



Adjunction of tamsulosin or mirabegron before semi-rigid ureterolithotripsy improves outcomes: prospective, randomized single-blind study

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Abstract

Objective To evaluate efficiency and safety of adjunct tamsulosin and mirabegron therapy before semi-rigid ureteroscopy for ureteral stones.

Materials and methods In this prospective, randomized, single-blind and multicentric study, participants were randomized into three groups. Group 1 was the control, participants in Group 2 used tamsulosin, and those in Group 3 used mirabegron. Operations were performed 7 days after drug administration. In all clinics, a 6/7.5-Fr ureteroscope with a laser power source for lithotripsy was used.

Results After excluding participants whose stones spontaneously passed, who discontinued medication due to adverse events and who were lost to follow-up, 186 participants were included in the final analysis. Mean age, gender, laterality, stone distribution and mean stone surface area were similar between groups. The number of participants requiring balloon dilatation was higher in the control group (23.8%) than in the tamsulosin (8.2%) and mirabegron (6.5%) groups ($p=0.006$). Successful access rate was lower in the control group (81%) than in the tamsulosin (96.7%) and mirabegron (95.2%) groups ($p=0.003$). Stone-free rate was lower in the control group (77.8%) than in the tamsulosin (90.2%) and mirabegron (95.2%) groups ($p=0.01$). Complication rates were similar among groups.

Conclusions Tamsulosin or mirabegron use for 1 week before semi-rigid ureteroscope increases stone access and the stone-free rate. Tamsulosin or mirabegron can be used with safety and efficacy before ureteroscopy for ureteral stones.

Keywords Semi-rigid ureteroscopy · Tamsulosin · Mirabegron

Introduction

Documentation of the use of the rigid retrograde ureterorenoscopy was first published in 1980 [1]. Since then, ureteroscopy has been the standard treatment method for ureteral stones, with a high success rate [2]. Miniaturizing the

ureteroscope and the use of lasers increased the success rate considerably, but stone access and achievement of stone-free status was not demonstrable in a significant number of cases [3, 4]. Advancing a rigid ureteroscope into a non-dilated ureter may be difficult and cause complications [5]. Balloon dilatation may provide access to stones, but not in all cases, and ureteral perforation might occur [6].

The ureter contains alpha-1 and beta adrenergic receptors. Alpha-1 adrenergic stimulation increases ureteral contractions, and beta adrenergic stimulation provides relaxation [7, 8]. Our hypothesis was that alpha-1 adrenergic blockade and beta adrenergic stimulation may provide ureteral relaxation; therefore, the ureteroscope may advance more easily, providing increased access to stones. Tamsulosin is an alpha-1 adrenergic blocking drug used for lower urinary tract symptoms [9]. Mirabegron is a beta-3 adrenergic agonist drug used for treatment of overactive bladder [10].

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The main goal of the study was to evaluate efficiency and safety of adjunct tamsulosin and mirabegron therapy before semi-rigid ureteroscopy for ureter stones.

Materials and methods

This prospective, randomized, single-blind and multicentric study was performed between June 2017 and August 2018 in three different urology departments in Turkey. All the participants, between 18 and 75 years old, and female who were not pregnant, were scheduled to undergo ureteroscopy for ureteral stones. After completing informed written consent, participants were divided into three groups using block randomization tables in a 1:1:1 ratio. Exclusion criteria were acute azotemia, stones larger than 2 cm, solitary kidney, drainage due to urinary tract infection, impacted status, bilateral ureterolithotripsy or stones in more than one location. Participants were also excluded if the planned procedure was a second operation, and their first, failed operation was not part of the study. The review board committees of Ankara Training and Research Hospital approved the study protocol.

The study is single blind, and medication protocols were given to the participants by secretaries of the departments to prevent the urologists from knowing which medications were assigned to each participant. The three protocols were (1) diclofenac 50 mg, (2) tamsulosin 0.4 mg (Flomax[®], Astellas Pharma Inc., Tokyo, Japan) and diclofenac 50 mg and 3) mirabegron 50 mg (Betmiga[®], Astellas Pharma Inc., Tokyo, Japan) and diclofenac 50 mg. The use of the drugs was explained to the participants. Diclofenac was only to be taken in case of pain, and tamsulosin or mirabegron was to be taken once daily. The table of block randomization was prepared by a bio-statistician, and the secretaries were instructed to abide by the provided block randomization table. Using one diclofenac tablet once was accepted as the definition of one dose of analgesic. Operations were performed 7 days after initiation of the drugs. All participants were questioned about the correct use of the drugs.

Non-contrast computed tomography with 5-mm slides was done before the operations. The stone surface area was calculated by 3D tomography software. Stone locations were classified as lower ureter, middle ureter or upper ureter. Three urologists performed operations in three different departments. These three urologists worked in the same clinic during urology training and were taught the same ureterolithotripsy technique. All of them used 6/7.5-Fr semi-rigid ureteroscopes (Richard Wolf GmbH, Knittlingen, Germany). A laser power source was used for lithotripsy. The first department used Sphinx Jr 30 (Lisa Laser, USA), the second used Dornier Medilas H Solvo (Olympus, Germany), and the third used Litho Laser (Quanta System, Italy). The

sensor tip guide wire was inserted into the ureter, then the ureteroscope was inserted into the ureter using the railway technique. When we accessed the stone, the guide wire inside the ureteroscope was taken out, and the stone was fragmented by laser. Stone pieces were removed from the ureter by basket catheter if possible and necessary. Dilatation with a high-pressure balloon catheter (12 Fr, 4 cm UroMax; Microvasive/Boston Scientific Corp., Natick, MA) was performed when the ureteroscope could not pass the ureterovesical junction. In cases of an inaccessible stone, a double-J stent was inserted, and the operation was finalized. Computed tomography was repeated 4 weeks after the operation.

Successful access was achieved when the ureteroscope entered the ureter and accessed the stone. When the participant was stone free by computed tomography 4 weeks after the procedure, the operation was defined as successful. Complications were classified by the Clavien–Dindo system. Only grades II or more were recorded. Perforation, formation of a false lumen and mucosal hemorrhage requiring the operation to end were defined as complications. A double-J stent was inserted when necessary (for ureter injury, residual stone, impacted stone, extended operation time, mucosal edema, etc.) for 4 weeks. Any prescribed alpha blocker or anticholinergic medications were not given to participants who required a double-J stent after the operation.

Recorded details included participant's age and gender; stone's laterality, location and surface area; whether balloon dilatation was needed; successful access rates; successful operation rates; operation times and complication rates. The study's power was calculated using Power and Sample Size Calculation software, version 3.1.6, setting the statistical difference at 15%, with a possibility of 10% of participants withdrawing from the study (alpha: 0.05, power: 0.90). The participant number for each department was calculated by ureteroscopy frequency for each department. Comparison of numerical data was completed with the Student's *t* test for paired groups and the one-way analysis of variance (ANOVA) for three-way groups. Analysis of non-numerical data was done using the Pearson Chi squared test. After the Chi squared test was employed to assess effects, a two-value logistic regression analysis was performed. A *p* value of less than 0.05 was accepted as statistically significant.

Results

The study was planned to include a total of 201 participants, with 67 in each group. After excluding participants whose stones spontaneously passed, who stopped medication due to adverse events and who were lost to follow-up, 186 participants were included in the final analysis. The control group (Group 1) was comprised of 63 participants, the tamsulosin

group (Group 2) was comprised of 61 participants and the mirabegron group (Group 3) was comprised of 62 participants (Fig. 1).

The mean age of participants was 41.3 ± 13.3 (18–72) years, mean stone surface area was 54 ± 31 mm² and mean operation time was 33.7 ± 9.2 min. Of the participants, 121 were male and 61 were female; interestingly, 93 stones were

located on the right and 93 on the left. Stone location distribution was 44 (23.7%) in the upper ureter, 37 (19.9%) in the middle ureter and 105 (56.5%) in the lower ureter. Patient distribution for each group by stone location, mean stone surface area, need for balloon dilatation, successful access, stone-free rate and complication rate was similar in each urology department (Table 1).

Fig. 1 Study design and including of participations

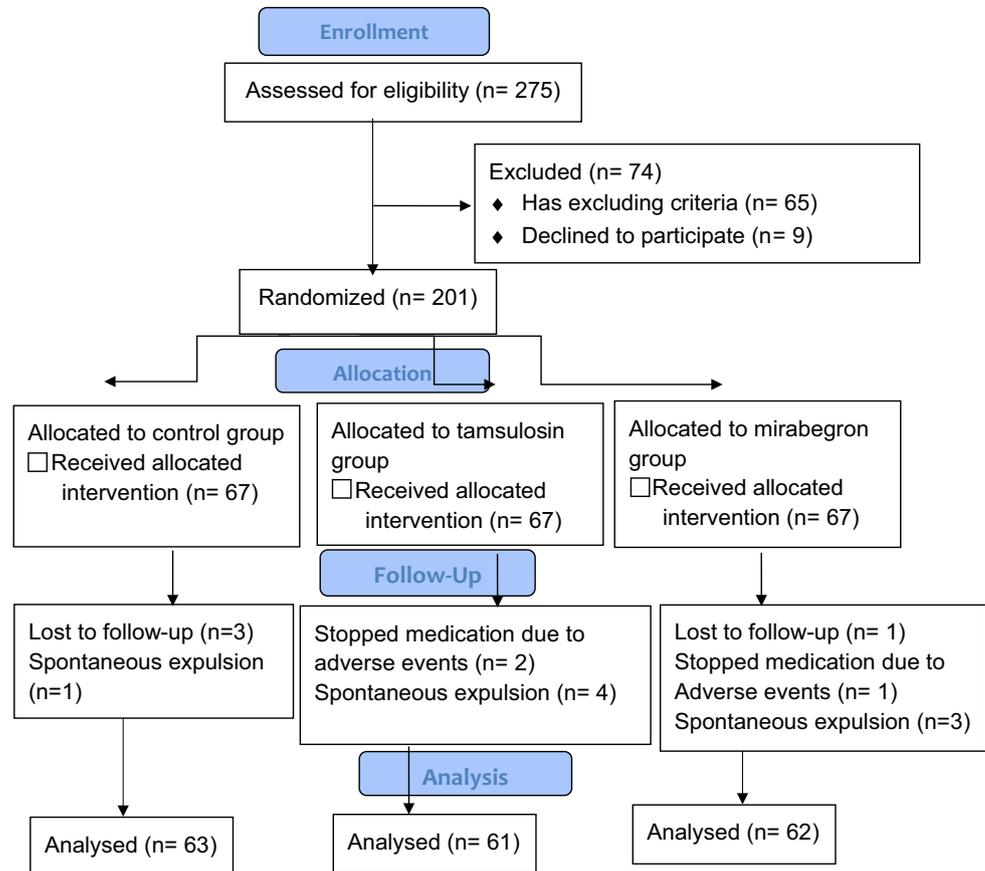


Table 1 Patients’ details and comparison of each department

| | 1 | 2 | 3 | <i>p</i> value | Total or mean |
|--|-----------|-----------|-------------|----------------|---------------|
| Total patient number (<i>n</i>) | 65 | 70 | 51 | | |
| Patient number (<i>n</i>) | | | | | |
| Control | 20 | 24 | 19 | 0.943 | 63 |
| Tamsulosin | 22 | 24 | 15 | | 61 |
| Mirabegron | 23 | 22 | 17 | | 62 |
| Localization | | | | | |
| Upper | 18 | 17 | 9 | 0.668 | 44 |
| Middle | 11 | 16 | 10 | | 37 |
| Lower | 36 | 37 | 32 | | 105 |
| Mean stone surface (mm ²) ± sd | 48.8 ± 30 | 61.2 ± 45 | 57.4 ± 44.8 | 0.192 | 55.8 ± 40.3 |
| Balloon dilatation need (<i>n</i>) (%) | 7 (10.8%) | 9 (12.9%) | 8 (15.7%) | 0.735 | 24 (12.9%) |
| Successful access (%) | 90.8 | 90 | 92.2 | 0.92 | 90.9 |
| Stone-free at the end of 4th week (%) | 87.7 | 88.6 | 86.3 | 0.931 | 87.6 |
| Complications (<i>n</i>) (%) | 2 (3%) | 2 (2.8%) | 0 | 0.46 | 4 (2.2%) |

Stone access was not achieved for 17 participants (9.1%). The ureteroscope could not be passed to the intramural ureter portion for ten participants and could not be passed to the middle or proximal portion for seven participants. Additionally, total or partial fragmented stone not removed from the ureter during the operation was still present at the end of the fourth week for six participants, so stone-free status could not be achieved for 23 (12.4%) participants. Complications occurred with four participants (2.2%); three were ureteral perforations and one was a hemorrhage, all of which required termination of the procedure. Adverse events were seen in 22 (36%) patients in the tamsulosin group. Only two participants discontinued taking tamsulosin because of hypotension. Twenty patients experienced an ejaculation disorder, and those patients continued to take the medication. One participant discontinued mirabegron because of hypertension.

Mean age, gender, laterality, stone location distribution and mean stone surface area were similar among groups. Mean doses of analgesic taken during the week prior to the operation were also similar (Table 2). The need for balloon dilatation was higher in the control group (23.8%) than the tamsulosin (8.2%) and mirabegron (6.5%) groups ($p=0.006$). The rate of successful access was lower in the

control group (81%) than the tamsulosin (96.7%) and mirabegron (95.2%) groups ($p=0.003$). The stone-free rate was lower in the control group (77.8%) than in the tamsulosin (90.2%) and mirabegron groups ($p=0.01$). Complication rates and mean operation times were similar among groups (Table 2).

We divided participants in terms of stone location. Proximal or middle ($p=0.042$) and distal ureter locations ($p=0.007$) showed statistically significant differences among groups in terms of stone-free rates (Table 3).

Discussion

Use of alpha-1 blockers before ureteroscopy is a relatively new subject. Zhu et al. [11] published a study in which tamsulosin was used as adjunct therapy before ureteroscopy. Afterwards, many papers published, and all of them reported that alpha-1 blockers (tamsulosin and silodosin) increased access to stones and contributed to stone-free rates [5, 12, 13]. All of these studies have the same hypothesis: alpha-1 adrenoceptors are present along the full length of the human ureter, and alpha-1 adrenoceptor blockade decreases contractions and causes relaxation in the ureter [14]. Alpha-1D

Table 2 Comparison of the demographic, characteristics and operative outcomes

| | Control | Tamsulosin | Mirabegron | <i>p</i> value |
|---|-------------|-------------|-------------|----------------|
| Patients nu (<i>n</i>) | 63 | 61 | 62 | |
| Mean age (years) ± sd | 39 ± 14.6 | 42.1 ± 11.4 | 42.8 ± 13.5 | 0.244 |
| Gender (male/female) | 42/21 | 42/19 | 41/21 | 0.944 |
| Side (right/left) | 36/27 | 28/33 | 29/33 | 0.377 |
| Localization (upper/middle/lower) | 17/12/34 | 14/10/37 | 13/15/34 | 0.42 |
| Mean stone surface (mm ²) ± sd | 53.9 ± 43.5 | 56.5 ± 22.4 | 51.5 ± 22.5 | 0.679 |
| Mean doses of analgesic ± sd | 1.6 ± 1.1 | 1.4 ± 1 | 1.2 ± 1 | 0.32 |
| Balloon dilatation needing (<i>n</i>) (%) | 15 (23.8) | 5 (8.2) | 4 (6.5) | 0.006* |
| Successful access (%) | 51 (81) | 59 (96.7) | 59 (95.2) | 0.003* |
| Stone-free at end of 4th week (%) | 49 (77.8) | 55 (90.2) | 59 (95.2) | 0.01* |
| Complications (<i>n</i>) (%) | 2 (3.2) | 1 (1.6) | 1 (1.6) | 0.799 |
| Mean operation time (min) ± sd | 30.9 ± 6.6 | 33 ± 9.4 | 33 ± 8.3 | 0.268 |

**p* value is significant under 0.05

Table 3 Comparison of access to stone and stone free rate in terms of stone localization

| | Control | Tamsulosin | Mirabegron | <i>p</i> value |
|----------------------------------|---------|------------|-------------------|----------------|
| Proximal and middle ureter Stone | | | | |
| Access to stone rate (%) | 75.8 | 91.7 | 92.7 | 0.079 |
| Stone free rate at 4th week (%) | 72.4 | 75 | 92.7 [†] | 0.042 |
| Distal ureter stone | | | | |
| Access to stone rate (%) | 85.3 | 100 | 97 | 0.02* |
| Stone free rate at 4th week (%) | 82.3 | 100 | 97 | 0.007* |

**p* value is significant under 0.05

[†]it is statistically different than control group

adrenoreceptors are more densely present in the ureter than 1A and 1B adrenoreceptors, and all three receptor types are denser in the distal ureter than in other parts [15]. However, ureteral contractions depend mainly on alpha-1A receptors [16]. Tamsulosin is more specific to alpha-1A than 1D [9]. Tamsulosin causes ureteral relaxation, so its use before ureteroscopy can improve outcomes [5, 17]. Beta adrenergic receptors are present in the smooth muscle and urothelium of the ureter, and beta-2 and beta-3 are especially responsible for relaxation [8]. The β_3 androgenic receptor number decreases when a stone blocks the ureter lumen, and it causes smooth muscle contraction; the β_2 number remains stable [18]. We believe that β_3 androgenic stimulation by mirabegron can cause relaxation before ureteroscopy and improve outcomes, just like tamsulosin.

Pre-operative adjunct tamsulosin therapy was performed by Ahmed et al. [5], and they reported that stone access rates were 87.9% vs. 93.8%, and stone-free rates were 86.1% vs. 92.6%, in control and study groups, respectively. In the study, stone access rates were 81, 96.7 and 95.2% and stone-free rates were 77.8, 90.2 and 95.2% in the control, tamsulosin and mirabegron groups, respectively. Ahmed et al. [5] reported that tamsulosin improved ureterolithotripsy outcomes in proximal ureteral stones. In that study, tamsulosin and mirabegron improved outcomes in proximal, middle and distal ureteral stones. Stone-free rate was between 77 and 92% for all ureteral stones [19, 20]. The stone-free rate was 77.8% in the control group. Stone location, size and impaction status were predictive factors for outcomes [21]. Stone location and size were similar among groups, and impacted stones were excluded from study.

Elashry et al. [22] reported that balloon dilatation was necessary in 59.5% of participants, but they used a 9.5-Fr ureteroscope; in our study, we used a 6-Fr ureteroscope. In the CROES study, the mean for balloon dilatation was 33.7% when a ≤ 8 -Fr ureteroscope was used [21]. In that study, balloon dilatation was necessary for 23.8% of the control group and it was a statistically significant increase compared to the tamsulosin (8.2%) and mirabegron (6.5%) groups. The use of balloon dilatation in our study seems to be lower than in existing literature, and we think this difference is because of ureteroscope size; the size used in our study was 6/7.5 Fr. Nevertheless, this statistical finding shows that the balloon dilatation may be needed even with small caliber ureteroscopes. Clavien grade II or more was recorded as complication. The complication rate of our study (2.2%) was similar to the CROES study (3%), which was very large [21].

Tamsulosin and mirabegron were given to the participants for 7 days, because both drugs achieve therapeutic levels at the 5th day [23, 24]. We wanted to keep the serum blood level therapeutic for at least 3 days. Adverse events occurred in 22 participants (36%) who used tamsulosin. Of these adverse events, ejaculation disorders occurred in 20

participants, but the drug was not discontinued. Tamsulosin administration was discontinued for two (3.3%) participants because of hypotension. Only one participant taking mirabegron experienced an adverse event, hypertension, and the drug was discontinued. It was discovered that the participant had idiopathic hypertension but did not use a prescribed antihypertensive drug regularly. We expected the operation time to be longer in the control group because our hypothesis was that ureter relaxation by medication (tamsulosin or mirabegron) provides further manipulation facility. However, operation time was similar between groups. The reason for this was the short duration of the operation in patients in which access could not be achieved, because the control group contained more patients who could not provide access. Operations were performed by three urologists, and none of them used a flexible ureterorenoscope. This may be seen as a study flaw. However, participant characteristics and outcomes were similar among clinics (Table 1). All three urologists were trained in the same clinic and have similar levels of experience. We do not believe that using a flexible ureterorenoscope would have changed the outcomes because flexible ureterorenoscopes and rigid ureteroscopes have the same calibers. The main reason for residual stones was unsuccessful access, and none of the stones migrated to the kidney.

Conclusions

Using tamsulosin or mirabegron for one 1 week before rigid ureteroscopy increased the stone-free rate and overall access to stones. Adverse events were seen in very few participants, and none of them were fatal. Tamsulosin or mirabegron can be used with safety and efficacy before ureteroscopy for ureteral stones.

Compliance with ethical standards

Conflict of interest No conflict of interest was declared by the authors.

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