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ORIGINAL PAPER

Role of combined use of potassium citrate and tamsulosin in the management of uric acid distal ureteral calculi

Osama El-Gamal · Mohamed El-Bendary · Maged Ragab · Mohamed Rasheed

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Abstract In this article, we investigated the effect of the combined use of tamsulosin and potassium citrate (Uralyt-U®) for the treatment of uric acid stones in the distal ureter. The study was designed as a prospective, double blind randomized controlled trial. A total of 191 adult patients with radiolucent distal ureteral calculi were recruited. We included patients with solitary stones ≥5 mm with mild or moderate hydronephrosis and a normal contralateral tract. The patients were randomized into four equal groups (the placebo, tamsulosin, Uralyt-U®, and the combined treatment groups). The patients were treated for a maximum duration of 4 weeks or until stone expulsion. The stone size in all groups ranged from 5 to 11 mm (7.69 ± 1.7 mm). The total expulsion rate of the stones was significantly lower in the control group (26.1%) compared with that of any of the other three groups (68.8, 58.7, and 84.8% respectively) ($P < 0.05$). Meanwhile, the difference between the Uralyt-U® group and the combined treatment group was also statistically significant ($P < 0.05$). When we studied the patients with stones >8 mm as a separate subgroup to find the effect of the used drugs on the relatively large stones, we detected that the expulsion rate of these stones was significantly higher in the patients who received the combined treatment in comparison with any of the other three groups ($P < 0.05$). In conclusion, the use of urinary alkalization with tamsulosin can increase the frequency of spontaneous passage of distal ureteral uric acid stones especially those of 8–11 mm.

Keywords Ureter · Calculi · Uric acid · Tamsulosin

O. El-Gamal · M. El-Bendary (✉) · M. Ragab · M. Rasheed
Department of Urology, Tanta University,
El-Bahr St., Tanta, Egypt
e-mail: Mbendary@hotmail.com

Introduction

The management of distal ureteral calculi represents every day practice of all urologists worldwide. The stone size is an important parameter for the decision making in these cases. Stones less than 5 mm have a very high probability (71–98%) for spontaneous passage. Therefore, conservative therapy is recommended if the symptoms are controlled [1, 2]. Patients with larger stones (5–10 mm) have a lower rate for spontaneous expulsion (25–53%) [3]. However, the use of alpha blockers or calcium channel blockers has been found to augment the passage of these calculi [4–9]. On the other hand, the minimally invasive therapies as extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (URS) have been widely introduced for management of the distal ureteral calculi. However, despite the recent advances in these techniques, they are not risk free and are quite expensive [10–12]. Therefore, they should be reserved for cases with failed or those unsuitable for the medical therapy. Lastly, the uric acid stones comprise a significant proportion of urinary stones and have an additional advantage in the medical therapy that they are amenable to chemolysis by alkalization of the patient's urine [13]. The current study was performed to evaluate the results of the combined use of tamsulosin and potassium citrate for the treatment of uric acid distal ureteral calculi.

Patients and methods

This study was carried out in Tanta University Hospital during the period from October 2006 to October 2010. After approval of the local ethical committee, we recruited adult patients with radiolucent distal third ureteral stones and an informed consent was obtained from each one. All

patients had complete history taking, physical examination, complete urine analysis, urinary pH in 24-h urine, serum creatinine, serum uric acid, plain X-ray of the urinary tract (KUB), abdomino-pelvic ultrasonography (U/S), and non-contrast spiral computed tomography (CT). We included only patients with solitary stones ≥5 mm with Hounsfield units between 200 and 350. The stone size was determined as the largest diameter in the CT study. In addition, a normal contralateral tract was also a prerequisite to enroll the patient in this project. The exclusion criteria of this study involved patients with severe hydronephrosis (the degree of hydronephrosis was based on the radiological finding in the U/S and CT studies that were carried out by an expert radiologist), previous ipsilateral ureteral surgery, pregnancy and cases on calcium channel blockers, corticosteroids, or other alpha blockers.

Treatment modalities

In this study, we used tamsulosin in a dose of 0.4 mg in the morning after breakfast. Urinary alkalization was achieved via the sodium–potassium-hydrogen citrate (Uralyt-U® from Cid – Madaus, Germany). This therapy was given daily in three divided doses to get a urinary pH between 6.2 and 6.8. The first dose involved one measure-spoonful (this equals to 2.5 g: each 1 g contains 4.4 mEq of potassium citrate) in the morning. This was repeated in the midday and two measure-spoonfuls were given in the evening. The last dose was modified according to the pH test of the patient's urine that was done by the patient himself.

Study groups

Patients were prospectively randomized through a computer generated randomization process into four equal groups. The first one was the placebo control group, the second received tamsulosin only, the third was given Uralyt-U® only, and the fourth had both the drugs. The investigators and the patients were blinded to the treatment given, until the end of the study. This was achieved via preparing a placebo powder to be similar to the Uralyt-U® and placebo capsules to be like the tamsulosin capsules. Thereafter, we prepared small boxes that contained the active drug or its matching placebo from each of the two studied drugs. Therefore, the contents of these boxes were one of the following: two active drugs, two placebos or only one active drug, and one placebo. The boxes were prepared by other personnel and the investigators received the boxes without any identification of their contents to give them to the enrolled patients. Meanwhile, the test of the urine pH that was done by the patient himself did not give the patient any indication about the composition of the powder because even with the use of the citrate powder the patient might need two measure-spoonfuls at night.

All patients were advised to increase fluid intake to more than 2 l per day and to receive intramuscular injection of 75 mg of diclofenac sodium to relieve the pain episodes. The patients were allowed to get the IM dose in any nearby hospital or General Practitioner (GP) clinic. In addition, the patients with hyperuricemia (uric acid >7.2 mg/dl in males and >6.2 mg/dl in females) were given a daily dose of 300 mg allopurinol (in the period in which they were enrolled) and were instructed to consume a low purine diet (decrease red meat, fish, and poultry). The treatment in all groups was continued for a maximum of 4 weeks or until expulsion of the stone. All patients were instructed to filter their urine to avoid missing the passed stones and to contact us if they have frequent pains or a febrile episode.

Follow up

After 2 weeks

At this visit, all the patients were evaluated by complete history taking, physical examination, complete urine analysis, serum creatinine, and abdomino-pelvic U/S. The U/S was replaced by a non-enhanced spiral CT if the patient claimed stone passage during his history taking. This CT was done to confirm that the patient is stone free, and if this was the case, he reached the end point of the study and was considered as a successful case. On the other hand, the patients who developed severe hydronephrosis or febrile urinary tract infection or had frequent attacks of renal colic that enforced them to seek surgical treatment were considered as failed cases. These failed cases received appropriate treatment and were scheduled for URS. Lastly, the rest of patients were allowed to continue their treatment as described before.

After 4 weeks

The eligible patients for this follow up were evaluated in the same way as the previous visit but the non-enhanced spiral CT was done for all of them. If this study showed the presence of the previously treated stone, the patient was reported as a failed case and vice versa. Lastly, all of the stones that passed spontaneously or extracted by the URS were subjected to chemical analysis.

Statistical analysis

The data were collected and analyzed by the Student's *t* test, ANOVA test, or Pearson chi-square test as appropriate with $P < 0.05$ considered statistically significant. All

Table 1 Demographic data of all groups

	Group I ($n = 46$)	Group II ($n = 48$)	Group III ($n = 46$)	Group IV ($n = 46$)	Significance (P value)
Age (years)					0.26
Mean ± SD	36.2 ± 6	35.3 ± 5.7	36.5 ± 6.5	37.8 ± 6.6	ANOVA test
Sex (M/F)	34/12	32/16	30/16	28/18	0.61
					Chi-square test
Urinary pH					0.66
Mean ± SD	5.55 ± 0.22	5.52 ± 0.19	5.53 ± 0.22	5.57 ± 0.15	ANOVA test
Hyperuricemia					0.66
No (%)	10 (21.7%)	8 (16.7%)	12 (26.1%)	8 (17.4%)	Chi-square test
Stone size (mm)					0.89
Mean ± SD	7.7 ± 1.63	7.9 ± 1.93	7.8 ± 1.63	7.7 ± 1.65	ANOVA test

these tests were done by the computer software SPSS 10.0 for Windows® (Chicago, Illinois).

Results

The total number of patients eligible to our inclusion criteria was 276 cases and 191 of them gave consent to participate in this study. These patients were randomized in the four groups: 48 in the first group, 49 in the second one, and 47 in each of the other two groups. However, 5 cases were lost to follow up (2 in the control group and one in each of the other three groups) and, therefore, they were excluded from our statistical analysis. The four groups were comparable regarding the age, sex, urinary pH, the mean stone size, and the percentage of patients with hyperuricemia (Table 1). The stone size of all patients ranged from 5 to 11 mm with a mean of 7.69 ± 1.7 mm. Tamsulosin was well tolerated by the patients with no significant side effects. On the other hand, the bad taste of Uralyt-U® was the main complaint in most of the patients who used it but all of them were able to continue it to the end of the study.

The analgesic needs (over the total of time the patient was enrolled) in the four groups are shown in Table 2 and our statistical analysis revealed that the tamsulosin and the combined treatment groups had a significantly lower number of injections when compared with the other two groups. On the other hand, we have got 12 cases that had frequent attacks of renal colic (6, 2, and 4 cases in the first three groups, respectively) and these patients were scheduled for URS. There were also two patients who developed acute pyelonephritis (the first one was in the control group and the other was in the Uralyt-U® group) and they were treated with appropriate antibiotics, and then scheduled for URS. These 14 patients (12 with frequent attacks of renal colic and 2 with acute pyelonephritis) were considered as failed cases.

Table 2 Analgesic needs over the total of time the patient was enrolled

Groups	Analgesic needs (no. of injections) Mean ± SD	Significance (P value) t test
Group I	2.46 ± 1.6	I vs. II: 0.000
		I vs. III: 0.44
Group II	0.58 ± 0.87	I vs. IV: 0.000
Group III	2.2 ± 1.6	II vs. III: 0.000
Group IV	0.63 ± 0.85	II vs. IV: 0.79
		III vs. IV: 0.000

The collected data from all the patients after 4 weeks of follow up showed spontaneous stone passage in 111 patients in the four groups. The expulsion rate was 26.1% in the control group and the corresponding figures in the other groups were 68.9, 58.7, and 84.8%, respectively (Table 3). Some of these patients were able to collect the stones (76 patients in the four groups) and the others (35 patients) failed to do so but the CT study was completely free in all of them. The statistical analysis revealed that the expulsion rate in the first group was significantly lower than that of the other three groups ($P < 0.01$). Meanwhile, when we compared the tamsulosin group with the third and the fourth one we could not detect any significant difference between them. On the other hand, the difference between the Uralyt-U® group and the combined treatment group was statistically significant ($P = 0.01$) in favor of the latter one (Table 3).

In order to assess the effect of our medications on different stone sizes, we stratified the stones in all the patients according to their size and the 8 mm was found to be median size of these stones. When we studied stones ≤8 mm, we detected 24, 24, 26, and 20 cases in the four groups, respectively. The mean size of these stones was 6.4 ± 0.1 mm with no significant difference between the four groups ($P = 0.09$). The success

Table 3 Expulsion rate of stones in the four groups

	Group I	Group II	Group III	Group IV	Significance (P value) Chi-square test
All stones (5–11 mm)					
Successful/total	12/46 (26.1%)	33/48 (68.8%)	27/46 (58.7%)	39/46 (84.8%)	I vs. II: 0.000
					I vs. III: 0.003
					I vs. IV: 0.000
					II vs. III: 0.4
					II vs. IV: 0.09
					III vs. IV: 0.01
Stones of 5–8 mm					
Successful/total	10/24 (41.7%)	21/24 (87.5%)	20/26 (76.9%)	18/20 (90%)	I vs. II: 0.002
					I vs. III: 0.02
					I vs. IV: 0.001
					II vs. III: 0.5
					II vs. IV: 1
					III vs. IV: 0.4
Stones of 8.1–11 mm					
Successful/total	2/22 (9.1%)	12/24 (50%)	7/20 (35%)	21/26 (80.8%)	I vs. II: 0.004
					I vs. III: 0.06
					I vs. IV: 0.000
					II vs. III: 0.4
					II vs. IV: 0.04
					III vs. IV: 0.002

rate of spontaneous passage of these small stone was 41.7, 87.5, 76.9, and 90% in the four groups respectively. This rate was significantly lower in the control group compared with that of each of the other three groups ($P < 0.05$) but the difference between the three treated groups was statistically insignificant (Table 3).

On the other hand, the number of patients with stones >8 mm was 22, 24, 20, and 26 in the four groups, respectively. The mean size of these stones was 9.2 ± 0.9 mm (range 8.1–11 mm) with no significant difference between the four groups ($P = 0.07$). The expulsion rates of these stones were 9.1, 50, 35, and 80.8% in the four groups respectively. This rate was significantly lower in the control group compared with that of each of the second and the fourth groups ($P < 0.05$, 0.001, respectively) (Table 3). In addition, the expulsion rate in the combined treatment group was significantly higher than that of either of the tamsulosin or the Uralyt-U® groups ($P < 0.05$ and 0.01) (Table 3). Lastly, the chemical analysis of the passed and the extracted stones showed that all of them were uric acid stones.

Discussion

The management of distal ureteral calculi involves the watchful waiting, the use of alpha blockers and some minimally invasive technique, such as ESWL and URS. In this study, we have used tamsulosin as a selective alpha 1A–1D blocker to treat the ureteral stones because of its high efficacy and low side effects [14–17]. Because stones less than 5 mm have a very high chance of spontaneous passage without any adjuvant treatment [1, 2], we excluded them from this study. On the other hand, it has been shown before that, the best candidates for the medical expulsive therapy are those with stones less than 1 cm [16] but the most suitable size for the chemolytic therapy of the distal ureteral calculi is not determined yet. Therefore, we did not put an upper limit for the stone size in this project, provided that the patient was fulfilling the other selection criteria. Consequently, we have got some patients with relatively large stones and the mean stone size of our patients (7.69 ± 1.71 mm) was more than that of some similar studies. In studies by Porpiglia et al., Autorino et al., and De Sio et al. [18–20], the mean stone sizes were 5.4, 6.5, and 6.9 mm, respectively.

Since the radiolucent stones are not always uric acid stones, we have selected cases with Hounsfield units between 200 and 350 to be coinciding with that of the uric acid stones [21] and the recovered stones were subjected to chemical analysis to identify the exact composition of them. However, despite that the X-ray crystallography and the infrared spectroscopy are superior to the chemical

analysis of the stones we could not use them in this study because of their unavailability in our hospital.

In this study, we excluded cases who were receiving calcium channel blockers, other alpha blockers or corticosteroids because these drugs might have an additional effect on stone expulsion. On the other hand, patients with hyperuricemia received allopurinol to decrease urate excretion. Despite the bad taste of Uralyt-U®, no patient discontinued it and this can be attributed to the short period of its use. The follow up in this study was specified to be 4 weeks only because it has been shown before that the rate of complications may be increased to up to 20% when symptoms exceed 4 weeks in duration [1]. In this study, we were not able to study the time needed for the stone expulsion in the different groups because some of the stones were passed unnoticed or showed complete dissolution by the chemolytic therapy and some patients failed to filter their urine in all times.

The analgesic needs in patients who received the alpha blocker were significantly lower than those who did not use it. This observation is in agreement with that reported by the other authors who studied the efficacy of tamsulosin in treatment of radio-opaque distal ureteral calculi [20]. On the other hand, in our project we have not studied the relation between the analgesic needs and the stone size because the four groups were comparable regarding this variable and identification of this relationship was beyond the scope of this study. Meanwhile, because the non steroidal anti-inflammatory drugs (NSAID) might have some effects on stone passage rate due to their anti-inflammatory effects, it may be claimed that they can affect the results of the studied drugs. Therefore, we have to clarify that we did not use the NSAID on regular basis but just during the attacks of the renal colic, so it is unlikely to have a significant effect on stone expulsion.

In this study, the tamsulosin group was found to have a significantly higher success rate compared with the control group. This is in agreement with many of the previous studies that confirmed the efficacy of tamsulosin in treating the distal ureteral calculi as those performed by Autorino et al. and De Sio et al. [19, 20]. However, in the current trial, the rate of stone expulsion with tamsulosin (68.8%) was lower than that reported by other similar studies (86, 88, 90%) [18–20]. This can be attributed to the relatively larger size of the stones in our patients as shown before. Therefore, when we investigated the patients with stones $\leq$8 mm as a separate category, the success rate of tamsulosin reached 87.5% which is comparable with those of the other studies. On the other hand, the statistical analysis of cases with stones >8 mm showed that the results of the tamsulosin and the combined treatment groups were significantly better than that of the control group. In addition, the success rate in the combined treatment (80.8%) was significantly higher than that of the tamsulosin group (50%). This significant increase in the expulsion rate of these stones may be explained by the chemolytic effect of Uralyt-U® that resulted in decreasing the stone size.

The use of potassium citrate to dissolve the renal uric acid stones is proved to be safe and effective but it usually necessitates a prolonged therapy of 3 months or more [22–24]. There are also some studies that showed this beneficial effect for the ureteral uric acid stones [25, 26].

However the association of pain, hydronephrosis, or urinary infection with the ureteral stones has limited the prolonged use of the chemolytic therapy to treat these patients. Therefore, when double pig-tail stents were inserted in these cases, it was possible to use Uralyt-U® for relatively long periods [25]. In accordance, the patients with stones >8 mm in our project who received Uralyt-U® alone, showed a low success rate (20%) after the 4-week therapy that might reflect the need of more time to achieve complete chemolysis of these stones. On the other hand, the addition of tamsulosin to Uralyt-U® allowed these patients to pass the stones before their complete dissolution. Therefore, the success rate for patients with large stones in the combined treatment group was significantly better than that of each of the other three groups.

However, it has been suggested by the previous studies that the suitable pH to dissolve the uric acid stones is from 6.2 to 6.8. Therefore, we adjusted the dose of potassium citrate to get this pH level but it will be interesting to find in another study if a higher urinary pH will be more beneficial to dissolve the uric acid stones in the lower ureter. This assumption might be applicable because these patients usually require the urinary alkalization for only a short period of time and thus there will not be enough time for the drawbacks of the higher urinary pH to develop.

Finally, because the uric acid stones are not the most common type of the distal ureteral calculi, we had got a small number of patients in our groups and subgroups. Therefore, more studies with larger numbers of patients are recommended to confirm our results.

Conclusion

Urinary alkalization with potassium citrate can be used with tamsulosin for treatment of distal ureteral uric acid stones especially the relatively large ones (8–11 mm), but good follow up is mandatory.

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