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Original Research Article

Comparison of safety and efficacy of silodosin versus mirabegron in medical expulsive therapy for lower ureteric stone: a prospective, open label and randomized controlled trial

Ira Sharma^{1*}, Atal Sood¹, Kulbhushan Sharma², Sushma Sawaraj¹, Nitin Patiyl¹

¹Department of Pharmacology, DRRPGMC Kangra at Tanda, Himachal Pradesh, India

²Department of Urology, DRRPGMC Kangra at Tanda, Himachal Pradesh, India

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*Correspondence:

Dr. Ira Sharma,

Email: sharmaira724@gmail.com

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ABSTRACT

Background: Urolithiasis the most common condition affecting genitourinary tract and affect 5 to 10% of population worldwide. Almost all ureteric stones are symptomatic, and patients need to receive immediate evaluation and pain relief treatment. Passage of stone is facilitated by medical expulsive therapy (MET). Overall, 71-98% for stones in the distal ureter that are 5 mm or smaller passes with MET while 29-98% for stones in the proximal ureter that are 5 mm or smaller passes with MET. Silodosin (alpha-1 adrenergic receptor antagonist) and mirabegron (β-3 agonist) were compared for stone expulsion and analgesic effects for symptomatic relief.

Methods: The study was conducted in the department of pharmacology and the department of urology at Dr. R. P. G. M. C., Kangra at Tanda Himachal Pradesh, India which is 700 bedded multispecialty tertiary health care from August 2023 to May 2024 and follow-up was done for 4 weeks after initiation of treatment, to compare the safety and efficacy of silodosin versus mirabegron in medical expulsion therapy for lower ureteric stone of size ≤10 mm in adults.

Results: In our study patients in silodosin treatment arm had a smaller number of colic episodes (mean 1.65±1.02) during MET as compared to group (mean 2.23±1.07) receiving mirabegron (p=0.011). Patients in silodosin group had significantly lower analgesic requirement (mean 2.10±1.58) as compared to patients in mirabegron (mean 3.30±1.96) which is also statistically significant (p=0.002). Patients in silodosin group had highly significant lower time for stone expulsion (mean 10.0±5.3) as compared to that in patients in mirabegron group (mean 15.7±7.1) (p=0.0004). Overall, incidence of side effects was similar in both groups.

Conclusions: Silodosin demonstrated superior efficacy over Mirabegron in terms of reducing colic episodes, analgesic requirement and stone expulsion time in the management of ureteric calculi. No significant adverse events were reported in either group during the study period

Keywords: Mirabegron, MET, Silodosin, Stone expulsion time

INTRODUCTION

Urolithiasis being the most common condition affecting genitourinary tract, its prevalence differ in different geographic regions globally. Global burden of the condition is estimated to affect 5 to 10% of population

worldwide.¹ In terms of prevalence and incidence, age and sex distribution, stone composition, and stone placement, the epidemiology of urolithiasis varies by geographic region. Climate, diet, and race have all been cited as explanations for these disparities. Additionally, the frequency, incidence, and distribution of lithiasis by age,

sex, and type have changed due to shifting socioeconomic circumstances, both in terms of the site and the chemical-physical makeup of the calculi.²

According to reports, the stone-forming belt crosses the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, Indonesia, the Philippines, Saudi Arabia, the United Arab Emirates, and Sudan.³ In North-Western part of India, two separate "stone belts" have been recognized. A single stone belt extends from Amritsar in North to Uttar Pradesh via Delhi and Agra. Another belt extends inward into Jabalpur in Central India from Jamnagar on West Coast.⁴

Anatomical positions of upper, middle/lower calyx, renal pelvis, upper, medium/distal ureter and urinary bladder can all be used to categorize stones. Stone location is defined upper ureteric if stone is located cranial to sacroiliac joint, mid ureteric if it is located over sacroiliac joint and lower ureteric if located caudal to sacroiliac joint.⁵

Almost all ureteric stones are symptomatic and patients need to receive immediate evaluation and pain relief treatment. Spontaneous passage of ureteric calculus depends on stone location, size, ureteric wall edema and ureteric spasm. Passage of stone is facilitated by MET. Overall, 71-98% for stones in distal ureter that 5 mm/smaller passes with MET while 29-98% for stones in the proximal ureter that are 5 mm or smaller passes with MET.⁶

MET has the distinct advantage to avoid invasive surgical or endourological procedure. These procedures require hospital admission and are associated with surgery and anesthesia related morbidities and long-term complications such as ureteric stricture and loss of renal function. Alpha-blockers are described by the American urological association (AUA) and the European urological association (EAU) as a good choice for a small group of patients who are at ease with the procedure and for whom prompt surgical stone removal is not necessary.⁷

Alpha-1 adrenergic receptors, muscarinic receptors, purinergic receptors, and histaminergic (H1) receptors along with serotonin, prostaglandin F2a, substance P, neurokinin A, neuropeptide Y and rho-kinase pathway play a role in ureter contraction.⁸ Alpha-1A adrenoreceptors are a principal contributor in phenylephrine-induced ureteral contraction in human isolated ureter.⁹

Contracting pathway

Alpha-1 adrenergic receptors, muscarinic receptors, purinergic receptors, and histaminergic (H1) receptors, along with serotonin, prostaglandin F2a, substance P, neurokinin A, neuropeptide Y, and the rho-kinase pathway, play a role in the contraction of the ureter.⁸

These are widely used in lower urinary tract symptoms. On the other hand, blocking alpha-adrenergic receptors in ureter helps the intraureteral pressure to decrease and the fluid passage per unit of time to increase.¹⁰

Beta-2/3 receptors, histaminergic (H2-H3) receptors with nitric oxide, prostaglandin (E1/E2), calcitonin gene-related peptide (CGRP), adenosine and vasoactive intestinal peptide (VIP) take part in relaxation.⁸

Relaxation pathway

Beta 3 receptors are commonly found in detrusor, participating in bladder relaxation. It has been shown that beta-2 and beta-3 adrenoreceptor subtypes are detected in the ureteral smooth muscle, mediating the adrenergic stimulation causing ureteral relaxation.¹¹ Urothelium and the interstitial cells themselves express beta-3 adrenoreceptors more than the ureteral smooth muscle. This indicates that beta-3 adrenoreceptors take part in the dynamics of the ureter. Beta-3 receptors are also found in ventriculi, human vasculature, brain, retinal endothelial cells, gastrointestinal tract, skeletal muscle and in brown and white adipose tissues. As compared, adipose tissues and urinary tract have higher density of the beta-3 receptors than other system.^{10, 11}

Sildosin

An alpha-1 adrenergic receptor antagonist that binds to the $\alpha 1A$ subtype with the highest affinity ($\alpha 1A$ -to-1B binding ratio is 162:1). The smooth muscle tone of the prostate, prostatic urethra, and bladder neck is regulated by $\alpha 1$ -adrenergic receptors. The $\alpha 1A$ subtype makes up around 75% of $\alpha 1$ -adrenoceptors found in the prostate.¹²

Mirabegron

Mirabegron tends to have an agonist effect on β_3 receptors and effects on storage phase of bladder and increases the bladder capacity without influencing the voiding phase and the bladder contractility. In contrast, antimuscarinics blocks the M3 cascade which contract detrusor. This effect, on the storage phase, is dependent and reduces the micro-motion in the detrusor.¹³ As mirabegron relaxes the ureteral muscles and dilates the ureter lumen by stimulating beta-3 adrenoreceptors, it serves as an effective and safe alternative for MET, which act with a totally different pathways.¹⁴

Primary objective

Primary objective was to compare the safety and efficacy of silodosin versus mirabegron for stone expulsion rate in lower ureteric stone of size ≤ 10 mm.

Secondary objective

Secondary objective was to compare the stone expulsion interval for MET with silodosin and mirabegron and

analgesic requirement in MET with silodosin and mirabegron.

METHODS

The study was randomized, prospective, open label, parallel group, comparative interventional study, conducted in the department of pharmacology and the department of urology at Dr. R. P. G. M. C., Kangra at Tanda India which is 700 bedded multispecialty tertiary health care.

Inclusion criteria

All the consenting adult patients of distal ureteric calculus of size less than 10 mm of different socio-economic strata were included in study.

Exclusion criteria

Patients not willing to give written informed consent, severe HDUN, multiple ureteric calculi, bilateral ureteric calculi, pregnancy, previous ureteric or bladder surgery, anatomical genitourinary tract abnormalities, uncontrolled hypertension (Systolic blood pressure >180 mmHg, diastolic blood pressure >110 mmHg), solitary functioning kidney, pyonephrosis were excluded from the study.

Study duration

The enrolment was done after registration with CTRI from August 2023 to May 2024 and follow was done for 4 weeks after initiation of treatment.

Study intervention

All the patients diagnosed with lower ureteric calculus of size ≤ 10 mm. registered in urology OPD, meeting the predefined inclusion criteria and after understanding the patient information sheet were made to understand thoroughly about the study and related aspects and then submitted informed consent for study were included.

Detailed relevant history was noted. Ultrasound KUB and X-ray KUB were done to determine location of stone, size of calculus and degree of HDUN. Any congenital malformation/anomalies of urinary tract, status of contralateral pelvicalyceal system and ureter or infective complications like pyelonephritis or pyonephrosis were evaluated with ultrasound KUB.

After a written informed consent, the participants were randomized with computer generated random number table to one group either A or B.

Patients in group A were given tablet silodosin 8 mg once 30 minutes after dinner. Patients in group B were given tablet mirabegron 50 mg once 30 minutes after dinner.

Fixed drug combination tablet tramadol 50 mg + paracetamol 325 mg were given as analgesic as per requirement in each group. The 15 tablets were given at the start of MET and patients were asked to keep record of number of tablets consumed and were asked to bring back empty blisters packs.

After starting treatment patients were asked to watch for lithuria (Instructed to pass urine in sieve and to collect stone).

Follow-up of each patient was done weekly for four weeks.

Before initiating the treatment, baseline investigations including complete hemogram were done and these investigations were repeated after completion of 4 weeks of treatment (for safety).

Measurement of outcome

On completion of 4 weeks of intervention the outcome was assessed on the basis of efficacy-Stone expulsion rate, total number of colic episodes and total number of analgesic tablet requirement. Safety-All the adverse events that occurred in subjects during study period were considered.

Statistical analysis was done using online statistics tool 'social science statistics'; available at <https://www.socscistatistics.com>. Qualitative data was calculated in the form of frequency and percentage. Quantitative data was presented as mean $\pm$ standard deviation (Mean $\pm$ SD). Student's t-test was used for comparing continuous variables between the two groups. Chi square or Fisher's exact probability test was used for comparing the qualitative data between the two groups. $P < 0.05$ was measured as statistically significant. An intention-to-treat analysis was done to compare the data.

RESULTS

The data collected was tabulated in Microsoft excel and analysed for various parameters and compared using appropriate statistical analysis tests using online 'social science statistics' software. Qualitative data was calculated in the form of frequency and percentage. Quantitative data was presented as mean $\pm$ standard deviation (Mean $\pm$ SD). Student's t test was used for comparing continuous variables between the two groups. Chi square or Fisher's exact probability test was used for comparing the qualitative data between the two groups. $P < 0.05$ was measured as statistically significant.

Total 104 patients were enrolled for the study out of which 5 were excluded, remaining 99 were randomized using computer generated numbers. 8 were lost to follow up, finally 91 patients were analysed.

Patients were randomly divided into two groups. The patients in group A were prescribed tablet silodosin 8 mg once daily and in group B tablet mirabegron 50 mg once

daily was prescribed. Comparison of demographic characters has been shown in Table 1.

Table 1: Comparison of demographic characteristics between two groups.

Variables	Group A, (n=51)	Group B, (n=40)	P value
Age (in years)	37.16±12.76	36.6±11.44	0.83
Male	44 (86%)	32 (80%)	0.42
Female	7 (14%)	8 (20%)	
Height (m)	1.63±0.08	1.66±0.08	0.13
Weight (kg)	64.92±4.62	64.1±2.94	0.31

Gender

Gender-wise both the groups were comparable (p=0.42).

Blood biochemistry

Comparison of blood biochemical parameters between two groups is shown in Table 2.

Hemoglobin (Hb)

On intragroup comparison there was no statistically significant difference between Hb levels. [Baseline versus 4 weeks follow-up: group A (p=0.65) and group B (p=0.52)].

Total leukocyte count (TLC)

On intragroup comparison there was no statistically significant difference between TLC levels. [Baseline versus 4 weeks follow-up: Group A (p=0.11) and group B (p=0.73)].

Platelet count

On intragroup comparison, there was no statistically significant difference between platelet counts. [Baseline versus 4 weeks follow-up: Group A (p=0.33) and group B (p=0.91)].

Fasting blood sugar (FBS)

On intragroup comparison there was no statistically significant difference between FBS levels. [Baseline

versus 4 weeks follow-up: group A (p=0.73) and group B (p=0.58)].

Serum urea and serum creatinine

On intragroup comparison there was no statistically significant difference between serum urea and serum creatinine levels.

SGOT and SGPT

On intragroup comparison there was no statistically significant difference between SGOT and SGPT levels.

Stone size

Stone sizes were statistically comparable between two groups at the time of diagnosis (p=0.94).

Colic episodes

After the treatment initiation colic episodes were significantly lower in group-A as compared to that in group-B. (*p=0.011) (Statistically significant) (Figure 1).

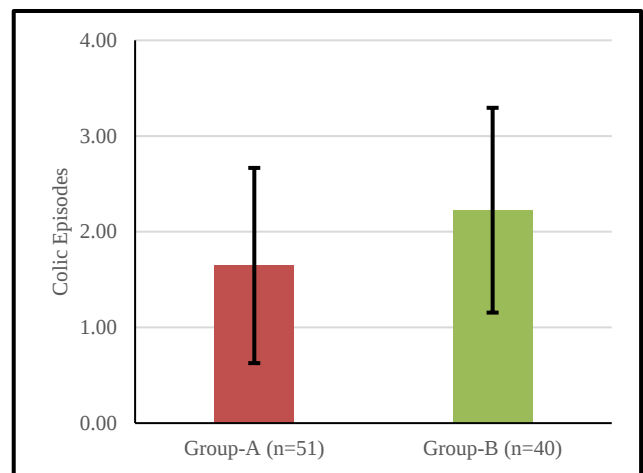


Figure 1: Comparison of colic episodes between two groups.

Analgesic requirement

In group A highly significant lower analgesia was required as compared to that in group B (*p=0.002) (Statistically significant) (Table 3).

Table 2: Comparison of blood biochemical parameters between two groups.

Variables	Group A, (n=51)	Group B, (n=40)	P value
Hb (g/dl), baseline	11.66±1.79	11.87±1.75	0.56
Hb (g/dl), after 4-weeks	11.7±1.58	11.65±1.48	0.47
TLC (/mm ³), baseline	7099.5±3616.24	6425±3164.1	0.35
TLC (/mm ³), after 4-weeks	6511.8±1418.8	6292.5±1162.3	0.42
Platelet count (thou/mm ³), baseline	255.8±128.6	220.6±103.6	0.15
Platelet count (thou/mm ³), after 4-weeks	246.8±118.3	219.2±90.8	0.21

Continued.

Variables	Group A, (n=51)	Group B, (n=40)	P value
FBS (mg/dl), baseline	95.3±6.52	97.13±12.94	0.41
FBS (mg/dl), after 4-weeks	95.67±6.96	95.65±11.05	0.99
S. urea (mg/dl), baseline	28.0±6.3	26.1±5.6	0.14
S. urea (mg/dl), after 4-weeks	27.4±3.3	26.4±3.4	0.16
S. creatinine (mg/dl), baseline	0.83±0.21	0.9±0.25	0.17
S. creatinine (mg/dl), after 4-weeks	0.77±0.18	0.86±0.14	0.11
SGOT (U/l), baseline	28.6±5.2	29.1±8.8	0.74
SGOT (U/l), after 4-weeks	29.4±5.4	31.2±8.6	0.24
SGPT (U/l), baseline	32.2±6.2	30.6±5.8	0.24
SGPT (U/l), after 4-weeks	30.8±7.8	30.3±4.0	0.20

Table 3: Comparison of analgesic requirement between two groups.

Variables	Group A, (n=51)	Group B, (n=40)	P value
Analgesic required (number of tablets of FDC tramadol 50+ paracetamol 325 mg)	2.10±1.58	2.10±1.58	0.002

Stone expulsion time

In group A very highly, significant lower time was there for stone expulsion as compared to that in group B (*p=0.0004) (statistically significant) (Figure 2).

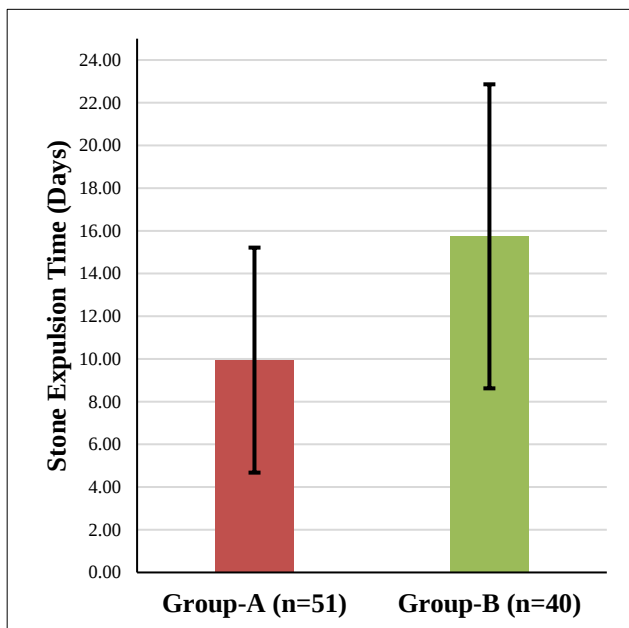


Figure 2: Comparison of stone expulsion time between two groups.

In group A 43 (84.3%) patients expelled the stone but 8 (15.7%) patients required URSL for stone removal.

In group B 31 (77.5%) patients expelled the stone but 9 (22.5%) patients required URSL for stone removal.

In group B higher number of patients (although statistically comparable) required surgical intervention i.e., URSL for stone removal although it was statistically insignificant.

Stone expulsion rate was significantly higher in silodosin group as compared to mirabegron group (*p=0.0007).

Safety

No complications occurred during treatment or operative procedures in any of the patients. Both the drugs were safe in terms of adverse drug effects.

DISCUSSION

The aim of our study was to evaluate the efficacy and safety of silodosin and mirabegron in MET for distal ureteric stones of size less than 10 mm.

Efficacy

In the present study we found that baseline and demographic parameters were comparable in both the groups. Mean age of the patients in group A (37.16±12.76) was comparable to that in group B (36.6±11.44); p=0.83.

Male preponderance was observed in both the groups, in group A it accounts 86% and in group B 80%. Higher incidence of stone diseases observed in male population in our study. Both the groups were comparable in terms of their height and weight. In our study mean BMI in group A was 24.55±2.23 kg/m² and in group B was 23.58±2.62 kg/m². BMI was comparable in both groups with the p=0.07.

Bayar et al studied mirabegron and silodosin in MET in which mean age in silodosin group was 40±15 years and in mirabegron group was 43±13.3 years. Male patients were 74% and female were 26% in silodosin group and in mirabegron group male patients were 86% and female were 14%.¹⁵

Sayed et al studied role on silodosin and mirabegron in MET. Mean age in silodosin group was 36.65± 6.81 years

and in mirabegron group was 38.62 ± 7.88 years which were comparable ($p=0.615$). In silodosin group male patients were 65.71% and female were 34.29%. In mirabegron group male were 62.86% and female were 37.14%.¹⁶

Baseline laboratory parameters on initial evaluation were comparable between two groups in terms on hemoglobin, TLC, platelet counts, FBS, urea, creatinine, liver function test SGOT/SGPT in our study.

In study conducted by Bayar et al base line biochemical parameters were comparable in both groups.¹⁵

In study conducted by Sayed et al pretreatment creatinine in silodosine group was 1.1 mg % and in mirabegron group was 1.06 mg % ($p=0.864$).¹⁶

In our study Stone sizes were comparable between two groups at the time of diagnosis, mean stone size was 6.44 mm in group A and 6.41 mm in group B ($p=0.94$).

Itoh et al studied role of silodosine in MET and compared to spontaneous expulsion. Mean stone size in silodosine group was 5.69 ± 2.31 mm in lower ureter.¹⁷

Solakhan et al studied role of mirabegron compared to placebo control in MET and mean stone size in this group was 6.29 ± 2.30 mm.¹⁸

Study by Kader et al compared silodosine, mirabegron and combination of both in three groups. mean stone size in silodosine and mirabegron were 7.44 ± 1.32 and 7.11 ± 1.25 respectively.¹⁶

Abdullah et al compared silodosine to tamsulosine in MET. Mean stone size in tamsulosine and silodosine group were 6 (4.3-7.6) and 6.55 (4.9-8.1) respectively.¹⁹

In our study patients in group A in silodosin treatment arm had less number of colick episodes (mean 1.65 ± 1.02) during MET as compared to group B (mean 2.23 ± 1.07) receiving mirabegron ($p=0.011$) in group A.

Salokhan et al studied efficacy of mirabegron in distal ureteric stone. Group 1 were given mirabegron with diclofenac and in group 2 only diclofenac. Number of colick episodes in group 2 were more as compared to group 1 (1.02 ± 0.52 vs 1.29 ± 0.57 , $p=0.49$).¹⁸

Bhori et al studied silodosine in MET in pediatric population and concluded than number of colick episodes were less in silodosine arm compared to control arm.²⁰

Abdulla et al in there RCT concluded that analgesic requirement in sildosin group was less than tamsulosin group (5.68 vs 8.4).¹⁹

Tang et al studied efficacy of mirabegron compared to placebo control group and found than in terms of renal

colick episodes and frequency of colicks were significantly lower in treatment arm as compared to control group.²¹

Safety

During treatment no serious adverse drug event was recorded in both the groups. Pre-treatment and post-treatment laboratory parameters were comparable in terms of complete hemogram, renal function test and liver function test. There was no significant change in weight in mirabegron treatment group.

This observation suggests that both drugs are safe in the given population.

Limitations

Keeping in view the prevalence of urolithiasis as 15% in Northern India, sample size of 196 or more could have yielded better results for extrapolation.

So larger sample size would have yielded better results for extrapolation to population. But due to time-bound nature of thesis study only 160 patients were enrolled to the study.

So, the study may be continued after due permission from Institutional Ethics Committee to achieve the target sample size and will be attached as supplementary note to this article in future.

CONCLUSION

Silodosin has proven to be statistically more effective in MET for stone expulsion in lower ureter ($p<0.05$) and is more proficient to control colic episodes ($p<0.05$) and analgesic requirement ($p<0.05$) than mirabegron in clinical setting.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee PRC approval vide letter no. D. No.-HFW-H(DRPGMC)PRC/2022 IEC no. IEC027/2023, CTRI no. REF/2023/08/071486.

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