (0.000)	1.469*** (0.000)
Observations	11355	11494	11454	11484	11242

Odds ratio; *p*-values in parentheses* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 3. Multivariate IPWRA analyses.

A. Bilateral versus Ipsilateral stone treatment					
	Stone Free	Retreatment and readmission	Long stay	Total complication	Operation time
B-URS	-0.051	0.056	0.044	0.028	1.363***
versus	[-	[-	[-	[-	[1.274,1.485]
I-URS	0.118,0.015]	0.011,0.122]	0.027,0.115]	0.018,0.074]	
Observation	2092	2134	2113	2125	2084
s					
B. Multiple versus single stone treatment.					
	Stone Free	Retreatment and readmission	Long stay	Total complication	Operation time
Multiple	-0.0666***	0.0481***	0.0348**	0.00831	1.228***
versus	[-0.083,-	[0.032,0.065	[0.012,0.058	[-	[1.194,1.261
Single	0.050]	]	]	0.004,0.020]	]
Observation	11176	11314	11246	11272	11065
s					

Numbers represent the Average Treatment Effect [Confidence Interval].

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Model A shows that having a B-URS over I-URS suggests a 5% lower SFR, 6% higher retreatment rates, 4% less long stay, 3% more complications, but most importantly, operation time is significantly longer in the B-URS group.

Model B shows that having multiple stones treated within on session is associated with 7% lower SFR, 5% higher retreatment rates, 3% less long stay, Moreover, operation time is significantly longer in multiple stone treatment. Higher complication rates are suggested.

Table 4: Summary of existing literature on URS for multiple ipsilateral and bilateral stones

Paper	Description & Stone size	Effect on SFR	Effect on operative time	Effect on complications
Bilgasem et al 2003	Retrospective study. (n=29) -Ureteric calculi and ipsilateral renal calculi -Mean renal stone size 5.7 mm	100% SFR at 1 month follow up	56.5 min (mean) 16.7 min (mean added time of for flexible ureteroscopy)	n/a
Alkan et al 2015	Retrospective study . (n=90) Group A -Ureteric calculi (distal or mid ureter) and ipsilateral calyceal stones -Mean ureteral stone burden 56.0 ±5.5 mm ² -Mean renal stone burden 83.7 ±11.3 mm ² Group B -Distal or mid ureteric calculi -Mean ureteric stone burden 54.8 ±6.1 mm ²	100% for ureteral stones in both groups 88.9% for renal stones	Longer for Group A vs Group B Mean difference 32.5 ± 1.2 min (p=0.001) 61.9 ± 3.4 (min) vs 29.4± 2.2 (min)	Similar Group A 17.8% Group B 15.5% (p=0.500)
Goldberg et al 2013	Retrospective matched study. (n=94) Group A -Ureteric calculi and ipsilateral renal calculi -Mean total stone burden of 52.9 mm ² Group B -Ureteric calculi -Mean total stone burden 47mm ²	Ureteric stone removal Group A 98% Group B 100% 85% for renal stones	Group A 68 min (mean) Group B 39 min (mean) (p<0.001)	Similar
Lai et al 2015	Retrospective matched study. (n=144) Group A -Ureteric calculi and ipsilateral renal calculi	Ureteral SFR- 100% in each group Renal SFR- 86.1%	Longer for Group A vs Group B Group A 72.4±21.3 (mean) Group B	Higher for Group A vs Group B (22.2% vs 13.9%) N/S

	<p>-Mean ureteric stone burden 67.2mm²</p> <p>Group B -Ureteric calculi</p> <p>-Mean ureteric stone burden 71.3mm²</p>		36.4±10.2 (mean) (p<0.001)	
Cocuzza et al 2009	<p>Retrospective study.(n=102)</p> <p>Group A -Ureteric calculi and ipsilateral renal calculi</p> <p>Group B -Ureteric calculi</p> <p>Mean renal stone size 10.7 +/- 6.4mm</p>	<p>Group A overall SFR- 81%</p> <p>Group A SFR w LP stones- 81%</p> <p>Group A SFR w multiple stones- 76%</p>	<p>Longer for Group A vs Group B</p> <p>Group A 67.9±25.9 min (mean) Group B 49.3±13.2 min (mean) (p<0.001)</p>	<p>Higher for Group A vs Group B</p> <p>(3.1% vs 2.5%) N/S</p>
Bansal et al 2016	<p>Retrospective study. (n=74)</p> <p>Bilateral renal calculi</p> <p>Mean stone size 11.7 ± 2.4 mm</p>	<p>Single session SFR 64 (86.4%)</p> <p>SFR after second session 72 (97.2%)</p>	51.1 min ± 15.3	5.4% overall 8/74 (grade I-II)
Atis et al 2013	<p>Retrospective study. (n=42)</p> <p>Bilateral renal calculi</p> <p>Mean stone size 24.09 ± 6.37 mm</p>	<p>Single session SFR 92.8%</p> <p>SFR after second session 97.6%</p>	51.08 min ± 15.22	4.7% overall 2/42 (grade I or II)