Management of Urolithiasis: An Update

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Burden of Urolithiasis

Urolithiasis—the formation of stones in the kidney, bladder, and/or urethra— is one of the most common urologic diseases worldwide, with an estimated prevalence ranging from 2% to 20% in different regions across the globe. Recent evidence suggests that the prevalence of urolithiasis is on the rise globally owing to various factors, including changes in social conditions, dietary habits, climate, and disease comorbidities.[1-3]

According to the Global Burden of Disease (GBD) 2019 study,[2] three countries, India, China, and the Russian Federation, were burdened by nearly half of global incident cases in 2019. India itself had the burden of over one-fifth of global incident cases of urolithiasis, followed by China and the Russian Federation. The distribution of total disability-adjusted life years (DALYs) attributed to urolithiasis followed a similar pattern to that in India, followed by China and the Russian Federation demonstrating the highest burden.

Clinical Presentations

Patients with urinary stones most commonly present with acute, severe pain that often radiates from the flank region to the abdomen and especially to the groin. This pain, known as renal or ureteric colic, is often sharp and severe in nature, and it is one of the most severe pain sensations known. The condition is often associated with urinary urgency, restlessness, hematuria, nausea, vomiting, and sweating.[1,4] Some patients may be asymptomatic, and are coincidentally diagnosed to have stones on diagnosis for some other illness.[5]

Risk Factors for Stone Formation

There are various types of kidney stones, with majority of stones being composed of calcium oxalate or phosphate (80%). Other stone types include uric acid (9%), struvite (10%), and cystine (1%) stones. The different types of stones occur due to varying risk factors, such as poor dietary habits including high salt intake, poor oral fluid intake, high animal-derived protein intake; prior personal and family history of stones; environmental factors; medications; and patient's medical history. A prior personal and family history of calculi often increases the patient's risk of developing subsequent stones.[6]

Diagnostic Evaluation

Initial evaluation of a patient with suspected urolithiasis usually starts with a urine analysis with microscopy.[6] Diagnostic confirmation following initial evaluation is often achieved through imaging modalities.[7] Renal ultrasound provides an ideal initial imaging modality to assess urolithiasis.[6] Non-contrast abdominal and pelvic CT scan is another common imaging technique to diagnose urolithiasis.[4] The STONE score is a validated risk assessment tool, which categorizes patients in a low, moderate, or high probability of having a stone using five criteria; sex, timing origin, nausea, and erythrocytes.[6]

Management of Urolithiasis

Management of patients with urinary stones depends on the patient's acute presentation and involves both conservative and surgical approaches. Surgical interventions, which may include shock wave lithotripsy (SWL), ureteroscopic stone removal, or percutaneous nephrolithotomy, are usually not required in cases of asymptomatic kidney stones. Some of the key approaches for urolithiasis management include watchful waiting, fluid and diet modifications, disease-specific therapies, and medical expulsive therapy (MET). Stone size is an important factor to be considered, since a trial of spontaneous passage is recommended for uncomplicated ureteral stones ≤10 mm. Medical expulsive therapy with α-adrenergic blockers, such as tamsulosin, can result in considerably higher passage rate of 5-10 mm ureteral stones.[6-9]

Role of Medical Expulsive Therapy: Focus on Tamsulosin

Medical expulsive therapy is an effective conservative treatment approach for the initial management of urinary

stones. It is a watchful approach that involves a combination of drugs to facilitate spontaneous passage of the urinary stones.[9,10] Among various drug classes, alpha-blockers are currently the only recommended monotherapy, with various guidelines, such as American Urological Association (AUA)/ Endourological Society Guideline and European Association of Urology (EAU) Guidelines endorsing the use of alpha-blockers to facilitate passage of ureteral stones < 10 mm in diameter in appropriately selected patients.[10-13]

Tamsulosin, a selective alpha-1 receptor antagonist, has been the most widely studied drug used in the treatment of ureteral stones with increased spontaneous stone expulsion.[14] Tamsulosin acts upon alpha adrenergic receptors on ureteral smooth muscles and dilatates the lumen and inhibits spasms, especially in the distal part of the ureter.[15] The pharmacotherapeutic advantage of tamsulosin is that it has equal affinity for both alpha-1a and alpha-1d receptors.[14] Likewise, it is effective in expulsion therapy and increases the passage rate for stones up to 10 mm.[16] Furthermore, not only it increases the rates of spontaneous stone expulsion but also decreases the time to stone expulsion.[14] Besides, it can also alleviate the amount of pain patients suffer while passing their stones.[17]

Salient Features of Tamsulosin

- High expulsion rate and short expulsion time for proximal ureteral calculi < 6 mm in size
- Highest stone free rate for distal ureteral stones in combination with alkalinization
- Effective in relieving renal colic, and facilitating and accelerating ureteral stone expulsion.

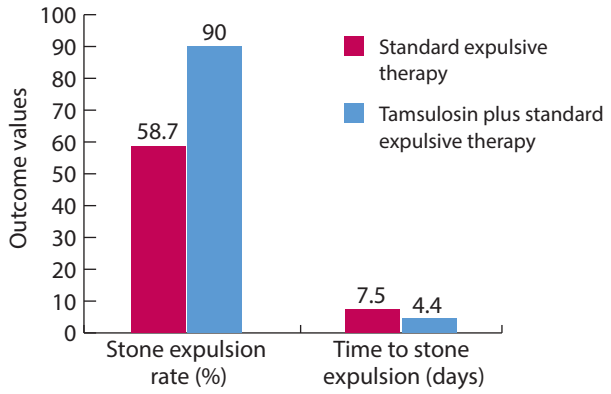
Adapted from: Guidelines on Urolithiasis. European Association of Urology 2021. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urolithiasis-2021.pdf. Accessed on 10/11//2022.

Clinical Evidences

De Sio and colleagues[18] demonstrated that addition of tamsulosin to a standard expulsive pharmacologic therapy for the treatment of distal-ureteral stones was associated with a significant higher expulsion rate (90%) than standard expulsive pharmacologic therapy only (58.7%). Addition of tamsulosin also resulted in shorter stone passage time (mean 4.4 days) versus standard therapy (mean 7.5 days) (Figure 1). Moreover, lower analgesic use was found in tamsulosin add-on group, as well as significantly fewer hospitalizations for recurrent colic. Thus, it could be concluded that tamsulosin is effective for the conservative management of uncomplicated distal-ureteral stones.[18]

Yencilek F et al[19] demonstrated in patients with proximal ureteral calculi that addition of tamsulosin to conservative approach led to considerable increase in stone expulsion rate and a decrease in time to stone expulsion. Among the stones <5 mm, patients receiving tamsulosin add-on to conservative approach had higher spontaneous passage rate (71.4%) than conservative approach only (50%) (Table 1). The study thus supports the use of tamsulosin in the proximal ureter stone management as well.

Figure 1: Effect of addition of tamsulosin to standard expulsive pharmacologic therapy for distal-ureteral stones



Adapted from: De Sio M, Autorino R, Di Lorenzo G, *et al*. Medical expulsive treatment of distal-ureteral stones using Tamsulosin: a single-center experience. *J Endourol* 2006;20:12-6.

Table 1: Efficacy of tamsulosin therapy on the spontaneous passage of proximal ureteral calculi

Outcomes	Conservative approach	Tamsulosin plus conservative approach
Stone expulsion rate	30%	**35.7%**
Spontaneous passage rate for stones <5 mm	50%	**71.4%**
Time to stone expulsion	11.6 ± 4.1 days	**8.4 ± 3.3 days**

Adapted from: Yencilek F, Erturhan S, Canguven O, *et al*. Does Tamsulosin change the management of proximally located ureteral stones? *Urol Res*. 2010;38(3):195-9.

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 (Box 1). The ADS advantage thus equates with less adverse effects on physiologic parameters.[20,21]

Box 1: Benefits of Tamsulosin with ADS technology

- 24 hours consistent drug release; lesser C_{max} related side effects
- Favorable efficacy/tolerability ratio
- Lower incidence of treatment emergent adverse events
- Independent of food intake
- Flexible dosing time; can be given anytime during the day without the risk of side effects
- Decreased risk of postural hypotension, especially in patients with cardiovascular comorbidities; thereby reducing the risk of cardiovascular events and falls and fractures.

Adapted from: 1. Speakman M. Efficacy and safety of Tamsulosin OCAS. BJU international 2006;98(2): 13-17. 2. Data on File

Box 2: Potassium citrate therapy for preventing stone recurrence: 2019 NICE recommendation

- Consider potassium citrate for adults with a recurrence of stones that are predominantly (more than 50%) calcium oxalate
- Consider potassium citrate for children and young people with a recurrence of stones that are predominantly (more than 50%) calcium oxalate, and with hypercalciuria or hypocitraturia
- Recommendations on dietary and lifestyle advice are to be followed along with potassium citrate therapy

Adapted from: Renal and ureteric stones: Assessment and management. Available at: https://www.nice.org.uk/guidance/ng118/chapter/Recommendations#preventingrecurrence. *Accessed on: 10/11/2022.*

Additional Considerations for Urolithiasis Management

Non-steroidal anti-inflammatory drugs (NSAIDs) have been used extensively in the management of patients with renal colic; however, while they may decrease pain, stone passage rate appears not to be impacted.[22] Additionally, their use may be associated with a number of adverse effects.[23] In this event, drotaverine, a phosphodiesterase inhibitor, has emerged as a well established directly acting, smooth muscle antispasmodic agent that brings about quick and effective pain relief in renal colic owing to its potent spasmolytic effect, lack of serious side effects, and non-inferior efficacy and safety as to diclofenac.[24-26]

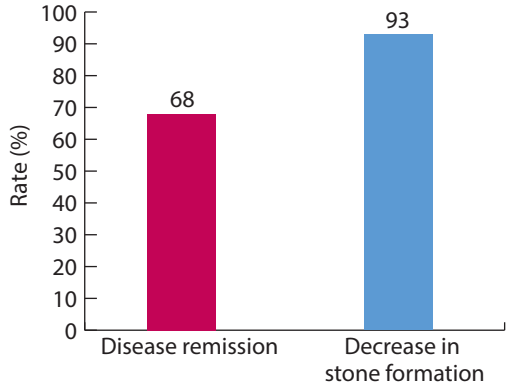
Urinary alkalization for dissolution of urinary stones

Urinary alkalization with administration of alkali has been clinically established as an important treatment approach for dissolution of stones.[27-29] Potassium citrate is a preferred alkalizing agent because of the avoidance of a high sodium load.[30] While alkalinising the urine, it offers the additional benefit of increasing urinary citrate which is an inhibitor of stone formation, thereby proving useful in patients with Ca-oxalate, cystine, and uric acid stones.[31] The recent NICE recommendations on use of potassium citrate for preventing stone recurrence is enumerated in Box 2.[32]

Effectiveness of long-term potassium citrate therapy

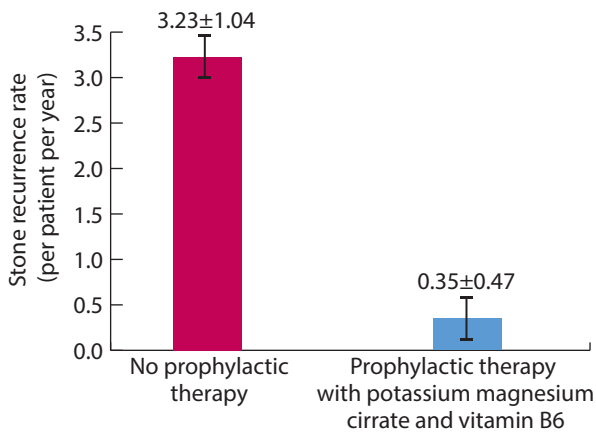
Robinson MR et al,[33] in a retrospective cohort study involving patients with urolithiasis, demonstrated a significant and durable change in urinary metabolic profiles following potassium citrate therapy. These changes, including increased urinary pH (5.90 to 6.46) and increased urinary citrate (470 to 700 mg/day) were observed as soon as 6 months after treatment onset. Also, there was a significant decrease in stone formation rate following initiation of potassium citrate from 1.89 to 0.46 stones per year ($p < 0.0001$). Overall, a 68% remission rate and a 93% decrease in stone formation rate were observed (Figure 2). Changes in urinary metabolic profiles were sustained for as long as 14 years of treatment. Findings of this study substantiated the long-term effectiveness of potassium citrate therapy in patients with recurrent nephrolithiasis.

Figure 2: Effectiveness of potassium citrate therapy in patients with recurrent nephrolithiasis



Adapted from: Robinson MR, Leitao VA, Haleblian GE, et al. Impact of long-term potassium citrate therapy on urinary profiles and recurrent stone formation. J Urol. 2009;181(3):1145-50.

Figure 3: Reduction in stone recurrence rate with potassium magnesium citrate and vitamin B6 prophylaxis



Adapted from: Reddy SV, Shaik AB, Bokkisam S. Effect of potassium magnesium citrate and vitamin B-6 prophylaxis for recurrent and multiple calcium oxalate and phosphate urolithiasis. Korean J Urol. 2014;55(6):411-416.

Combination therapy with potassium citrate, magnesium citrate and vitamin B6

Magnesium can increase the solubility of calcium oxalate in vitro; therefore, by enriching urine with magnesium, the rate of calcium oxalate crystal growth in vitro can be slowed. Thus, it seems plausible that magnesium therapy may be used to prevent stone recurrence. [34,35] Likewise, vitamin B6 deficiency has been linked to an increase in oxalate production and excretion, while vitamin B6 intake has been shown to have an inverse association with risk of stone formation.[36]

In this context, Reddy and colleagues[37] conducted a study to explore the effects of long-term treatment with potassium magnesium citrate and vitamin B6 prophylaxis in recurrent stone formers. A total of 247 Indian patients with hypocitraturia- and hyperuricosuria-induced recurrent calcium oxalate and calcium phosphate stones were followed prospectively for 3 years. Prophylaxis with potassium magnesium citrate yielded a sustained increase in 24-hour urinary citrate excretion from initially low values (221.79±13.39 mg/dL) to within normal to high limits (604.04±5.00 mg/dL) at the 6-month follow-up. Likewise, urinary pH elevated significantly from 5.62±0.2 to 6.87±0.01. Of note, there was a reduction in stone recurrence rate from 3.23±1.04 per patient per year to 0.35±0.47 per patient per year (Figure 3).

Clinical efficacy of the therapy following spontaneous passage or forced procedural clearance of symptomatic stones was also found to be better in the treated patients versus the controls who underwent similar procedures for their stones, thus underscoring the usefulness of this therapeutic combination.[37]

Conclusion

Urolithiasis, although being highly prevalent, presents a unique challenge to clinicians largely due to associated morbidity and recurrence. Although there have been several advances in the interventions for ureteral stones, the conservative approach continues to hold prominence as the initial therapy in a large subset of population, with MET acting as a substantial facilitator. Tamsulosin, an alpha blocker, is the most studied drug in MET; several studies have substantiated that tamsulosin increases stone passage rate in patients with urolithiasis. Additionally, urine alkalization is a standard treatment approach to dissolve urinary tract stones composed of uric acid and cystine. Potassium Citrate therapy has become one of the cornerstones of medical management of urinary tract stones owing to its immense potential for stone dissolution, prevention of recurrence and improved patient compliance. Supplementation of potassium citrate provides an alkali load, raises urine pH, enhances the citraturic effect, and reduces stone recurrence. Tamsulosin and potassium citrate combination therapy has yielded better outcomes in the treatment of uric acid stones.

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