The Role of Tamsulosin in the Management Of Lower Ureteric Stones.

Ayad Ali Al-Beer *

ABSTRACT:

BACKGROUND:

Recent Studies have reported outstanding results concerning medical expulsive therapy (MET) for distal ureterolithiasis in terms of stone expulsion and control of colic pain. While ureteral intracorporeal and extracorporeal shock wave lithotripsy are recognized to be effective, the role of MET has not yet been established for the treatment of this disease.

OBJECTIVES:

To evaluate the role of α1- adrenergic antagonist Tamsulosin in conservative therapy for patients with juxtavesical ureteral stones.

METHODS:

Sixty consecutive symptomatic patients with juxtavesical unilateral lower ureterolithiasis from the urologic consultation department in Baghdad Medical City were enrolled in this randomized prospective controlled study during the period from January 2005 to December 2006. Patients were randomly divided into two groups, group 1 (n=30) and group 2 (n=30). The two patient groups used oral diclofenac (25 mg orally twice daily) plus cotrimoxazole 2 times daily for 5 days and 75 mg diclofenac injected intramuscularly on demand. All patients were instructed to drink 2 L water daily. Group 1, served as the control group. Group 2 was given the α1 -blocker (tamsulosin) in addition to conservative treatment. Tamsulosin capsule (0.4 mg) was administered daily. The treatment duration was until stone expulsion or 28 days, whichever came first. During this period, all patients were evaluated weekly by urinary tract ultrasonography and serum createnine level, and were asked whether they experienced acute colic pain, to score the intensity of pain according to a visual analog scale (VAS), whether the calculus passed spontaneously, the day and time of stone expulsion, number of diclofenac injections, and finally any drug side effects. Statistical analyses were performed with Student's t test, ANOVA, and Mann-Whitney U test as appropriate. Correlation analysis was done using Spearman's rank test. Cox proportional hazard regression module was used to determine the predictive factors for expulsion.

RESULTS:

The stone expulsion rate was 70% for group 1 and 90% for group 2 (P=0.003). Mean stone size was 7.3 and 7.7 mm, respectively (P=0.24). Mean expulsion time, mean VAS of pain, mean attack of acute colic, and mean number of diclofenac injections were significantly less in patients used tamsulosin. Only therapy and stone size proved to be significantly predictive factors of stone expulsion (P<0.0001 and 0.001) respectively, while gender and age did not have any predictive value. Although side-effects, such as headache, abnormal ejaculation, and dizziness occurred more in patients who were given tamsulosin, no significant side-effects was detected so as to require exclusion of a patient from the study.

CONCLUSIONS:

Medical Expulsive Therapy (MET) for lower ureterolithiasis with tamsulosin during conservative treatment period is safe and effective as demonstrated by the absence of serious side effects and increased stone expulsion rate with early time. Also MET with tamsulosin affords an outstanding control of pain for patients while waiting for stone expulsion.

KEY WORDS: Ureteric Stone, Tamsulosin.

* Department of Surgery (Urology), Medical College, Baghdad University.

INTRODUCTION:

Ureteral stones occupy an important place in daily urological practice, usually causing an acute episode of ureteral colic by obstructing the urinary tract.
[1] Of all urinary tract stones, 20% are ureteral stones, and 70% of these stones are located in the distal portion of the ureter.[2,3] In the last 20 years the introduction and improvement of new, minimally invasive procedures (extracorporeal shock wave lithotripsy and ureteroscopy) for ureteral stones considerably changed the historical therapy for this disease, determining perhaps a substantial increase in treatment costs, whereas medical therapy (treatment regimens and various therapeutic agents), which is indicated for distal ureteral stones 5mm or smaller according to symptoms, is increasingly less considered [4-6]. Some groups have implemented an observational approach based only on the pharmacological control of pain, while others pharmacologically treat the possible causes of stone retention, such as edema, ureteral spasm and infection, trying to favor its expulsion.
[7-9] the majority of ureteral calculi can pass spontaneously and intervention is usually not required. Other published studies provide a variety of results regarding the spontaneous passage of ureteral stones. If the stone diameter is less than 4 mm, spontaneous passage is generally possible.
Ureteral calculi >6 mm have a 5% or less chance of spontaneous passage. Ureteral calculi located at the distal ureter have a 50% chance of spontaneous passage with only conservative observation.
The majority of stones generally pass spontaneously within a 6-week period after the onset of symptoms.[10,11] Therefore, it is difficult to make a decision between interventional therapy (shock wave lithotripsy or ureteroscopy) and conservative therapy. Several alternative measures other than oral hydration have been tried to increase the stone-free rate, both in watchful waiting patients and those who undergo SWL. Calcium-channel blocking agents and steroids have been commonly used to reduce muscular tonus and decrease the inflammation.
[12,13] Although they have had some effect on pain and stone movement, they also have severe side effects. Headache and asthenia may be mild, but hypotension and palpitations can result in treatment discontinuation.[13] Also, steroids may require a steroid taper. However, α1-adrenergic blockers are familiar drugs for urologists and are used for benign prostatic hyperplasia to reduce smooth muscle tonus.
Hancock[14] reported the Presence of α-adrenergic and β-adrenergic receptors in the human ureter, and additional studies revealed the prevalence of α1d-adrenergic receptors in the human ureter. [15,16] In a randomized study, Cervenakov et al. reported the spontaneous passing of stones in 80.4% of patients who were given the α1-blocker compared with 62.8% of patients without the α1-blocker. [17] They reported a significant statistical difference in the stone expulsion rate between the group treated with tamsulosin and the control group. Dellabela et al. reported that medical therapy using tamsulosin was effective in all patients treated for 4 weeks. [4] We performed a randomized, prospective controlled study to assess the possible role of the combined α-1a and α-1d selective antagonist tamsulosin[18] for facilitating the spontaneous expulsion of juxtavesical ureteral stones even larger than 5 mm and less or equal to 10 mm according to the potential role that the α1-adrenergic receptor might have in the pathophysiology of ureteral colic.

PATIENTS AND METHODS:

From January 2005 to December 2006, 60 patients from the urologic consultation department in Baghdad Medical City, Surgical Specialties Hospital, suffering from ureterolithiasis of the lower part of the ureter were included in this randomized prospective controlled study. The stone was at the left lower ureter in 32 patients and at the right ureter in 28 patients. No patients had a history of ipsilateral ureteric surgery, endoscopy, systemic disease or medication. Stone presence and characteristics were diagnosed with abdominal ultrasonography and stone size was measured along its longest axis in millimeters. An excretory urography was done for all patients at initial visit.
The patients were prospectively randomized into two groups of 30 patients. The two patient groups used oral Diclofenac (25 mg orally twice daily) as a non-steroidal anti-inflammatory drug plus cotrimoxazole 2 times daily for 5 days and 75 mg Diclofenac injected intramuscularly on demand.
All patients were instructed to drink 2 L water daily. Group 1, served as the control group.
Group 2 was given the α1 -blocker (tamsulosin) as an accelerator for the passing of the stone in addition to conservative treatment. Tamsulosin capsule (0.4 mg) was administered one hour after the same meal daily. Both groups were followed up for 4 weeks because the probability of spontaneous passage of the stone was higher during this period.

The treatment duration was until stone expulsion or 28 days, whichever came first. During the 4-week period, all patients enrolled were evaluated weekly by urinary tract ultrasonography and serum createnine level, and were asked whether they experienced acute colic pain, to score the intensity of pain according to a visual analog scale (VAS)[19,20] whether the calculus passed spontaneously, the day and time of stone expulsion, number of analgesic (Diclofenac) injections, and finally any drug side effects. In the VAS, we asked patients to express their perception of the intensity of the pain.

Patients were requested to define the colicy pain they experienced as a number between 0 and 10 by comparing the pain with the most severe pain they had ever experienced (0, no pain; 10, the most severe pain perceived). Patients who failed to expel the stone within 4 weeks underwent ESWL or ureteroscopy. To highlight possible stone expulsion, all patients were required to filter the urine.

Patients who expelled their stones underwent ultrasound examination to confirm stone passage. The criteria for treatment discontinuation as well as the need of hospitalization and/or intervention were pain uncontrolled by therapy, uroseptic fever and/or severe hydronephrosis, increased creatininemia (greater than 2 mg/dl), unsuccessful expulsion after 4 weeks and patient desire to remove the stone before day 28. All variables were expressed as mean values ± SD, or as numbers of patients and percentages. Statistical analyses were performed with Student's t test, ANOVA, and Mann-Whitney *U* test as appropriate. Correlation analysis was done using Spearman's rank test. Cox proportional hazard regression module was used to determine the predictive factors for expulsion.

A P-value of less than 0.05 was considered significant. Analyses were performed using SPSS software, version 9.0 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS:

Group 1 (control group) consisted of 21 males and 9 females with a mean age of 29.8±10.8 years (range 17 to 53), while group 2 (tamsulosin group) included 18 males and 12 females with mean age 30.6±9.3 (range 21 to 51). No statistically significant difference was observed in patients' age between the two groups; (P=0.7), neither with regard to sex difference; (P=0.43). Figure(1).

Mean stone size was 7.3±1.3 mm (range 5 to 9) for group 1 and 7.7±1.3 mm (range 6 to 10) for group 2; There was no statistical difference with respect to the average diameter of the stones between the two groups. (P=0.24) Table (1).

The stone expulsion rate was 70% (21 of 30 patients) for group 1 and 90% (27 of 30 patients) for group 2 with a mean expulsion time of 205.7±87 (range 96 to 336) hours for group 1 and 74.7±58.7 (range 12 to 216) hours for group 2.

Group 2 showed a statistically significant advantage in term of the stone expulsion rate (P=0.003) and expulsion time (P=0.001) Table (1).

It was identified that all patients in group 2 who expelled their stones did that within 10 days of oral tamsulosin treatment start.

Patients in group 1 had higher mean VAS (Visual Analogue Scale) 7.9±1 (range 6 to 9) than 3.9±1.2 (range 2 to 6) for patients taking tamsulosin in group 2 (P<0.0001).

Also the mean attack of acute colic was 3±1.4 (range 1 to5) in group 1 and 1.5±1 (range 0 to 3) in group 2 patients and this result was again with highly significant difference (P<0.0001). Table (1) .

The mean number of Diclofenac injections during therapy was 5.1±2 (range 3 to 9) for group 1 and 0.8 ± 1 (range 0 to 3) for group 2, showing significantly less analgesic injection use in group 2, (P<0.0001).

The univariate analysis using Cox proportional hazard model revealed that only therapy and stone size proved to be significantly predictive factors of stone expulsion (P<0.0001 and 0.001) respectively, while gender and age did not have any predictive value. When applying Spearman's rank test, good and strong correlations were observed between the use of tamsulosin and less VAS of pain (rho=0.867; P<0.0001), less attacks of acute colic (rho=0.496; P<0.0001), early expulsion time (rho=0.713; P<0.0001), and less Diclofenac injections (rho=0.861; P<0.0001).

Also there was good correlation between early expulsion time and smaller stone size in both groups (rho=0.439; P<0.0001).

9 patients (30%) in group 1 needed hospitalization because uncontrolled pain (3) or unsuccessful expulsion after 4 weeks of treatment (6).

2 of them underwent successful ESWL for their stones, and 7 patients were treated by ureteroscopy with pneumatic stone disintegration.

While 3 (10%) of patients in group 2 needed hospitalization for unsuccessful expulsion after 4 weeks of treatment and all them treated by ureteroscopy.

The mean stone size and age of the 3 patients who failed to expel their stones were not statistically different from other patients in group 2.
Although side-effects, such as headache, abnormal ejaculation, and dizziness occurred more in patients Who were given tamsulosin (P value< 0.05), no significant side-effects was detected so as to require Exclusion of a patient from the study, and medical intervention was not performed in any of the patients because of side-effects. Figure (2)

Table (1) Different Parameters Between the Two Groups.

Parameters	Group (1) *Control (n=30)*	Group (2) *Tamsulosin (n=30)*	P *value*
Mean mm stone size (range)	7.3 (5 - 9) mm	7.7 (6 - 10) mm	0.24*
Percent of expulsion (No. of patients)	70% (21)	90% (27)	0.003
Mean hours for expulsion (range)	205.7 (96 - 336) hours	74.7 (12 - 216) hours	0.001
Mean VAS of pain (range)	7.9 (6- 9)	3.9 (2 - 6)	<0.0001
Mean No. of acute colic attacks (range)	3 (1 - 5)	1.5 (0 - 3)	<0.0001
Mean No. of diclof. injections (range)	5.1 (3 - 9)	0.8 (0 - 3)	<0.0001

* P value <0.05 considered significant.

Table (2) Spearman's Rank Test Correlations

Spearman's rho	*Tamsulosin use*		*Stone size*	
	Correlation Coefficient	Sig. (2-tailed)	Correlation Coefficient	Sig. (2-tailed)
VAS of pain	.867**	.000**	.090	.492
Colic attacks	.496**	.000**	.066	.614
Time to expulsion	.713**	.000**	.493**	.000**
Diclofenac injections	.861**	.000**	.122	.353
Stone size	.124	.344	1.000	.

**: Significance at P<0.0001

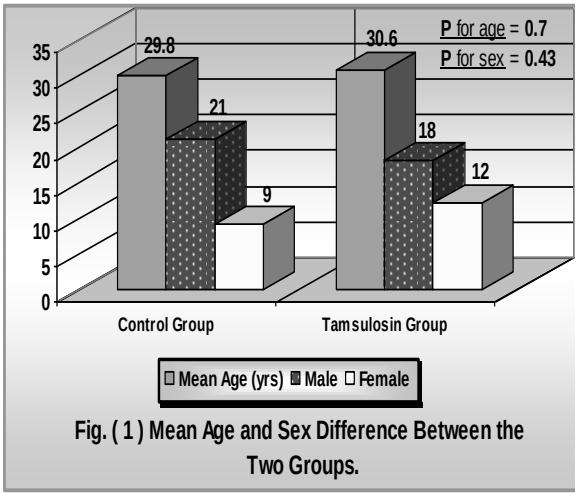

Fig. (1) Mean Age and Sex Difference Between the Two Groups.

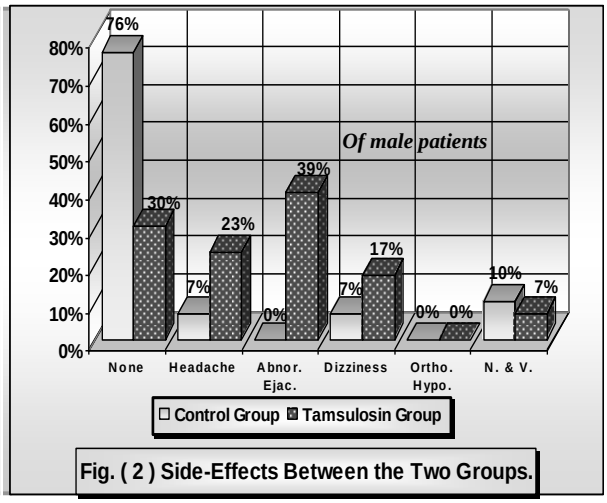

Fig. (2) Side-Effects Between the Two Groups.

DISCUSSION:

Medical therapy with tamsulosin was significantly more effective(90% of patients) in pushing out lower ureteric stones than in the control group (70% of patients) (P=0.003), and tamsulosin reduced the mean expulsion time from 205.7 hours in control group to 74.7 hours in tamsulosin group (P=0.001). it is probable to propose that the effect of tamsulosin on obstructed ureter is to create an increase in the intraureteral pressure gradient in the region of the stone by increasing the urine bolus above the stone as well as reduction in peristalsis below it in association with the decrease in basal and micturation pressure even at the bladder neck. For these reasons – that are mediated by α1-adrenoceptors blockage by tamsulosin – there would be a physically powerful force to expel the stone. Our results concerning stone expulsion rate and time were similar to what reported by Dellabela et al in 2003 in Italy. [4] It is worthwhile to mention that all patients who were given tamsulosin and expelled their stones did so within the period of 10 day of treatment initiation and no advantage – expulsion – was observed in continuation of tamsulosin therapy for the end of 4 weeks. This can be attributed to the fact that tamsulosin achieve a steady-state concentrations by the fifth day of once-a-day 0.4 mg oral dose.[21]The 3 cases of tamsulosin therapy failure can be explicated by the limited water intake by those patients as well as the history of severe recurrent lower urinary tact infections. We observed that patients who were given tamsulosin had significantly better outcome in that they had less VAS pain scores, less attacks of acute colic, and they used less NSAIDs injection during therapy. These findings made obvious that the effect of tamsulosin on the ureter was probably to decrease the frequency and amplitude of phasic peristaltic contractions that accompanying ureteric obstruction. Such results are compatible to the results of Resim et al in 2004 in Turkey [1], the findings of Dellabela et al in 2003 in Italy[4], and Porpiglia et al in 2004 in Italy[22]. Dellabela et al [4] stated that only therapy with tamsulosin affected stone expulsion in his group of patients. We have the same opinion in this aspect regarding our patients, but we found also stone size has a predictive value for stone expulsion. The smaller the stone, the greater the chance of expulsion with earlier time. This can be clarified by the fact that small stone requires less energy to push it down the ureter since the friction between the stone and ureteral wall is less than that of larger stone. No serious side–effects were encountered in any patient during the study, but it is valuable to point out that abnormal ejaculation – mainly retarded ejaculation – was observed in 39% of male patients in tamsulosin group. Patients get benefit from therapeutic option of tamsulosin for ureterolithiasis since it encourages early stone expulsion without the requirement of hospitalization or ordinary endoscopic treatments. Moreover, if patients with distal ureterolithiasis can carry on their every day activities with their home treatment, without the need for a great number of analgesic injections, it will be likely to advise medical expulsive therapy with tamsulosin to be an alternative to endoscopic treatment in selected patients as patients in our study groups. It is true that the simplification of therapeutic schemes makes patient treatment easier. **CONCLUSION:** Medical Expulsive Therapy (MET) for lower ureterolithiasis with tamsulosin during conservative treatment period is safe and effective as demonstrated by the absence of serious side effects and increased stone expulsion rate with early time. Also MET with tamsulosin affords an outstanding control of pain for patients while waiting for stone expulsion.

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