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Efficacy of Silodosin in comparison with Tamsulosin in the medical expulsive therapy for ureteral calculi

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Abstract
Objectives*: To compare the efficacy of silodosin (8mg) versus tamsulosin (0.4mg), both in terms of the stone expulsion rate and the time to stone expulsion.*
Settings and Design*: A prospective and randomized controlled study was conducted in the department of Urology, Surgical Sub-Specialties Hospital, Medical City Complex in Baghdad.*
Patients and Methods*: Starting from October 2013, till September 2014; a total of 96 patients (M=56; F=40) who were between age group of 18–50 years, who had unilateral, non–impacted, uncomplicated middle or lower ureteral stones which were ≤ 1cm, were enrolled in a prospective study and they were randomized into two groups. Group 1 received tamsulosin (0.4mg), and group 2 received silodosin (8 mg) for a maximum period of 4 weeks. The patients were followed up weekly or biweekly with imaging studies.*
Main outcomes and Measures*: The primary endpoint was the stone expulsion rate, and the secondary endpoint was the time to stone expulsion.*
Statistical Analysis*: Student t-test was used to compare continuous variables, and the Chi-square test was used for categorical variables.*
Results*: stone expulsion rate was observed in 59% of patients in group 1 and in 80% of patients in group 2, which was statistically significant. There was also significant difference between groups with regard to mean time to stone expulsion.*
Conclusion*: Silodosin was more effective than tamsulosin with regard to stone expulsion rate and with a less mean time to stone expulsion.*
Keyword*: ureteric stone, silodosin, tamsulosin, medical expulsive therapy.*

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I. Introduction

Urinary stones have afflicted humankind since antiquity, with the earliest literary quotations to stone disease, describing symptoms and prescribing treatments to dissolve the stone, are observed within the medical texts of Asutu in Mesopotamia between 3200 and 1200 BC [(1)].

Ureteral stones occupy an important place in daily urological practice, that causing an acute attack of ureteral colic by obstructing the ureter. [(2)]

Of all urinary tract stones,ureteralstonesare 20% and 70% of these stones are located in the distal portion of the ureter. [(3)]

There has been a paradigm shift in the management of the ureteral calculi in the past decade, with the introduction of minimally invasive techniques and newer drugs [(4)]. An excellent results withrecent studies have reported with the medical expulsion therapy for the distal ureteral calculi, with alpha 1 `blockers [(5)].

Treatment Methods of ureterolithiasis:
I. Observation (also termed "watchful waiting"and"expectant management").
II. Medical expulsive therapy (MET).
III. Shock wave lithotripsy (SWL).
IV. Ureteroscopy (URS).
V. Percutaneous Antegradeureteroscopy (PAURS).
VI. Laparoscopic surgery.
VII. Open surgery [6, 7].

Indications for active removal of ureteral stones:
1. Stones with low likelihood of spontaneous passage {for example: stones associated with ureteric stricture,stones> 1 cm } [6].
2. Persistent pain despite adequate analgesic medication [7].
3. Persistent obstruction [7].
4. Renal insufficiency (bilateral obstruction,or single kidney,renal failure) [6].
5. The patient's employment (machinery, pilots) [4].

Medical expulsive therapy (MET):

Patients who have newly diagnosed ureteric stoneswho have no indication for active removal of ureteric stones (listed above) and of less than **10 mm** in size, may be offered appropriate medical therapy to facilitate stone passage during observation (Medical Expulsive Therapy) i.e. {the administration of drugs to facilitate stone passage} [6].

There is growing evidence that (MET) can be efficacious [6]. And the use of (MET) has become an accepted practice [2]. Meta-analyses have shown that patients with ureteral stones mangewithnifedipineor α-blockers are more likely to pass stones with less episodes ofureteiccolic than those not tacking such therapy [5, 8]. Tamsulosin, anadrenoceptorantagonist($\alpha_{1A,}$ α_{1D})iseffective medical agentsand the most popular one, which is used for the expulsive therapy (probably because of itslack of a need for dose titration upon initiation of treatmentand the excellent tolerability) [6]. Silodosin, a recently introduced selective α_{1A}adrenoceptor antagonist, has shown promising results with fewer side effects and a better efficacy [9].

Factors affecting medical expulsion therapy:
1. Stone size: MET is less likely to increase the stone-free rate,due to the high likelihood of spontaneous passage of stones up to ~5 mm,. [10-13]
2. Stone location: The vast majority of trials have investigated distal ureteral stones. [4] One randomized clinically controlled trial (RCT) has assessed the effect of tamsulosin on spontaneous passage of proximal ureteral calculi 5-10 mm [14]. The main effect was to encourage stone migration to a more distal part of the ureter. [14]
3. Medical expulsive therapy after extracorporeal shock wave lithotripsy (SWL): Clinical studies and several meta-analyses have shown that MET after SWL for ureteral or renal stones can expedite expulsion and increase stone free rate and reduce analgesic requirements. [15-17]
4. Medical expulsive therapy after ureteroscopy: Medical expulsive therapy following holmium: YAG laser lithotripsy increases stone free rates and reduce colic episodes. [18]
5. Duration of medical expulsive therapy treatment: Most studies have had duration of 30 daysor1 month [19].

Alpha 1 adrenoceptors (ARs) are a class of proteins belonging to the G protein-coupled receptor family [20]. Molecular heterogeneity in $\alpha_1$adrenoceptors has been widely documented by gene cloning technologies and three different subtypes have been cloned,according to the indications of the International Union of Pharmacology,pharmacologically characterized and named α_{1A}, α_{1B}, and α_{1D} [21].

The distribution of these α1 adrenoceptors in human ureter was studied using quantitative real-time PCR and α1 adrenoceptors was found that each ureteral region was endowed with mRNA encoding $\alpha_1$adrenoceptors subtypes, although with differences in terms of the amount expressed and receptor distribution [21].The α_{1A} subtype accounted for about 38% of total adrenoceptors[22].The α_{1D} subtype mRNA was highly expressed in each ureteral region, accounting for about 54% of total adrenoceptors mRNA [22]. The α_{1B} subtype accounted for about 8%[21]. In the proximal and middle ureter, the distribution of adrenoceptors was $\alpha_{1D} \geq \alpha_{1A} > \alpha_{1B}$, like that of the total ureter [22]. The α_{1D} subtype expression was significantly higher than the α_{1A} subtype expression. In the distal ureter, the distribution of adrenoceptors was $\alpha_{1D} > \alpha_{1A} > \alpha_{1B}$[22].The distal ureter expressed the highest amount of α_{1D}adrenoceptors subtype [22].

Alpha1A-adrenoceptors that is primarily located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra.Silodosin is a highly selective forthese receptors. Blockade of these alpha$_{1A}$-adenoceptors causes smooth muscle in these tissues to relax [23].

Silodosin has been demonstrated in vitro that the $alpha_{1A}$: $alpha_{1B}$ binding ratio of silodosin is (162:1) which is extremely high [(24)].it has a substantially lower affinity for $alpha_{1B}$-adrenoceptors that are primarily located in cardiovascular system [(23)].

Tamsulosin exhibits selectivity for both $alpha_{1A}$ and $alpha_{1D}$ receptors over the $alpha_{1B}$adrenoceptor subtype [(26).] These three AR subtypes have a distinct distribution pattern in human tissue [(22)]. Tamsulosin hydrochloride is an $alpha_1$adrenoceptor (AR) blocking agent used for the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) [(25)]. Whereas approximately 70% of the alpha1-receptors in human prostate are of the $alpha_{1A}$ subtype, the human bladder contains predominantly the $alpha_{1D}$ subtype while blood vessels express predominantly $alpha_{1B}$ subtype [(27)].

Aim of Study

The objective of this study was to compare the efficacy tamsulosin (0.4 mg)versussilodosin (8 mg), once daily, both in terms of the stone expulsion rate and the time to stone expulsion.

II. Patients And Methods

Starting from October 2014, till September 2015; a total of 96 patients (F=56; M=40) who were in the age group (17–60)years, and hadnon–impacted, unilateral, uncomplicated loweror middle ureteral stones which were ≤ 0.9cm, were enrolled in a prospective study and they were randomized into two groups.

The patients were selected at the urology unit, in Surgical Sub-Specialties Hospital, Medical City Complex in Baghdad.

The Study Exclusion criteria:

1. Diabetes Mellitus.
2. Urinary tract infection.
3. Severe hydronephrosis.
4. Hypotension.
5. Ureteral strictures.
6. Multiple stones.
7. Solitary kidney.
8. Current use of any type of alpha-blocker.
9. Asthma and gastrointestinal ulcers.
10. Stones larger than 10 mm in greatest dimension.

The sample size of the study was arbitrarily determined. The patients were diagnosed by unenhanced computed tomography (CT) scans and re-evaluated withultrasonography, plain X–ray and unenhanced (CT) scans whenever they were necessary. The stone size was calculated on the CT scan by using a digital ruler and the greatest dimension of the stone was taken into consideration as the stone size.

All the patients provided informed written consents and they were properly informed about the study in which they would be enrolled.

The patients were randomly allocated into two treatment groups of 48 patients each. The patient demographics in the two groups,in terms of the size of the stones in the two groups, their locations in terms of the laterality and their locations in the ureter. GroupA received tamsulosin (0.4 mg) daily, whereas Group B received silodosin (8 mg) daily, for a maximum period of 6 weeks.

All the patients were prescribed the 50 mg diclofenac tablet on demand for pain relief. The patients were advised that on experiencing an episode of unbearable ureteric colic, they should immediately report to us. The patients were followed up weekly or 3 times weekly with X–rays of the abdomen and the pelvis and ultrasonography. The patients were instructed to record the time and date of the stone passage. The follow up continued until the stone spontaneously passed, as reported by the patient, or for a maximum period of 6 weeks. The primary endpoint was the stone expulsion rate and the secondary endpoints were the stone expulsion time.

The stone expulsion rate was defined as the percentage of patients that spontaneously pass their stones within the follow up period (i.e.6 weeks), whereas the stone expulsion time was defined as the number of days from the random allocation to the stone expulsion.

The statistical analysis was performed by using the Student's t-test to compare continuous variables between the two groups, and the Chi–square test was used for categorical variables. A p value of < 0.05 was considered to be statistically significant.

III. Results

Four patients in Group A and six patients in Group B were lost to follow-up, with 86 patients remaining for per-protocol analyses. No significant differences were found between the groups with respect to age, stone size, or stone location (Table 1). Spontaneous stone expulsion was observed in 26 of 44 patients (59%) in Group A and in 34 of 42 patients (80%) in Group B (P=0.027). The stone expulsion rate was significantly higher in Group B than in Group A. There was also a significant difference between the groups with regards to the mean stone expulsion time (p= 0.01). The mean expulsion time was 19.5 ± 7.5 days in Group A vs. 12.5 ± 3.5 days in Group B (Table 2).

In table (1) we notice that despite the random allocation of the patients into the two treatment groups, the difference in stone size, stone location, sex of the patients and laterality was not significant; meaning that the difference in these variables is negligible, and there was no bias in patients' randomization.

(Table 1): Demographic data of the two study groups

NO. of patients	**Group A (n=44) (tamsulosin)**	**Group B (n=42) (silodosin)**	**P value**
Sex: **Male** **Female**	 25 19	 27 15	0.47
Mean age± SD(years)	37±11	35±10	0.22
Mean stone size±SD(mm)	6.9±1.9	7.0±2.1	0.51
Stone location: **Left** **Right**	 23 21	 25 17	0.49
Stone position: **Lower ureter** **Mid ureter**	 18 26	 23 19	0.19
None of the differences are statistically significant.			

(Table 2): Results according to treatment

Endpoint	**Group A (n=44) (tamsulosin)**	**Group B (n=42) (silodosin)**	**P value**
Primary end point: Stone expulsion rate	26/44 (59%)	34/42 (80%)	0.027
Secondary end point: Time to stone expulsion (days).	19.5±7.5	12.5± 3.5	0.01
Both differences are statistically significant			

IV. Discussion

Ureteral colic, which is mainly due to stones, represents 1 to 2% of the emergency room admissions [(28)].With the introduction of effective medical therapeutic agents in the market,there has been a significant improvement in the medical management of the ureteral calculi [(5, 8, 12)].

Several studies findings indicate that alpha blockers facilitate ureteral stone passage while nifedipine may provide a marginal benefit [(6)]. These have demonstrated that this approach may facilitate and accelerate the spontaneous passage of ureteral stones [(2, 5, 15)].Similar findings have been reported by Hollingsworth and associates, who recently performed a meta-analysis of studies involving alpha blockers or nifedipine in patients with ureteral stones [(29)]. The likelihood of a ureteral stone passage is dependent on several factors, which include the stone size and the location and the ureteral conditions [(12-14)]. Ibrahim AI *et al.* has demonstrated that stone passage rates between 71–98% for the distal ureteral stones which are less than 5 mm and from 25–53% for those which are between 5 and 10 mm [(30)].

The role of adrenergic receptors in the human ureter was first described in 1970. [(31)] It was shown later, that the alpha–adrenergic receptors were classified into three different subtypes of α_{1A}, α_{1B} and α_{1D}, of which the distribution in the human ureter was $\alpha_{1D}>\alpha_{1A}>\alpha_{1B}$ [(22)].

It was also shown that the alpha-adrenergic receptor agonists had a stimulatory effect on the ureteral smooth muscle, whereas the beta-adrenergic receptor agonists had an inhibitory effect [(32)].The alpha-adrenergic receptor agonists prevent the uncoordinated muscle activity which is seen in renal colic, while maintaining ureteral peristalsis, which might facilitate a spontaneous stone passage [(33)]. The alpha blockers mainly produce relaxation of the distal human ureter by reducing the ureteric smooth muscle tone rather than completely ablating its activity [(33)]. Two meta–analyses provided a high level of evidence for the clinical benefit of the alpha blockers in the patients with distal ureteral calculi, in which the patients who were given alpha blockers had 52% and 44% greater likelihoods of stone passage than those who were not given such treatment. [(29, 34)]

The treatment effect on the expulsion rate was partially lost, as the sizes of the stones decreased, because of the high spontaneous expulsion rate of the small stones [(4)]. By way of example only, De Sio*et al*.,

Wang *et al*., and Yilmaz*et al*. reported better stone expulsion rates (81%, 79%, AND 90%,respectively) in patients who received 0.4 mg tamsulosin daily than in controls (54%, 53%, AND 58%,respectively)[35-37]. Although most of the studies used tamsulosin, which is a selective α_{1A}/α_{1D} adrenergic receptor antagonist, the efficacies of the other alpha blockers such as doxazosin, terazosin, alfuzosin and naftopidil were also indicated [36, 38,39].Wang *et al*., Yilmaz*et al*., and Agrawal*et al*. demonstrated the efficacy of α1-adrenoceptor antagonists in the management of lower ureteral stones regardless of the type of alpha-blocker used [36,37, 40].

Many studies have been published on α1-adrenoceptors in the human ureter since the first report in 1970,Malin*et al*. first described the presence of α- and β-adrenoceptors through the entire length of the human ureter and the physiological response (increased tone and frequency of contractions) of the ureter when exposed to α adrenoceptor agonists [31]. In 2005, Sigala*et al*. found that α_{1D}- and α_{1A}-adrenoceptors were expressed in significantly larger amounts than α_{1B}-adrenoceptors in the human ureter, and these authors also demonstrated that the distal ureter expressed a greater amount of α1-adrenoceptor mRNA than the proximal and middle ureter [41]. Itoh*et al*. reported that α_{1D}-adrenoceptor mRNA is more highly expressed than α_{1A}-adrenoceptor mRNA in each region of the ureter [33].

According to their results, an α_{1D}-adrenoceptor blocker can be expected to be more effective for the expulsion of ureteral stones than an α_{1A}-adrenoceptor blocker [22, 41]. However, Tomiyama*et al*. reported that, in the hamster ureter, ureteral contraction was mediated mainly by α_{1A}-adrenoceptors, even though α_{1D}adrenoceptors were more prevalent [42]. Recently, it was found that α_{1A}adrenoceptors is the main participant in phenylephrine-induced ureteral contraction in the human isolated ureter [43].**Our results indicate that an α_{1A}-adrenoceptor blocker is more effective than an α_{1D}-adrenoceptor blocker with respect to stone expulsion rate and the time to stone expulsion suggesting more clinical usefulness of α_{1A}-adrenoceptor blockers.**

Silodosin was approved for BPH by the US Food and Drug Administration in October 2008 [44]. Silodosin is a highly selective α_{1A}-adrenoceptor antagonist, which has 56-fold affinity for α_{1A}-over α_{1D}-adrenoceptors [33].

Our study has compared the efficacy betweentamsulosinandsilodosin and our results are also very encouraging with stone expulsion rate of (80%) in group B who received silodosin (8 mg) compared to (59%) of group A who received tamsulosin (0.4 mg) which was a significant difference (P value =0.027). Regarding the incidence of the retrograde ejaculation, which is the most common side effect of silodosin (which has been stated to be very common among other side effects) [45-49], there has been a consensus among many urologists, that its occurrence should be considered as a sign of the efficacy, rather than an adverse effect of the treatment [45]. Silodosin appears to relax the smooth muscles ofthe genital tractand the lower urinary tract enough to induce a retrograde ejaculation [46]. This was reflected in the finding that the patients who had the greatest relief from the lower urinary tract symptoms had a higher likelihood of the retrograde ejaculation [46]. This observation suggests that the retrograde ejaculation is actually an indirect indicator of the relaxation of the smooth musculature thatinducedbysilodosin[48]. The advantage of the medical expulsive therapy is important, because the risks which are related to a surgical intervention are not trivial [50]. Studies have reported the overall complication rates after ureteroscopic lithotripsies to be 11–22%, with major complications such as ureteral perforations, avulsions and strictures occurring during 4–6% of the procedures [50]. Urinomas and sub capsular bleeds have been reported in16–33% of the patients who are treated with shock wave lithotripsy (ESWL) [51].

Therefore the medical expulsive therapy should be offered as a cost-effective treatment for the patients with distal ureteral calculi, who are amenable to a waiting management.

Limitations encountered during study were: (1) Relatively small sample size, and (2) The cost of silodosin was much higher than any available alpha blocker.

V. Conclusions

From this study we identified that:

1. Silodosin (as an example of a selective α_{1A}-adrenoceptor antagonist) was more effective than tamsulosin (as an example of an α_{1D} and α_{1A}-adrenoceptor antagonist) with respect to stone expulsion rate for ureteral stones and the time to stone expulsion, despite the abundance of α_{1D}-adrenoceptors in human ureter.
2. A conservative approach should be considered as an option in the management of the uncomplicated, small, distal ureteral calculi.

VI. Recommendations

1. We recommend the use of silodosin in the medical expulsive therapy for ureteric stones, since it is clinically superior to tamsulosin in this type of therapy.
2. Further studies on medical expulsive therapy for ureteric stones, are required to determine the superiority of α_{1A}adrenoceptor antagonist (silodosin) versus α_{1D}/α_{1A}adrenoceptor antagonist (tamsulosin). These studies should include larger sample size.

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