Update on Medical Expulsive Therapy of Urinary Stones

Reviewed by:

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Introduction

Urolithiasis remains a major issue regarding health and well-being of individuals, with a life time risk of developing urinary stones ranging between 5 and 12% in Europe and in America, respectively.[1] The condition affects more men as compared to women. The incidence of urolithiasis seems to peak in the 3rd and 4th decades, with prevalence increasing with age until approximately the age of 70 years.[2] In India, 12% of the population is expected to have urinary stones, out of which 50% may end up with loss of kidneys or renal damage.[3] The burden may be relatively more in northern India, where nearly 15% of the population suffers from kidney stones. Furthermore, amongst the population, the anatomical location of stones may also exhibit differential distribution. Generally, almost 20% of the urinary tract stones are found in the ureters, with majority (70%) being located in the lower third of the ureter.[4]

Clinical presentation

The symptoms of urinary stones vary widely, and may include a frequent urge to urinate, painful urination, hematuria, and dysuria.[5] Some patients may be asymptomatic, and are co-incidentally diagnosed to have stones on diagnosis for some other illness. However, symptomatic patients may often present with pain, hematuria or infection. Typically, an obstructing urinary stone in the upper part of ureter or in renal pelvis is associated with severe flank/abdominal pain accompanied by nausea and vomiting. When the stone is present in the middle or lower segments of ureter, the pain often radiates downwards to the inguinal and/or perineal region. Stones located in the terminal segment of ureter may be accompanied by frequent urination and dysuria. Hematuria may be seen with any of these pain patterns; while chills and fever are present in cases of infection.[5] In some cases, stones can cause potentially serious complications.

Management of urinary stones

Management of urinary stones requires individualization, and may encompass observation, dietary management, disease-specific therapies, and medical expulsion therapy (MET) of stones. Clinical presentation, proper history, and laboratory investigations may help to identify whether one would require medical treatment, or urgent procedural or surgical intervention like shock wave lithotripsy (SWL), ureteroscopy, open surgery, laparoscopic stone removal, or percutaneous nephrolithotomy (PCNL).

Medical expulsion therapy

The management of patients having ureteral calculi has changed dramatically in the current era with minimal invasiveness being the primary focus of concern, so far selection of any treatment modality is concerned. In this event, although the management depends upon the severity of obstruction and degree of renal function deterioration, conservative therapy is generally the first approach. MET is a watchful approach that makes use of a combination of drugs to facilitate spontaneous passage of the ureteric calculi, and can be used successfully for a considerable number of patients.[6]

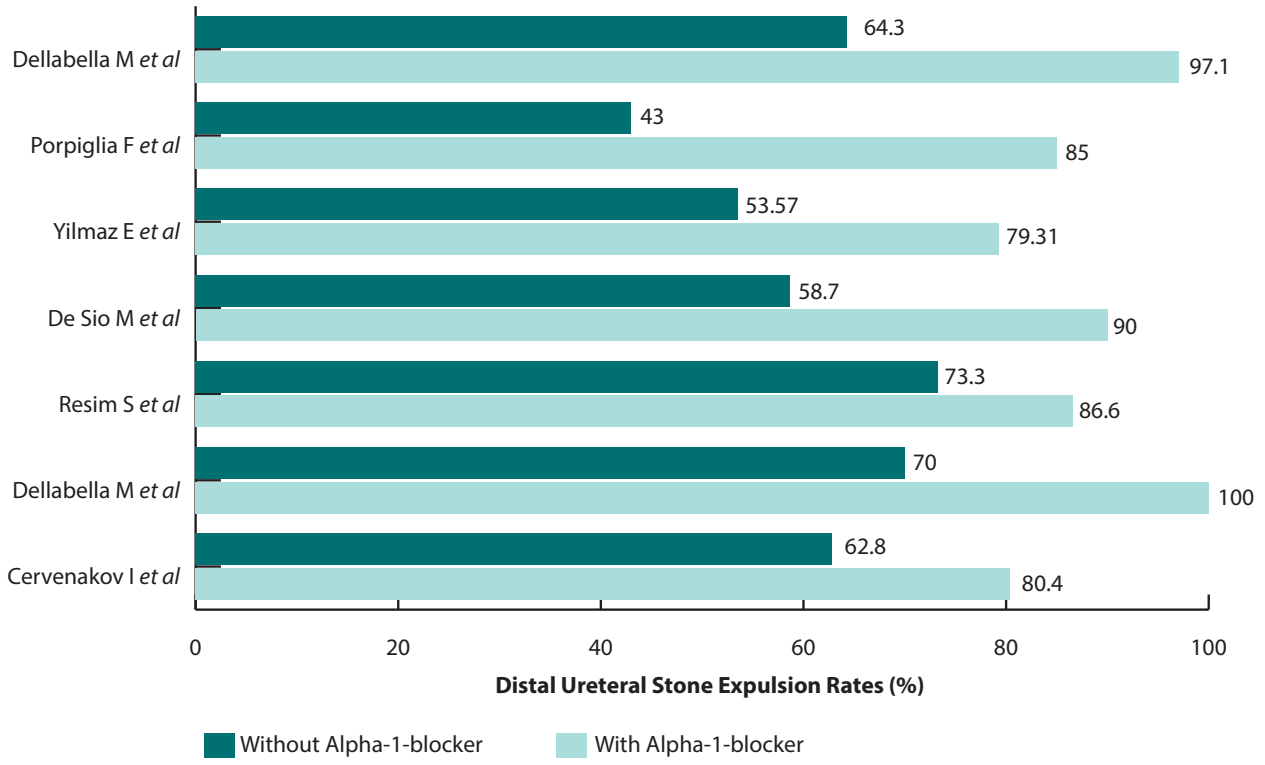
In fact, approximately 90% of stones less than 5 mm and 15% of stones between 5 and 8 mm pass spontaneously within 4 week; though findings indicate that MET can be considered for stones up to 10 mm.[7,8] The American Urological Association (AUA)/Endourological Society Guideline strongly

recommends that patients with uncomplicated ureteral stones less than 10 mm should be offered observation, and those with distal stones of similar size should be offered MET with alpha-blockers.[9] Likewise, European Association of Urology (EAU) guidelines on diagnosis and conservative management of urolithiasis also recommends MET to support spontaneous stone expulsion.[10] The meta-analysis by Hollingsworth *et al*[11] had also demonstrated that patients given medical therapy (with either a calcium channel antagonist or alpha-blocker) had a 65% greater likelihood of stone passage without intervention. MET is thus an option for facilitation of urinary-stone passage for patients amenable to conservative management, potentially obviating the need for surgery.

Several agents evaluated for MET include the calcium channel blockers, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and alpha1-adrenergic receptor antagonists, with differential outcomes. For instance, studies comparing the calcium channel antagonist nifedipine against Tamsulosin seem to indicate that both drugs are useful, but Tamsulosin is more efficacious.[12,13] Steroids may also be useful as medical expulsive agents in distal ureteric stones, but there is no evidence to support the use of corticosteroids as monotherapy for MET. In fact, there is even insufficient data to support the use of corticosteroids in combination with alpha-blockers as an accelerating adjunct.[10]

Thus, among the options available for MET, alpha-blockers are a particularly promising class of stone-expulsive agents, and may in fact be the preferential mode of medical therapy.[14] They decrease the tension and release the spasm of smooth muscles, thus make a faster passing of calculi from the terminal part of the ureters possible;[15] and in this event, they seem to be superior to calcium-channel inhibitors in facilitating stone passage.[10] Figure 1 shows the rates of stone expulsion for distal ureteral stones in patients treated with alpha-1-blocker vs. patients treated with standard medical expulsion therapy without alpha-1-blocker.[12-19]

Figure 1. Rates of stone expulsion for distal ureteral stones in patients treated with alpha-1-blocker vs. patients treated with standard therapy without alpha-1-blocker



The graph shows that spontaneous passage rates vary from 43-73%, but increase up to 100% with the addition of MET using an alpha-blocker drug. These improvements are generally statistically significant.

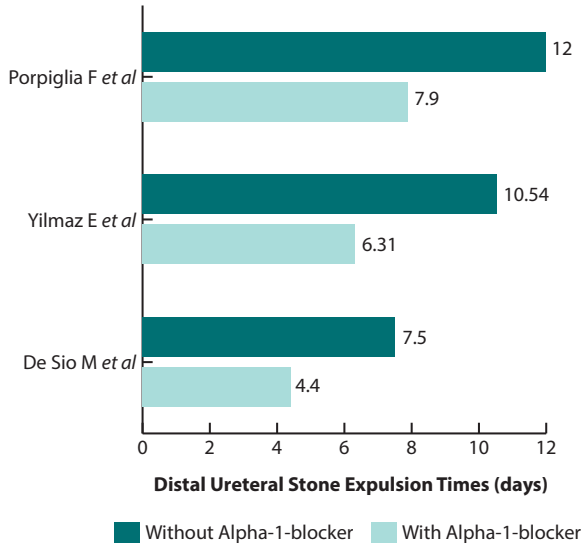
Source: Lipkin M, Shah O. The Use of Alpha-Blockers for the Treatment of Nephrolithiasis. *Rev Urol.* 2006;8(Suppl 4): S35-42.

Tamsulosin – the most commonly studied alpha-blocker for stone expulsion

Amongst alpha-blockers, Tamsulosin has been the most commonly studied drug used in the treatment of ureteral stones with increased spontaneous stone expulsion.[14] The drug works by acting on the alpha adrenergic receptors that are densely located in the smooth muscles of ureter. While alpha-1a-receptors predominate in bladder outlet, prostate, and proximal urethra; alpha-1d-receptors are seen in lower ureter and detrusor muscle of bladder. The pharmacotherapeutic advantage of Tamsulosin is that it has equal affinity for both alpha1a and alpha1d receptors.[14] Like this, it is effective in expulsion therapy and increases the passage rate for stones up to 10 mm.[20] Furthermore, not only it increases the rates of spontaneous stone expulsion but also decreases the time to stone expulsion (Figure 2).[12,14,18,19] Besides, it can also alleviate the amount of pain patients suffer while passing their stones.

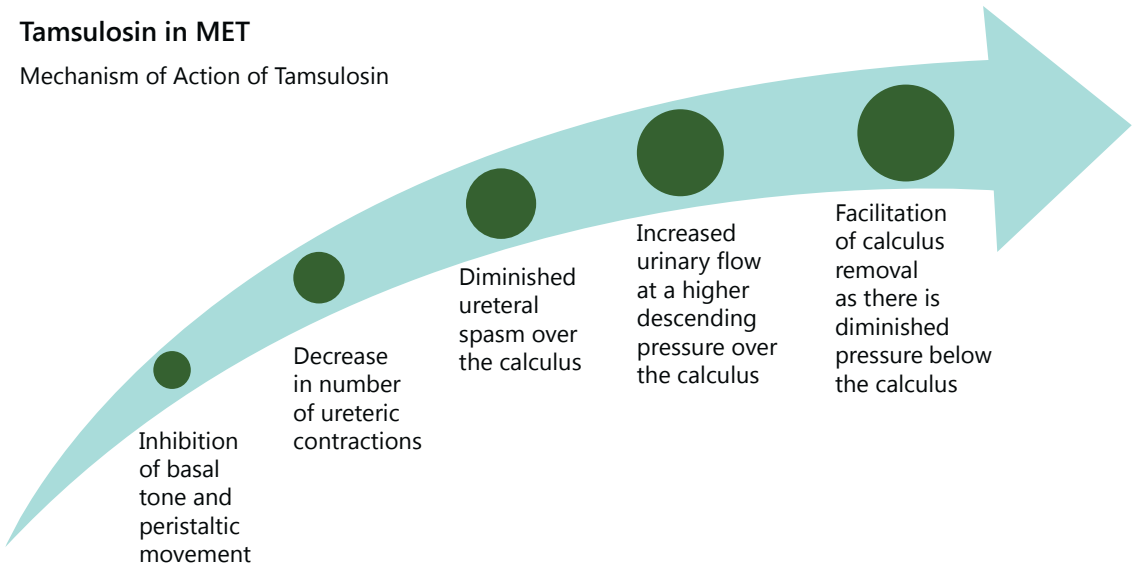
Several trials have been conducted to evaluate the efficacy of Tamsulosin in the management of ureteral stones. Table 1 summarizes some of these studies supporting the drug's efficacy in the management of ureteral stones.[21-25] In one

Figure 2: Time to stone expulsion for distal ureteral stones in patients treated with alpha-1-blocker vs. patients treated with standard medical expulsion therapy without alpha-1-blocker



Source: Lipkin M, Shah O. The Use of Alpha-Blockers for the Treatment of Nephrolithiasis. *Rev Urol.* 2006;8(Suppl 4): S35-42.

How Tamsulosin Facilitates Medical Expulsion Therapy



Tamsulosin decreases the frequency of peristaltic contractions by decreasing the resting tone and interference with ureteric contractions thus causing early stone passage, decreased colics and therefore decreased analgesic requirement

Table 1: Some of the clinical studies supporting the efficacy of Tamsulosin in ureteral stone			
Study	**Objective of the study**	**Results of the study**	**Conclusion drawn**
2012 (meta-analysis of clinical studies)	Evaluate the efficacy of Tamsulosin, in the treatment of ureteral stones with or without shockwave lithotripsy (SWL) in Korean patients.	43% higher expulsion rate was seen with Tamsulosin when compared to the control group.	Treatment with Tamsulosin augments the stone expulsion rate for ureter stones with or without SWL in a Korean population is successful.[21]
2012 (systematic review and meta-analysis of randomized controlled trial)	Evaluate the efficacy of Tamsulosin as a medical expulsive therapy of ureteral stones.	Compared with calcium channel blockers, there was a higher stone expulsion rate in Tamsulosin.	Tamsulosin is a safe and effective medical expulsive therapy choice for ureteral stones. It should be recommended for most patients with distal ureteral stones before stones are 10 mm in size.[22]
2012 (prospective, randomized, comparative study)	Evaluate and compare the efficacy of Tamsulosin (0.2 mg and 0.4 mg) and alfuzosin (10 mg) in the treatment of lower ureteral stones.	The spontaneous stone passage rate through the ureter was higher and the stone expulsion time was faster in the patients treated with Tamsulosin and alfuzosin.	Tamsulosin at 0.2 mg and 0.4 mg proved to be safe and effective.[23]
2012 (prospective randomized study)	Evaluate the efficacy of Tamsulosin in the management of distal ureteral stones in children.	87.8% of stone-free rate was seen in patients treated with Tamsulosin when compared to placebo group (64.2%).	Tamsulosin demonstrated no clinically significant adverse effect, while proving to be a safe and effective treatment option for distal ureteral stones in children.[24]
2012 (prospective, double blind randomized controlled trial)	Evaluate the efficacy of the combined use of Tamsulosin and Potassium citrate for the treatment of uric acid stones in the distal ureter.	84.8% of stone expulsion rate was seen in combined therapy when compared with control group (26.1%).	The use of urinary alkalization with Tamsulosin can increase the frequency of spontaneous passage of distal ureteral uric acid stones especially those of 8-11 mm.[25]

Source: References 20-24

study of Tamsulosin in renal colic, up to 100% expulsion rate was seen in the treatment group as compared to 70% in the control group.[16] In this study, the mean expulsion time in the treatment group was 65.7 hours compared with 111.1 hours for the control group. The mean stone size was 6.7mm in the treatment group, compared with 5.8 mm in control subjects. Thus, a first cycle of MET with Tamsulosin 0.2 mg could be considered as an option in the management of single lower ureteral stone.[23]

Overall, there is thus ample data to support the use of Tamsulosin in medical management of distal ureter stones. Nevertheless, there is also evidence showing that administration of Tamsulosin can facilitate the spontaneous passage rate of stone less than 5 mm in proximal ureteral calculi, and the relocation of the stones between 5 and 10 mm to more distal part of the ureter. This study was conducted on 92 patients, who were randomly divided into two groups.[26] Patients in group 1 were followed with classical conservative approach, while those in group 2 additionally received Tamsulosin 0.4 mg/day during 4 weeks follow-up. The results showed that stone expulsion rates had statistically significant difference between Tamsulosin receivers and non-receivers, and time to stone expulsion period was also shortened in those receiving Tamsulosin. The study thus supports the use of Tamsulosin in the proximal ureter stone management as well.

Tamsulosin with ADS technology – Tamsulosin with ADS technology is an innovation designed to ensure continuous and consistent release of the drug throughout the entire length of gastrointestinal tract (GIT), including the colon

where water is poorly available. This appears to overcome the limitation of conventional formulations, which depend on the presence of water in GIT to release the active ingredient. The ADS technology would result in a more constant exposure to Tamsulosin over 24 hours with a smaller peak-to-trough fluctuation than conventional formulations; and also reduces/eliminates the dependency on food, which may help in a more consistent absorption profile and patient tolerability and compliance.[27] The ADS advantage thus equates with less adverse effects on physiologic parameters.

Benefits of Tamsulosin with ADS technology

- Consistent drug release over 24 hours, and thus lesser C_{Max} related side effects
- Favourable efficacy/tolerability ratio
- Lower incidence of treatment emergent adverse events
- Independent of food intake
- Can be given anytime during the day without risk of side effects

Additional consideration

NSAIDs like diclofenac have been used extensively in the management of patients with renal colic; however, while they may decrease the pain and hospital admissions, the stone passage rate appears not to be affected.[28] Besides, their use may be associated with several unwanted side-effects.[29] NSAIDs may therefore be preferably avoided during the treatment phase. Drotaverine, a phosphodiesterase inhibitor may be a better option for pain relief in renal colic because of its potent spasmolytic effect with no serious side-effects, and non-inferior efficacy and safety as analgesic to diclofenac.[30,31]

Fluid and dietary management

A low urine volume is an important risk factor in urinary stone formation;[32] and hence, increasing the fluid intake together with dietary changes could be important measures for preventing recurrence of urinary stones at least in certain stone formers.[33,34] Urine flow of more than 1 ml/kg/hour alleviates the risk of supersaturation for calcium oxalate, calcium phosphate and uric acid, thus protecting from the formation of corresponding kidney stones.[35] Adequate fluids like water, barley water, sharbat, aerated water and fruit juice should therefore be advised in accordance with body size.

Dietary components also influence the biochemical parameters of stones such as oxalate, uric acid and calcium sodium. Therefore, oxalate-rich foods like cucumber, green peppers, beetroot, spinach, soya bean, chocolate, popcorn, and sweet potato should be avoided, given the finding that a small reduction in urinary oxalate is associated with significant reduction in the formation of calcium oxalate stones.[8] Similarly, the benefits of protein restriction are enormous for stone formers.[35]

Urinary alkalization for dissolution of urinary stones

Urine pH is an important factor that strongly influences the formation of various types of kidney stones; a low urine pH can promote calcium, oxalate and uric acid stones.[36] Thus, patients with uric acid stones who do not require urgent surgical intervention for reasons of pain, obstruction, or infection can often have their stones dissolved with alkalization of the urine. Prior to the advent of effective urinary alkalinizing agents, it was necessary to rely on diet to alter urinary pH, though this could rarely be accomplished effectively. Also, it is difficult to follow for most patients. The practice has now been largely outdated by advent of better alkalinizing agents. Care in deliverance of therapy is however necessary since a high pH without alkali therapy may increase the risk of struvite stones from a urinary tract infection.

The dosage of the alkalizing agent should be adjusted to maintain the urinary pH between 6.5 and 7.0. Urinary pH of more than 7.5 should be avoided because of the potential deposition of calcium phosphate around the uric acid calculus, which would make it undissolvable.[37] Potassium citrate is a preferred alkalizing agent because of the avoidance of a high sodium load; sodium loading can increase urine calcium excretion, offsetting the benefits of raising urine citrate.[38] Potassium citrate may avoid the complication of calcium salt precipitation, and therefore, is likely to be more effective in preventing the calcium stones.[39,40] Studies have shown that urinary alkalization with Potassium citrate is a well tolerated and highly effective treatment, resulting in dissolution of non-obstructing uric acid stones.[41] Potassium citrate helps in chemodissolution of uric acid and cystine stones and is useful in prevention of the stone recurrence in general, and in those who have undergone SWL or percutaneous nephrolithotomy.[42]

Conclusion

Urinary tract stone disease is common in humans, and requires individualized therapy. While several advances have been made in the interventions for ureteral stones, the conservative approach still holds significance as the

first therapy in a large number of patients. Pharmacological management (MET) and urine alkalization is safe and effective method of managing the urinary stones. Tamsulosin, an alpha blocker, is the most studied drug in MET with several evidences supporting its effectiveness in increasing the stone passage in patients with urinary stone disease. Combination therapy of Tamsulosin and Potassium citrate has shown better results in the treatment of uric acid stones.

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