A Review of the Role of Silodosin as Medical Expulsive Therapy for Ureteral Stones

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Abstract

Urolithiasis is a chronic human condition that has immense public health importance and it poses a tremendous economic burden on our society. Medical expulsive therapy (MET) for the treatment of ureteral stones has emerged as a cost-effective approach. In the last few years, a number of drugs have been introduced and used successfully as MET for the expulsion of small, uncomplicated ureteral calculi. Using a selective α-adrenoceptor blocker for MET has emerged as an effective treatment approach and is widely used for ureteral stones. Silodosin, a selective α-blocker, has a higher selectivity for the α1A receptor as compared to other agents in the class. The objective of this review is to determine the efficacy and safety of Silodosin in MET as compared to placebo and Tamsulosin.

Keywords: Ureteral Stone Expulsion, Urolithiasis, alpha-1 adrenoceptor blocker, Silodosin, Tamsulosin

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Introduction

Owing to its high prevalence and occurrence, urolithiasis is a major health-care concern and it accounts for a large economic burden on our society. It is a multifactorial and recurrent disease that is often encountered in routine clinical practice. Urolithiasis is the third most common urinary tract disease after urinary tract infections and pathologic condition of the prostate.[1] Around 5-10% of the population suffers from urolithiasis. The increasing prevalence of ureteric stones in this era is of great concern as it is associated with diminished quality of life.[2]

In Asia, urolithiasis affects about 1 -19.1% of the population. However, the prevalence and occurrence in various countries or areas have varied over the years due to differences in socio-economic status and geographic locations. The prevalence of urolithiasis is 5-19.1% in West Asia, Southeast Asia, South Asia, as well as some developed countries (South Korea and Japan), whereas in most of East Asia and North Asia, it is only 1-8%. In South Asia, the prevalence of urolithiasis is much higher due to high temperatures and excessive exposure to sunlight.[3]

In India in the 1960s, the incidence was lower than 40/100000, but it grew dramatically to 930/100000 three decades later. The rate of recurrence after 3–5 years ranges from 21-53%. [3] Renal stones are most prevalent

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between 20 and 40 years of age and are 3 times higher in men than in women.[4] 22% of all urinary tract stones are in the ureter, 68% of which are found in the distal ureter. This article will focus primarily on distal ureteral stones. [4]

Treatment of Ureteral Stones

The appropriate treatment approach is determined by the size, location and composition of the stone, severity of the obstruction and symptoms. [4] In the last decade, there has been a paradigm shift in the management of ureteral stones, with the introduction of lesser invasive methods and availability of newer pharmacological agents. [5]

Minimally invasive therapies, such as extracorporeal shock wave lithotripsy and ureterolithotripsy, represent effective treatment modalities. These procedures nonetheless imply high costs and are not risk-free. In up to 50% of cases, a watchful waiting approach has been reported to be associated with spontaneous stone expulsion but some complications may occur, such as urinary tract infections, hydronephrosis and colic events. As a consequence of improvements in pharmacological treatment, the use of a proactive waiting strategy has been expanded, which can minimize symptoms and promote stone expulsion.[2] Medical expulsive therapy (MET) has emerged as an alternative strategy and is becoming increasingly popular since it effectively reduces symptoms and facilitates stone expulsion. [1,2]

Efficient MET offers many possible benefits. First, it can decrease the duration of symptoms associated with ureteral stone, and thus the risk of complications such as urinary tract infection (UTI), hydronephrosis, and impairment of kidney function. Secondly, MET can potentially decrease the use of more invasive interventions, such as ESWL and ureteroscopy, and thus may decrease the rate of possible complications associated with these procedures. Finally, MET is likely to spare scarce healthcare resources, such as doctor's time and hospital beds. [6]

Several randomized trials have confirmed the efficacy of MET pertaining to the reduction in pain associated with stone passage, increase stone expulsion rate, decrease the stone expulsion time, decrease the need for analgesics and reduce the need for surgery. MET has now become an accepted treatment tool, involving the use of several drugs acting on ureter by different mechanisms. [2]

Clinical evidence suggests that MET should be indicated when calculi are small (≤10 mm), located in the distal part of the ureter, and with no clinical evidence of infection and pain. [7]

MET with various drugs belonging to pharmacological classes like alpha-blockers, calcium channel blockers (CCBs) and phosphodiesterase-5 inhibitors (PDEI) has been described in the literature. [8] Alpha-1 blockers are the most frequently used class of drugs for MET.

α_1 - Blockers in MET

The α-blockers were initially developed for the management of hypertension; however due to their relaxing properties on the urinary tract and the bladder, they are now used successfully in the management of benign prostatic hyperplasia (BPH). Their usage in the treatment of distal ureteral stones originated from the idea that they could induce a selective relaxation of the ureteral smooth muscle, which could inhibit ureteral spasms and dilate the ureteral lumen, thereby facilitating the stone passage. [5]

Various α-blockers like Silodosin, Tamsulosin, Naftopidil, Terazosin, Doxazosin have been used for MET.

α1-adrenergic receptors are located throughout the human ureter. The function of α1-adrenergic receptors situated in the human ureter was first described in 1970 by Malin et al. Stimulation of the α1-adrenergic receptors with agonists increases the force of ureteral contraction and the frequency of ureteral peristalsis, whereas antagonism of the receptors with α1-blockers has the opposite effects. [2,9,10]

α1 blockers decrease the force of ureteral contraction, the frequency of peristaltic contractions, and increase the amount of fluid bolus transported down the ureter. These responses aid in the passage of ureteral stone. [9]

Clinical evidence suggests that α1-blockers are highly effective in increasing the expulsion rate of distal ureteral stones, reducing the time to stone passage, and decreasing the amount of pain medication needed during the passage of stones. The role of α1 -blockers in MET has been well described. [8,9]

The meta-analysis conducted by Thijs *et al*, included 67 studies with 10,509 participants overall. Result based on overall analysis showed that treatment with alpha blockers result in a large increase in stone clearance (risk ratio (RR) 1.45, 95% confidence interval (CI) 1.36 to 1.55). Patients treated with α-blockers experience shorter stone expulsion times (mean difference (MD) -3.40 days, 95% CI -4.17 to -2.63), less diclofenac (MD -82.41, 95% CI -122.51 to -42.31), and likely

require fewer hospitalisations (RR 0.51, 95% CI 0.34 to 0.77), corresponding to 69 fewer hospitalisations (95% CI 93 fewer to 32 fewer) per 1000 participants. A predefined subgroup analysis (test for subgroup differences; P = 0.002) suggests that effects of alpha-blockers may vary with stone size, with RR of 1.06 (95% CI 0.98 to 1.15; P = 0.16; I^2 = 62%) for stones 5 mm or smaller versus 1.45 (95% CI 1.22 to 1.72; P < 0.0001; I^2 = 59%) for stones larger than 5 mm. [6]

Sridharan *et al* conducted a meta-analysis comparing effectiveness of α-blockers, CCB, PDEI and spasmolytics in MET. A total of 114 studies for systematic review and 108 studies for the network meta-analysis were included. α-blockers, PDEI, and combined α-blockers and corticosteroids had significantly increased stone expulsion rate (SER) and shorter stone expulsion time (SET) than placebo or standard of care. α-blockers have the highest probability of being the 'best' in the pool with regard to SER. This effect persisted in patients with stones ≥ 5 mm, children, after shockwave lithotripsy, proximal ureteric stones and distal ureteric stones. Statistically significant increase in the expulsion rate and shorter expulsion time with α-blockers, PDEI and combined α-blockers with corticosteroid was observed. It was concluded that of these interventions, α-blockers have the high probability of being the 'best'. [20]

Role of α_1 Receptor Subtype in Ureter

The α1 adrenergic receptor is a G protein-coupled receptor. Pharmacologic studies and receptor cloning have identified at least three α1 adrenergic receptor subtypes: α_{1A}, α_{1B}, α_{1D}. [11]

Sigala *et al*, conducted molecular and pharmacological characterization of α1 receptors subtypes in human ureter. The result suggested that α_{1A}, α_{1B} and α_{1D} receptors are present in the human ureter, although the amount expressed differed. The human ureter was endowed with each α1 receptor subtype, although α_{1D} and α_{1A} receptors were prevalent over α_{1B} receptors.

It has also been shown that the highest density of α1 receptors is in the distal ureter in comparison to medial and proximal ureters. [12]

Itoh *et al*. reported that α_{1D}-adrenoceptor mRNA is more expressed in each region of the ureter than α_{1A} receptor mRNA and the highest amount of α_{1D} receptors are expressed in the distal ureter. Also, the distribution of alpha receptors in the ureter was $\alpha_{1D} \geq \alpha_{1A} \geq \alpha_{1B}$. [13]

Table 2: Distribution of α1-adrenoceptor (AR) subtypes in the human ureter. [13]

α_1 receptor subtype	Percentage (%)
α_{1D}	54%
α_{1A}	38%
α_{1B}	8%

These results suggest that α_{1D} receptor blockers may be effective in the expulsion of ureteral stones than a α_{1A} receptor blocker. However few animal studies have confirmed that ureteral contraction is mainly mediated via α_{1A} receptor even though α_{1D} are more prevalent in ureter.[14,15] Sasaki et al conducted an in-vitro study on ureteral specimens obtained from patients undergoing nephrectomy. The results suggested that the α_{1A} subtype plays the predominant role in contraction in the human ureter than the α_{1D} receptor. [16]

The explanation pertaining to the predominant role of the α_{1A} receptor and low involvement of the α_{1D} receptor in ureteral contraction can be explained by the fact that α_{1A} receptor subtype is expressed both on the cell surface and intracellularly whereas the α_{1D} subtype is expressed only intracellularly having little or no expression on the cell membrane in human ureteral smooth muscle. In addition, the α_{1D} receptor is constitutively active and is thus localized to intracellular compartments involved in the re-

Table 1: Studies demonstrating the efficacy (stone expulsion rate and time) of alpha blockers compared to placebo.

	Stone Expulsion Rate (SER)			Stone Expulsion Time (SET)		
	With α_1-Blocker	**Without α_1-Blocker**	***P Value***	**With α_1-Blocker**	**Without α_1-Blocker**	***P Value***
Cervenakov [21]	80.4%	62.8%	*N/A*	*N/A*	*N/A*	*N/A*
Dellabella [22]	100%	70%	0.001	65.7 hrs	111.1 hrs	*0.02*
Resim [23]	86.6 %	73.3%	0.196	*N/A*	*N/A*	*N/A*
De Sio M [24]	90%	58.7%	0.01	4.4 days	7.5 days	0.005
Yilmaz [25]	76-79%	53.57%	0.03-0.04	5.75 - 6.31 days	10.54 days	0.03-0.04
Porpiglia [26]	85%	43%	<0.001	7.9 days	12 days	0.02
Dellabella M [27]	97.1%	64.3%	< 0.0001	72 hrs	120 hrs	<0.0001
Itoh et al [28]	52.2%	30.4%	0.036	10.27 days	15.19 days	0.0058
Sur et al [29]	52%	44%	0.2	NA	NA	NA

cycling of receptors. [16, 17,18]

Since α_{1A} receptor plays an important role in ureteral smooth muscle contraction, drugs blocking α_{1A} receptor are effective in relaxing ureteral smooth muscles and thereby facilitate the expulsion of ureteral stones.

In the clinical study conducted by Tsuzaka *et al* to determine the efficacy of selective α_{1D} adrenoceptor antagonist Naftopidil and the selective α_{1A} -adrenoceptor antagonist Silodosin, it was observed that α_{1A}-adrenoceptor blocker was more effective than an α_{1D}-adrenoceptor blocker with respect to stone expulsion rate, suggesting more clinical usefulness of α_{1A}-adrenoceptor blockers. [19]

Silodosin in MET

Silodosin is a highly selective α_{1A}-receptor antagonist indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). [30]

Silodosin has the highest uro-selectivity of all the α1 receptors known to date. [1]

Silodosin has a low affinity for α_{1B}-adrenoceptors in the cardiovascular system. In vitro, the affinity of Silodosin for α_{1A}-adrenoceptors was approximately 580-fold greater than for α_{1B} -adrenoceptors and approximately 55-fold greater than for α_{1D} -adrenoceptors. By contrast, Tamsulosin had 15-fold greater affinity for α_{1A}-versus α_{1B} - adrenoceptors and 3- fold greater affinity for α_{1A} versus α_{1D} -adrenoceptors. [30]

Table 3: Selectivity of α-blockers

	Silodosin [30]	Tamsulosin[31]	Alfuzosin [32]	Naftopidil [31]
α_{1A}	580	15	0.5	0.372
α_{1D}	55	3.8	1.4	1.78
α_{1B}	1	1	1	1

High α_{1A} selective of Silodosin suggests that it has the potential to cause ureteral smooth muscle relaxation, while minimizing undesirable CVS side effects like postural hypotension.[1]

Meta- analysis conducted by Wei *et al*, indicated that Silodosin was superior to placebo or Tamsulosin in the management of distal ureteral calculi with better control of pain. The safety profile of Silodosin was similar to Tamsulosin, though retrograde ejaculation was worse for Silodosin use. It was conclude that Silodosin might have potential as a MET for ureteral stones.[2]

In the study conducted by Sur *et al*, no significant differences between the Silodosin and placebo groups were observed for passage rate of all stones (52% vs 44%, respectively; p = 0.2). However, the passage rate of distal ureteral stones was significantly higher with Silodosin than placebo (69% vs 46%, respectively; p = 0.01). Significant differences were not observed for emergency room (ER) visits, hospital admission, or use of analgesics.[29]

Itoh *et al*, conducted a prospective randomized study to evaluate the effects of Silodosin as a MET for distal ureteral stones. The expulsion rate for stone ≥ 5 mm was 17.9 % (n=28) for patients receiving 2 L of water (control) and 75.9% (n=29) for the patients receiving Silodosin along with 2 L of water daily (P = 0.001). The expulsion time was 13.40 ± 5.90 and 9.29 ± 5.91 days, respectively (P = 0.012). Analgesics were required 1.5 ± 3.1 and 0.3 ± 0.9 times, respectively (P = 0.382). [35]

Silodosin vs Tamsulosin

Dell'Atti L. compared the effectiveness of Silodosin and Tamsulosin in the expulsion of distal ureteral stones measuring 4 to 10 mm. A total of 136 patients (aged 18 years or older) were enrolled in the study. Group 1 (67 patients) received Tamsulosin 0.4 mg daily and group 2 (66 patients) received Silodosin 8 mg daily for 3 weeks. A significant increase in the expulsion rate was found in patients treated with Silodosin (80.3%, 53 out of 66) in comparison to Tamsulosin (61.2%, 41 out of 67 patients); Silodosin showed a statistically relevant advantage in terms of stone expulsion rate (p: 0.003) as well as in terms of expulsion time (weeks) (p: 0.002). No severe complications were recorded. [7]

Yuan-Pin *et al*, conducted a meta-analysis to assess the efficacy and safety of Silodosin compared to Tamsulosin for treating ureteral stones <10 mm in diameter. Sixteen randomized controlled studies (RCTs) and observational studies with 1824 patients were included in the study. Silodosin achieved significantly higher expulsion rates than Tamsulosin (pooled risk difference (RD): 0.13, 95% confidence interval (CI): 0.09 to 0.18). A subgroup analyses showed that Silodosin had a significantly higher expulsion rate on stone sizes of 5±10 mm than Tamsulosin (pooled RD: 0.14, 95% CI: 0.06 to 0.22, I2 = 0%). The superior effect was not observed on stone sizes <5 mm. Patients receiving Silodosin also probably had a significantly shorter expulsion time (pooled mean difference (MD): -2.55 days, 95% CI: -4.06 to -1.04, I2 = 85%) and may have fewer pain episodes (pooled MD: -0.3, 95% CI: -0.51 to -0.09) but a higher incidence of retrograde ejaculation by 5% compared to those receiving Tamsulosin.

It was concluded that compared to Tamsulosin, Silodosin provided significantly better stone passage

Table 4: Various studies demonstrating the efficacy (stone expulsion rate and time) of Silodosin compared to placebo and other α blockers.

Study	Experimental group (Sample size and Dose)	Control group (Sample size and Dose)	Duration of treatment	Stone location and size range	Outcome examined	Result
Itoh et al [28]	Silodosin N= 95 Dose- 8 mg /day	Blank control N= 92	8 weeks	Symptomatic unilateral ureteral calculi of less than 10 mm	-Stone Expulsion rate -Stone Expulsion time -Need for analgesics	**Mean Expulsion Time** • **Overall** - 15.19 ± 7.14 days for Control group and 10.27±_ 8.35 days for Silodosin group • **For distal ureteral stones** – 13.40 ± 5.90 days for Control group and 9.29 ± 5.91 days for Silodosin group. • **For stones of 1–5 mm in diameter** - 14.28 ± 6.35 days for Control group and 9.56 ±8.45days for Silodosin group • **For stones of 6–9 mm in diameter** - 21.00 ± 9.9days for Control group and 11.33 ± 8.31days for Silodosin group. **Mean Expulsion Rate** **For stones of 6–9 mm in diameter -** 30.4% for Control group and 52.2% for Silodosin group.
Sur et al [29]	Silodosin N=115 Dose -8 mg /day	Placebo N=117	4 weeks	Unilateral ureteral calculus of 4–10 mm.	-Stone Expulsion rate -Stone Expulsion time	Stone Expulsion rate • Silodosin – 52 % • Placebo – 44%
Tsuzaka et al [19]	Silodosin N= 31 Dose -8 mg /day	Naftopidil N =33 Dose-50 mg/day	6 weeks	Symptomatic unilateral ureteral calculi of less than 10 mm	-Stone Expulsion rate -Stone Expulsion time	Stone Expulsion rate Silodosin – 81 % Naftopidil – 61% No significant differences were noted in stone expulsion time
Gupta et al [5]	Silodosin N= 50 Dose -8 mg /day	Tamsulosin N= 50 Dose - 0.4 mg/day	4 weeks	unilateral, uncomplicated middle or lower ureteral stones less than 10 mm	-Stone Expulsion rate -Stone Expulsion time	Stone Expulsion rate • Silodosin – 82 % • Tamsulosin – 58% No significant differences were noted in stone expulsion time. Lower analgesic use was found in Silodosin group.
Dell'Atti et al [7]	Silodosin N= 66 Dose -8 mg /day	Tamsulosin N= 67 Dose-0.4 mg/day	3 weeks	Single, unilateral, radiopaque, proximal ureteral stone (range 4-10 mm in size)	-Stone Expulsion rate -Time to expulsion	Stone Expulsion rate • Silodosin – 80.3 % • Tamsulosin – 61.2% Silodosin showed a statistically significant advantage in terms of expulsion time (weeks) (p: 0.002)
Kumar et al [4]	Silodosin N=90 Dose -8 mg /day	Tamsulosin N=90 Dose-0.4 mg/d Tadalafil N=90 Dose - 10 mg OD	4 weeks	Distal ureteric stones of size 5-10 mm	-Stone Expulsion rate -Stone Expulsion time -Analgesic use	Stone Expulsion rate • Silodosin – 83.3 % • Tamsulosin – 64.4% • Tadalafil – 66.7% Stone Expulsion time • Silodosin – 14.8 ± 3.3 days • Tamsulosin – 16.5 ± 4.6 days • Tadalafil – 16.2 ± 4.2 days Analgesic use (mg) • Silodosin – 195 ±10.2 • Tamsulosin – 220 ±10.8 • Tadalafil – 215 ± 12.4
Elgalaly et al [33]	Silodosin N=55 Dose -8 mg /day	Tamsulosin N=56 Dose-0.4 mg/d	4 weeks	Unilateral distal ureteric stones of ≤10 mm	-Stone Expulsion rate -Stone Expulsion time -Analgesic use	Stone Expulsion rate • Silodosin – 83% • Tamsulosin – 57% There were fewer ureteric colic episodes and less analgesic requirement in Silodosin group.
Imperatore	Silodosin	Tamsulosin	4 weeks	Unilateral	-Stone Expulsion rate	Stone Expulsion rate

contd../-

Table 4 continue

et al [34]	N=50 Dose -8 mg /day	N=50 Dose-0.4 mg/d		distal ureteric stones of ≤10 mm	-Stone Expulsion time	• Silodosin – 88% • Tamsulosin – 82% Stone Expulsion time • Silodosin – 6.7 days • Tamsulosin – 6.5 days
Itoh et al [35]	Silodosin N=56 Dose -8 mg /day	Blank Control N=56	4 weeks	Symptomatic unilateral distal ureteral calculi of less than 10 mm	-Stone Expulsion rate -Stone Expulsion time -Analgesic use	Stone Expulsion rate • Silodosin – 72.7% • Control – 55.3% Stone Expulsion time • Silodosin – 9.29 ± 5.91 days • Control – 13.40 ± 5.90 days Analgesic required • Silodosin – 0.3 ± 0.9 times • Control – 1.5 ± 3.1 time
Gharib et al [36]	Silodosin N=75 Dose -8 mg /day	Tamsulosin N=75 Dose-0.4 mg/d	4 weeks	Single unilateral stone 10 mm or less	-Stone Expulsion rate -Stone Expulsion time	Stone Expulsion rate • Silodosin – 82.4% • Tamsulosin – 61.5% Stone Expulsion time • Silodosin – 9.4 ± 3.8 days • Tamsulosin – 12.7 ± 5.1 days
Wang et al [37]	Silodosin N=62 Dose -8 mg /day	Control (N= 61)	2 weeks	Radiopaque distal ureteral stones less 10 mm in size	-Stone Expulsion rate -Stone Expulsion time	Stone Expulsion rate • Silodosin – 72.42% • Control – 54.1% Stone Expulsion time • Silodosin – 6.31 ± 2.13 days • Control – 9.73 ± 2.76 days

for patients with ureteral stones (particularly for sizes of 5~10 mm), shorter expulsion times, and fewer pain episodes but caused a higher incidence of retrograde ejaculation.[38]

Silodosin - Safety and Tolerability

Silodosin is generally well tolerated with the majority of reported adverse events being of mild severity and did not require cessation of therapy in any patient.[2, 30]

The most common adverse effect reported with Silodosin is retrograde ejaculation. However, retrograde ejaculation resolves completely within a few days of discontinuing treatment.[1]

Regarding the incidence of the retrograde ejaculation, there is 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. Silodosin appears to relax the smooth muscles of the lower urinary tract and the genital tract enough to induce a retrograde ejaculation. 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 retrograde ejaculation. This observation suggests that the retrograde ejaculation is actually an indirect indicator of the relaxation of the smooth musculature induced by Silodosin.[5]

Dizziness, orthostatic hypotension, headache, nasal congestion, backache, diarrhoea and abnormal ejaculation are also reported with the usage of Silodosin.[2]

Orthostatic hypotension is commonly associated with nonselective α_1 adrenoceptor antagonists such as doxazosin and terazosin. However, Silodosin was associated with a low risk of orthostatic hypotension in clinical trials. The incidence of orthostatic hypotension was 1.3% in Silodosin recipients and 1.1% in placebo recipients in the pooled analysis of the US and European trials. [30]

The low risk of orthostatic hypotension associated with Silodosin is presumably reflective of its high selectivity for α_{1A} adrenoceptors over α1B adrenoceptors. [30]

Retrospective analysis carried out by Imperatore et al found that Silodosin is associated with a lower incidence of peripheral vasodilation-related side effects such as orthostatic hypotension and dizziness but a higher incidence of retrograde ejaculation compared with Tamsulosin.[34]

Conclusion

Ureteral colic, which is mainly due to ureterolithiasis, is one of the major causes of the hospital emergency admissions. MET has emerged as an alternative strategy for the initial management of selected patients with distal ureteric stones. Analysis of various RCTs and Meta- analysis indicates that Silodosin as a part of MET is an effective and safe treatment option for ureteral stones with a low occurrence of side effects. Also, Silodosin was found to be clinically superior to Tamsulosin, both in terms of the stone expulsion rate and the stone expulsion time. However, more high-quality trials with larger sample sizes are needed to further explore the role of Silodosin in the treatment of distal ureteral stones.

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