

## THE ROLE OF $\alpha$ 1-BLOCKERS IN THE MEDICAL EXPULSIVE THERAPY FOR URETERAL CALCULI - A PROSPECTIVE CONTROLLED RANDOMIZED STUDY COMPARING TAMSULOSIN AND SILODOSIN

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### Abstract

In patients with newly diagnosed ureteral stones under 10 mm, observation is an optional initial treatment. The aim of this prospective trial was to evaluate the efficacy of tamsulosin and silodosin associated with anti-inflammatory drugs by comparison with anti-inflammatory therapy alone in the medical expulsive treatment of uncomplicated ureteral stones. A total of 150 patients over 18 years with unilateral, uncomplicated ureteral stones under 1cm were enrolled in a randomized prospective trial. Subjects in Group I were given tamsulosin 0.4 mg once daily and diclofenac sodium 50 mg/12 h, those in Group II were given silodosin 8 mg once daily and diclofenac sodium 50 mg/12 h and patients of third group of study only received the anti-inflammatory medication. In all three groups, drug administration was continued until the patients were rendered stone-free by intervention or spontaneous stone expulsion, or for a maximum of 4 weeks. Stone expulsion rate was 76% in Group I, in 82% in Group II and 54% in Group III. The statistical analysis demonstrates significant higher expulsion rate in both study groups by comparison to control group. The difference between the expulsion rates of cases from the tamsulosin and silodosin groups did not reach statistical significance. The use of tamsulosin and silodosin in medical expulsive treatment of ureteral stones proved to be safe and effective. The efficacy of both drugs seems to be similar.

### Rezumat

Pacienții cu calculi ureterali nou-diagnosticați, sub 1 cm pot beneficia de tratament conservator. Obiectivul studiului a fost reprezentat de evaluarea eficacității tamsulosinului și silodosinului asociate cu anti-inflamatoare, în comparație cu anti-inflamatoarele în monoterapie în tratamentul medical expulsiv al litiazei ureterale necomplicate. Un număr de 150 de pacienți peste 18 ani, cu litiază ureterală unilaterală, necomplicată, sub 1 cm au fost randomizați într-un studiu prospectiv randomizat. Pacienții din Grupul I au primit tamsulosin 0,4 mg pe zi și diclofenac sodic 50 mg/12 ore, cei din Grupul II, silodosin 8 mg zilnic și diclofenac sodic 50 mg/12 ore iar cei din Grupul III doar tratament anti-inflamator cu diclofenac sodic. Administrarea medicației a continuat până la eliminarea sau extragerea calculului ori pe o perioadă maximă de 4 săptămâni. Rata de eliminare a calculilor a fost de 76% în Grupul I, 82% în Grupul II și 54% în Grupul III. Analiza statistică a demonstrat rate de expulsie semnificativ mai mari în ambele grupe de studiu comparativ cu pacienții din grupul de control. Diferențele între rezultatele administrării tamsulosinului și silodosinului nu au fost semnificative statistic. Utilizarea tamsulosinului și silodosinului în cadrul tratamentului medical expulsiv este eficientă și sigură. Eficacitatea celor două medicamente pare a fi similară.

**Keywords:** medical expulsive therapy, silodosin, tamsulosin, ureteral stone

### Introduction

Ureteral stones have a significant impact on patients' quality of life. Renal colic is common in

urological practice, being one of the most important issues encountered by urologists in emergency clinical settings. It leads to a requirement for

analgesia, time off work and, often, repeated hospital admissions for therapeutic interventions.

In the past decade, with the introduction of minimally invasive procedure and newer drugs, the management of these cases has substantially changed.

According to the European Association of Urology Guidelines, in patients with newly diagnosed ureteral stones under 10 mm, and if active removal is not indicated, observation with periodic evaluation is an optional initial treatment.

The likelihood of ureteral stone passage varies between 46-85% for stones under 5 mm and 36-58% for calculi with a size of 5 to 10 mm [1].

In order to facilitate the stone passage, appropriate medical therapy may be used. Various drugs, including nifedipine, glyceryl trinitrate, prostaglandin synthesis inhibitors, corticosteroids, have been investigated as spasmolytic agents that would facilitate the expulsion of ureteral stones [2].

In the stone migration process, ureteral activity is modulated by the sympathetic nervous system [3]. As a consequence,  $\alpha$ 1-blockers decrease the tension, release the spasm of smooth muscles, and reduce the obstruction and irritation symptoms in the lower urinary tract [4]. Tamsulosin was already evaluated by a large number of trials, being the most commonly used  $\alpha$ 1-blocker in medical expulsive therapy (MET). The efficacy of Silodosin, a uroselective  $\alpha$ 1-blocker, marketed for the first time in 2006, was assessed in a limited number of studies.

The aim of this prospective trial was to evaluate the efficacy of tamsulosin and silodosin associated with anti-inflammatory drugs by comparison with the anti-inflammatory therapy alone in the medical treatment of symptomatic, uncomplicated ureteral stones.

### Materials and Methods

The study was performed in the Department of Urology of "Sf. Ioan" Emergency Clinical Hospital, Bucharest, Romania, between February 2013 and December 2013. A total of 150 patients over 18 years old with unilateral, non-impacted, uncomplicated ureteral stones under 1cm were enrolled in this prospective trial.

The study was conducted after approval from the local ethics committee.

Patients with fever, urinary tract infection, high-grade hydronephrosis, hypotension, acute or chronic renal failure, single kidney, urinary congenital anomalies, multiple or bilateral ureteral stones, a history of open surgery or endoscopic procedures in the urinary tract, diabetes, peptic ulcer, or concomitant treatment with  $\alpha$ - or  $\beta$ -blockers, calcium antagonists, steroid, nitrates,

pregnant or lactating women were excluded. Also, patients requiring immediate stone removal were not included in the study.

The patients were properly informed about the study, including the attendant risks of medical expulsive therapy and associated drug side effects. Afterwards they provided informed written consents.

The patients were prospectively randomly assigned into three equal groups of 50 subjects. The randomization process was achieved by means of sealed envelopes equally nominating one of the three treatment alternative. Allocation concealment was performed using the SNOSE method (sequentially-numbered, opaque, sealed envelopes). The initial evaluation protocol was based on physical examination, serum creatinine, urinalysis, urine culture, ultrasonography, plain X-ray of the kidneys, ureters, and bladder (KUB) or non-contrast computed tomography (CT).

The stone size was calculated on the first KUB or CT. The greatest dimension of the stone was taken into consideration as the stone size.

The patient demographics in the three groups, in terms of age, gender, stones size, location and laterality were documented.

Subjects in Group I were given tamsulosin 0.4 mg once daily and diclofenac sodium 50 mg/12 h, those in Group II were given silodosin 8 mg once daily and diclofenac sodium 50 mg/12 h and patients of third group of study only received the anti-inflammatory medication. Anti-inflammatory drugs were administrated regularly for 1 week and then on demand up to a maximum of 2 times per day.

In all three groups, drug administration was continued until the patients were rendered stone-free by spontaneous stone expulsion or intervention, or for a maximum of 4 weeks.

The patients were instructed to record the date and time of the stone passage as well as the number of renal colics.

The mean number of pain episodes was calculated by dividing the number of renal colics by the numbers of follow-up days.

Absences of stone expulsion at the end of the study or intervention before the end of the study as the result of uncontrollable pain or adverse events were considered failed therapy.

Patients were followed at 14 +/- 2 days and at the end of the study with urinalysis, KUB and ultrasonography in order to evaluate the stone position and the degree of hydronephrosis.

The primary endpoint was the stone expulsion rate and the secondary endpoints were stone expulsion time, rates of the interventions (retrograde ureteroscopy, extracorporeal shock wave lithotripsy, or ureteral stenting), the pain control and side effects. The expulsion time was defined as the

number of days from the randomization to the stone expulsion.

The statistical analysis was performed by using the ANOVA and Chi-square test. A p value of < 0.05 was considered to be statistically significant. The SPSS-16 software was used for the statistical analysis of the data.

## Results and Discussion

All the patients from the three groups completed the study. There was no significant difference between the groups with respect to the patients' age, the stone size and their location. The demographic characteristics of the patients are summarized in Table I.

**Table I**

The demographic characteristics of the three groups

Characteristic	Group I (tamsulosin)	Group II (silodosin)	Group III (control)	p value
Age (years)	43.5 ± 13.31	44.26 ± 13.00	45.14 ± 11.58	0.811
Sex (male / female)	27 / 23	31 / 19	26 / 24	0.566
Laterality (left / right)	26 / 24	28 / 22	21 / 29	0.3534
Location (upper / middle / lower)	2 / 18 / 30	3 / 14 / 33	3 / 15 / 32	0.9171
Stone size (mm)	5.08 ± 2.09	5.32 ± 2.09	5.1 ± 2.02	0.813

A spontaneous stone expulsion during the 4 weeks follow-up period was observed in 38 of the 50 patients (76%) in Group I, in 41 patients (82%) in Group II and in 26 patients (54%) in Group III. The statistical analysis demonstrates significant higher expulsion rate in both study groups by comparison to control group. The difference between the expulsion rates of cases from the tamsulosin and

silodosin groups did not reach statistical significance (Table II).

The same differences were noted for calculi over 5 mm. For stones under 5 mm, even if the expulsion rates in patients receiving  $\alpha$ -blockers were superior to those only under anti-inflammatory treatment, the differences were not statistically significant.

**Table II**

Treatment outcome parameters in the three groups

Endpoint	Group I	Group II	Group III	p value
Stone expulsion rate	38 / 50 (76%)	41 / 50 (82%)	26 / 50 (54%)	0.012 group I vs III 0.0014 group II vs III 0.4616 group I vs II
Stone expulsion rate (< 5 mm)	21 / 24 (87.5%)	24 / 26 (92.3%)	16 / 23 (69.5%)	0.0558 group I vs III 0.0014 group II vs III 0.5710 group I vs II
Stone expulsion rate (> 5 mm)	17 / 26 (65.3%)	17 / 24 (70.8%)	10 / 27 (37%)	0.0390 group I vs III 0.0187 group II vs III 0.6801 group I vs II
Mean time to expulsion (days)	9 ± 5.26	7.82 ± 5.16	12.03 ± 6.22	0.0467 group I vs III 0.0060 group II vs III 0.3218 group I vs II
Number of pain attacks	234 / 928	201 / 749	489 / 1456	0.00001 group I vs III 0.0012 group II vs III 0.4518 group I vs II
Hospital readmission for active removal	1 / 50	2 / 50	7 / 50	

Hospital readmissions with consecutive intervention and discontinuation of the medication due to uncontrollable pain occurred in 7 patients: 1 patient (2%) in Group I, 2 patients (4%) in Group II, and 7 patients (14%) in Group III.

No severe complications were recorded in the three groups. One patient (2%) in Group I recorded an episode of hypotension, which did not require suspension of the therapy. Retrograde ejaculation during the treatment occurred in and 3/27 patients in Group I and 5/31 patients in Group II.

Urolithiasis affects 4% to 15% of the world population, and the incidence of this disease is increasing [5].

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 (NSAID) tablets or suppositories [6] may help reduce inflammation and risk of recurrent pain [7].

Even if in Romania none of the  $\alpha$ -blockers are an indication in the treatment of ureteral lithiasis, the European Guideline recommends these drugs like the first line option for medical expulsive therapy. Tamsulosin is the most commonly used  $\alpha$ -blocker for the medical treatment of ureteral stones [7]. More recently introduced in the clinical practice, silodosin seems to provide at least similar results [8].

A first description of the adrenergic receptors role in the human ureter was performed in 1970 [9]. The  $\alpha$ -adrenergic receptors were classified into three different subtypes of  $\alpha 1A$ ,  $\alpha 1B$  and  $\alpha 1D$ . This adrenoceptor subtypes are localized in the human ureter irrespective of location [10]. The expression levels of subtypes are different according to level of ureter and subtype. According to Itoh *et al*, the distribution in the human ureter is  $\alpha 1D > \alpha 1A > \alpha 1B$  [11].

Activation of  $\alpha 1$ -adrenoceptors leads to ureteral contraction *via* activation of phospholipase C, which in turn leads to the formation of second messengers (inositol triphosphate (IP3) and diacylglycerol (DAG)). IP3 is involved in the mobilization of calcium from the sarcoplasmic reticulum, whereas DAG increases calcium influx across the cell membrane *via* the activation of protein kinase C [12].

The rationale behind the  $\alpha$ -blocker use is that stimulation of the  $\alpha 1$  receptors in the ureter increases the force of ureteral contraction and the frequency of ureteral peristalsis. Thus, the  $\alpha 1$ -adrenergic antagonists are able to inhibit basal tone and peristaltic frequency, dilating the ureteral lumen and facilitating stone passage [13].

Tamsulosin is considered a first line option because it provides a very good tolerability, and does not imply the need for dose titration upon initiation of treatment. The tamsulosin displays selectivity for  $\alpha 1a$  and  $\alpha 1d$  adrenoceptors [13]. In several studies, the density of  $\alpha 1d$  adrenergic receptors in the ureteral smooth muscle cells is greater than that of other adrenergic receptors [12].

However, limited direct comparative data indicates that other  $\alpha$ -blockers such as alfuzosin, doxazosin, and terazosin can be similarly effective [14, 15], suggesting a possible class effect.

A meta-analysis published in 2011 [16] showed that compared to standard therapy or placebo, tamsulosin had significant benefits, being associated with both higher stone expulsion rate and reduction of the expulsion time. The expulsion rate was statistically different ( $p < 0.001$ ) between the treatment and control groups. The mean expulsion time was also statistically different ( $p = 0.02$ ) between the treatment and control groups.

Our results confirm these data, the expulsion rates being significantly higher in the  $\alpha$ -blockers groups. Reductions in the need for analgesic therapy, hospitalization and surgery were also significant.

Adverse events [17] rarely led to patients withdrawing from MET and were reversible after discontinuation of the drug administered [18]. In our study, none of the patients withdraw from the study due to adverse events.

Silodosin received its first marketing approval in Japan in May 2006. A first study published in 2011

by Itoh *et al* [19] on 187 patients compared the use of silodosin with the watchful waiting in patients with ureteral calculi less than 10 mm. The stone expulsion rate was 72.7% for the patients receiving silodosin by comparison with 55.3% for the watchful waiting group.

The differences in expulsion rate were more obvious for calculi  $\geq 5$  mm (75.9 % vs 17.9 %) by comparison to those  $< 5$  mm (92.9 % vs 69.2 %).

In a recent comparative study, spontaneous stone expulsion was observed in 58% of the patients receiving tamsulosin and in 82% of the patients from the silodosin group, which was statistically significant. There was also a significant difference between the groups with regards to the mean stone expulsion time [8].

In our study, the differences in the expulsion rates in both groups receiving  $\alpha$ -blocker did not reach clinical significance.

The stones up to 5 mm have a high likelihood of spontaneous passage without medical expulsive therapy. In our study, for stone under 5 mm the differences between the expulsion rates in the tamsulosin (87.5%) and silodosin (92.3%) by comparison to the control group (69.5%) did not reach statistical significance. In this way were explained the results of the study performed by Thomas Hermans in 2009, in which tamsulosin treatment did not improve the stone expulsion rate in patients with distal ureteral stone  $< 7$  mm [20].

However, even in these cases patients may benefit from supportive analgesic effect. MET does reduce the need for analgesics.

An explanation could be the fact that  $\alpha$ -blockers also block the conduction of visceral referred pain to the central nervous system, acting on C-fibres or sympathetic postganglionic neurons [21].

## Conclusions

Medical expulsive therapy should be offered as a treatment for patients with ureteral calculi under 10 mm who are amenable conservative management. 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.

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