

COMPARATIVE RESEARCH BETWEEN SOLIFENACIN-TAMSULOSIN *VERSUS* TAMSULOSIN ALONE IN EXPULSION OF JUXTAVESICAL URETERAL STONES

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Abstract

The European Association of Urology Guidelines (EAU) recommends medical expulsive therapy using alpha-blocking medication for the treatment of pelvic ureteral stones smaller than 10 mm if urinary drainage is not mandatory. We performed a randomised, prospective study to assess whether the combination of tamsulosin and solifenacin provides additional benefits over tamsulosin alone in the expulsion treatment of pelvic ureteral stones. A total of 236 patients were included in this study. Patients in group A received tamsulosin 0.4 mg/day, while patients in group B received tamsulosin 0.4 mg/day and solifenacin 10 mg/day. The main groups were divided into subgroups according to the size of the calculus- subgroups A1 and B1 - patients with calculi between 5 - 6 mm and A2 and B2 - patients with calculi between 7 - 8 mm in size. Patients in subgroups A2 and B2 had shorter expulsion intervals of the calculus compared to patients in subgroups A1 and B1 (5.2 days vs. 3.81 days and 6.42 days vs. 3.79 days), required lower doses of NAIDS (2.95 tablets/day vs. 1.82 tablets/day and 3.1 tablets/day vs. 2.05 tablets/day) and presented an improvement in symptom scores. Our data suggest that the combined treatment of tamsulosin and solifenacin brings benefits to medical expulsion therapy of pelvic ureteral stones.

Rezumat

Ghidul Asociației Europene de Urologie (EAU) recomandă pentru tratamentul calculilor ureterali pelvini mai mici de 10 mm, tratamentul de expulzie utilizând medicația alfa-blocantă, dacă drenajul urinar nu este necesar. Am efectuat un studiu prospectiv, randomizat pentru a observa dacă asocierea solifenacina-tamsulosin aduce beneficii suplimentare comparativ cu monoterapia cu tamsulosin în tratamentul de expulzie al calculilor ureterali pelvini. În acest studiu au fost înrolați 236 pacienți. Pacienții din grupul A au primit tratament cu tamsulosin 0,4 mg/zi în timp ce pacienții din grupul B au primit asocierea tamsulosin 0,4 mg/zi-solifenacină 10 mg/zi. Grupurile principale au fost subdivizate în funcție de dimensiunea calculilor. Subgrupurile A1 și B1 au cuprins pacienți cu calculi de 5 - 6 mm iar subgrupurile A2 și B2, pacienți cu calculi de 7 - 8 mm. Pacienții din subgrupurile A2 și B2 au prezentat intervale de timp mai mici de expulzie a calculilor comparativ cu cei din subgrupurile A1 și B1 (5,2 zile vs. 3,81 zile și 6,42 zile vs. 3,79 zile), au necesitat doze mai mici de AINS (2,95 comprimate/zi vs. 1,82 comprimate/zi și 3,1 comprimate/zi vs. 2,05 comprimate/zi) precum și o ameliorare a scorurilor simptomatice. Rezultatele obținute în acest studiu sugerează că tratamentul combinat aduce beneficii suplimentare în tratamentul de expulzie al calculilor ureterali pelvini.

Keywords: expulsive therapy, pelvic ureteral stone, tamsulosin, solifenacin

Introduction

The epidemiological aspects of urolithiasis differ depending on geographical area, gender, age and race [1]. There has been an increase in the incidence and prevalence of the stone disease in Europe over the last few years. Thus, in Germany, it was observed that the prevalence of the disease increased from 4% (1979) to 4.7% (2011) [2], with similar percentages being reported in Iceland [3], while in some areas of Greece the prevalence is significantly higher - up to 15% [4]. An epidemiological study conducted at the University of Pisa estimates an annual incidence of renal colic

at 3.1 cases/1000 inhabitants. These data are similar to those indicated by the National Hospital Medical Care Survey (NHAMCS), which estimates that over 1.1 million patients in the United States each year present to the emergency department for colic pain. [5, 6].

Medical expulsive therapy (MET) has become routine in urological practice. The most studied drugs which can be used in the treatment of distal ureteral stones are alpha-blockers. According to European Urology Association Guidelines [7], American Urological Association and Endourological Society Guidelines

[8], expulsion treatment may be recommended for any patient with a pelvic ureteral stone smaller than 10 mm in diameter (level of evidence 1a) if active removal is not an emergency.

The efficacy of expulsion treatment using tamsulosin has been demonstrated in numerous meta-analyses and single-centre randomised controlled trials [9-13]. However, on the other hand, two extensive multicentre studies challenge the usefulness of this medication, proving a limited or even the lack of utility regarding the ureteral passage of urinary stones [14, 15]

Assuming that the juxtavesical location of ureteral calculi can be associated with intense urinary symptomatology, we attempted to assess whether the control of low urinary tract symptoms by adding an antimuscarinic drug to the alpha-blocker changes the evolution of the patient when the calculus is located in the proximity of the bladder. All patients received the same non-steroidal anti-inflammatory drug by request. None of the patients received antibiotic therapy in accordance to the EAU guidelines and the principles of rational use of antibiotics [7, 16].

Materials and Methods

Study design

Between January 1st, 2022, and February 1st, 2022, patients with renal colic secondary to a pelvic ureteral stone, were evaluated in the Emergency Department of the Urology Clinic of "Dr. C.I. Parhon" Hospital Iași, Romania.

Every patient signed an informed consent form for inclusion in the study. The study was conducted following the Declaration of Helsinki. The initial evaluation protocol involved clinical examination associated with paraclinical tests (serum creatinine and urea levels, blood count, C-reactive protein, and urine analysis) as well as imaging investigations (ultrasonography and kidney-ureter-bladder radiography). The inclusion criteria in this study were: the radiologically documented presence of a calculus in a juxtavesical position, a dimension of the calculus between 5 - 8 mm, and the possibility of follow-up throughout treatment. All patients were informed of the potential risks of MET and any possible side effects of the medications used. Exclusion criteria were the presence of significant uretero-hydronephrosis, the presence of significant inflammatory syndrome (modified C-reactive protein, leucocytosis with neutrophilia, serum creatinine > 1.5 mg/dL, patients with solitary kidney (functional, surgical or congenital), pregnancy or active cancers. All patients were advised to filter their urine at home to highlight the stone expulsion.

We randomly assigned the patients, in a chronological manner, into two groups. Patients in group A received tamsulosin 0.4 mg/day, while patients in group B received tamsulosin 0.4 mg/day in combination with solifenacin 10 mg/day. Patients from both groups

simultaneously received Rowatinex® 2 tablets 3 times daily.

We divided the two main groups into subgroups in accordance with the size of the calculus - subgroups A1 and B1 comprising patients with stones between 5 mm and 6 mm in maximum diameter, while subgroups A2 and B2 patients with stones between 7 mm and 8 mm in maximum diameter.

All patients received written instructions regarding the restriction of water intake during flares of pain and the administration of nonsteroidal anti-inflammatory drugs during these flare-ups. All patients were evaluated for pain progress under the indicated treatment using the Visual Analog Scale (VAS), assessed before starting treatment, at 3, and at 7 days after starting treatment. Urinary symptoms were assessed (before and after treatment, 3 to 7 days after initiation of treatment) using the USS (Urinary Sensation Scale). The USS is a valuable tool for assessing the symptoms encountered in patients with overactive bladder, both in men and women, validated in a large number of patients by Coyne *et al.* [17]. We also assessed the need for pain-killer drugs to control the pain, as well as the presence of side effects associated with medication and the number of episodes of pain exacerbation and subsequent patient presentations. The absence of elimination of the stone at the end of two weeks of follow-up or the need for endourological intervention was considered a failure of MET.

Statistical analysis

The statistical analysis was performed using the t-Student and Chi-square tests. A p-value of < 0.05 was considered statistically significant.

Results and Discussion

After applying the exclusion criteria, 250 patients were initially enrolled in this study, which were subsequently randomised into one of the two study groups. Fourteen patients did not present for evaluation and follow-up. For this reason, they were excluded from the study. The mean age of patients in group A1 was 39.98 years, A2 40.87 years, and for patients in group B1 the mean age was 44.16 years, while in group B2 was 42.64 years. We did not find any significant differences between the distribution of patients by gender ($p > 0.05$) nor regarding the size of the calculi.

Also, there were no statistically significant differences in the expulsion rates for each main group. The 47 patients (19.9% of the total) in whom no ureteral passage occurred through MET during the follow-up period, required another form of treatment. Table I shows the main characteristics of the two groups.

Regardless of the treatment, there were no values that reached the threshold of statistical significance in terms of the rate of expulsion of stones. The average expulsion time in subgroup A1 was 5.2 days, while in subgroup B1, the average period between the treatment

initiation and the occurrence of the ureteral passage was 3.81 days ($p < 0.05$). In subgroup A2 the time to

stone expulsion was 6.42 vs. 3.79 days in subgroup B2 ($p < 0.05$).

Table I

The characteristics of patients related to study groups

	Subgroup A1	Subgroup A2	Subgroup B1	Subgroup B2	*p	§p
Number	80	40	79	37	> 0.05	> 0.05
Mean age (SD years)	39.98 (12.54)	40.87 (10.21)	44.16 (14.47)	42.64 (10.91)	> 0.05	> 0.05
Gender					> 0.05	> 0.05
Female	35	9	36	12		
Male	46	31	43	25		
M:F Ratio	1.31	3.44	1.19	2.08		
Average calculi size (SD mm)	5.25 (0.72)	7.6 (0.49)	5.7 (0.48)	7.16 (0.37)	> 0.05	> 0.05
Stone free rate	65 (81.2%)	26 (65%)	69 (87.3%)	29 (78.3%)	> 0.05	> 0.05
Lack of expulsion	15 (18.8%)	14 (35%)	10 (12.7%)	8 (21.6%)		
Average time to expulsion (days)	5.2	6.42	3.81	3.79	0.0001	0.0001
Average NAIDS consumption (tablets/day)	2.95	3.1	1.82	2.05	0.0001	0.0001
Hospital re-evaluation (%)	9 (11.25%)	12 (30%)	7 (8.86%)	10 (27.02%)	> 0.05	> 0.05

* p represents the statistical analysis of subgroup A1 vs. subgroup B1; § p represents the statistical analysis of subgroup A2 vs. subgroup B2;

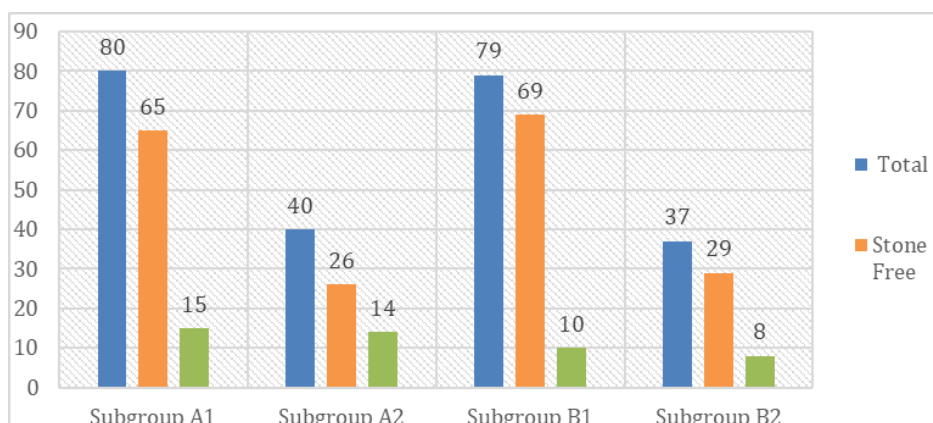


Figure 1.

MET efficiency

Regardless of the size of the stone, patients receiving combination therapy with tamsulosin and solifenacin required a lower number of pain-killer drugs compared to tamsulosin monotherapy. Nine patients (11.25%) in group A1, seven in group B1 (7.59%), twelve (30%) in A2, and ten in B2 (27.02) were re-evaluated at the hospital for the onset of nephritic colic without clinical or paraclinical degradation, intramuscular administration of hydrochloride tramadol 50 mg was sufficient to obtain analgesia, and patients subsequently continued expulsion treatment.

In 47 patients, the expulsion of the stone did not occur. Of the 47 patients, 35 (74.5%) were referred for extracorporeal lithotripsy, and the rest twelve required the insertion of a JJ stent due to the presence of the inflammatory syndrome. Extracorporeal lithotripsy was performed with a Dornier Sigma Compact electro-magnetic device.

All patients presented postprocedural stone-free status. Patients undergoing ureteral catheterisation were treated with retrograde ureteroscopy with a stone-free rate of 100%.

Table II

Patients outcomes by subgroups

	Subgroup A1	Subgroup A2	Subgroup B1	Subgroup B2	*p	§p
Number	80	40	79	37	> 0.05	> 0.05
VAS before initiating treatment	7.73	7.75	7.97	7.97	> 0.05	> 0.05
VAS 3 days after initiating treatment	5.38	5.97	4.3	3.56	0.00015	0.0003
VAS 7 days after initiating treatment	4.07	4.6	2.08	1.72	0.0001	0.0001
USS before initiating treatment	3.2	2.9	3.13	2.45	> 0.05	> 0.05
USS 3 days after initiating treatment	2.45	2.52	2.07	1.78	0.004	0.006
USS 7 days after initiating treatment	2.2	1.95	1.41	1.29	0.0001	0.0001

* p represents the statistical analysis of subgroup A1 vs. subgroup B1; § p represents the statistical analysis of subgroup A2 vs. subgroup B2

Data regarding the location of ureteric stones in patients at the moment of first urologic consultation are relatively heterogeneous. Eisner *et al.* in a retrospective research demonstrate that from 94 patients with renal colic, 60.6% of the stones were located at the ureterovesical junction at the time of presentation in the emergency department, the percentage was superior to other locations – ureteropelvic junction 10.6%, proximal ureter 23.4%, intersection with external iliac artery 1.1% [18]. Different percentages are reported by Moon *et al.*, They demonstrate in a group of 246 patients that 36.2 % of the stones are present at the ureterovesical junction and 37% at the upper lumbar ureter [19], while El-Barky *et al.*, in a group of 300 patients with ureteral lithiasis demonstrates the presence of the stone at the ureterovesical junction in only 16% of patients [20].

Malin *et al.* demonstrated the presence of adrenergic receptors in the ureteral mucosa, especially α -receptors, the blockage of which results in a reduction in the amplitude and frequency of ureteral peristalsis [21]. Sakamoto and Itoh demonstrated by immunohistochemistry research that most α -receptors in the pelvic ureter are subtype D, the other subtypes being less represented [22, 23].

Dellabella *et al.* demonstrated in a group of 60 patients with radiologically documented juxtavesical ureteral lithiasis that the use of tamsulosin is associated with an increase in the expulsion rate (90%) and a decrease in the need for hospitalisation [24]. In a study that compares the efficacy of tamsulosin with silodosin, Georgescu *et al.* reported similar expulsion rates for the two types of α -blockers, 76% and 82% [25]. These data are similar to our results, with an expulsion rate of 81.2% (subgroup A1) and 65% (subgroup A2).

Five types of muscarinic receptors (M1 - M5) are described in the human body. About 80% of the muscarinic receptors in the bladder are represented by the M2 subtype and 20% by the M3 subtype. Despite the abundance of M2 receptors, the stimulation of M3 receptors is responsible for the contractility of the bladder. Solifenacin is a strong muscarinic receptor antagonist with high selectivity for the M3 subtype of the smooth muscle. This increased selectivity allows the use of solifenacin in the treatment of low urinary symptomatology in overactive bladder syndrome [26, 27]. According to EAU Guidelines, solifenacin is used as a first-line treatment for overactive bladder [28]. Sakamoto *et al.* demonstrated through immunohistochemistry studies and rt-PCR that all types of muscarinic receptors (M1 - M5) are present in the distal ureteral mucosa and in the bladder mucosa in the proximity of the ureterovesical junction, the amount of M5 receptors is insignificant [22].

To our knowledge, it is the first time when the solifenacin-tamsulosin combination was used to facilitate the expulsion of pelvic ureteric stones. In a previous study, Lv *et al.* noted that the addition of tolterodine, a nonselective

antimuscarinic, to α -blocker treatment did not bring additional benefits in terms of the rate of calculi expulsion [29]. This is also observed by Ertuhan *et al.*, who, using the same pharmacological combination, obtained expulsion rates of 70%, with approximately similar results [30]. In our study, the expulsion rate in the subgroups of patients receiving combined treatment of tamsulosin and solifenacin was higher compared to the monotherapy subgroups but without statistical significance.

Following the analysis of the subgroups, we found that in both patients with stones of 5 - 6 mm and those with stones of 7 - 8 mm who received solifenacin and tamsulosin, the time to stone expulsion was shorter compared to patients who received monotherapy with tamsulosin. However, our data on time to stone expulsion are slightly different from those obtained by Itoh *et al.*, who noted 9.29 days using silodosin as a central element of expulsion treatment, noting that the authors did not differentiate stones depending on size [31]. Different results are also reported by Lee *et al.*, who show that for stones smaller than 6 mm, it takes up to 14 days for the expulsion to occur [32]. In a previous comparative study between α -blocker medications and potassium citrate, we also found higher stone-free rates for tamsulosin when used to treat pelvic stones, but with equal stone-free rates when the calculi were located on the lumbar ureter [33].

Lv *et al.*, using only tolterodine without the association of an α -blocker in the treatment of pelvic ureteral stones, observed that its administration is not associated with shortened expulsion time [29]. Contrary, our data show that the combination of solifenacin-tamsulosin reduces the time to stone expulsion for both 5 - 6 mm and 7 - 8 mm stones categories.

Regarding the pain symptomatology evaluated by VAS as well as the urinary symptomatology determined by the juxtavesical location of the stones, evaluated by USS, we found that at 3 days, and respectively at 7 days from the start of treatment, patients who received the α -blocker-antimuscarinic therapy combination showed a marked improvement in these parameters compared to patients who received only α -blocker treatment. Analysing the four subgroups, we found that the combined treatment with tamsulosin-solifenacin reduced VAS and USS for both 5 - 6 mm and 7 - 8 mm stones. Our findings are sustained by the results obtained by Lv *et al.*, who used the same parameters and obtained an improvement in symptom scores [29]. Also, in our research, the patients receiving combination therapy required a smaller dose of anti-inflammatory drugs, to control pain, as opposed to patients receiving only α -blocker medication, both for 5 - 6 mm and 7 - 8 mm stones providing an advantage regarding the ever-increasing sales and usage of over-the-counter NSAIDs [34]. Our results are different from those obtained by Ertuhan *et al.* They did not find it necessary to administer a reduced dose of NSAIDs in patients

receiving combination therapy [30]. According to our results, the only side effect that was more common in patients using the solifenacin-tamsulosin combination was xerostomia (5% vs.17.3%), with the remaining side effects having similar frequencies in both groups. A similar xerostomia incidence in patients treated with solifenacin doses of 5 mg and 10 mg, respectively, was reported by Chapple *et al.* [35]. However, Warde *et al.*, in a comparative study, found the presence of xerostomia in 35% of solifenacin-treated patients [36]. A disadvantage of the combined treatment can be represented by the significantly higher costs. According to the prices in our country, the patients who received treatment with tamsulosin only paid an average of 3 euros/week, while the patients who received combination treatment paid 10 euros/week [37].

One of the best-documented works on the cost-effectiveness of expulsion treatment by Bensalah *et al.* shows that in 2008, the price of a tamsulosin tablet in the United States was about \$2, meanwhile performing an ureteroscopy involves more than \$4,000/patient. The same authors state that the cost of expulsion treatment is estimated at \$77 in Germany. In contrast, ureteroscopy costs more than \$ 2,000, concluding that expulsion treatment is a cost-effective strategy and should be considered whenever we are facing a patient who does not need urinary drainage [38]. One of the limitations is the absence of a group of patients receiving Rowatinex[®]-only treatment or placebo, and on the other hand, we have the limitation of the relatively small number of patients, but the research is still ongoing.

Conclusions

When used for the expulsion of ureteral stones located near the bladder, with sizes between 5 - 8 mm, the pharmacological combination of tamsulosin-solifenacin proves to be effective and safe. In our study, the combination of solifenacin-tamsulosin significantly reduced the pain and urinary symptoms of the patient with a juxtavesical stone and improved the rate of expulsion of stones, but without statistical significance from this point of view. Further studies using a placebo or NSAID may help certify the results of our research.

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Conflict of interest

The authors declare no conflict of interest.

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