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## **ORIGINAL ARTICLE**

## Prospective, Non-randomized Study of Clinical Outcome in Patients With Primary Versus Delayed Ureteroscopy for Proximal Ureteric Stone (PRIDE Study)

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#### ABSTRACT

Introduction: Conventionally, proximal ureteric stone is managed with stenting followed by a definitive delayed treatment. This approach requires multiple hospital visits. Primary ureteroscopy has been employed to expedite the treatment as a single-stage procedure. Methodology: This prospective, non-randomized, cohort study assessed the efficacy and safety of primary (P-URS) versus delayed ureteroscopy (D-URS) in the management of proximal ureteric stone. A total of 176 consecutive patients with unilateral proximal ureteric stone >3mm were included in the final data analysis (95 P-URS and 81 D-URS). The decision to proceed with P-URS or D-URS was based on initial presentation and surgeon's expertise. Stone free was defined as no visible residual fragments on the kidney, ureter and bladder (KUB) radiograph which was performed 6 weeks post-operatively. Primary outcome was stone free rate. Secondary outcomes include operative duration, length of hospital stay and rate of complications. **Results:** D-URS had a higher stone free rate (96.3%) compared to P-URS (74.7%) but overall operative duration, length of stay and rate of complications were comparable between these 2 groups. All complications from D-URS were UTI-related (8.6%) Conclusion: P-URS for proximal ureteric stone is a safe and feasible option accepting the lower stone free rate compared to D-URS.

## INTRODUCTION

Urolithiasis, or urinary tract stone is a major health problem worldwide. There has been a stone forming belt stretching across the West Asia, Southeast Asia, South Asia as well as several developed countries, including South Korea and Japan, with prevalence ranging from 5% to 19.1% (Liu et al., 2018). Unfortunately, the Borneo part of Malaysia (Sarawak and Sabah) is not spared from this "stone-belt". A recent epidemiological study of urolithiasis in Sarawak found a prevalence of 4.4%, with the commonest age group being 24 –64 years (Perumal et al., 2023). Another study in Sabah revealed that ureteric stone alone (excluding multiple sites) accounts for 18% of all urolithiasis (Cheema et al, 2022). Intervention on ureteric stones poses a significant burden on healthcare cost and national economy, both directly and indirectly through follow-up appointments and absence from work.

Conventionally, ureteric stone is managed firstly with stenting followed by a definitive treatment later such as delayed ureteroscopy (D-URS) or extracorporeal shock wave therapy (ESWL). However, this approach requires multiple hospital visits and thus, exacerbating the burden on individual and healthcare system. Increasingly, primary ureteroscope (P-URS) has been employed to expedite the definitive management of ureteric stone as a single-stage procedure.

While distal and mid ureteric stones are deemed easy to access using ureteroscope, proximal ureteric stone remains a challenge for most endourologists, even the most experienced ones. A number of studies have looked at the role of P-URS (Arcaniolou et al., 2017), but none was specific to proximal ureteric stone. This prospective, nonrandomized, cohort study is the first study in modern literature to assess the efficacy and safety of primary versus delayed ureteroscopy in the management of proximal ureteric stone.

## **MATERIALS AND METHODS**

Between March 2022 and December 2023, 178 consecutive patients from a tertiary urological referral center were recruited in a prospective but non-randomized manner, where they were diagnosed with unilateral proximal ureteric stone >3mm requiring surgical intervention. Proximal stone was defined as a stone above the upper border of pelvic brim. Children <18 years old, pregnant ladies and patients with ongoing active infection were excluded from this study. Two patients were excluded from final data analysis due to pyonephrosis upon stone fragmentation. The decision to proceed with primary or delayed ureteroscopy was based on initial presentation (severe colic or infection would mandate drainage first) and surgeon's expertise. Sample size was calculated based on previous similar study (Elderwy et al., 2018) where stone free rate for P-URS and D-URS were 0.75 and 0.87 respectively. Using formula for comparative study (Sharma et al., 2020), the sample size needed to achieve 95% confidence level with a power of 80% was 162 patients with 81 in each group. Final data analysis included 176 patients in total (95 for P-URS and 81 for D-URS).

This study was approved by MREC (Medical Research and Ethics Committee) of Ministry of Health Malaysia (NMRR ID-22-01294-KA2).

Initial non-contrasted computed tomography (CT) scans and kidney, ureter and bladder (KUB) radiography were performed for all patients to determine the size and location of ureteric stone. KUB radiography-radiolucent stones were excluded from this study. All procedures were performed by a urologist or a senior trainee under supervision of a single consultant urologist. All patients underwent the procedure either under spinal or general anesthesia based on anesthetist's experience and clinical judgement. Ureteroscope used was a Richard-Wolf 6.5/7Fr semi-rigid ureteroscope. Stone fragmentation was performed with

low power Holmium:YAG laser (Jena Surgical Multipulse Ho 35W). The decision to leave a stent post operatively was left to surgeon's discretion. Duration of operation and length of hospital stay post operatively were noted.

Stone free status was defined as no visible residual fragments on the KUB radiography which was performed 6 weeks after operation. Any post-operative complications were noted.

Data analysis was done using SPSS version 24 (SPSS, Chicago, IL, USA). Categorical data were assessed using  $\chi^2$  and Fisher's exact test. Continuous data were analyzed using the independent t-test assuming that the data were normally distributed. The statistical significance level was set at 0.05.

## RESULTS

A total of 176 patients were included in the final data analysis. Among these 176 patients, 95 underwent P-URS and 81 underwent D-URS. Mean age of patients for P-URS was 52 years (SD 12) compared to 54 years (SD 13) in D-URS group. Both groups had similar proportion of male and female patient. P-URS had 47 male (49%) while D-URS had 44 male (54%) (p=0.411). P-URS had 45 right-sided stone (47%) while D-URS had 41 right-sided stone (51%) (p=0.185). The mean stone size for P-URS group was 13.31mm (SD 4.31) compared to D-URS which was 13.23mm (SD 5.48) (p=0.924) (Table 1).

URS for Ure- teric Stone (n=176)	Primary (n=95) ± SD	Delayed (n= 81) ±SD	95% Confidence Interval (p-val- ue=0.05)
Mean age, years	52±12	54±13	0.217 (-6.272 to 1.434)
Gender	Male=47 Female=48	Male=44 Female=37	0.411
Location	Right=45 Left=50	Right=41 Left=40	0.185
Stone Size (mm)	13.31±4.31	13.23±5.48	0.924 (-1.387 to 1.528)

#### Table 1: Patient and stone demographics.

In terms of stone outcomes, D-URS had performed better with a stone free rate (SFR) of 96.3% (78 patients) compared to 74.7% (71 patients) for P-URS. These results were statistically significant (p=0.000) (Table 2).

URS for Ure- teric Stone (n=176)	Primary (n=95) ± SD	Delayed (n= 81) ±SD	95% Confidence Interval (p-val- ue=0.05)	
Stone Free Rate, (100%)	Yes=71 (74.7%) No=24 (25.3%)	Yes=78 (96.3%) No=3 (3.7%)	15.648 (p=0.000)	
Operation duration (min)	47.47±18.31	48.40±18.78	0.743 (-0.921 to 2.802)	
Stay duration (hours)	22.48±10.72	29.20±31.14	0.05 (-13.441 to 0.015)	
Stenting	Yes=95 (100%) No=0 (0%)	Yes=73 (90.1%) No=8 (9.9%)	7.685 (p=0.002)	
Complica- tions	Yes=5 (5.3%) No=90 (94.7%)	Yes=7 (8.6%) No=74 (91.4%)	0.786 (p=0.55)	
Severity (Clavien-Din- do Grading)	No=90 (94.7%) Grade 2 (UTI)=1 (1.1%) Grade 2 (Stent- Irritation)=1 (1.1%) Grade 1 (Irrigation)=2 (2.1%) Grade 2 (Transfu- sion)=1 (1.1%)	No=74 (91.4%) Grade 2 (UTI)=7 (8.6%)	9.004 (p=0.016) 8.369 (p=0.018)	
Unsuccessful Reason	No=71 (74.7%) Impacted=5 (5.3%) Retropul- sion=14 (14.7%) Difficult Maneuver=5 (5.3%)	No=78 (96.3%) Impacted=2 (2.5%) Retropul- sion=1 (1.2%)	16.874 (p=0.000) 17.545 (p=0.000)	

#### Table 2: Operative outcomes.

In terms of operative outcomes, both P-URS and D-URS had similar mean operative duration (minutes) which was 47.47 (SD 18.31) and 48.40 (SD18.78) respectively (p=0.743). Patients from P-URS group had a mean post-operative length of stay (hours) of 22.48 (SD 10.72) compared to D-URS group which was 29.20 (SD 31.14) (p=0.05). 100% of P-URS patients had stenting post-operatively compared to 90.1% of D-URS patients (Table 2).

In terms of complications, P-URS group had 5 cases (5.3%) while D-URS group had 7 cases (8.6%) (p=0.786). These results were statistically not significant. All 7 cases with complications from D-URS group were urinary tract infection (UTI) compared to only 1 case from P-URS group. All of the complications were minor (Clavien-Dindo grade 2 and below). The most common unsuccessful reason for P-URS was retropulsion of stone (14 cases) (Table 2).

In terms of efficacy of different level of surgeon, both trainee and specialist groups had achieved similar SFR (85.6% for trainee and 83.1% for specialist) (p=0.199). The differences were not statistically significant (Table 3).

## Table 3: Level of surgeon.

URS for Ure- teric Stone (n=176)	Primary (n=95) ± SD	Delayed (n= 81) ±SD	95% Confidence Interval (p-val- ue=0.05)
Stone Free Rate, (100%)	Yes=95 (85.6%) No=16 (14.4%)	Yes=54 (83.1%) No=11 (16.9%)	0.199 (p=0.670)

## DISCUSSION

Our prospective, non-randomized study has shown that P-URS for proximal ureteric stone had a lower stone free rate (SFR) compared to D-URS, with similar operative duration, length of hospital stay and rate of complication. Another study conducted in UK looking at P-URS versus D-URS for ureteric stone at all locations had shown similar results with comparable SFR (Mckay et al., 2021). Data from a retrospective study in New Zealand had also shown that emergency P-URS is a feasible approach in managing acute ureteric colic for stones in all locations with a success rate of 72% (Zargar-Shostari et al., 2015).

As far as we know this is the first study to focus on ureteroscopic management of proximal ureteric stone. Unstented patients especially young female and proximal ureteric stone were the least likely to be accessed primarily (Fuller et al., 2016). In our study, there were total of 24 unsuccessful cases for P-URS (14 cases due to retropulsion, 5 cases due to stone impaction and 5 cases due to difficult maneuver). These results reflected the challenges that endourologists had to face during manipulation of proximal ureteric stone. The risk of proximal fragment migration is influenced by the pressure of the irrigant fluid, type of energy source used for intracorporeal lithotripsy, site and degree of calculus impaction, and degree of proximal ureteral dilatation (Hendlin et al., 2008). A stone could be deployed to reduce the risk of proximal stone retropulsion (Bastawisy et al., 2011). Pre-operative alpha blockers could improve ureteroscopic outcome based on a recent meta-analysis (Bhojani et al, 2024). With the advent of smaller, flexible ureteroscopes and better LASER equipment, we have a reason to believe that the stone free rate for P-URS would be improved in the near future.

Both P-URS and D-URS in our study have shown similar complications rates (5.3% versus 8.6%) and all complications were considered minor. This is in concordance with other larger studies (de la Rosette et al., 2014). Another study reported a lower rate of complication (2.83%) with proximal stone ureteroscopy, but ureteral access sheath (UAS) was used in 22% of the patients (Lazarovich et al., 2023). UAS was not used in our study due to extra cost and risk of ureteric perforation. Most complications included transient hematuria and urinary tract infection (UTI) which resolved with conservative management. Surprisingly, in our study, the complications from D-URS were all UTI-related. This was probably associated with prolonged indwelling stent. A recent study had shown that preoperative stenting was

significantly associated with post-URS urinary tract infection (16.9% versus 7.1%) (Pereira et al., 2023). Female gender, preoperative positive urine cultures and stone recurrence were significant risk factors (Pereira et al., 2023). Another study has demonstrated that a stent dwelling time of more than two months was associated with an increased risk of postureteroscopic febrile UTI (Geraghty et al., 2022). We advise to obtain pre-operative cultures prior to ureteroscope and treat accordingly in case of prolonged indwelling stent.

Our study has shown that there was no difference in terms of SFR for different level of surgeon. The slight reduction for SFR in specialist group was probably due to selection bias as specialist would have taken on more challenging cases based on pre-operative imaging. However, it should be safe to say that P-URS could be performed by trainee with equivalent outcome to specialist.

P-URS could have positive impact on patient's quality of life, total work-day loss and healthcare expenses. P-URS avoided the initial admission for pre-stenting and stent-related complications during the waiting period for definitive operation especially in public hospital. The stent post P-URS could be easily removed during outpatient visit in 2 weeks. On cost evaluation, a UK study has shown that average total treatment cost for emergency stenting (delayed intervention) was 5900 Euro compared to 4450 Euro for P-URS group (Wani et al., 2021). In long run, P-URS could be the most cost-effective option to deal with ureteric stones provided that facilities and suitable endourological experience are available.

The placement of indwelling stent has variable degree of impact across all general health domains. Many patients report fatigue, dependence to perform daily activities, and even reduce their social life while presenting symptoms associated with the stent (Bargues-Balanza et al., 2022). P-URS totally avoided the stent-irritation symptoms during the waiting period for D-URS.

## CONCLUSION

Primary URS for proximal ureteric stone is a safe and feasible option accepting the lower SFR compared to delayed URS. Primary URS avoided the stent-irritation symptoms during the waiting period for D-URS. Primary URS should be attempted provided that the facilities and expertise are available. Further studies are required to identify patients that are not favorable for primary URS in the setting of proximal ureteric stone.

## **CONFLICT OF INTEREST**

The authors declared no conflicts of interest.

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