

The use of tamsulosin as adjunctive treatment after ESWL in patients with distal ureteral stone: do we really need it?

Results from a randomised study

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Abstract Our study aimed to define the position of tamsulosin as adjunctive therapy in patients with stones of the distal ureter who had undergone extracorporeal shock wave lithotripsy (ESWL). In total, 61 consecutive patients (38 men and 23 women) with single distal radiopaque ureteral stone of ≥ 6 mm of diameter were enrolled. After ESWL patients were randomized in two groups. Non-steroidal anti-inflammatory drug (supp. diclofenac 50 mg) was given to both groups upon demand. In group B, all patients (30) received additionally tamsulosin 0.4 mg every day. Follow-up visits were performed 1, 2, 3 and 4 weeks after ESWL. Evaluation included a KUB plain film and an ultrasound examination. Efficacy was evaluated in terms of success rate, stone-free rate, expulsion time of the fragments and use of diclofenac. Two patients from the tamsulosin group experienced dizziness and one was withdrawn. The success rate was 58.06 and 66.66% for the control and the tamsulosin group, respectively, while the corresponding values for stone-free rate were 51.6 and 63.33%, respectively. The mean expulsion time of the fragments was 13.22 days for group A and 12.95 days for group B. These results did not achieve statistically significant difference ($P > 0.05$). The mean diclofenac dose was 118.9 mg in group A and 56.9 mg in group B. This difference was statistically significant ($P = 0.02$). Despite the relatively small number of patients, our data indicate that the use of tamsulosin after ESWL in this specific subgroup of patients does not result in improved

success and stone-free rate and expulsion time. In contrast, a significantly reduced need for analgesics was found.

Keywords Tamsulosin · Ureteral stones · Extracorporeal shock wave lithotripsy · Expulsive treatment · Randomised

Introduction

Several studies have demonstrated the utility of pharmacological therapy in promoting spontaneous ureteral stone passage and in reducing the time for and pain associated with stone expulsion. Pharmacological therapy includes calcium channel blockers, corticosteroids, analgesic and anti-inflammatory drugs [1–4]. The use of α_1 -adrenergic antagonists has been recently introduced in the treatment of urolithiasis [2–8]. The theory is that since α_1 -adrenergic receptors are the most abundant receptors in ureteral smooth muscle cells, and α_1 -adrenergic antagonists inhibit basal tone, peristaltic activity, and ureteral contractions, they may affect stone passage. Current available data demonstrate that α -blockers seem to be a safe and effective expulsive therapy for the management of small distal ureteral stones. The next reasonable step is to explore if α -blockers in combination with other treatments (such as extracorporeal shock wave lithotripsy, ESWL) or in special situations (such as pregnancy) may yield superior benefit. In this regard, few studies have evaluated the role of tamsulosin after ESWL, but still data remain limited while in addition a discrepancy is observed in the reported efficacy [9–11]. For this reason, we conducted this prospective, randomized study to evaluate the efficacy of tamsulosin as adjunctive treatment in patients with stones of the distal ureter who underwent ESWL.

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Patients and methods

Between June 2005 and September 2006, 64 consecutive patients with single radiopaque distal ureteral stone (defined as those below the sacral–iliac joint) of ≥ 6 mm of diameter underwent ESWL for the first time and were considered for this study. Maximum diameter of stone was measured on plain KUB X-ray. All ESWL treatments were performed in our Department with the Dornier S Lithotripter II (Dornier MedTech System GmbH, Wessling, Germany).

Patients were randomized in two groups based on the last digit (even/odd) of their personal hospital code number. Exclusion criteria included hypotension, ulcer, therapy of benign prostatic obstruction with α -blockers and presence of a double J stent previously placed. Patients' permission was obtained after they had read a summary of the protocol and agreed to comply with the follow-up schedule. The possibility of side effects and undesired events was discussed and patients were encouraged to report them immediately. Hydration (fluid intake of at least 2 l a day) was recommended to all patients and non-steroidal anti-inflammatory drug (supp. diclofenac 50 mg) was given to both groups upon demand. In group A, diclofenac was the only prescribed medication. In group B, all patients received additionally tamsulosin (0.4 mg per os) every day during the follow-up period. All patients were followed-up for up to 1 month. When treatment was judged to be successful, patients were released. Follow-up visits were scheduled 1, 2, 3 and 4 weeks after ESWL. Evaluation included a KUB plain film and an ultrasound examination of the urinary tract to assess the presence of hydronephrosis.

Efficacy was evaluated in terms of success rate, expulsion time of the fragments and use of diclofenac. Success rate was defined as the percentage of patients who rendered stone free or had clinically insignificant residual fragments (asymptomatic fragments less than or equal to 3 mm in diameter). Insignificance of residual fragments was evaluated by two of the investigators who were not blinded to treatment group. Expulsion time was considered as the visit at which treatment was classified to be successful.

It was estimated that for a significance level (α) of 0.05 and effect size of 0.35, a sample size of 64 patients was required to reach a 0.8 power in our study.

The differences between the two groups were tested using the Chi-square test and the Mann–Whitney *U* test. $P < 0.05$ was considered to indicate significance. Analysis was performed on an intention-to-treat basis with the assumption that dropouts failed to pass their stones.

Results

In total 61 eligible patients (38 men and 23 women) were enrolled into this randomized study. Group A included 20

men and 11 women with a mean age of 49.2 years (from 30 to 72 years) while group B consisted of 18 men and 12 women with a mean age of 48.8 years (range 27–73 years). The mean stone diameter before ESWL was 8.3 and 8.5 mm for group A and B, respectively. The average number of shocks waves per ESWL session was 3,050 in group A (range 2,700–3,500) and 3,100 in group B (range 2,600–3,500). There was no statistically significant difference between the two groups in terms of age, gender, mean stone size and mean number of shock waves. Detailed data are presented in Table 1.

In group A, one patient was lost to follow-up and another one from the same group was given a nephrostomy catheter due to the development of urinary infection in the presence of hydronephrosis and he was considered as a failure. Two patients (one man and one woman) from the tamsulosin group experienced dizziness. The female patient refused to continue and was withdrawn from the protocol; she was considered as a failure. Figure 1 presents the flow diagram of participants through each stage of the study.

The success rate was 66.66% (20 of 30 patients) and 58.06% (18 of 31 patients) for the tamsulosin and the control group, respectively. Stone-free rate was 63.33% (19/30) for group B and 51.6% (16/31) for group A. These results did not achieve a statistically significant difference ($P > 0.05$). The mean expulsion time of the fragments was 13.22 days (range 7–21 days) for the control group and 12.95 days (range 7–28 days) for the tamsulosin group. There was no statistically significant difference in expulsion time ($P > 0.05$). Figure 2 shows the distribution of patients at each follow-up visit.

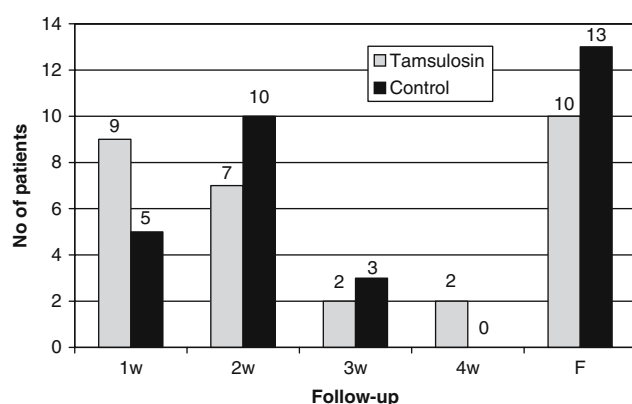
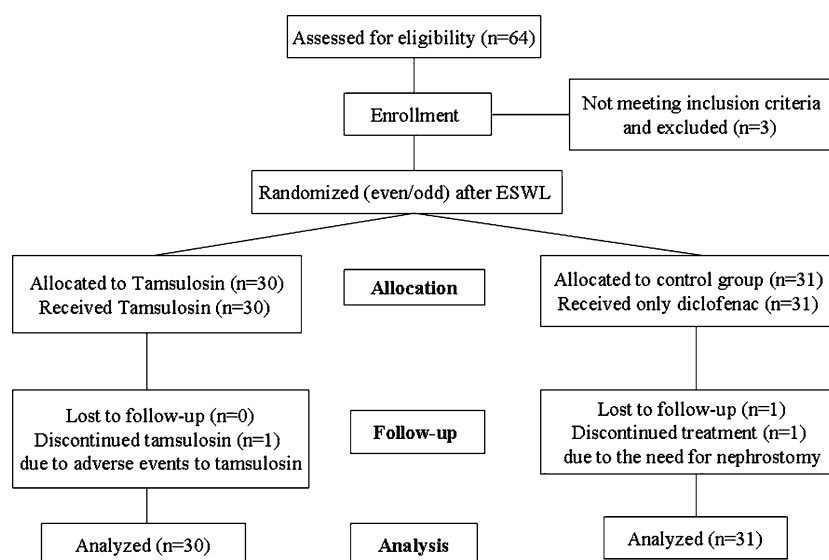
The mean diclofenac dose was 118.9 mg (from 0 to 350 mg) per patient in group A and 56.9 mg (range 0–250 mg) per patient in group B. This difference was statistically significant ($P = 0.02$).

Discussion

The steadily increasing number of publications on the role of α -blockers in the treatment of urolithiasis is suggestive of the interest in medical expulsive therapy. Limitations of

Table 1 Comparison of patients characteristics, expressed as mean value and range

	Group A	Group B
Patients (<i>n</i>)	31	30
Age (years)	49.2 (30–72)	48.8 (27–73)
Gender (male/female)	20/11	18/12
Stone size (mm)	8.3 (6–12)	8.5 (6–13)
Shock waves	3,050 (2,700–3,500)	3,100 (2,600–3,500)

Fig. 1 The flow diagram of the present study**Fig. 2** Successfully treated patient at each follow-up visit (weeks) and failures (F)

studies on the efficacy of α -blockers have been identified by Michel and de la Rosette, including different treatment arms with several combinations of drugs, small numbers of patients resulting in limited statistical power, different follow-ups and lack of vigorous randomization procedures [12]. However, a recent meta-analysis of nine randomised controlled trials suggests that treatment with a calcium channel blocker or an α -blocker improves the chance of spontaneous expulsion of small distal urinary stones by 65%, obviating the need for surgical treatment [13].

Potentially, a further application of expulsion therapy might be the passage facilitation of the fragments after ESWL. The stone-free rate of ESWL treatment for lower ureteral stones ranges between 54 and 91% and depends on the stone size and composition [14–16]. In addition, it has been reported that fragmentation of these stones may not be sufficient for complete stone clearance due to spasm of smooth muscles, submucosal edema, and pain that affect migration of ureteral stone [9]. Kupeli et al. [9] evaluated the impact of tamsulosin on the clearance of lower ureteral

stones and found that the adjunctive administration of tamsulosin after ESWL to patients with low ureteral stones could increase the stone-free rate to 70.8%, compared to 33.3% of patients who underwent only ESWL. Gravina et al. [10] demonstrated that ESWL in association with tamsulosin is more effective (78.5%) than ESWL alone (60%) for the management of patients with renal stones. Interestingly, when patients were stratified according to stone size, the success rate was significantly greater in the tamsulosin group for stones larger than 10 mm (81%) compared to the controls (55%) but this difference was not significant for stones less than 10 mm (75 vs. 68%). In addition, the use of tamsulosin for the management of patients who developed steinstrasse after ESWL did not result in significant improvement of spontaneous passage rate and expulsion time [11].

The present study was designed to prospectively investigate the role of tamsulosin as adjunctive therapy after ESWL of distal ureteral stones. The clinical success was 66.66 and 58.06% for the tamsulosin and the control group, respectively. Our results did not demonstrate a significant advantage from the use of tamsulosin in contrast to the findings of Kupeli et al. [9]. Although the success rate of the tamsulosin patients was similar in the Kupeli study (70.8%) and ours (66.66%), the main difference was found in the success rate of the ESWL group (33.3 vs. 58.06%). Plausible explanations for this discrepancy include use of different lithotripters, definition of success rate and different follow-up periods. It is well accepted that the key for expulsion is the fragmentation of stones, which may be affected by the machine type. The Dornier Lithotripter S II was used in all our cases. In addition, in most studies success rate was defined as the percentage of patients who were stone free, while in the present study patients who had clinically insignificant residual fragments were also classified as

successfully treated. In our opinion avoidance of over-treatment of asymptomatic fragments less than 4 mm that can pass spontaneously represents a reasonable approach, since the risk for stone recurrence and re-growth from persisted fragments of distal ureteral stones was found to be 2.7% at 5 years [17].

Tamsulosin was shown to improve the clearance of large renal stones after ESWL compared to smaller stones [10]. These large stones often generate larger fragments that migrate less easily. Therefore, it seems that the size of fragments may play a role in the success rate. In our study the mean size of stones was less than 9 mm for both groups and this may represent a possible explanation for our results.

Another difference was that Kupeli et al. [9] performed a single follow-up examination at the 15th day while our patients were followed-up for 4 weeks. In general, treatment duration and follow-up in the published series on medical therapies facilitating ureteral stones passage range from 1 to 6 weeks. Different follow-up may result in controversial clinical outcomes.

A consideration of our study is the risk to be underpowered, since one could argue that effects that are smaller than the specified medium effect size could not be considered negligible. Which choice is considered appropriate depends on the theoretical context of the research, related results published previously, and cost–benefit considerations. In contrast, it is well known that a statistically significant result is not always translated to a clinically significant result.

Previous studies on active pharmacological management of ureteral stones have reported a statistically significant difference in expulsion time compared to conventional treatment [3–5, 7, 8, 18]. In these studies, only pharmacological treatment was given to facilitate stone passage, therefore calculi were intact and patients could record precisely the time of stone expulsion. In the present study, ESWL caused fragmentation of the stones, thus it was difficult for patients to recognize the expulsion time. Therefore, expulsion time was defined to be the visit at which treatment was classified to be successful. Our results showed that expulsion time was similar for both treatment arms (12.95 days for the tamsulosin group and 13.22 days for the controls). An interesting finding in our series was that at the 4-week follow-up visit, stone-free patients were recorded only in the tamsulosin group (Fig. 1). Although the number is small (two patients), this may indicate that prolongation of tamsulosin therapy could yield an increased stone-free success rate. This assumption is also supported by the findings of Gravina et al. [10] on the use of tamsulosin after ESWL of renal stones that showed a continuous increase in the success rate in the treatment group during the 3-month follow-up. Therefore, the question that arises is which the ideal duration of treatment should be.

A benefit from the use of tamsulosin in our study was the significant decrease in the analgesic use of diclofenac. The mean dose of diclofenac was 118.9 and 56.9 mg for the control and the treatment group. Our finding is in agreement with those in previous studies that have demonstrated a decrease in the number of ureteral colic episodes, the intensity of pain and the use of analgesics [7, 8, 18, 19]. Since colic pain is related to ureteral spasm, it seems that tamsulosin could decrease the algogenic stimuli by decreasing the frequency of peristaltic contractions during expulsion. Thus, these results indicate the possibility of home management and a loss of fewer working days.

All currently available studies on the α -blocker treatment of urolithiasis have used tamsulosin, possibly because of its excellent tolerability and the lack of need for dose titration upon initiation of treatment, which allows administering a fully effective dose immediately. The side-effect profile of tamsulosin includes dizziness, rhinitis, and diarrhea although the incidence of side effects has been reported to be low [2, 7, 11]. However, not all studies systematically report on the side effects of the administered treatment regimen. In the present study, 2 of the 30 (6.66%) patients experienced dizziness and one of them (3.33%) dropped out of the protocol. It is also interesting that similar to previous studies retrograde ejaculation has not been reported probably due to the short observation time and the decrease in coitus frequency owing to colicky pain [11].

In their recent meta-analysis Hollingsworth et al. [13] recognized the need to identify all available data in order to avoid publication bias although negative studies are less likely to be submitted and published than positive ones. In this framework, our study offers significant insight into the position of medical expulsive treatment after ESWL, despite the relatively low patient numbers of the present study, a limitation inherent in all analogous studies.

Conclusions

Our data indicate that adjunctive medical therapy with tamsulosin given after ESWL of distal ureteral stones does not affect the success and stone free rate and the passage time of fragments. On the contrary, adjunctive administration of tamsulosin can reduce the total analgesic consumption after an ESWL procedure in this specific subgroup of stone patients. However, it is obvious that further multi-center randomized studies with a larger number of patients are required to draw solid conclusions on the current position of tamsulosin in the management of patients who undergo ESWL.

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