

Indications for Intervention in Patients Undergoing Ureteroscopic Therapy for Ureteric Calculus: A Cross-sectional Study

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ABSTRACT

Introduction: Urolithiasis is one of the most common urological problems worldwide. The fastest treatment modality to achieve stone clearance of ureteral stones is Ureteroscopic Lithotripsy (URSL). However, it is negated by both the cost burden and potential risk to the patient. Medical Expulsive Therapy (MET) is a treatment option for upto 10 mm stones but has failure rates of 40-60% in the literature.

Aim: To analyse the various indications for surgery, whether MET was used or not, if used-its details, operative findings at ureteroscopy including the reason for the failure of MET.

Materials and Methods: A cross-sectional study consisting of 72 patients with ureteric calculi undergoing URSL was analysed from June 2017 to December 2018 at Mazumdar Shaw Medical Centre, Bangalore, Karnataka, India. Indications were assessed at the time of admission. During ureteroscopy, factors like impaction, distal obstruction, and unusual findings were studied, which could have contributed to the failure of MET. The Chi-square test was used as a test of significance for categorical data. The Analysis of Variance (ANOVA) test was

used as a test of significance to identify the mean difference between continuous variables. The p-value of <0.05 was considered statistically significant.

Results: The mean age in the study was 41.65±13.4 years (range 20-69 years), and the mean stone size was 10.03±3.34 mm. Large stone was the most common indication (41, 56.9%, p=0.004), followed by failed MET (35, 48.6%). Even though MET could have been continued for four weeks in 17 patients (23.6%), they were taken up for surgery. The impaction rate was 70.8% (51), with 48.6% (35) being large impacted stones and 22.2% (16) being small impacted stones. The overall stone clearance rate was 68 out of 72 (94.4%).

Conclusion: Large stone size (≥10 mm) and failed MET were the main indications for surgery. One reason for the failure of MET was not waiting for a duration of four weeks. During ureteroscopy, impaction of the stone, irrespective of size, was the most common finding and was the reason for the failure of MET. Ureteric stones on MET should not be neglected as there are reasons for the failure of MET, and they will require URSL after four weeks.

Keywords: Failed Medical Expulsive Therapy,, Laser Lithotripsy, Ureteroscopy

INTRODUCTION

Urinary stones are among the most common urological problems worldwide and have been an ancient source of serious morbidity. The prevalence of urinary stones is approximately 1%-5% in Asia, 5%-9% in Europe, and 13% in the United States [1]. On average, 12% of individuals across populations have a history of urinary stones, with an overall recurrence rate is approximately 50% [2]. The recurrence interval changes over time, with 10% recurrence within one year, 35% within five years, and 50% within 10 years [3]. The annual incidence of stone formation is estimated to be 1,500 to 2,000 cases per million people [4]. Stone incidence appears to have steadily increased in recent years and may be linked to dietary changes (especially increased protein and mineral intake), race or ethnicity, and region of residence [5]. The peak incidence age generally falls between 20 and 50 years [6].

The most expedient treatment modality for achieving ureteral stone clearance is surgery-URSL. However, this is countered by both the financial burden and potential risks to the patient. MET is a treatment option for stones up to 10 mm, but the literature reports failure rates of 40-60% [7-9]. While there are studies questioning the role of alpha blockers in MET [7,9], it remains common practice for suitable patients in our country.

Numerous studies on URSL and MET can be found in the literature, but no similar study has been done previously. Generally, for ureteric stones >10 mm, URSL is performed, while for 5-10 mm stones, either MET or URSL is considered. These studies discuss the drugs used, the varying success rates of MET, and the advantages and disadvantages of URSL, particularly for stones sized 5-10 mm. The

decision to consider surgical or medical therapy for such stone sizes depends on multiple factors and can often be uncertain.

In this study, by selecting cases undergoing intervention, the authors will be able to select the cases in which MET has failed, in addition to large ureteric stones. The purpose of the current study was to determine the percentage of indications represented by each of these groups. Subsequent analysis could shed light on potential preventive measures or predictive factors for this subset of failures. Identifying markers that could predict failures in advance might lead to a more evidence-based implementation of such therapies.

MATERIALS AND METHODS

A cross-sectional study of patients undergoing ureteroscopic intervention for ureteric calculus at Mazumdar Shaw Medical Centre, NH, Bangalore, Karnataka, India, was conducted from June 2017 to December 2018. This study was conducted after obtaining clearance from the ethical committee of the institute (NHH/AEC-CL-2017-174), and informed written consent was obtained from the patients. After considering the inclusion and exclusion criteria, a total of 72 cases were included in the study.

An ideal candidate for MET [10-15] would be a well-motivated patient with a unilateral, solitary, ureteric calculus <10 mm in size, well-controlled symptoms, access to emergency medical services if required, and no Urinary Tract Infections (UTI), renal dysfunction, distal obstruction, or other co-morbidities that would make the patient unsuitable for the approach. EAU recommends considering α-blockers as part of MET as one of the treatment options for (distal) ureteral stones >5 mm [16].

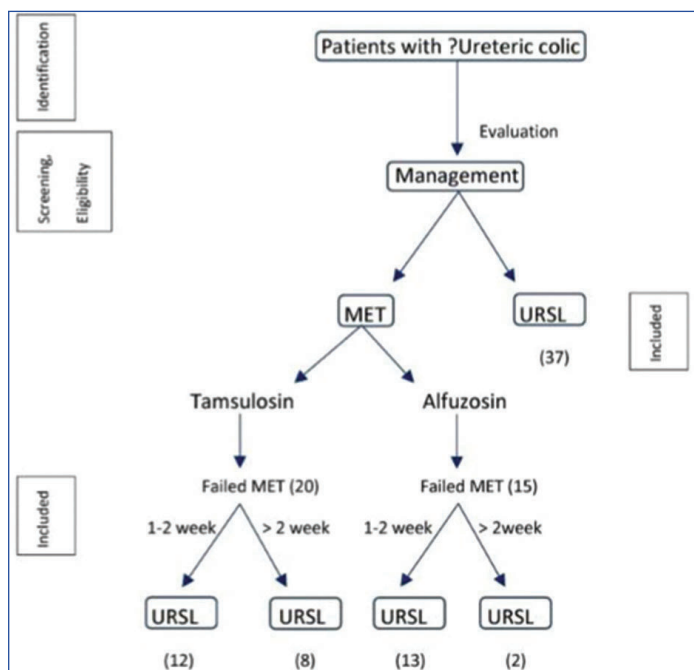
At our institution, the standard of care is to pursue MET if the patient is deemed suitable. Hence, large majority of patients undergoing ureteroscopic intervention for calculus at our institution have had a failed MET, apart from having large ureteric stones. Failed MET cases considered in the study for 5-10 mm stone size are shown in [Table/Fig-1].

Those who developed recurrent pain on MET and analgesics
Those failed to pass stone after 4 weeks of MET
Those developing UTI on MET
Worsening renal dysfunction
Those not tolerating alpha blockers
Patient refusal

[Table/Fig-1]: Failed Medical Expulsive Therapy (MET) considered in the study.

Inclusion criteria: All patients undergoing URSL for stone clearance at our centre, including those with large stones (>10 mm), failed MET, refractory pain, renal insufficiency (renal failure, bilateral obstruction, or a single kidney), residual stone, and patient request, were included in the study.

Exclusion criteria: Patients undergoing additional procedures, e.g. RIRS (Retrograde Intrarenal Surgery) simultaneously, those undergoing only DJ stenting for ureteric calculi, pregnant women, contraindications or allergies to α -blockers, and those did not consent were excluded from the study [Table/Fig-2].



[Table/Fig-2]: Flowchart of the subjects recruitment. URSL: All patients undergoing URSL for different-different reasons eg. failed MET or direct URSL were included in the study

Procedure

The indication for surgery was assessed at the time of admission. A thorough evaluation of the patient through history, examination, investigations (including laboratory values and CT KUB (Plain)), and review of prior records was conducted. A conservative trial with MET for a maximum of four weeks was taken as sufficient duration. Tamsulosin 0.4 mg in males, 0.2 mg in females, and Alfuzosin 10 mg in both males and females were administered. Depending on the duration for which the patients received alpha-blocker therapy, they were further sub-categorised into

- those who had not received MET (37 cases, 51.4%),
- those who received it for 1-2 weeks only (25 cases, 34.7%),
- those who received it for more than two weeks (10 cases, 13.9%) [Table/Fig-2].

The URSL procedure was carried out under spinal anaesthesia or general anaesthesia in a few patients. Ureteroscopy was done with a 6.4/7.8 Fr semi-rigid ureteroscope. Intraoperatively, fluoroscopy was used for a retrograde ureterogram/pyelogram. Stone fragmentation was achieved with a luminous holmium laser [17,18]. Retropulsion devices were not used for upper ureteric stones during ureteroscopy. At the time of ureteroscopy, factors like impaction, distal obstruction, and any unusual findings (e.g., kinks, narrow ureteric orifice, narrow lower ureter) were documented in the proforma, which could have contributed to the failure of MET. If the stone could be fragmented during ureteroscopic intervention using a luminous holmium laser, it was considered successful therapy, and these cases were included in the study.

Cases where the stone could not be fragmented for any reason were considered unsuccessful therapy and were excluded from the study. Patients were followed until discharge for postoperative recovery, and any complications observed were recorded in the study. Complete fragmentation of the stone by laser during ureteroscopy with no residual fragments on X-ray was considered complete clearance.

STATISTICAL ANALYSIS

Categorical data were represented in the form of frequencies and proportions. The Chi-square test was used as a test of significance for categorical data. Continuous data were represented as mean and standard deviation. The ANOVA test was used as a test of significance to identify the mean difference between quantitative variables. A p-value of <0.05 was considered statistically significant after assuming all the rules of statistical tests. The Microsoft (MS) excel and SPSS version 22.0 (IBM SPSS Statistics, Somers NY, USA) were used to analyse data.

RESULTS

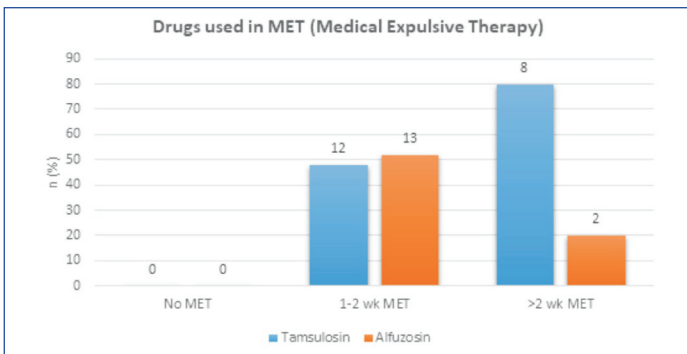
Overall, males constituted 58 (80.6%) cases, and females 14 (19.4%). There was no significant difference between gender and the different study groups (p=0.58) [Table/Fig-3].

	No MET (n=37, 51.4%)	1-2 wk MET (n=25, 34.7%)	>2 wk MET (n=10, 13.9%)	Total (n=72)	z-value	p-value
Gender (M/F)	31 (83.8%)/6 (16.2%)	19 (76%)/6 (24%)	8 (80%)/2 (20%)	58 (80.6%)/14 (19.4%)	0.58	0.75
Age (years)	43.68±14.48	40.96±11.44	35.90±12.94	41.6±13.4	1.4	0.25
Symptom Duration-Wk	9.77±13.21	14.88±23.91	13.80±16.39	12±17.93	0.65	0.5
S. Creatinine	1.32±0.79	1.08±0.42	0.96±0.29	1.19±0.64	1.8	0.17
Stone Size (Largest Dimension) in mm	11.55±3.04	8.32±2.84	8.73±3.16	10.01±3.35	9.8	<0.0001
Hospital stay (Days)	3.08±0.68	2.88±1.05	3.0±0.94	3±0.85	0.4	0.7

[Table/Fig-3]: Descriptive statistics (Mean±SD).

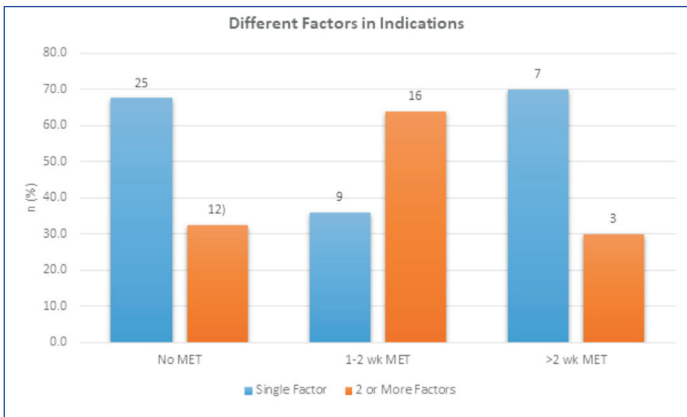
In the present study, only 3 (8.6%) patients could finish four weeks of the MET schedule. None of the patients had intolerance for alpha-blocker therapy. The authors had 35 (48.6%) patients in whom MET had failed. Out of these patients, 20 (57.1%) had received Tamsulosin, and 15 (20.8%) had received Alfuzosin. MET failure was most commonly seen in the 1-2 week group with 25 (71.4%) cases, 13 (52%) cases with Alfuzosin, and 12 (48%) cases with Tamsulosin [Table/Fig-4].

Indications for URSL included different factors, with a single factor being considered most common in the non-MET group (25, 67.6%). Multiple factors were considered most common in the



[Table/Fig-4]: Drugs used in Medical Expulsive Therapy (MET).

1-2 week group (16, 64%) and the non-MET group (12, 32.4%). Overall, a single factor was considered in 41 (56.9%) cases, and multiple factors were considered in 31 (43.1%) [Table/Fig-5].



[Table/Fig-5]: Different factors in indications.

The largest stone was the most common indication, with 41 (56.9%) cases. Other common indications consisted of failed MET group with 35 (48.6%) cases and the renal dysfunction group with 14 (19.4%) cases. Although MET could have been continued for four weeks in 17 (23.6%) patients, they were taken up for surgery [Table/Fig-6].

Indications	No MET (n=37, 51.4%)	1-2 wk MET (n=25, 34.7%)	>2 wk MET (n=10, 13.9%)	Total (n=72)
Large stone	28 (75.7%)	10 (40%)	3 (30%)	41 (56.9%)
Failed MET	0	25 (100%)	10 (100%)	35 (48.6%)
Renal Dysfunction	10 (27%)	3 (12%)	1 (10%)	14 (19.4%)
Refractory pain	3 (8.1%)	3 (12%)	0	6 (8.3%)
Multiple calculi	2 (5.4%)	3 (12%)	0	5 (6.9%)
Bilateral Ureteric stones	4 (10.8%)	1 (4%)	0	5 (6.9%)
Pyuria	1 (2.7%)	0	0	1 (1.4%)
Solitary functioning kidney (SFK)	1 (2.7%)	0	0	1 (1.4%)
Residual stone	1 (2.7%)	0	0	1 (1.4%)
Patient request	0	1 (4%)	0	1 (1.4%)

[Table/Fig-6]: Indications for ureteroscopy.

In the present study, failed MET was considered in the following cases (which were either single or overlapping with another factor):

- Those who developed recurrent pain on MET and analgesics (31, 88.5%) were the largest group seen.
- Those who failed to pass the stone after 4 weeks of MET (3, 8.6%).
- Those developing UTI on MET (0).
- Worsening renal dysfunction (overlapped with three cases in recurrent pain while on MET and one case who failed to pass the stone after four weeks of MET, 4, 11.4%).

- Those not tolerating alpha blockers (0).
- Patient refusal (1, 2.9%).

Overall, in the study, 61 (84.7%) cases had a single stone, 6 (8.3%) cases had two stones, and 5 (6.9%) cases had multiple stones in the ureter. During URS, stones were most commonly seen in the lower ureter in 42 (58.3%) cases. In the upper ureter, they were seen in 23 (31.9%) cases, and in the mid-ureter, 15 (20.8%) [Table/Fig-7].

URS-site	No MET (n=37, 51.4%)	1-2 wk MET (n=25, 34.7%)	>2 wk MET (n=10, 13.9%)	Total (n=72)
Upper ureter	15 (40.5%)	6 (24%)	2 (20%)	23 (31.9%)
Mid-ureter	7 (18.9%)	2 (8%)	6 (60%)	15 (20.8%)
Lower ureter	19 (51.4%)	20 (80%)	3 (30%)	42 (58.3%)

[Table/Fig-7]: Ureteroscopy- site of stone.

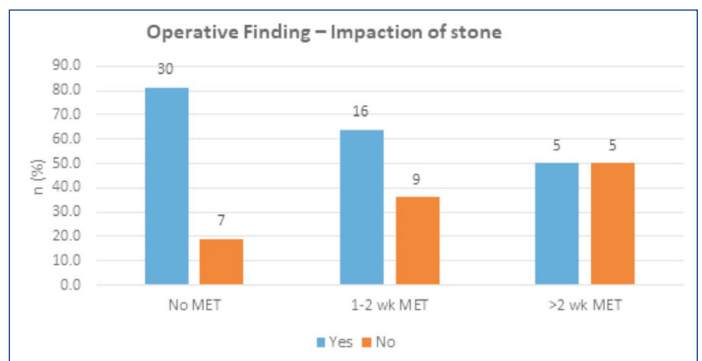
Large impacted stones were the most common finding in 35 (48.6%) patients, while 9 (12.5%) had large un-impacted stones. Unusual findings noted were small impacted stones (22.2%), kinks (5.6%), multiple stones (5.6%), and narrow ureteric orifice/ureter (9.7%, one case of duplex system with a narrow ureter).

The data suggests that longer durations of MET may lead to fewer large impacted stones (>2 week group, large impacted stone 1 (10%) but large un-impacted stone 2 (20%)), reduced chance of finding a narrow ureteric orifice or narrow lower ureter (1-2 week group 4 (16%) but for >2 weeks 1 (10%)), with a higher likelihood of normal findings during surgery. However, the relationship between MET duration and other operative findings like kinks, multiple stones is less clear [Table/Fig-8].

Operative findings	No MET (n=37, 51.4%)	1-2 wk MET (n=25, 34.7%)	>2 wk MET (n=10, 13.9%)	Total (n=72)
Large impacted stone	25 (67.6%)	9 (36%)	1 (10%)	35 (48.6%)
Large un-impacted stone	4 (10.8)	3 (12%)	2 (20%)	9 (12.5%)
Small impacted Stone	5 (13.5%)	7 (28%)	4 (40%)	16 (22.2%)
Kink	2 (5.4%)	1 (4%)	1 (10%)	4 (5.6%)
Multiple stone	1 (2.7%)	3 (12%)	0	4 (5.6%)
Narrow Ureteric orifice/Ureter	2 (5.4%)	4 (16%)	1 (10%)	7 (9.7%)
Nothing Abnormal (Normal)	4 (10.8%)	2 (8%)	2 (20%)	8 (11.1%)

[Table/Fig-8]: Operative findings suggestive of failure of MET.

The authors defined impaction as contrast±guidewire not passing beyond the stone as Impaction. Impaction was most commonly found in the non-MET group with 30 (81.1%), followed by the 1-2 week group with 16 (64%). The overall impaction rate in the present study was 51 (70.8%), where 35 (48.6%) were large impacted stones and 16 (22.2%) were small impacted stones [Table/Fig-9].



[Table/Fig-9]: Operative finding- impaction of stone.

DISCUSSION

Although the majority of <1-cm stones pass spontaneously, this can take time and cause significant pain. The surgical treatment modalities to achieve stone clearance of ureteral stones are ESWL

(seldomly used), URSL, RIRS, or PCNL (for migrated stones), open/lap ureterolithotomy (rarely used). URSL is most commonly used; however, it is negated by both the cost burden and potential risk to the patient. The overall complication rate after URS is 9-25% [19-21]. Therefore, urologists have attempted to treat ureteric stones more conservatively and have tried various pharmacotherapies to facilitate spontaneous passage. Subsequently, this gave rise to MET [22], but it too has a failure rate of 40-60% in the literature [7-9].

A number of factors must be considered in determining the optimal treatment for patients with ureteral calculi. These factors may be grouped into three broad categories: 1) stone factors (location, size, composition, presence, and degree of obstruction); 2) clinical factors (symptom severity, patient's expectations, associated infection, solitary kidney, abnormal ureteral anatomy, coagulopathy and obesity); and 3) technical factors (available equipment and cost) [23]. Hence, these factors are assessed before considering a patient with ureteric stone for MET or URSL.

There is a 68% chance of passage for ureteral stones 5 mm or smaller, and an estimated 47% chance for stones 6 to 10 mm in size [19]. These rates may be enhanced with MET using either calcium channel blockers (such as nifedipine) or, more commonly, α -receptor blockers (such as tamsulosin); however, the utility of MET remains controversial (Pickard R et al., Furyk JS et al., Hollingsworth JM et al., Ye Z et al.) [7,24-26]. There appears to be limited, if any, benefit with MET for stones less than 5 mm. For distal ureteral stones 5 mm and greater, there may be up to a 57% increase in spontaneous stone passage with MET, as well as a shorter time to stone passage and a potential reduction in pain medication needed during stone passage [23]. Ibrahim AK et al., in their study titled "To compare the efficacy of tamsulosin and alfuzosin as MET for ureteric stones," had a failure rate of 15% for the Tamsulosin group and 25% for the Alfuzosin group [27].

Even though MET is controversial, at our institution, the standard of care is to pursue MET if the patient is deemed suitable. Hence, the large majority of patients undergoing ureteroscopic intervention for a calculus at our institution were failures of MET. The surgical intervention rate fell by 20.8% in the >2-week MET group compared to the 1-2 week group. This might suggest that the longer the duration of MET (4 weeks), the less likely a need for interventional management.

MET failure should be considered after four weeks of MET [28]. As per the present study, these patients can be broadly divided into four groups: 1) it fails because the patient would not have been suitable for such therapy; 2) it could be that the patient was suitable for the therapy but the duration of therapy was inadequate; 3) it failed despite being adequate duration therapy in a suitable patient; 4) patients who did not tolerate the therapy.

Ureteroscopic intervention for ureteric calculi has been well addressed in the literature [29,30] and guidelines (EAU, AUA, CUA [16,31,32]). There are well-defined indications for intervention. In the present study, URSL was mainly required in patients with stone size 10 mm and more 41 (56.9%), failed MET 35 (48.6%), Renal dysfunction 14 (19.4%). A few patients with multiple stones, refractory pain, and bilateral ureteric stones needed URSL. Rare instances like solitary functioning kidney, residual stones, or patient request also required URSL. The single most important factor for the failure of MET found during ureteroscopy was an impacted stone 51 (70.8%). This impaction finding is more compared to the study by Takazawa R et al., [33]. In the failed MET group, Ureteroscopy also revealed other interesting but uncommon findings like kinks, multiple stones, narrow ureteric orifice, and duplex systems with a narrow ureter.

Complications during and following ureteroscopy are not uncommon despite the enormous evolution of instruments in the ureteroscopic armamentarium during the last two decades. Ureteral stent discomfort, ureteral wall injury, and stone migration are the most reported complications. Incidence rates of these and other complications vary extensively between the reviewed reports [20,34-43]. This may be because many complications usually do not require intervention

and standardised reporting systems are seldom used. Even though minor complications occasionally require intervention, they increase the cost and duration of the intervention or hospitalisation and may result in major complications if not recognised. Severe complications like urosepsis, multi-organ failure, and death are rare but may be under-reported as well, with only 21 death cases reported worldwide to date for the latter [44]. This may give urologists an un-warranted sense of security when performing ureteroscopy [45].

Post-operative complications occurred in 3.5-4.6% of patients and varied according to location, with the highest rate reported for multiple locations. The most common postoperative complication was fever, with a rate of 1.3-3.0%, followed by Urinary Tract Infection (UTI) at 0.6-1.8% and bladder cramps at 0.2-0.7% [21]. There is evidence suggesting a risk of postoperative urosepsis of up to 5% [46,47]. Ureteric perforation seen in 0.7-4.6% [36, 47-49]. Ureteral avulsion and strictures are rare (<1%) [45].

In the present study, there were no intraoperative complications like ureteric perforation, ureteric avulsion, and significant bleeding. One patient (1.4%) in the post-operative period developed sepsis, which was treated with appropriate antibiotics, and he recovered. Residual fragments were identified on X-ray KUB before stent removal and were seen in 4 out of 59 (6.8%) patients ($p=0.002$). As the stone clearance was satisfactory during the URSL procedure, X-ray KUB was not done in 13 (18%) patients. The overall stone clearance rate was 68 out of 72 (94.4%). This stone clearance rate was comparable to studies by Purpurowicz Z and Sosnowski M (90.9%), Sofer M et al., (98.3%), and Li YC et al., (95%) [50-52].

Overall, the authors suggests considering URSL directly for stones larger than 10 mm. For stones measuring 5-9 mm, consider MET or URSL based on the merit of the case depending on various factors determining the decision. Patients on MET need to be closely followed up as there are reasons for the failure of MET, and if it fails, they need to undergo definitive URSL treatment. Future research could focus on predicting success or failure of MET through imaging or scoring systems, as well as using 3D measurements of stone size before considering MET.

Limitation(s)

Small volume, single-center study, blinding couldn't be done. In the MET group, not all patients completed four weeks of treatment.

CONCLUSION(S)

The most common indications for URSL were large stones (>10 mm) and failed MET. Not completing four weeks of MET could be one of the reasons for the failure of MET. During ureteroscopy, the most common finding, irrespective of stone size, was the impaction of the stone, which was the reason for the failure of MET. Ureteric stones that failed to respond after four weeks of MET will require URSL as there are reasons for the failure of MET.

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