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UROLITHIASIS

Comparing silodosin and mirabegron as medical expulsive therapy for distal ureteral calculus: a prospective, randomised study

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Introduction In this study we aimed to compare the efficacy of mirabegron and silodosin as medical expulsive therapy (MET) for distal ureteric calculus ≤10 mm.

Material and methods A total of 114 patients who met the inclusion criteria were prospectively randomised into 2 groups, 58 patients in the silodosin group and 56 patients in the mirabegron group. The drugs were given for a maximum of 4 weeks. The primary endpoint was the stone expulsion rate, and secondary endpoints were stone expulsion time and number of pain episodes.

Results There were no statistically significant differences between the two groups in terms of mean age, gender, mean stone size, side, or hydronephrosis. Both groups exhibited similar rates of stone expulsion and expulsion time. Regarding pain management, the frequency of renal colic episodes was significantly lower with mirabegron compared to silodosin (2.3 ±0.2 vs 1.9 ±0.2, P <0.0001). Six patients were excluded from the study due to adverse drug reactions: 4 (6.15%) in the silodosin group (retrograde ejaculation, hypotension) and 2 (3.27%) in the mirabegron group (hypertension).

Conclusions In among patients with distal ureteric stones measuring 5–10 mm, mirabegron did not demonstrate superiority in stone expulsion rate or expulsion time compared to silodosin. However, mirabegron significantly reduced the frequency of renal colic episodes. Therefore, mirabegron may be considered a preferable option for medical expulsive therapy for distal ureter stones over silodosin.

Key Words: efficacy ‹› medical expulsive therapy ‹› mirabegron ‹› silodosin ‹› ureteral calculi

INTRODUCTION

The prevalence of ureteric calculus was about 20% of all urolithiasis cases, with 70% of stones located at distal ureter, globally [1]. In India, the overall prevalence of urolithiasis was 7.9% [2], and the occurrence of distal ureteric calculus per se was 5.5% [3].

As per the available literature, various agents have been used as medical expulsive therapy (MET) for distal ureteric stones, like alpha-1 receptor blockers, calcium channel blockers, and (phosphodiesterases) PDE-5 inhibitors [4]. The beta-3 adrenergic receptors (β3-AR) are located in the smooth muscles and epithelium of the ureter. Their stimulation leads to relaxation of smooth muscles via an effect on the urothelial function [5]. Several studies similarly confirmed that mirabegron, a selective beta-3 receptor agonist, can act as a medical expulsive therapy for ureteral stones [6–8]. Hence, this study analyses the effectiveness of mirabegron as a medical expulsive therapy for distal ureteric calculus.

MATERIAL AND METHODS

This was the prospective, cohort, double blind, randomised study conducted from May 2022 to April

2023 after obtaining approval from the institutional Ethics Committee (EC/NEW/INST/2020/961). The inclusion criteria were patients aged ≥18 years, with distal ureteric stone of size 5–10 mm in maximum diameter, diagnosed on ultrasonography (USG), of the kidney, ureter, or bladder (KUB), or non-contrast computed tomography KUB (if required). Exclusion criteria were active urinary tract infection, severe hydronephrosis, bilateral or multiple unilateral ureteric stones, solitary kidney, renal insufficiency, uncontrolled hypertension (systolic blood pressure ≥180 mmHg, diastolic blood pressure ≥110 mmHg), previous ureter and urinary bladder surgery, patient on alpha-blocker or anticholinergic to lower urinary tract symptoms, hepatic dysfunction, ureteric strictures, pregnancy, and those who opted out of the study.

In total 126 patients were recruited in the study, of whom 114 were included in the final analysis [Figure 1]. After obtaining written informed consent, patients were randomised into 2 groups based on sequentially numbered, opaque, sealed envelope (SNOSE) technique. In group A, silodosin 8 mg once daily was prescribed (control group), and in group B, mirabegron 50 mg once daily was prescribed. The drugs were continued until stone expulsion or 4 weeks. All the patients were advised to take 2.5 to 3 litres of water daily and a diclofenac 50 mg tablet orally for pain episodes. They were advised to sieve their urine for any stones. The primary endpoint of this study was the stone expulsion rate, and secondary endpoints were stone expulsion interval, rates of interventions, and pain episodes. Patients were followed up weekly for 4 weeks by USG, after which ureteroscopic lithotripsy (URSL) was performed for patients whose stones were not expelled. Stone analysis was performed on all collected stones.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS v.23.0) for MS Windows was applied for statistical calculations. A p value <0.05 was accepted as statistically significant, and the power of the study was 0.90. The required sample size per group was 55. Mean and standard deviation were calculated for continuous variables. The chi-square test and Mann-Whitney U test were used to compare the groups.

RESULTS

The 114 patients were divided into 2 groups: silodosin (58 patients) and mirabegron (56 patients). There

Table 1. *Demographic characteristics of the silodosin and mirabegron groups*

Characteristics Mean ±SD or n (%)	Silodosin (n = 58)	Mirabegron (n = 56)	P value
Gender			
Female	19 (32.76)	20 (35.71)	0.739
Male	39 (67.24	36 (64.29)	
Side			
Left	15 (30)	25 (47.17)	0.074
Right	35 (70)	28 (52.83)	
Hydronephrosis			
No	12 (20.69)	9 (16.07)	0.631
Yes	46 (79.31)	47 (83.92)	
Age (years)	32.5 ±9.67	33.12 ±7.84	0.706
Size (mm)	6.8 ±1.56	7.1 ±1.37	1.96

n – number of patients; SD – standard deviation

Table 2. *Comparison of outcomes between the silodosin and mirabegron groups*

Outcome Mean ±SD or n (%)	Silodosin (n = 58)	Mirabegron (n = 56)	P value
Stone expulsion rate	47 (81.03)	46 (82.14)	0.879
Stone expulsion time (weeks)			
1	12 (25.53)	13 (28.26)	0.767
2	20 (42.55)	22 (47.83)	0.609
3	14 (29.79)	9 (19.57)	0.253
4	1 (2.13)	2 (4.35)	0.617
Pain episodes (per day)	2.34 ±0.20	1.94 ±0.18	<0.0001

n – number of patients; SD – standard deviation

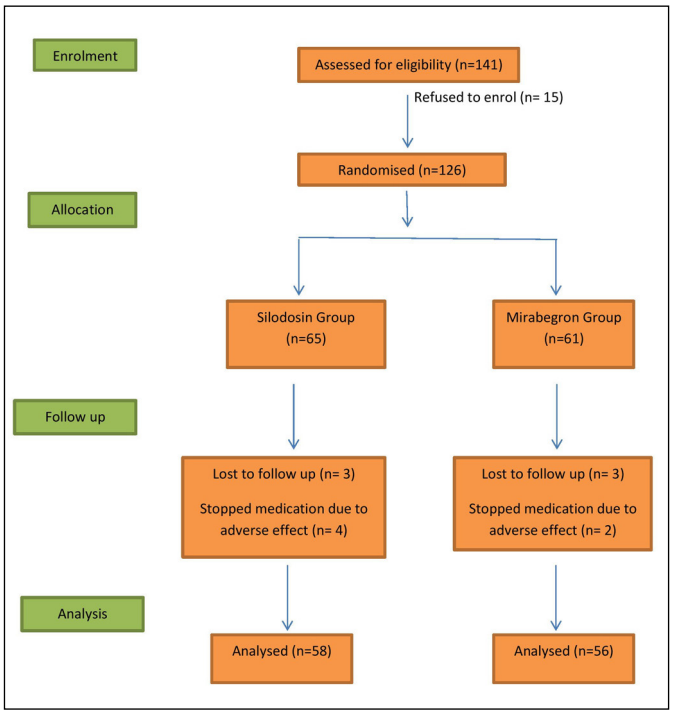

Figure 1. *Flowchart of study design.*

was no statistical difference between the 2 groups in mean age, gender, mean stone size, side, or hydronephrosis (Table 1).

The differences in the clinical outcome of the studied groups are shown in Table 2. The stone expulsion rate was statistically similar among both the groups (Table 2). The stone expulsion time was shorter in the silodosin group than in the mirabegron group in the first week (25.5% vs 28.2%, p = 0.767), second week (42.5% vs 47.8%, p = 0.609), and the fourth week (2.13% vs 4.35%, p = 0.617), but was not statistically significant.

In terms of pain episodes per day, patients in the silodosin group experienced significantly more pain than those in mirabegron group (2.34 ±0.20 vs 1.94 ±0.18, p <0.0001) (Table 2) and less analgesic was required. URSL was performed at the end of fourth week in patients who could not pass their stones [silodosin group: 11 (18.97%), mirabegron group: 10 (17.86%), p = 0.879]. All the patients were stone free after the surgery.

Adverse drug reactions leading to discontinuation of the medication occurred in 6 patients: 4 in the silodosin group (retrograde ejaculation, hypotension) and 2 in the mirabegron group (hypertension). All these patients were excluded from the final analysis (Fig. 1).

DISCUSSION

Adrenoceptors are widely distributed in the bladder and ureter. Alpha adrenergic receptors are densely present in the distal ureter [9], which relaxes the ureter while concomitantly maintaining the antegrade peristaltic movement, and hence helps in stone passage [10]. The meta-analysis suggested that the alpha-blockers significantly increase the stone expulsion rate of distal ureteric stones [11]. According to the literature, silodosin has better stone free rates, shorter stone expulsion time, and fewer pain episodes than tamsulosin [12, 13]. Studies showed that various patient-reported outcome measure tools have been developed for the evaluation of ureteric stone diseases which are more patient-centric. They assess the health-related quality of life in the form of questionnaires [14, 15].

The bladder detrusor smooth muscle relaxation is mainly mediated by the cyclic adenosine monophosphate (cAMP) pathway. Mirabegron is a potent and selective β3-AR agonist. It increases the cAMP concentrations in rat bladder tissue and leads to bladder relaxation [16]. Mirabegron relaxes the detrusor muscle during the storage phase of the urinary bladder fill-void cycle by activation of β3-AR, which increases the capacity of the bladder [17]. It has a half-life of 50 hours. It is mainly metabolised in liver and excreted in both urine and faeces [18]. The common side effects of mirabegron are raised blood pressure, tachycardia, dry mouth, urinary tract infections, constipation, headache, back pain, and dizziness [19]. Presently, mirabegron is approved for the treatment for overactive bladder [20].

Studies have shown the expression of beta-3 receptors in the smooth muscles and urothelial cells of the ureter. The expression of beta-3 adrenoceptor in the dilated ureter were significantly less than the normal ureter, which leads to a compensatory increase in smooth muscle contraction to propel the urine through obstruction [21]. The literature further showed that β-adrenergic receptor agonists inhibit the ureteral smooth muscle contraction leading to ureteral dilatation by downgrading the peristaltic activity of the ureteral smooth muscle [22], and they could help in stone passage. Tomiyama et al. revealed that β adrenoceptor agonist significantly lowered the intraureteric pressure caused by acute ureteral obstruction, and hence increased the urinary flow in dogs [23]. These studies supported that mirabegron could be used as an expulsive therapy for distal ureteric stones.

Bayar G et al. [24] did not find a statistically significant difference in stone expulsion rates of distal ureteric stones between silodosin- and mirabegron-administered patients (p = 0.391). In the present study also, the stone expulsion rate of both groups were similar (silodosin [81.03%] and mirabegron [82.14%]), without statistical significance (p = 0.879). A study by Tang QL [8] showed that the stone expulsion rate was statistically significant in patients with stone size ≤5 mm with mirabegron and tamsulosin combination.

The patients were followed up for 4 weeks. The stone expulsion time was always less in the silodosin group as compared to the mirabegron group, except in the third week (Table 2). However, we did not find a statistically significant difference. But our findings correlate with the previous studies. Bayar G et al. [24] reported that the stone expulsion time was 7.1 days for the silodosin group and 9.2 days for the mirabegron group, and not statistically significant. Another study by Solakhan M [7] found no statistical difference between mirabegron and control groups according to stone expulsion time in distal ureteric calculus (p = 0.979). According to them, the stone expulsion time was 7.64 days in the mirabegron group and 7.68 days in the control group. There is downregulation of beta-3 adrenoceptors in the dilated ureter [21]. This is a possible explanation of the lack of a valid association between the silodosin and mirabegron groups in terms of stone expulsion time.

In the current study, the mirabegron group (mean [SD] 1.94 [0.18]) had significantly fewer pain

episodes per day than the silodosin group (mean [SD] 2.34 [0.20]) ($p < 0.0001$). Our results were consistent with previous studies. A study by Tang QL [8] found significantly fewer pain episodes with mirabegron in the tamsulosin group (mean [SD] 1.3 [0.5]) when compared with the control group (mean [SD] 1.6 [0.7]) ($p = 0.022$). Another study [16] reported that the analgesic requirements were significantly lower in the mirabegron group (mean [SD] 1.8 [1.9]) in patients with distal ureteric stones as compared to the control group (mean [SD] 3.6 [2.3]) ($p = 0.004$).

In our study, a total of 6 patients left the study due to adverse drug reactions: 4 (6.15%) patients in the silodosin group and 2 (3.27%) in the mirabegron group. The reasons for discontinuation of drug in the silodosin group were as follows: 3 patients had retrograde ejaculation and one patient had hypotension. The other studies also had similar incidence rates (4–15%) of adverse drug events with silodosin [25, 26]. The reason for which mirabegron was abandoned was hypertension. Furthermore, the studies on mirabegron as an MET for distal ureteric stone had similar rates of adverse events (1.6–10%) [24, 27].

The limitations of this study were single centre, small sample size, and mean follow up of 4 weeks. Therefore, this study also suggests a multi-centric, larger sample with a longer period of follow-up. Moreover, this study did not evaluate the effect of drugs on stone expulsion according to the stone size. So, this may be an error when calculating the stone expulsion rate. In addition, a CT scan was not used for follow-up in any of the patients, which could be fallacious for residual stones.

CONCLUSIONS

This study concludes that among patients with distal ureteric stones ranging in size from 5 to 10 mm, mirabegron does not improve either the stone expulsion rate or the stone expulsion time when compared with silodosin. However, mirabegron does significantly reduce renal colic episodes, consequently decreasing the need for analgesics. Therefore, we propose that mirabegron may serve as a better choice for medical expulsive therapy of distal ureteric stones compared to silodosin.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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