Urol Res (2012) 40:537–542
DOI 10.1007/s00240-011-0455-x

ORIGINAL PAPER

Does the use of doxazosin influence the success of SWL in the treatment of upper ureteral stones? A multicenter, prospective and randomized study

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Received: 18 August 2011 / Accepted: 22 December 2011 / Published online: 7 January 2012

Abstract The objective of the study is to investigate the effect of doxazosin, administered to the subjects who underwent SWL due to upper ureteral stones, on therapeutic outcomes. The study enrolled the patients with a radio-opaque stone ≥5 mm in upper ureter. Patients were randomized into two groups: the first group underwent SWL following the diagnosis and they were recommended to receive oral hydration. The second group underwent SWL after initiating alpha blocker (doxazosin controlled-release tablet 4 mg/day) and drug therapy was continued until that the patient has been stone free. Parameters of SWL procedure, Steinstrasse, pain score at admission, time to stone passage, the complications developed, the additional procedures that were administered and number of hospital visits done due to pain during the treatment were recorded. A total of 79 patients were enrolled to the study. The subjects evaluated included 35 patients, who received an alpha blocker and 44 patients who did not receive an alpha blocker. For both groups, the level of energy applied per SWL session, the diameter of the stone, the number of hospital visits done due to pain, pain score and the need for analgesia were found to be similar ($p > 0.05$). The group of doxazosin was more advantageous in terms of stone-free rate, the need for additional procedures and Steinstrasse ($p < 0.05$). In conclusion, the addition of doxazosin to SWL therapy administered for upper ureteral stones reduces Steinstrasse, and thereby, the need for additional procedures and increases post-treatment stone-free rate. A positive effect of doxazosin on the time to stone passage was not shown.

Keywords SWL · Doxazosin · Ureteral stone

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Introduction

Urinary stone disease is one of the most common reasons for Urology referrals, affecting 5–10% of the total population [1]. SWL, which was introduced in early 1980s, became one of the treatments of choice for renal and ureteral stones [2]. Despite the developments in endourological methods, SWL is still the treatment of choice in majority of the urinary calculi [3]. The success of SWL depends on the type of the lithotriptor used, the size of the stone and the location of the stone [4]. Although new SWL devices have many new features, none of them could catch up with the success rate of the first generation HM3 (Dornier, MedTech, Germany), which is about 77–99%, in the total excretion of stone [5, 6]. Therefore, many efforts have been spent to increase the success rates. During the last few years, a number of studies concluded that alpha blockers, which are used for the treatment of BPH, could also be used for the treatment of ureteral stones [7], facilitating the stone passage [8–10]. However, the outcome of alpha blockers treatment for upper ureteral stones has not been studied. To elucidate this issue, a multicenter, randomized prospective study was designed.

Materials and methods

Patients with renal colic, who were admitted to the emergency departments or Urology clinics between April 2009 and October 2010 and whose kidney–ureter–bladder (KUB) graphs revealed upper ureteral stones were enrolled. To achieve a problem-free SWL procedure, radio-opaque ureteral stones were chosen. All patients were evaluated based on a detailed history, physical examination, urinary analysis and, if necessary, the laboratory findings, which included urinary culture, serum level of urea, creatinine levels and whole blood counts. Patients were evaluated with ultrasonography once, and because SWL was performed in the early period, this information was sufficient for the treatment decision. The purpose of initial ultrasonographic examination was to determine the degree of hydronephrosis. Exclusion criteria were abnormal renal anatomy and function, the use of medications that may lead to stone formation, pregnancy or suspicion of pregnancy, distal obstruction, history of previous urinary stone surgery, hydronephrosis higher than grade 1, presence of coagulopathy, active urinary system infection, history of hypersensitivity for doxazosin, serum creatinine level >2 mg/dl, existence of more than one ureteral stone, hypotension and pain that could not be controlled with an analgesic.

Each patient was informed about the study and a signed consent was obtained.

Four urology departments from three hospitals on the Anatolian side of Istanbul participated in the study. Patients were randomized into two groups according to a computer-based randomization schedule. The first group underwent SWL within the first 24 h after the diagnosis, and the second group received alpha blocker treatment initially (doxazosin controlled-release tablet 4 mg, once a day) and then underwent SWL within 24 h. Both groups were treated on with the same SWL device (Siemens Lithoscope^{TM}, Germany). All patients were prescribed oral diclofenac sodium on demand. The treatment with alpha blocker was continued until the patients are stone free or for maximum of 14 days. All patients were advised a fluid intake that would provide urine output of at least 2 l daily and to observe their urine for stone passage by filtering it.

If, during the follow-up, an effect on stone was not observed, or there was a fever above 38.5°C, pain uncontrolled with an analgesic, a continuous increase in serum creatinine level or a stone which did not pass within 2 weeks after being fragmented, additional procedures, such as emergent ureteroscopy, were performed. If, during the follow-up visit after the first session, the stone was not influenced or the stone was fragmented into pieces equal to or larger than 6 mm, a second session of SWL was performed 3 days after the first procedure. A standard SWL treatment of 3,000 shocks/session was planned in each patient. However, the stone was observed to have completely fragmented during the procedure in some patients, and the SWL treatment was terminated earlier. The procedure was performed at a frequency of 90 shocks per minute, by gradually increasing the speed to reach the half of the maximum energy during the first 500 shocks, using electromagnetic energy-sourced SWL devices (Siemens Lithoscope^{TM}, Germany).

The patients were evaluated on days 1, 3, 5, 7, 10 and 14 post procedure, and their stone status was checked using KUB radiography. A stone-free status was considered as a total absence of opacity on the KUB graphy. The most senior urologist in the institution checked the stone status, and he was blinded to the patient.

The age and gender of all patients, radiologically determined longest diameters of stone, number of pain episodes and the need for parenteral analgesics during these episodes were recorded. During this period, pain scores were evaluated using visual analog scale (VAS). For the patients, the number of re-admission to the hospital due to pain, stone-free rates, time to stone clearance and additional procedures required during the therapy were recorded. Patients' blood pressures were measured before treatment and each visit after treatment.

As SWL parameters, number of sessions administered, number of shock waves, total amount of energy administered per session and complications which developed after SWL were recorded.

Statistical analysis

Patients were compared as groups of two for categorical data using χ^2 test and quantitative data were compared using Mann–Whitney U test. Significance level was considered as $p < 0.05$. Power analysis was done, using confidence interval (alpha error level) of 5 and 80% statistical power (1-beta error level), 32 patients were sufficient for each group.

Results

Initially, a total of 90 patients were planned to be enrolled to the study, but eventually 79 patients completed the study. Although the first group was consisted of 33 males and 11 females, the second group was consisted of 25 males and 10 females. Although the number of patients was not equal between the groups, intent-to-treat analysis was performed and the groups were considered as equal.

It was observed that the stone was totally removed in 35 of 44 patients (79.5%), who did not receive alpha blocker and in 33 of 35 patients (94.3%), who received alpha blocker. Nine of 44 patients who did not receive alpha blocker (20.4%) and 2 of 35 patients (5.7%) who received alpha blocker) underwent URS as an additional procedure.

Data regarding the age, stone diameter, VAS score, number of hospital admissions due to pain, time to stone passage and SWL parameters are given in Table 1. Two groups were similar in terms of these parameters, except for age.

At the end of the procedure, the groups were different for the rate of Steinstrasse formation, the need for additional procedure and being stone free ($p < 0.001$). Analgesic needs of the groups were similar. Data are given in Table 2.

None of the patients, who were initially labeled as "stone free" subsequently passed more fragments later on. All the stones were radiopaque, therefore, KUB was sufficient for the decision of stone free, computed tomography or intravenous urography was not utilized. Stone analysis confirmed that all of the stones in study population was radio-opaque calcium oxalate stones.

Mean pre- and post-treatment systolic blood pressure was 113.97 ± 6.52 and 113.18 ± 6.65 mmHg in group 1, while 110.28 ± 5.28 and 109.14 ± 4.61 mmHg in group 2. Mean pre- and post-treatment diastolic blood pressure was 67.84 ± 5.43 and 67.16 ± 4.50 mmHg in group 1, while 66.57 ± 4.67 and 65.00 ± 4.20 mmHg in group 2, respectively. Blood pressure changes were not clinically and statistically significant in both groups ($p > 0.05$).

Discussion

Urinary calculus disease is still a serious health problem worldwide. Ureteral stones account for 20% of all urinary tract calculi. Stone diameter is considered an important criterion for spontaneous stone passage. Although the ureteral stone with a diameter <4 mm may spontaneously pass, the likelihood for passage of ureteral stone with a diameter >6 mm is <5% [11, 12].

Today, SWL is one of the first-line therapy modalities used for the treatment of ureteral stones, but the rates of recurrent therapy and adjuvant interventions are high. The excretion of stone fragments formed after SWL depends on many parameters, such as the diameters of the fragments, narrow sites of the ureter, ureteral peristalsis, hydrostatic pressure proximal to the stone, edema due to the stone, presence of urinary tract infection and the muscular spasm where the stone was impacted [13, 14]. The two most important factors that facilitate the spontaneous stone

Table 1 Comparison of the groups for numerical data

	Group 1[a]	Group 2[b]	p[c]
Age	30.95 ± 9.68	38.35 ± 11.41	**0.003**
Stone diameter (mm)	8.30 ± 2.51	9.06 ± 1.45	0.086
VAS	6.59 ± 1.58	6.89 ± 1.02	0.323
Number of admission	0.52 ± 0.62	0.51 ± 0.70	0.796
Time to stone passage (day)	3.61 ± 2.70	4.14 ± 1.78	0.322
Number of SWL sessions	1.23 ± 0.47	1.26 ± 0.98	0.284
Number of shocks	2,403.41 ± 797.84	2,501.12 ± 831.40	0.212
Energy (J)	76.61 ± 11.79	79.66 ± 9.29	0.093
n	44	35	

[a] SWL group

[b] SWL + doxazosin group

[c] Using Mann–Whitney U test

Table 2 Comparison of the groups for categorical data

	Group 1[a]	Group 2[b]	p[c]
Need for analgesics (yes/no)	30/14	29/6	0.431
Outcome (stone free/failure)	35/9	33/2	**<0.001**
Need for additional procedure (no/URS)	35/9	33/2	**<0.001**
Steinstrasse (no/yes)	37/7	35/0	**<0.001**
n	44	35	

[a] SWL group

[b] SWL + doxazosin group

[c] Using χ^2 test

passage are hydrostatic pressure proximal to the stone and the caliber of the ureter at stone location [15]. This knowledge was shown with the rabbits by Sivula and Lehtonen, but not confirmed with human studies [16]. Edema, urinary tract infection, spasm and ureteral peristalsis are the factors that may be influenced by medical therapy [11]. Medical therapy interfering with these factors may facilitate stone passage.

The effects of sympathetic nervous system on the ureteral function have been proven with the demonstration of adrenergic receptors in the ureter [17]. In ureteral smooth muscle, alpha adrenergic receptor concentrations are higher than other adrenergic receptors [18]. Alpha adrenergic receptor stimulation leads to the contraction of smooth muscles in the area in which they are localized [19]. Therefore, alpha adrenergic stimuli also decrease the passage of urine through the ureter. However, alpha adrenergic antagonists may decrease the frequency of ureteral peristalsis, which, in turn, increases the urine passage through the ureter, increasing the proximal hydrostatic pressure [20]. This is why the alpha adrenergic antagonists are recommended to facilitate the passage of lower ureteral stones [2–11, 21]. It was reported that the addition of tamsulosin to SWL therapy increased stone-free rate from 46.2 to 74.5% [22]. The greater the diameter of the calculus, the more marked the contribution of the alpha blocker to stone-free ratio gets. In the same study, it was also reported that alpha blocker shortened the time to calculus clearance. Based on the results obtained from this study, alpha blocker significantly decreases the time to stone clearance and the number of ureteral colic episodes occurring after SWL [22]. In our study, we found that doxazosin had no significant effect on the time to stone clearance or on the number of hospital admissions due to colicky pain. This might be because the density of alpha adrenergic receptors in upper ureter is lower than that in distal ureter [23].

Liatsikos et al. [24] investigated the correlation between the rate of spontaneous stone passage and the diameter and the location of the stone, and found a linear correlation between the diameter of stone and spontaneous stone passage. It was reported that the excretion rates of the stones located in middle and lower parts of the ureter were higher regardless of the diameter of the stone [25]. In a randomized, placebo controlled and double-blind study conducted by Hermann et al. it was reported that, with the stones $\leq$7 mm, the excretion rates were not influenced by the use of tamsulosin [26]. Because the mean stone diameter of our patients was above this value, we thought that the spontaneous passage of the stones would be difficult and we expected the subjects to benefit from the treatment with doxazosin. However, in our study, the treatment with doxazosin did not shorten the time to stone clearance. This might be because the diameters of the stones in the doxazosin group were greater, although this difference was statistically insignificant. In a meta-analysis evaluating the effect of alpha blockers on stone clearance after SWL, it was reported that tamsulosin was successful and shortened the time to stone excretion [27]. In the study performed by Kobayashi et al. in which the majority of the cases were upper ureteral calculi, no correlation was detected between the diameter of the stone and the time to stone clearance [28]. This suggests that the evidence showing a correlation between the rate of stone clearance after SWL and the diameter of the stone was not convincing and that larger studies are warranted. In our study, we found that doxazosin had no significant effect on the time to stone clearance. In the same meta analysis, it was concluded that the use of an alpha blocker provided lower pain scores and that the need for analgesics was less. In addition, it was suggested that alpha blockers had a protective role against secondary interventions for the stone and associated complications. In another study performed with doxazosin, it was reported that doxazosin increased the pain tolerance and decreased the frequency of colic episodes [29]. In our study, despite a numerically lower need for analgesics in the group that received alpha blockers, no statistically significant difference was found between the groups. However, less need for URS in the group that received doxazosin is consistent with the results obtained from aforementioned studies. The number of patients requiring additional treatment procedures was smaller in alpha blocker group. This suggests that stones must be fragmented into smaller pieces in alpha blocker group, but no such measurement was performed in this study. Further studies may be useful to focus on this issue.

There are few studies that evaluate the efficacy of doxazosin in the treatment of ureteral stones. Most of them evaluated the efficacy of doxazosin on lower ureteral stones [30–34]. Seitz et al. [35] found five studies that were comparing doxazosin with a control group and they suggested that doxazosin was useful for stone clearance. In two studies, in which the use of doxazosin after SWL was evaluated and compared with placebo, the efficacy of alpha blockers was noted [32, 36]. In our study, we demonstrated that doxazosin had a positive effect only on stone-free rate and Steinstrasse. This might be the due to the fact that our subjects had upper ureteral stones.

None of our study participants reported any adverse effect related to short term use of alpha blockers. Doxazosin controlled release form was used in this study. Therefore, the antihypertensive effect of this drug is minimal in normotensive individuals as shown in previous studies [37, 38]. All adverse events whether voluntarily reported by the subjects or observed by the investigator were recorded at each study visit. In our study, no patients

underwent hypotensive effect requiring termination of treatment.

Regarding age distribution, group 2 was older than group 1. The emergence of the gap between two groups completely resulted from randomization. However, the age difference between the two groups (30 and 38) was not different enough to change the results of this treatment. Because both groups consisted of young adult patients without hypertension.

The most important limitation of our study is the fact that small number of patients and the absence of a placebo control group may be other limiting factors of our study. No comments on the impact of the stone composition on disintegration could be made since stone fragments for every patient were analyzed and all was same content: calcium oxalate. Although there is an age difference between the groups, both groups included young adults, and an 8-year discrepancy between the mean age values should not cause any potential bias that could affect data analysis.

Conclusion

In our study, the addition of doxazosin to SWL in the treatment of upper ureteral stones did not decrease the time to stone clearance. Furthermore, it did not affect the hospital admissions due to colicky pain and analgesic use. Interestingly, in the group that received doxazosin, no Steinstrasse was observed and the need for additional procedures was less. More studies including larger number of patients and studying different alpha blockers are needed.

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