Medical expulsive therapy for distal ureteric stones: Tamsulosin versus silodosin

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Summary Objectives: To compare the efficacy and safety of tamsulosin and silodosin in the context of medical expulsive therapy (MET) of distal ureteric stones.

Patients and methods: Observational data were collected retrospectively from patients who received silodosin (N=50) or tamsulosin (N=50) as MET from January 2012 to January 2013. Inclusion criteria were: patients aged ≥ 18 years with a single, unilateral, symptomatic, radiopaque ureteric stone of 10 mm or smaller in the largest dimension located between the lower border of the sacroiliac joint and the vesico-ureteric junction. Stone expulsion rate, stone expulsion time, number of pain episodes, need for analgesics use, incidence of side effects were compared.

Results: Stone-expulsion rate in the silodosin and in the tamsulosin groups were 88% and 82%, respectively (p not significant). Mean expulsion times were 6.7 and 6.5 days in the silodosin and tamsulosin group, respectively (p not significant). Mean number of pain episodes were 1.6 and 1.7 in the silodosin and tamsulosin group, respectively (p not significant). The mean number of analgesic requirement was 0.84 and 0.9 for the silodosin and tamsulosin group, respectively (p not significant). Overall, incidence of side effects was similar in both groups. Patients taking silodosin experienced an higher incidence of retrograde ejaculation but a lower incidence of side effects related to peripheral vasodilation when compared to patients taking tamsulosin. Subgroup analysis demonstrated significantly lower mean expulsion times and pain episodes in patients with stones ≤ 5 mm in both groups.

Conclusions: Tamsulosin and silodosin are equally effective as MET for distal ureteric stones sized 10 mm or smaller. MET with silodosin is associated with a lower incidence of side effects related to peripheral vasodilation but an higher incidence of retrograde ejaculation when compared to tamsulosin.

KEY WORDS: Silodosin; Tamsulosin; Medical expulsive therapy; Stones.

Submitted 26 August 2013; Accepted 15 January 2014

Introduction

Ureteric stones account for 20% of urinary tract stones and about 70% of them are found in the lower third of the ureter at presentation (1). To date, minimally invasive therapies, such as extracorporeal shock wave lithotripsy and ureterolithotripsy, represent efficacious treatment modalities in almost all cases. Nevertheless, these procedures imply high costs and are not risk-free (2). A watchful waiting approach has been reported to be associated with spontaneous stone expulsion in up to 50% of cases but some complications may occur such as urinary tract infections, hydronephrosis and colic events (2). In recent years, the use of the expectant approach for distal ureteric stones has been extended thanks to the use of adjuvant medical expulsive therapy (MET), that is able to reduce symptoms and facilitate stone expulsion. In 1970, Malin et al. demonstrated the presence of alpha and beta adrenergic receptors (AR) in the human ureter (3). Alphal are the most abundant AR subtypes at the level of ureteric smooth muscle cells (4). Itoh et al. demonstrated that three types of alpha1 AR are expressed in the human ureter (alpha1A, alpha1B and alpha1D) (5-7). Antagonists of these receptors have been proved to decrease ureteric basal tone, peristaltic activity, and contractions thus decreasing intraureteric pressure and increasing urine transport (5). Three metaanalyses have confirmed a positive effect of alpha-blocker therapy on the stone expulsion rates (8-11). Alphablockade has been proved to improve the likelihood of spontaneous stone passage, and to decrease both the time to stone passage and analgesic requirements (12). According to European Association of Urology Guidelines, alpha-blockers or nifedipine are recommended for MET (grade of recommendation A) (13). Patients who elect for MET should have well controlled pain, no clinical evidence of sepsis, and adequate renal functional reserve (13). The alpha1A/D selective alpha-blocker tamsulosin has been demonstrated to be a safe and effective drug that enhances spontaneous passage of distal ureteral stones sized 10 mm or smaller (8). Recent studies have demonstrated that the alpha1A subtype plays the major role in mediating phenylephrine-induced contraction in

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the human isolated ureter (7). *Kobayashi et al.* found that the selective alpha1A adrenergic receptor antagonist, silodosin, was more effective than the selective alpha1D adrenergic receptor antagonist, BMY-7378, for noradrenaline-induced contraction in the human ureter (14). Silodosin is effective as MET for ureteric stones (16). According to *Tsuzaka et al.*, silodosin was clinically superior for stone expulsion when compared to the selective α1D AR antagonist naftopidil (16). To date, however there are no clinical studied that compare silodosin to tamsulosin as MET for lower ureteric stones. We aimed to compare the efficacy of tamsulosin and silodosin as MET for symptomatic, uncomplicated distal ureteric stones.

MATERIALS AND METHODS

Observational data were collected retrospectively from patients who received silodosin or tamsulosin as MET from January 2012 to January 2013. Inclusion criteria were: patients aged \geq 18 years with a single, unilateral, symptomatic, radiopaque ureteric stone of 10 mm or smaller in the largest dimension located between the lower border of the sacroiliac joint and the vesicoureteric junction as assessed on intravenous urography. Exclusion criteria were: renal insufficiency, urinary tract infections, high-grade hydronephrosis, previous therapies for the stone, solitary kidney, history of ureteral surgery or previous endoscopic procedures, concomitant calcium-antagonists or corticosteroids medications, ureteric strictures, cardiovascular diseases, incomplete data. The following data were recorded and compared: patients demographics, stone size and side, type of MET, stone expulsion rate, stone expulsion time, number of pain episodes, need for analgesics use, incidence of side effects. Patients who experienced stone expulsion before first medication, or who were lost to follow-up were excluded from the analysis. Statistical analysis of mean values was carried out with the Student t test and the chi square test. Subgroup analysis was performed according to stone size \leq or > 5 mm.

and with ultrasonography. Absence of stone expulsion after day 28 was considered failed therapy.

Discontinuation of MET and intervention within 28 days from the start of the MET due to uncontrollable pain, adverse events, urinary tract infections, acute renal failure, or the patient's desire for stone removal were also considered failed therapy. Baseline patients characteristics in both study arms are reported in Table 1. The two groups were comparable in terms of mean age, mean stone size, stone side. Moreover, the number of patients with smaller stones (≤ 5 mm) and larger (> 5 mm) stones were also comparable in both groups. Spontaneous stone expulsion within 28 days was observed in 41 patients in the tamsulosin arm (82%) and in 44 patients in the the silodosin arm (88%) without statistically significant differences (Table 2). Hospitalization and ureteroscopy were required in 3 patients belonging to the tamsulosin arm and in 2 patients belonging to the silodosin arm. Six patients in the tamsulosin arm and 3 in the silodosin arm experienced unsuccessful expulsion after 4 weeks of treatment and required ureteroscopy. Not statistically significant differences emerged in terms of mean expulsion

Table 1.Baseline patients' characteristics in both treatment groups.

| | Tamsulosin | Tamsulosin Silodosin | | | |
|---|--------------|----------------------|------|--|--|
| Mean age, year (range) | 53.5 (33-77) | 50.1 (30-77) | n.s. | | |
| Ureteric stone side | | | | | |
| Left n (%) | 27 (54) | 21 (42) | n.s. | | |
| Right n (%) | 23 (46) | 29 (58) | n.s. | | |
| Gender n (%) | | | | | |
| Male | 50 (100) | 50 (100) | n.s. | | |
| Mean stone size, mm (range) | 6.7 (3-10) | 6.5 (3-10) | n.s. | | |
| Size n (%) | | | | | |
| ≤ 5 mm | 22 (%) | 24 (48) | n.s. | | |
| > 5 mm | 28 (%) | 26 (52) | n.s. | | |
| n.s.: not statistically significant difference. | | | | | |

Table 2.Overall results.

| | Tamsulosin | Silodosin | P value |
|---|------------|------------|---------|
| Expulsion rate n (%) | 41 (82) | 44 (88) | n.s. |
| Expulsion time days mean (range) | 6.5 (3-9) | 6.7 (3-9) | n.s. |
| Pain episodes mean (range) | 1.7 (0-4) | 1.6 (0-4) | n.s. |
| Need for analgesics | 0.9 (0-3) | 0.84 (0-3) | n.s. |
| Side effects (n %) | | | |
| Retrograde ejaculation | 1 (2) | 8 (16) | < 0.05 |
| Side effects related to peripheral vasodilation | | | |
| Dizziness | 4 (8) | 1(2) | n.s. |
| Nasal congestion | 3 (6) | 1 (2) | n.s. |
| Postural hypotension | 3 (6) | 1 (2) | n.s. |
| Headache | 3 (6) | 1(2) | n.s. |
| Total | 13 (26) | 4 (8) | < 0.05 |
| Total side effects | 14 | 12 | n.s. |

RESULTS

Overall, data from a total of 100 patients which met inclusion and exclusion criteria were recorded.

Of them, 50 patients (50%) received a prescription of a daily single dose of tamsulosin 0.4 mg for 28 days and 50 (50%) a prescription of a daily single dose of silodosin 8 mg for 28 days.

All patients were advised to drink a minimum of 2 L of water daily and to use symptomatic therapy with injection of 75 mg diclofenac on demand.

All patients were advised to filter their urine to detect spontaneous stone passage and to stop taking the medications when the stone was expulsed. Patients were followed up weekly with x-ray of the kidney, ureter, and bladder region

| | Table : | 3. | | | |
|---------------------|----------|-----------|----|-------|-------|
| Results of subgroup | analysis | according | to | stone | size. |

| | | Tamsulosin | | | Silodosin | | |
|--------------------------------------|------------|------------|--------|------------|------------|--------|--|
| | ≤ 5 mm | > 5 mm | р | ≤ 5 mm | > 5 mm | р | |
| Expulsion rate n (%) | 20 (90.90) | 21 (75) | n.s. | 23 (95.83) | 21 (80.76) | n.s. | |
| Expulsion time days mean (range) | 5.4 (3-8) | 7.7 (6-9) | < 0.05 | 5.7 (3-8) | 7.9 (6-9) | < 0.05 | |
| Pain episodes mean (range) | 1.1 (0-3) | 2.1 (0-4) | < 0.05 | 1.1 (0-4) | 2.0 (0-4) | < 0.05 | |
| Need for analgesics | 0.8 (0-3) | 0.9 (0-3) | n.s. | 0.6 (0-2) | 1.0 (0-3) | n.s. | |
| n.s.: not statistically significant. | • | | | | | | |

time, mean number of pain episodes and need for analgesics (Table 2). Overall, the incidence of side effects was similar in both groups. They were mild and did not require cessation of therapy in any patient. The incidence of retrograde ejaculation was significantly higher in the silodosin arm while the incidence of side effects related to peripheral vasodilation (dizziness, postural hypotension, headache, nasal congestion) were significantly higher in the tamsulosin arm (Table 2). Results from subgroup analysis according to stone size are reported in Table 3. The mean expulsion times and the mean number of pain episodes were significantly lower in patients with smaller stones, in both treatment arms.

DISCUSSION

Advances in endourology have diverted the management of ureteric stones by open surgery to minimal invasive methods like extracorporeal shock wave lithotripsy and ureterorenoscopy. Nevertheless, these techniques are not risk-free. MET has recently emerged as an alternative strategy for the initial management of selected patients with distal ureteric stones (17). The stimulation of the alpha1 AR in the ureter increases the force of ureteric contraction and the frequency of ureteric peristalsis. Blockade of alphal AR inhibits basal tone, reduces peristaltic amplitude and frequency, and decreases intraluminal pressure while increasing the rate of fluid transport and the chances of stone expulsion. Alpha1A and alpha1D are the AR subtypes that are more densely expressed in the distal ureter (18). Tamsulosin has been widely studied in the context of MET for patients with distal ureteric stones smaller than 10 mm. It has been proved that tamsulosin increases stone expulsion rates, decreases pain, reduces mean time to stone expulsion and decreases analgesic usage when compared to placebo (1,5, 19-21). However, a possible class effect has been supported by trials demonstrating increased stone expulsion rates using tamsulosin, doxazosin, terazosin, alfuzosin, and naftopidil (5, 13). Itoh performed the first prospective randomized study evaluating the use of silodosin in the management of ureteric stones ≤ 10 mm (15). Tsuzaka compared the efficacy of the selective alpha1D AR antagonist naftopidil and the selective alpha1A AR antagonist silodosin in the management of symptomatic ≤ 10 mm ureteral stones (16). To our knowledge, we compared for the first time tamsulosin and silodosin in the context of MET for distal ureteric stones. Spontaneous stone expulsion rates without MET

in patients with distal ureteric stones ≤ 10 mm have been reported to vary between 35.2% to 61% with mean expulsion times ranging from 9.87 to 24.5 days (1, 5, 19-21). Tamsulosin enhances stone expulsion rates and mean expulsion times in this subset of patients with reported values ranging from 79.31% to 89.5% and from 6.31 to 12.3 days, respectively (1, 5, 19-21). Stone expulsion rate in patients with distal ureteric stones treated with silodosin has been reported to be 72.7% with mean expulsion time of 9.29 days (15). Tsuzaka et al. reported a stone expulsion rate significantly higher in patients treated with silodosin than naftopidil (84% vs 61%, respectively) without significant differences in terms of stone expulsion time or rate of interventions (16). Results from the present study demonstrate stone expulsion rates and stone expulsion times in patients treated with tamsulosin that are within the published ranges. Patients treated with silodosin exhibit stone expulsion rates and mean expulsion times that are comparable to those reported in the tamsulosin arm. However, stone expulsion rates and times with silodosin in the present study are better than that reported by other authors (15). Stone size has been identified as an important predictive factor for ureteral stone expulsion. The probability for distal ureteric stones to pass spontaneously is as high as 71-98% for stones ≤ 5 mm and only 25-51% for stones > 5 mm. Studies on MET with sub analysis according to stone size demonstrated higher expulsion rates for stones ≤ 5 mm with respect to larger stones (1, 19). Stone expulsion rate of 89.5% and 70% in patients treated with tamsulosin with stone size ≤ 5 mm and > 5 mm, respectively, have been reported (1). Results from the present study demonstrated higher expulsion rates in patients with stones ≤ 5 mm and this was true for both patients treated with tamsulosin and silodosin. However the difference was not statistically significant. Most trials on MET for lower ureteric stones with tamsulosin demonstrated significant lower mean number of pain episodes with respect to placebo (1, 5, 19-21). This difference may be attributable to the accelerated stone expulsion with a consecutive shorter time at risk for painful events. However, a true analgesic effect of tamsulosin has been also reported. Results from the present study in terms of mean number of pain episodes and need for analysics are within the published ranges for tamsulosin and similar data have also emerged for silodosin. Safety issues and adverse events spectra differ considerably between the available alpha-blockers. Adverse side effects commonly reported with different alpha1 AR blockers include dizziness, headache, asthenia, postural hypotension, syncope, rhinitis, sexual dysfunction (22, 23). Alpha1 AR subtypes are implicated in blood vessel contraction. The main alphal subtype in the large vasculature is the alpha1B AR. The blockage of this receptor is mainly responsible for side effects related to peripheral vasodilation, such as postural hypotension, dizziness, and headache (24-26). The alpha1D subtype is predominant and functional in human epicardial coronary arteries, and its inhibition might mediate coronary vasodilation (26). Studies indicate differences among the various alpha1 blockers in terms of cardiovascular side effects (22). Studies of pharmacy databases in Europe suggest that the administration of alphal AR blockers increases the incidence of hip fractures (chosen as a surrogate for clinically important orthostatic hypotension) (25).

Further analysis with regard to the precise alpha1 AR antagonists prescribed suggests that avoidance of alpha1B AR blockade may result in fewer overall hip fractures (25). Interestingly, alphal AR expression increases with aging, with the ratio of alpha1B: alpha1A increasing (25). Alpha1 AR inhibitors with higher selectivity for the alpha1A subtype have been developed in order to reduce the cardiovascular side effects, while maintaining efficacy on urinary tract (26). Tamsulosin preferentially blocks alpha1A and alpha1D AR, with a 10-fold greater affinity than for alpha1B AR. In contrast, silodosin is highly selective for alpha1A AR, with a 162fold greater affinity than alpha1B AR and about a 50-fold greater affinity than for alpha1D AR. The weak cardiovascular effects of silodosin have been demonstrated in many in vivo models (26). Studies conducted recently have suggested that silodosin as a consequence of its high subtype selectivity is less likely than tamsulosin to have significant cardiovascular side effects either when used alone or in combination with other agents, which may affect blood pressure (24). An important characteristic of silodosin is the lack of clinically relevant or statistically significant changes in blood pressure or heart rate versus placebo (24). However, a minor but statistically significant difference versus placebo was observed with tamsulosin (24). In a study by Yu HG et al., tamsulosin treatment resulted in a significant reduction in mean systolic blood pressure relative to the negligible change of silodosin (27). The incidence of orthostatic hypotension with silodosin has been reported to be < 3% (28). In a study by Marks et al., the proportions of patients with treatment emergent orthostatic hypotension were similar for silodosin (2.6%) and placebo (1.5%) (29). Results from the present study demonstrate higher incidence of retrograde ejaculation in patients treated with silodosin but lower incidence of side effects related to peripheral vasodilation when compared to tamsulosin. The incidence of side effects is similar to that reported by other authors (23). The lower incidence of side effects related to peripheral vasodilation associated with silodosin use make it more suitable for older patients (24). By contrary, according to literature data, retrograde ejaculation does not appear to be particularly bothersome and only a small percentage of patients reporting this adverse effect enrolled in clinical studies discontinued treatments because of it (23). Furthermore, this effect is fully and promptly reversible within a few days after discontinuation of treatment (23). By contrary, cardiovascular side effects may have a greater clinical relevance especially in older patients. The main limit of the present study is the retrospective design. Further studies are needed to elucidate the efficacy of silodosin as MET for distal ureteric stones.

CONCLUSIONS

In conclusions, tamsulosin and silodosin are safe and effective treatments that enhance spontaneous passage of distal ureteric stones sized 10 mm or smaller. They appear to have similar profiles in terms of expulsion rates and times, mean number of pain episodes and need for analgesics. Or study demonstrate a lower incidence of side effects related to peripheral vasodilation and an higher incidence of retrograde ejaculation with silodosin thus making this drug mainly suitable for older patients.

ACKNOWLEDGEMENT OF FINANCIAL SUPPORT

There are no financial support.

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