

## Efficacy of Medical Expulsive Therapy in Renal Calculi Less than or Equal to 5 Millimetres in Size

Sudarshan Daga, Vinayak Wagaskar\*, Harshawardhan Tanwar, Umesh Shelke, Bhushan Patil, Sujata Patwardhan

**Purpose:** Natural history and modality of treatment for asymptomatic renal calculi less than or equal to 5 millimetres in size is still unknown. Many options are available ranging from medical expulsive therapy to minimally invasive surgery. Till date no study has focussed on this very common but asymptomatic issue. Hence, this study is undertaken to evaluate efficacy of medical expulsive therapy in renal calculi less than or equal to 5mm in size.

**Materials and Methods:** A prospective, parallel group, randomized study was carried out from 1st June 2014 to 31st May 2015, with total of 100 patients, 50 patients in each group. Patients with renal stones less than or equal to 5mm were included in the study. Group A Patients were administered medical expulsive therapy which included tamsulosin 0.4 mg daily at night time, furosemide 20mg, spironolactone 50mg in a single morning dose, and syrup potassium magnesium citrate 20Meq per dose three times a day for 12 weeks while group B patients were given placebo. The primary outcome variable was number of patients achieving clearance of stone during 12-week treatment period in both groups.

**Results:** No statistically significant differences in age, gender, stone size, and calyceal stone location was found between the two treatment arms. A spontaneous stone expulsion rate of 50% (at 6 weeks) and 86% (at 12 weeks) was noted in group A versus 28% (at 6 weeks) and 38% (at 12 weeks) in group B. Less number of pain episodes and less analgesic medication was required in group A as compared to group B.

**Conclusion:** Medical Expulsive therapy for 12 weeks significantly improves stone free rates in renal calyceal calculi less than or equal to 5mm.

**Key words:** diclofenac sodium; furosemide; spironolactone; tamsulosin; urolithiasis.

### INTRODUCTION

Urolithiasis affects almost varied population all over world<sup>(1,2)</sup>. Estimated world risk is 10%-25%<sup>(1,3)</sup>. Natural history, progression and best modality of treatment for asymptomatic renal calculi less than 5mm is still not known. Occupations like Air force, Navy, Army and Bus Drivers, requires stone free status to join duty. Available treatment options are observation, medical expulsive therapy (MET), Shockwave Lithotripsy (SWL), retrograde intra-renal surgery (RIRS), Micro-percutaneous nephrolithotomy (PCNL), ultra mini-PCNL. Cost of operative treatment is higher than non operative modalities like observation and MET<sup>(4)</sup>. Several medications have being evaluated over the last 10 years for medical management of renal stones<sup>(5)</sup>. Meta-analysis have demonstrated effectiveness of MET in post SWL procedure with added analgesic effect<sup>(6,7,8)</sup>. Medline searches did not yield any published study relating to use of medical expulsive therapy for asymptomatic renal calyceal calculi less than 5mm in size. Karabacak et al. demonstrated presence of  $\alpha 1$  receptors and their subtype in renal pelvis and calyces<sup>(9)</sup>. They suggested that use of  $\alpha 1$  blockers (tamsulosin) for treatment of renal calyceal stones may be implicated<sup>(9)</sup>. After search of Medline data base, we did not find any study performed with respect to MET for

particularly asymptomatic renal calyceal calculi and hence this is among the first prospective, randomized single institutional studies to evaluate efficacy of medical expulsive therapy for asymptomatic renal calyceal calculi  $\leq 5$ mm in size. The purpose of this study was to evaluate efficacy of medical expulsive therapy for asymptomatic renal calyceal calculi  $\leq 5$ mm in size.

### MATERIALS AND METHODS

A prospective, parallel group, randomized study was carried out from 1st June 2014 to 31st May 2015. With a total of 100 patients, 50 patients in each group. Institutional Ethical Committee approval (EC-OA-105/2013) was taken. Patients who fulfilled our inclusion/exclusion criteria during study period were included and assigned into two groups by simple random method. Each patient was chosen entirely by a chance and had equal chance of being included in either group. A written informed consent was taken from all the patients. Inclusion criteria: All patients with asymptomatic or history of a single episode of renal colic with well controlled pain by analgesics, age  $>18$  years, and stone size  $\leq 5$  mm in renal calyces were included in the study. These asymptomatic patients came to us with ultrasonography Kidney-Ureter-Bladder (USG KUB) performed outside for other reasons

Department of Urology, King's Edward Memorial Hospital, Mumbai, India\*Correspondence: King's Edward Memorial Hospital, Mumbai, India.

\*Correspondence: King's Edward Memorial Hospital, Mumbai India.

Tel: +91-9890906273 Email: vinayakwagaskar@kem.edu.

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**Table 1.** Distribution of patients in the groups with respect to age, sex, side affected and size of stone.

	GROUP A(MET)	GROUP B (PLACEBO)	P value
Age, years; mean±SD(range)	35.14 ± 11.43 (17-68)	32.66 ± 10.24 (16-70)	0.443
Sex Male	31	32	0.8
Female	19	18	0.8
Side Right	38	36	0.25
Left	24	34	0.25
Stone Size, mm; mean ± SD	4.274 ± 1.06	4.49 ± 0.99	0.634

and were incidentally detected to have renal calculi. Exclusion criteria: Patients with stone greater than 5mm, solitary kidney, ureteric stone, distal ureteric stricture or subtle ureteric stricture like those with history of prior ureteroscopy or history of Bilharziasis, bladder stone, pregnant female, recurrent stone formers, chronic renal failure, aberrant ureteral anatomy (e.g., ureteral ectopia, ureterocele and mega ureter), sensitivity to the drugs used in MET, presence of renal stones more than 3 in number and patients with urinary tract infection were excluded from the study. We also excluded patients with recurrent stone formers as these patients usually have underlying metabolic abnormality and their treatment would have an influence on the results of our study. We did not include patients with clinical insignificant residual fragments (CIRF). Each patient was evaluated with history, physical examination, and laboratory investigations like haemoglobin, complete blood count, blood urea nitrogen level, serum creatinine, serum electrolyte, urine C/S, X-Ray Kidney-Ureter-Bladder (KUB) and ultrasonography (USG) KUB. Literature supports that there is no significant difference in evaluation of urolithiasis by USG and computed tomography KUB10. USG KUB was done by the same physician in all patients. CT KUB Plain was done only when stone was visualized on ultrasound and was not seen on X-ray KUB. Group A Patients were given medical expulsive therapy which included capsule tamsulosin 0.4 mg daily at night time, tablet furosemide 20mg, spironolactone 50mg single morning dose, and syrup potassium magnesium citrate 20Meq per dose three times a day for 12 weeks while group B patients were given placebo. Both groups were given dietary advice including water intake >3litre/day and tablet diclofenac sodium 50mg as per severity of pain. The primary outcome variable was number of patients achieving clearance of stone during the 12-week treatment period in both groups. Secondary variables included expulsion rate

for different calyceal location, and incidence of pain in both groups. Expulsion rate was measured objectively by performing USG KUB after 6 weeks and after 12 weeks. Side effects were evaluated from start of study till completion. Side effects such as dizziness, nausea, headaches and retrograde ejaculation (in male patients) in patients taking tamsulosin; muscle weakness and lethargy in patients taking furosemide and altered bowel habits, nausea and vomiting in patients taking potassium magnesium citrate syrup were explained to them. All patients were asked to follow up at 6 and 12 weeks. These patients were also informed to refer if they experienced any of above side effects. Primary and secondary variable were evaluated at each visit. Primary physician evaluated the patients during study time. He was concealed about the group of the patients. Outcome variables such as pain or stone free-rate was measured separately each time and measured again in the next follow-up visits. Imaging techniques included USG KUB, X-ray Kidney-Ureter-Bladder (KUB) at 6 and 12-week follow up visit. Imaging data were recorded for noting variables like stone size and location.

#### Statistical Analysis

Since no data was available for sample size calculation, a universal sampling method was used. Accordingly, 50 patients in each group were selected. The Null hypothesis assumed there was no difference between MET and placebo group on the effect of stone passage. Data was recorded on Microsoft excel 2010. Chi-square test with two tail distribution was used to compare two groups, *P*-value < .05 was considered as significant.

## RESULTS

No statistically significant differences in age, gender, stone size, and calyceal stone location were found between the two treatment arms (Table 1). Median stone size in entire study group was 4.7 mm (inter-quartile range [IQR]: 2.0-5mm).

**Table 2.** Percentage of stone clearance achieved in the two groups at 6 weeks and at 12 weeks

No. of patients achieved complete Clearance at	Group A(MET)	Group B(Placebo)	P value
6 weeks	25(50%)	14(28%)	0.04
12 weeks	43(86%)	19(38%)	<0.01

**Table 3.** Calyceal-wise stone clearance rates in the two groups.

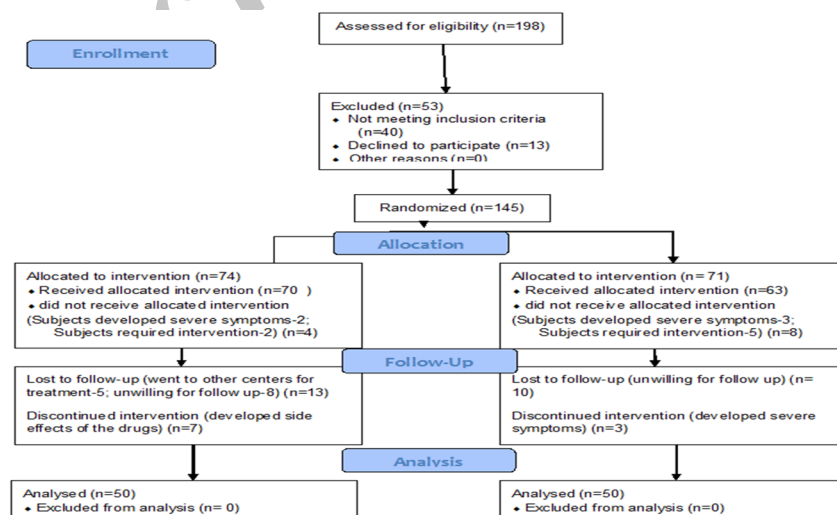
Stone free rate at	Calyceal Location	Group A(MET)	Group B(placebo)	P value
6 weeks	Superior Calyx	66.66%(10/15)	45.46%(10/22)	0.3
	Medial Calyx	63.41%(26/41)	47.83%(22/46)	0.2
	Inferior Calyx	50%(9/18)	50%(9/18)	0.7
12 weeks	Superior Calyx	93%(14/15)	45.46%(10/22)	<0.01
	Medial Calyx	90.25%(37/41)	60.87%(28/46)	<0.01
	Inferior Calyx	78%(13/18)	55.56%(10/18)	0.4

A spontaneous stone expulsion rate (**Table 2**) of 50% (at 6 weeks) and 86% (at 12 weeks) was noted in group A and 28% (at 6 weeks) and 38% (at 12 weeks) in group B. Expulsion rate noted for different calyceal location at 6 weeks and 12 weeks are shown in Table 3. With significant less number of pain episodes in group A as compared to group B, only 8 patients (16%) in group A required analgesic as compared to 19 (38%) in group B which was statistically significant ( $P < .05$ ). Patients were asked to bring back empty strips of medication to evaluate compliance with medication at each visit. Expulsion rates in respect to number of patients achieving stone free status achieved statistical significance at 6 weeks ( $P = .04$ ) and 12 weeks ( $P < .01$ ) (**Table 2**). However, clearance rate in respect to number of stone from each calyx achieved statistical significance at 12 weeks only for superior and middle calyces (**Table 3**).

## DISCUSSION

Many patients with renal calculi  $\leq 5$ mm remain asymptomatic. Evaluation of ureteral smooth muscle physiology and obstruction caused by urinary stones signifies that  $\alpha$ -blockers can facilitate stone expulsion<sup>(11-13)</sup>. Distribution of  $\alpha 1$  receptors and their subtypes has

been confirmed by Karabacak et al. in human pelvis and calyces<sup>(9)</sup>. Meta-analysis has confirmed use of  $\alpha$ -blockers (tamsulosin) to achieve clearance of residual stone in post surgical cases<sup>(14-16)</sup>. Use of diuretics like furosemide has been shown to be effective in expulsion of the calcium fragments and also diuresis would further fasten expulsion of small stones<sup>(17)</sup>. Expectant management is followed for renal calculi less than 5 mm in size which are likely to pass spontaneously by follow up every 6 month<sup>(8)</sup>. However, there is level IIb/B evidence that for small  $\leq 5$ mm calculi after SWL when followed expectantly, a significant number would require intervention or have symptomatic episodes during follow-up. Burgher and co-workers has described that stone  $> 4$ mm were 26% more likely to fail observation than patients with smaller solitary calculi<sup>(18)</sup>. Hubner et al. reported that 83% of 62 patients with asymptomatic calyceal stone required intervention within 5 years of diagnosis. Only 10% remained symptom free after 10 years<sup>(19)</sup>. Karabacak et al.<sup>(9)</sup> had described density expression of  $\alpha$ -1 receptor subtypes for renal pelvis and calyces which were  $\alpha$ -1D  $>$   $\alpha$ -1A  $>$   $\alpha$ -1B. No difference was observed in the receptor expressions in pelvis with calyces. However, receptor

**Figure 1.** Patients' flow diagram.

density for each calyx was not mentioned in study, which would have helped in predicting whether inferior calyx had less density of receptors which might be the reason for lower expulsion rate in our study. Soygur et al. have concluded that use of potassium citrate in post SWL lower pole calculi aided in spontaneous passage of stone and increasing clearance rates<sup>(20)</sup>. Gravina and colleagues studied the efficacy of tamsulosin as an adjunctive therapy after SWL for renal stones<sup>(21)</sup>. At 12 weeks, clinical success was achieved in 78.5% of patients receiving tamsulosin and 60% of patients not receiving tamsulosin ( $P = .037$ ). The stones ranged in size from 4 mm to 20 mm<sup>(19)</sup>. However lower pole calculi were not included in the study group. Mean stone size in our study was 4.7 mm and the most commonly reported stone location was middle calyx (65.9%) followed by superior calyx (31.66%) and inferior calyx (27.27%). On subgroup analysis, expulsion rate of above 90% was achieved after 12 weeks for superior and middle calyceal calculi and 78% for inferior calyceal calculi. Overall number of patients achieving complete clearance of stone at 12 weeks was 43 out of 50 (86%) which was statistically significant. Stone expulsion was significantly ( $P < .05$ ) better with MET than with placebo (86% vs. 38%); with an absolute benefit (AB) of 48%; number needed to treat (NNT) was 4 in our study. Four studies showed a beneficial effect for  $\alpha$ -blockade for renal stones treated with SWL<sup>(21-24)</sup>. Han et al. demonstrated a significant expulsion rate and decreased analgesic requirement with use of tamsulosin for upper ureteral stones after SWL<sup>(25)</sup>. In a prospective study of 70 patients performed by Arrabal-Martin M et al.<sup>(26)</sup>, it was found that tamsulosin significantly increases stone expulsion rate (85.7%) as compared to hydration therapy (54.3%) in patients with distal ureteric calculi less than 10 mm. Three double-blinded RCTs did not demonstrate significant differences in expulsion rate for MET using alfuzosin or tamsulosin for lower ureteral stone versus placebo<sup>(27-29)</sup>. However average stone size in these 3 study groups were 3.8 mm in Pedro et al.<sup>(27)</sup>, (2.9mm -3.2mm) in Vincendeau et al.<sup>(27)</sup> and (3.8mm -4.1 mm) in Hermanns et al.<sup>(29)</sup>. With stone size less than 4mm there is higher chances of stone passing spontaneously<sup>(8)</sup>, therefore decreased efficacy of MET is expected. In these studies,  $\alpha$ -blockers still reduced time to stone passage, pain scores, and need for analgesia<sup>(28)</sup>. Similarly, Ferre et al.<sup>(30)</sup> failed to demonstrate a significant higher expulsion rate in the tamsulosin group. Again, mean stone size was 3.6 mm. Meta-analysis of 33 trials (3105 patients) examined  $\alpha$ -blockers (most often tamsulosin) or calcium channel blockers (nifedipine) in patients with renal stones (primarily < 10 mm; frequently distal ureter)<sup>(31)</sup>. Stone expulsion was significantly ( $P < .001$ ) better with MET than with placebo (80% vs. 54%); absolute benefit (AB) of 26%; number needed to treat (NNT) of four<sup>31</sup>. The more distal the stone, the lesser time required for expulsion. Skolarikos A et al.<sup>(32)</sup> performed meta-analysis and demonstrated efficacy of  $\alpha$ -blockers in stone clearance. They have also concluded that  $\alpha$ -blockers significantly reduce the time to stone elimination, the intensity of pain, the formation of steinstrasse, and the need for auxiliary procedures. Similarly, efficacy of  $\alpha$ -1D receptor blockers in clearance of distal ureteric stones has been proven by other studies<sup>(33)</sup>. European<sup>(34)</sup> and US<sup>(35)</sup> guidelines for urolithiasis recommend MET as an option when the fol-

lowing criteria are met: newly diagnosed ureteral stone < 10 mm in patients without need for urgent urologic intervention; and well-controlled pain, no sepsis, good renal function, and following with periodic imaging to monitor stone position and assess hydronephrosis.

The secondary variable of number of events of pain was significantly lower in MET group versus placebo. Patients in MET arm required less analgesia than patients in the placebo arm. No serious complications were recorded in both groups. The common side effects of tamsulosin are dizziness, nausea, diarrhoea, headache and retrograde ejaculation. In our study the only adverse effect noted was dizziness in 4 patients and nausea in 3 patients in MET group over a period of 12 weeks which was well tolerated. Patients with residual calculi in both groups after 12 weeks were managed with other modalities like SWL, or RIRS. With recent understanding of distribution of alpha adrenoreceptors in renal calyces and pelvis, the present study is one of the first to compare the efficacy between MET and placebo on renal calyceal calculi  $\leq 5$ mm in size. The results suggest that treatment with use of MET in patients with  $\leq 5$ mm renal calculi when taken for 12 weeks is effective in achieving stone clearance, implying a higher number of patients achieving complete clearance and better pain management. Being an initial step to address small renal calculi and use of medical therapy which is better than observation and less morbid than invasive procedure certain limitations of this study are: single institutional study and small population size; a multicenter placebo controlled double blind study will be able to validate results observed in our study. Other limitations include the use of X-ray KUB and USG KUB to detect residual calculi when CT Scans should be the imaging of choice to detect the calculus. MET as a combine treatment of alpha blocker with diuretics and potassium citrate therapy was given to treatment group which has a confounding effect, however MET achieved a significant expulsion rate and better patient tolerability of all drugs with minimal side effects. Stone composition and metabolic evaluation was not addressed which would have been helpful to evaluate patients completely and starting specific medical therapy according to stone composition and addressing and minimizing future recurrences. Our study fails to address difference between spontaneous passage and MET for small stones.

## CONCLUSIONS

Medical Expulsive therapy for 12 weeks significantly improves stone free rates in renal calyceal calculi less than or equal to 5mm. However, further randomized studies are required to document these findings.

## CONFLICTS OF INTEREST

None declared.

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