

COMPARATIVE ASSESSMENT OF THE BENEFITS OF POTASSIUM AND MAGNESIUM TRIBASIC CITRATE *VERSUS* TAMSULOSIN IN NEPHROLITHIASIS PATIENTS

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Abstract

Nephrolithiasis is a major health issue. Present guidelines recommend conservative treatment for calculi less than 5 mm. Over the years, various therapeutic regimens to facilitate spontaneous passage of stones have been used without reaching a consensus in this respect. We aimed to compare the efficacy of potassium and magnesium tribasic citrate which has metaphylactic indications with that of a selective alpha-blocker as medical expulsion therapy. The preliminary results of this ongoing study showed that in patients with pelvic ureteric lithiasis, the alpha-blocker-based expulsion treatment was significantly more effective than that based on potassium and magnesium tribasic citrate. As for asymptomatic lumbar ureteric lithiasis below 7 mm in diameter, the alpha-blocker and potassium and magnesium tribasic citrate treatment showed similar results.

Rezumat

Nefrolitiază este o problemă majoră de sănătate. Ghidurile de practică recomandă tratamentul conservator pentru calculii ureterali mai mici de 5 mm. De-a lungul anilor, diferite regimuri terapeutice pentru tratamentul de expulzie au fost utilizate fără a se ajunge la un consens. În studiul de față am comparat eficiența citratului de magneziu și potasiu care are indicații metafylactice cu cea a unui alfablocant selectiv în tratamentul de expulzie. Rezultatele preliminare ale acestui studiu aflat încă în desfășurare arată că la pacienții cu litiază ureterală pelviană, tratamentul de expulzie cu alfablocante este semnificativ mai eficient decât cel bazat pe citrat de magneziu și potasiu. În ceea ce privește litiază ureterală lombară asimptomatică (calculi < 7 mm în diametru), alfablocantul și citratul de magneziu și potasiu au dovedit eficiență similară.

Keywords: alpha-blocker, potassium and magnesium citrate, urolithiasis, expulsion therapy

Introduction

Nephrolithiasis is a major health problem, with statistics estimating an incidence varying between 5 - 15% of the world's population, and a recurrence rate higher than 50%, the males being more frequently affected than women [1, 2].

Nowadays, a significant proportion of cases is represented by the presence of calculi with “borderline” dimensions (4 - 7 mm), a situation that gives rise to discussions on the choice, as primary treatment option, between medical expulsion therapy (MET) and modern endourological treatment like shock wave lithotripsy (SWL) or retrograde ureteroscopy (URS) [3]. The guidelines recommend conservative treatment for calculus less than 5 mm. Coll *et al.* demonstrated that patients with calculi of up to 5 mm have

spontaneous passage chances of about 75% regardless of stone location [4]. Segura *et al.* noticed that the chances of passing for a stone less than 5 mm located in the distal ureter range from 71 to 98%, while for those of 5 - 10 mm with the same location the chances are between 25 - 53% [5]. On the other hand, the small size of the calculus is not a guarantee for its spontaneous passage. Approximately 5% of patients with the stone diameter of 2 mm require endourological interventions, while for those with a stone greater than 4 mm the percentage may reach 50% [6]. However, in clinical practice, several factors such as the time needed to eliminate the calculus, the urinary tract infections, the recurrence of pain or the impact of obstruction on kidney function cannot be predicted [7]. Furthermore, these aspects are even more increased in patients with previous renal

impairment undergoing or not dialysis to whom the adequate treatment management, including the follow-up, still represents a matter of debate [8, 9]. For patients with ureteral stones that are expected to pass spontaneously, the Guideline of European Association of Urology states that non-steroidal anti-inflammatory drugs (NSAIDs) tablets or suppositories may help to reduce inflammation and risk of recurrent pain [9, 10]. Over the years, various therapeutic regimens for the treatment of expulsion have been used without reaching a consensus in this respect [4].

That is why we aimed to compare the efficacy of the new drugs with metaphylactic indications that contain a substantial amount of citrate along with other known crystallization inhibitors (pyridoxine, magnesium) with the selective alpha-blocker medication (tamsulosin) used in medical expulsion therapy for several years, in order to find out if we can improve the spontaneous elimination rate of ureteral calculi with diameters below 7 mm.

Materials and Methods

Study design

We have enrolled 168 patients with unilateral lumbar and pelvic lithiasis less than 7 mm in diameter diagnosed in the Department of Urology at "Parhon" Hospital, Iași, Romania, between September 2016 and December 2017. The study was conducted after the approval of the local ethics committee and the patients have signed informed written consents. We monitored and evaluated patients within three months after enrolling each in one of three randomized groups: group A - tamsulosin, group B - combination of potassium-magnesium citrate and pyridoxine (KMg citrate - B6) and group C - placebo (diuretic tea).

We have included patients over 18 years of age diagnosed by imaging tests, with a lumbar or pelvic ureter stone having the largest diameter < 7 mm. The stone size was calculated on the first KUB (Kidney, Ureter and Bladder X-ray) or CT (Computerized Tomography). In all patients, the ureteral calculi were either newly diagnosed or had migrated to the ureter after extracorporeal shock wave lithotripsy (ESWL), ureteroscopy or PCNL (percutaneous nephrolithotomy). Depending on the location of ureteral stones, patients were divided, from the beginning, in two large cohorts: those having lumbar ureteral

calculi (LUC patients) and those with pelvic ureteral calculi (PUC patients), respectively. Depending of the size of stones, patients were also classified as having calculi between 3 - 4 mm ("x" group) or between 5 - 7 mm ("y" group). In both cohorts (LUC and PUC), patients were randomly assigned to one of three groups: group A (tamsulosin, 0.4 mg, once daily, for up to 3 months), group B (a fixed combination of potassium citrate 25 mEq + magnesium citrate 5 mEq + pyridoxine 25 mg, noted as KMg citrate - B6, 1 sachet, twice daily, dissolved in 500 mL of water/tea for up to 3 months) and group C, the control group, which received the recommendation of drinking diuretic teas, minimum 2 liters *per day*, up to a maximum of 3 months.

Patients with fever, urinary tract infection, high-grade hydronephrosis, hypotension, acute or chronic renal failure, urinary congenital anomalies, single kidney, multiple or bilateral ureteral stones, history of open surgery or endoscopic procedures in the urinary tract, diabetes, peptic ulcer, concomitant treatment with α - or β - blockers, calcium antagonists, steroid, nitrates, and also pregnant or lactating women were excluded. In addition, patients requiring immediate stone removal were not included in the study. At enrolment, each patient received a file of liquid-intake and dietary instructions, according to their situation; they were also warned to come to the hospital in case of pain or fever.

Statistical analysis

The statistical analysis was performed using the ANOVA and Chi-square tests. A p value of < 0.05 was considered statistically significant. The SPSS.16 software was used.

Results and Discussion

From a total of 168 patients initially enrolled in the study, only 141 cases were able to complete the research: 67 patients with LUC, and 74 patients with PUC. In the LUC cohort, 24 patients were randomly assigned to group A, 22 patients to group B, and 21 patients to group C. From the PUC cohort, 24 patients were enrolled in group A, 27 patients in group B and 23 patients in group C. The distribution of the patients depending the stone size and location is presented in Table I.

Table I

Distribution of patients who completed the study, depending on treatment type and stone size and location

Location	Tamsulosin	KMg citrate - B6	Tea
LUC	24 (x = 14, y = 10)	22 (x = 12, y = 10)	21 (x = 12, y = 9)
PUC	24 (x = 12, y = 12)	27 (x = 15, y = 12)	23 (x = 13, y = 10)
Total	48	49	44

LUC = lumbar ureteral calculi, PUC = pelvic ureteral calculi

As previously noted, during the study 27 patients (10 in group A, 9 in group B and 8 in group C) were

excluded. We lost contact with 7 of the patients; in 20 cases the drop out was determined by recurrent pain

or pyelonephritis which emerged endourological interventions (Table II).

From the total of 141 patients, 71 were male and 70 women; the age varied between 19 - 78 years, with a

mean of 45.67 years. Patients' outcome in groups A, B and C was registered as favourable: "stone-free" or unfavourable: "unpassed stone" (Table III).

Table II

Distribution of patients excluded from the study according to treatment type, stone size and location, and reason for exclusion

Stone location	Tamsulosin	KMg citrate - B6	Tea	The reason for exclusion
PUC	1 (y)	3 (y)	6 (2x + 4y)	URS - 2 SWL - 4 JJ stent insertion - 4
LUC	4 (1x + 3y)	2 (y)	4 (1x + 3y)	URS - 5 SWL - 2 JJ stent insertion - 3

URS = ureteroscopy; SWL= shockwave lithotripsy; JJ stent insertion = double "J" ureteral stent insertion, LUC = lumbar ureteral calculi, PUC = pelvic ureteral calculi

Table III

Patients' outcomes by groups

	Group A		Group B		Group C	
	Tamsulosin stone-free	Tamsulosin unpassed stone	KMg citrate - B6 stone-free	KMg citrate - B6 unpassed stone	Tea stone-free	Tea unpassed stone
PUC	16 (66.66%)	8 (33.34%)	21 (77.77%)	6 (22.23%)	4 (17.39%)	19 (82.61%)
LUC	11 (45.83%)	13 (54.17%)	9 (40.90%)	13 (59.10%)	6 (28.57%)	15 (71.43%)
Mean age (years)	45.2	44.57	46.26	44.15	47.42	51.44
Mean initial serum creatinine (mg/dL)	0.86	0.97	0.94	0.87	0.81	0.70
Mean final serum creatinine (mg/dL)	0.84	0.82	0.84	0.83	0.75	0.77
Mean initial urinary density	1017.77	1018.57	1019	1021.66	1018.43	1017.14
Mean final urinary density	1017.85	1017.5	1015.45	1015	1017.75	1017
Mean initial urinary pH	6.33	6.21	5.55	5.61	5.5	6.03
Mean final urinary pH	6.14	5.57	7.05	6.53	5.69	6.28
Hypertension	6	4	1	4	4	5
Diabetes	1	4	7	1	6	8
Dyslipidemia	6	7	6	6	2	4
Mean stone size (mm)	5.3	5.71	4.89	5.61	4.88	5.72

LUC = lumbar ureteral calculi, PUC = pelvic ureteral calculi

In the group with LUC, there were no significant differences regarding the outcome between tamsulosin and KMg citrate - B6 ($p = 0.73$), tamsulosin *versus* tea ($p = 0.23$) or KMg citrate - B6 *versus* tea ($p = 0.39$) (Table III). In the case of patients with PUC, the results at 90 days were different, as follows: there was a significantly higher passing rate in patients who received KMg citrate - B6 compared to the tea group ($p = 0.000021$) or tamsulosin compared to the tea group ($p = 0.000637$), but no significant differences

were found for stone passing rate in KMg citrate - B6 treated patients when compared with those treated with tamsulosin ($p = 0.37$) (Table III).

We noticed that patients treated with tamsulosin or KMg citrate - B6 who became stone-free after the 3 months of the study had initially smaller stones than those who did not eliminate the calculi (Table IV). Nevertheless, the difference was not significant (tamsulosin free *versus* unpassed: $p = 0.14$; KMg citrate - B6 free *versus* unpassed: $p = 0.06$).

Table IV

Distribution of stone-free patients by stone size

Location	Stone size	Tamsulosin	KMg citrate - B6	Tea
LUC	x	7	6	3
	y	4	3	3
PUC	x	10	15	3
	y	6	6	3

LUC = lumbar ureteral calculi, PUC = pelvic ureteral calculi

Final urinary pH was significantly influenced by the treatment with KMg citrate - B6 (5.57 *versus* 6.84; $p = 0.00001$) and herbal tea (5.76 *versus* 6; $p = 0.045$), but not by tamsulosin treatment (6.28 *versus* 5.85; $p = 0.161$).

The urinary density was not influenced by tamsulosin treatment (1018.12 *versus* 1017.27; $p = 0.359$). Although tea consumption involved an increased fluid intake and the mean final urine density was lower than the initial value (1018.15 *versus* 1017.74), the difference was not of statistic importance ($p = 0.392$). Only the treatment with KMg citrate - B6 resulted in a significant decrease in urinary density (1020.71 *versus* 1015.22; $p = 0.000014$) (Table III).

There were no significant differences between groups regarding the incidence of hypertension ($p = 0.33$) or dyslipidaemia ($p = 0.79$), but the incidence of diabetes was significantly different between groups ($p = 0.037$, $\chi^2 = 6.5577$) (Table III).

In the group with PUC, we found no statistically significant difference of gender between patients stone-free and those with unpassed stone ($p > 0.05$). In the group with LUC, there was no significant difference of gender between tamsulosin group and the tea group ($p = 0.47$, and $p = 0.77$, respectively), but in the KMg citrate - B6 treated patients we noticed a significantly higher elimination rate for males ($p = 0.035391$, $\chi^2 = 4.4262$) (Table V).

Table V

Distribution of gender in the studied groups

		Group A		Group B		Group C	
		Tamsulosin stone-free	Tamsulosin unpassed stone	KMg citrate - B6 stone-free	KMg citrate - B6 unpassed stone	Tea stone-free	Tea unpassed stone
PUC	Women	4	4	12	2	1	8
	Men	12	4	9	4	3	11
LUC	Women	8	11	2	10	2	6
	Men	3	2	6	4	4	9

LUC = lumbar ureteral calculi, PUC = pelvic ureteral calculi

Urinary stone disease is one of the most common reasons for visiting the urologists. Although in humans, the mechanism of ureteral stone passage is not fully understood, two of the most important predictors of stone passage are the stone size and the location. After a long period, in which the expulsion treatment offered a wide range of rather empirical alternatives, from olive oil to antispasmodics or from various diuretic teas to terpene combinations, the last 20 years have brought to the forefront debates about treating MET with alpha-blockers.

The rationale for using alpha-blockers for MET is that alpha adrenergic receptors are present in high density within the distal ureter. There are three types of receptors in the distal ureter: $\alpha 1A$, $\alpha 1B$, and $\alpha 1D$. The receptor with the highest density is $\alpha 1D$ and therefore it is not surprising that specific antagonists of this receptor have been developed. Alpha-blockers are used for MET because they tend to decrease intra-ureteral pressure and increase fluid passage which might facilitate stone passage. Although tamsulosin has been the most studied alpha-blocker in MET, according to Yilmaz *et al.*, tamsulosin, terazosin, and doxazosin were equally effective in distal stone expulsion in comparison to the control group [6]. Georgescu *et al.* compared the efficacy of tamsulosin *versus* silodosin in 150 patients with unilateral, non-impacted, uncomplicated ureteral stones under 1 cm and showed that the use of tamsulosin and silodosin proved to be safe and effective, as demonstrated by the increased stone expulsion rate, decreased expulsion time, reduced pain attacks and side effects. The efficacy of both drugs seems to be similar [11]. In a

meta-analysis published by Campschroer *et al.*, which included thirty-two studies (5864 participants), the stone-free rates were significantly higher in the alpha-blocker group when compared to standard therapy. More than that, the use of alpha-blockers reduced the number of pain episodes, the need for analgesic medication and hospitalization [12].

In our study, after 90 days of treatment, 56.25% of patients who received tamsulosin (group A) and 61.22% from those who received KMg citrate - B6 (group B) were stone-free, while in the control group (group C) we had only 22.72% elimination of calculi.

We had a lower percentage of stone-free patients in the alpha-blocker group, for the same size of stones when compared with the results reported by Yilmaz *et al.* (79.31% after one month) or Ye *et al.* (86%) [6, 13]. On the other hand, the percentage of stone-free patients in our control group was significantly lower than that of Ye *et al.* (79%). Although Ye *et al.* reported that tamsulosin-treated patients required lower use of analgesics compared with placebo and significantly relieved renal colic, in our study there was no significant difference between groups regarding the failure of therapy and exclusion from the study [13]. In a more recent meta-analysis conducted by Amer *et al.*, studies performed from 1990 to 2016 showed small overall benefit for α -blockers as MET for ureteric stones, and no benefit with calcium channel blockers. Paradoxically, alpha-blockers showed a greater benefit for large (> 5 mm) ureteric stones and those located in the distal ureter, but no benefit for smaller or more proximal stones. Alpha-blockers are also associated, according to the authors, with a

greater risk of side-effects compared to placebo or calcium channel blockers [14]. In our study we also noticed that the alpha-blocker was more efficient on pelvic stones rather than on lumbar stones.

Regarding the stone size, Amer *et al.* showed that alpha-blockers have greater benefits for large (> 5 mm) distal ureteric stones compared to calcium channel blockers. Similar findings have been reported by Ye *et al.* who, in a very large cohort, demonstrated the superiority of alpha-blocker treatment compared to placebo on large (> 5 mm) distal ureteric stones ($p < 0.001$) [13, 14]. Although in our study we did not have significant different expulsion rates between groups function of stone size, we cannot draw a relevant conclusion because of the relative small number of patients. This is also the case of the study performed by Hermanns *et al.* in 2009, who found that the treatment with tamsulosin did not improve the stone expulsion rate in patients with distal ureteral stone < 7 mm [15].

It is the first time, to our knowledge, that citrate-based medication was used to facilitate the expulsion of ureteric stones. Citrate is well known as a potent inhibitor of the crystallization of calcium salts. The therapy with citrate salts is commonly prescribed in clinical practice in order to increase urinary citrate and to reduce stone formation rates, and, up to now, citrate was not studied alone, but only in combination with other drugs, which is irrelevant for our study. Daga *et al.* compared 2 groups of patients: one group who received tamsulosin 0.4 mg daily at night time, furosemide 20 mg and spironolactone 50 mg in a single morning dose, for 12 weeks, and placebo group. The authors monitored caliceal stones less than 5 mm and they noted that stone expulsion rate was 50% at 6 weeks and 86% at 12 weeks in medication-treated group *versus* 28% at 6 weeks, and 38% at 12 weeks in placebo group. Reduced number of pain episodes and less analgesics were required in medication-treated group when compared to placebo group [16].

In our patients, the potassium and magnesium citrate significantly increased urinary pH, compared to alpha-blockers, and it was similarly efficient on proximal ureteral stone passage.

By our knowledge, there are no studies regarding the influence of potassium and magnesium citrate on stone passage of ureteric stones. We can only assume, for the moment, that urinary pH can influence ureteral peristalsis. In an animal model, Smith *et al.* showed that intracellular alkalisation inhibited the amplitude of the action potential, therefore decreased the excitability of the cell [17].

It is also known, that urine alkalisation can influence lower urinary tract symptoms. Sönmez *et al.* evaluated the effects of sodium bicarbonate administered orally in female patients with lower urinary tract symptoms (LUTS) who had acidic urine. The authors used

different symptomatic scores and concluded that urine alkalisation with NaHCO₃ in women with LUTS and acidic urine pH had a significant level of positive effects on symptoms and symptom scores [18]. Further studies are needed to show if increasing the urine pH can play a role in MET.

Regarding the period of treatment we have followed the recommendation of Stoller and Meng, who postulated that the expulsion treatment should last between 2 and 4 weeks [19]. Miller and Kane noticed that 95% of stones ≤ 4 mm pass within 40 days. During this period, pain, gastrointestinal intolerance, or signs of urinary infection (fever, cloudy urine, etc.), should be monitored [20]. We have decided to call patients to verify after 4 weeks if no events occurred (intense pain, fever that would justify the change of the therapeutic strategy).

Even if it was not the goal of our study, the use of other drugs like calcium channel blockers for MET are still debatable. Calcium ion is involved in generating the action potential and therefore may increase ureteral contractility; consequently, calcium channel blockers are expected to have an inhibitory effect on ureteral peristalsis. *In vitro* and in animals, verapamil, diltiazem and nifedipine have shown their inhibitory effect on ureteral contractility. Of these, nifedipine seems to be the most effective [5].

The conflicting results of the SUSPEND study rise the question of the use of medical expulsive therapy [21]. The authors randomized 1167 patients with ureteric stones to tamsulosin 400 μ g, nifedipine 30 mg, or placebo administered daily for up to 4 weeks. They concluded that there was no difference between the active treatment and placebo ($p = 0.78$), or between tamsulosin and nifedipine ($p = 0.77$). Extensive subgroup analysis of the data also failed to show any difference between the active treatment and placebo for ureteric stones, irrespective of size or anatomical location of the stone within the ureter. Although well-designed and large research, the SUSPEND study was criticized, for its lack of confirmation of stone passage. Nevertheless, Furyk *et al.* reach to similar conclusions [22]; in their study, the authors reported comparable stone passage rates of 87% with tamsulosin and 81.9% in placebo, and also no differences in the time needed for the stone passage, analgesic requirements, or necessity for subsequent interventions.

Conclusions

Analysing the preliminary results of this ongoing study, we have found that for those patients with pelvic ureteric lithiasis without fever or underlying colic, the tamsulosin - based expulsion treatment is significantly more effective than that based on KMG citrate - B6, both treatments being more effective than diuretic teas.

For asymptomatic lumbar ureteral lithiasis below 7 mm in diameter, tamsulosin and KMG citrate - B6 treatment had similar results, however both superior to diuretic tea.

Regardless of the ureteral stone location (lumbar or pelvic), the calculi between 3 - 4 mm were eliminated faster and easier than those between 5 - 6 mm, which should be taken into account when planning the therapeutic strategy in this pathology. In all cases where the expulsion treatment failed, modern endourologic procedures have been successfully used without complications that could have been attributed to delayed minimally invasive treatment.

Further studies are needed to determine the role of alkaline urinary pH on ureteral peristalsis and whether the association of the studied expelling agents with each other or with a non-steroidal anti-inflammatory agent can accelerate the process of eliminating the ureteral stones.

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