Evolving Concepts in the Imaging and Management of Urolithiasis

Reviewed by:

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Introduction

Urinary stones are polycrystalline concretions occurring in the urinary tract of humans and may range in size from micrometers to several centimeters in diameter. Around 97% of urinary stones are found in the kidneys and ureters (kidney stones), the remaining 3% in the urinary bladder and urethra.[1]

Urolithiasis has gradually become a universal problem as it is known to affect patients across geographical, cultural, and racial boundaries. The prevalence of urinary stones has progressively increased in the industrialized nations, and a similar trend is being observed in developing countries.[2] This growing prevalence and incidence could be accounted to be due to change in lifestyle and improvements in diagnosis.[1] Available data has shown that urolithiasis affects about 12% of the world population at some stage in their lifetime and occurs more frequently in men than in women within the age of 20-49 years. In Indian population, about 12% of them are expected to have urinary stones and out of which 50% may end up with loss of kidney functions.[3]

Advancements in Diagnostic Investigations of Urolithiasis

With the increasing prevalence of uroliathiasis, utilization of imaging for diagnosis, treatment planning, and post-treatment follow-up has markedly increased.[2] Imaging has a critical role in the initial diagnosis, treatment planning and post-treatment surveillance of patients with urolithiasis.[4]

Non-contrast CT (NCCT) has come up as the reference gold standard for the initial and subsequent evaluation of patients with suspected kidney stones, superseding radiography and intravenous urography.[2,4]

NCCT has several advantages as compared to alternative imaging techniques such as plain radiography and ultrasound. The advantages include high sensitivity and specificity (>95% and >96%, respectively) for the detection of stones, easy availability, faster speed of acquisition and absence of need for administration of intravenous contrast.[4]

NCCT performed in the emergency department for clinical suspicion of urolithiasis accounts for nearly 22% of all CT examinations performed for evaluation of acute abdominal pain. Evidences had shown that nearly 55% of patients undergoing CT for the evaluation of acute flank pain did not have stone disease, and about 15% had other abnormalities that were detected.[2]

Stone Classification Based on Composition

Various factors such as familial, environmental, dietary, and systemic are associated with the pathogenesis of renal stones. Stones are composed of a combination of crystals (both inorganic and organic) and proteins. Calcium-based stones, which include calcium oxalate monohydrate, calcium oxalate dihydrate, and calcium phosphate stones, account for 70%–80% of upper urinary tract stones. Struvite stones account for 5%–15% of stones and are composed of magnesium ammonium phosphate. Uric acid stones are unique in as they can be dissolved with urinary alkalinization; they account for 5%–10% of stones and occur in acidic urine (pH<5.8). Other stones, including cystine, xanthine, and protein matrix stones, as well as drug (eg, triamterene, indinavir) induced calculi, account for less than 5% of stones.[2]

Clinical Perspective

Acute flank pain is the most common symptom associated with urolithiasis which is often relieved with the passage of the stone. Flank pain is caused by the stones that are impacted at the ureteropelvic junction, whereas stones lodged in the proximal ureter (between the ureteropelvic

junction and the iliac vessels) cause flank pain radiating to the genitals. Stones lodged at the ureterovesical junction produce voiding urgency and suprapubic discomfort, and they cause pain that radiates into the groin and genitals. Associated symptoms include gross or microscopic hematuria, nausea, and vomiting. Struvite stones often remain asymptomatic without causing obstruction.[2]

Recent Advancements in the Management of Urolithiasis

Factors Influencing Treatment Decisions

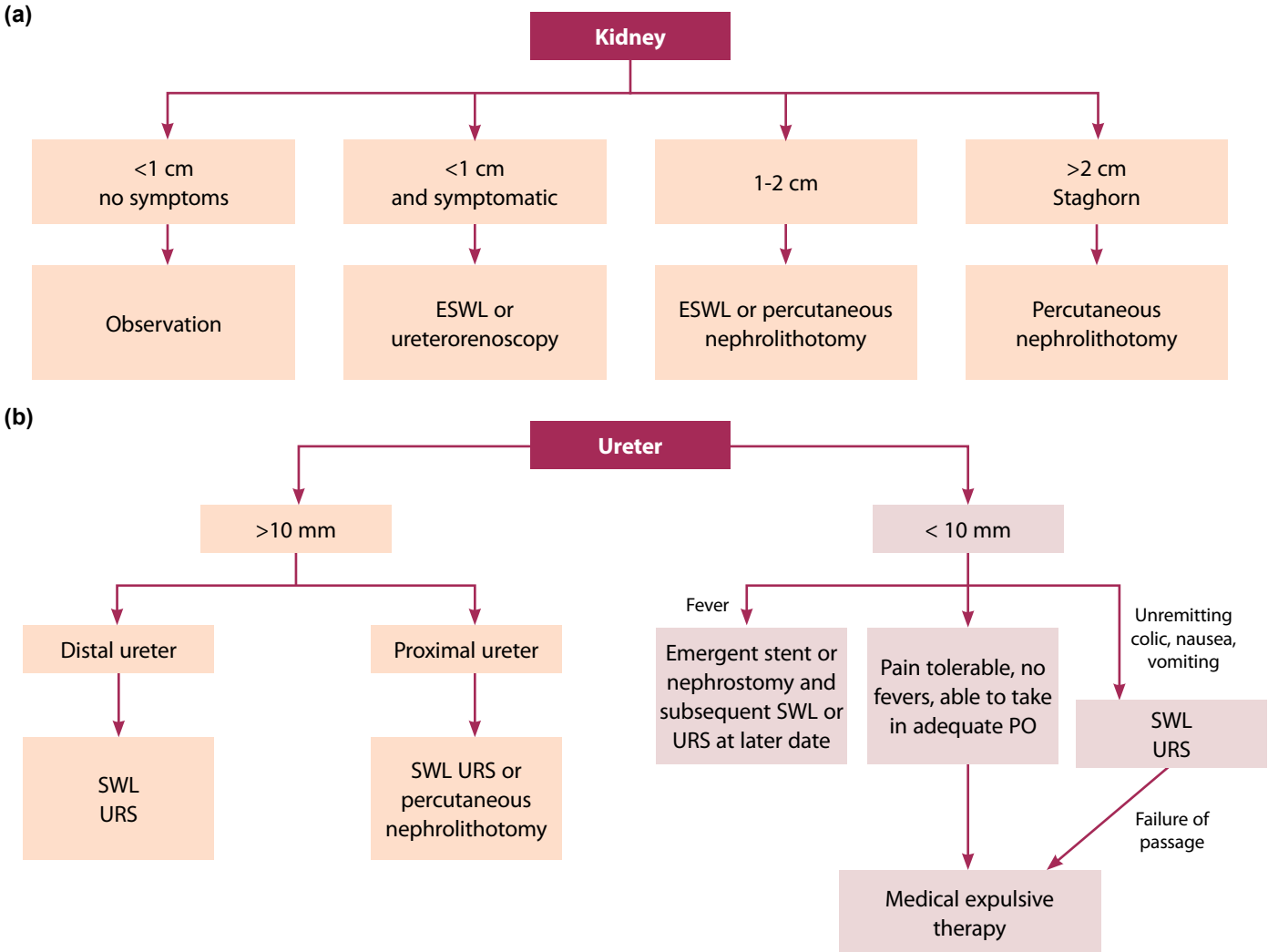
Stone location, size, and composition along with patient symptoms are the factors that impact the decisions regarding urologic intervention (Figure 1, 2). Renal stones may be treated with shock wave lithotripsy (SWL), ureteroscopy, or percutaneous nephrolithotomy (PCNL). Factors such as stone location, size and composition along with stone to skin distance are associated with the success of SWL, the least invasive of these three treatments.[2]

Ureteral stones treatment depends on stone size and type of interventional procedure. The first-line treatment is medical expulsive therapy (α-blockers or calcium channel blockers with or without steroids and nonsteroidal anti-inflammatory medications), as well as hydration and analgesia.[1]

Medical Expulsive Therapy

The most frequent strategy for treatment of urolithiasis presenting with acute renal colic is conservative management with the aim of achieving spontaneous passage of the urinary stone.[1] Medical expulsive therapy (MET) has been described as an effective conservative treatment option in the initial management of urinary calculi. It is a watchful

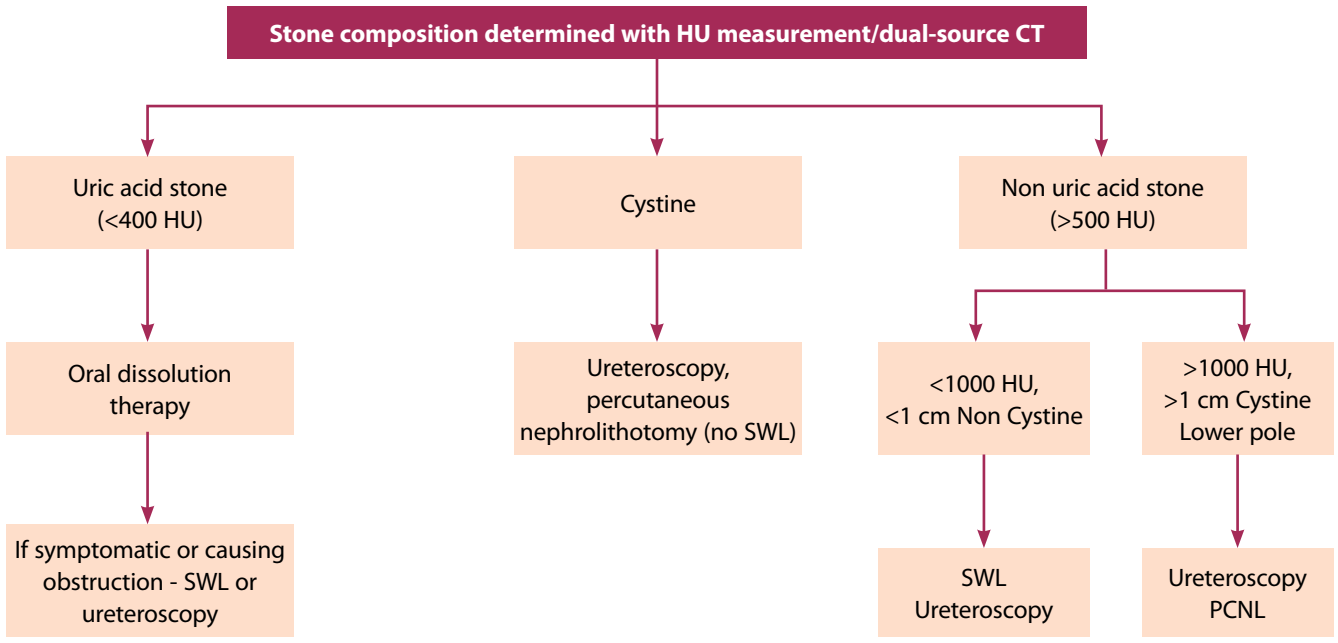
Figure 1: Treatment decisions based on stone location (kidney in a, ureter in b)



Abbreviations: ESWL = extracorporeal shock wave lithotripsy, PO = per os (by mouth),URS = ureteroscopy.

Adapted from: Kambadakone AR, Eisner BH, Catalano OA, Sahani DV. New and evolving concepts in the imaging and management of urolithiasis: urologists' perspective. *Radiographics.* 2010;30(3):603-23.

Figure 2: Treatment decisions based on stone composition



Abbreviations: SWL = shock wave lithotripsy, PCNL = percutaneous nephrolithotomy.

Adapted from: Kambadakone AR, Eisner BH, Catalano OA, Sahani DV. New and evolving concepts in the imaging and management of urolithiasis: urologists' perspective. *Radiographics.* 2010;30(3):603-23.

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.[5,6] Alpha-blockers, such as tamsulosin are currently the only recommended monotherapy, with current guidelines endorsing the use of alpha-blockers to facilitate passage of ureteral stones <10 mm in diameter in appropriately selected patients.[6,7] Alpha-blockers promote spontaneous passage and reduce episodes of colic.[7]

Tamsulosin – The Preferred Alpha-Blocker for Stone Expulsion

- 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[8]
- Tamsulosin acts upon alpha adrenergic receptors on ureteral smooth muscles and dilates the lumen and inhibits spasms, especially in the distal part of the ureter[9]
- The pharmacotherapeutic advantage of tamsulosin is that it has equal affinity for both alpha-1a and alpha-1d receptors[8]
- Likewise, it is effective in expulsion therapy and increases the passage rate for stones up to 10 mm[10]
- Furthermore, not only it increases the rates of spontaneous stone expulsion but also decreases the time to stone expulsion[8]
- Besides, it can also alleviate the amount of pain patients suffer while passing their stones.[11]

Acute renal colic secondary to ureteral stones

Renal colic, one of the most painful events in a person's life is associated with an acute pain related to the migration of calculi along the urinary tract and is one of the most common presentations of acute pain in emergency.[12,13] Increased pressure/tension in the renal pelvis and ureteral wall secondary to obstruction, renal capsule stretching, abnormal distention, and ureteral smooth muscle spasm leads to acute pain. It is this overpressure that stimulates local release of prostaglandins, which leads to vasodilatation, diuresis, and ureteral spasm.[12] Hence the priority should be given to manage the acute pain episode focusing on measures to decrease the severity of pain.[13] Furthermore, conservative treatment approach with appropriate pain control and medical expulsive therapy should be followed in patients with renal colic with close follow-up just in case it becomes an emergency.[14]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as standard analgesics and opioids as rescue medications in patients with renal colic. Furthermore,

phosphodiesterase (PDE) inhibitors such as drotaverine possess the potential to decrease ureteral spasm and pain as they inhibit the breakdown of cAMP and cGMP, enhancing smooth muscle relaxation.[13]

Also, EAU 2020 guideline states that NSAIDs and paracetamol are effective in the treatment of renal colic. Paracetamol should be used in the forefront in appropriate patients as recommended by the guideline as an alternative to NSAIDs. In cases where pain control cannot be achieved with paracetamol, the controlled use of NSAIDs may be an appropriate treatment approach in COVID-19 positive patients with renal colic with distal ureteral stones.[15]

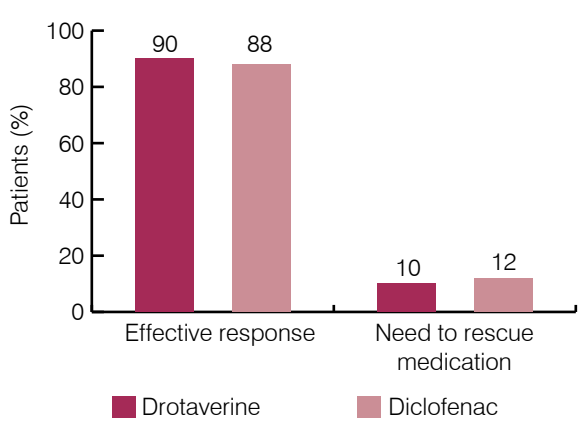
Drotaverine in acute renal colic

Drotaverine, an effective spasmolytic inhibits PDE type IV in the smooth muscle cells, accompanied by a mild calcium-channel blocking effect with no anticholinergic effect. In daily practice, it is generally used as a spasmolytic that can be administered orally, intramuscularly, or intravenously.[13]

Drotaverine has emerged as a well established directly acting, smooth muscle antispasmodic agent that brings about quick and effective pain relief. Not only in emergency, but Drotaverine provides effective pain-control in postoperative situations as well.[16]

Clinical studies have assessed efficacy and safety of intramuscular drotaverine hydrochloride in the setting of acute renal colic. A randomized, single-blind study was conducted that compared single intramuscular doses of drotaverine hydrochloride (80 mg) vs diclofenac sodium (75 mg) on 100 patients (50 in each arm) who presented to the emergency department (ED) with renal colic. It was observed that:

Figure 3: Comparison of efficacy of Drotaverine and diclofenac in colic pain



Adapted from: Dash A, Maiti R, Akantappa Bandakkanavar TK, Arora P. Intramuscular Drotaverine and Diclofenac in acute renal colic: a comparative study of analgesic efficacy and safety. *Pain Med*. 2012;13(3):466-71.

- Significant decrease was reported in VAS with both drotaverine (52.4%) and diclofenac (49%) at 30 minutes ($p<0.001$)
- Reduction of VAS at 60 minutes was 61.3% with drotaverine in comparison to 60.4% with diclofenac
- Forty-five patients (90%) in the drotaverine group and 44 (88%) in the diclofenac group found the therapy effective
- Need for rescue medication was in five patients of the drotaverine group and six patients in the diclofenac group (Figure 3).[13]

Also, the combination therapy with both ketorolac and drotaverine proved to have greater efficacy in reducing the pain intensity thus exhibiting effective pain regimen and reduced dissatisfaction in patients with renal colic.[14]

Drotaverine along with NSAIDs

Herein, the drug may be combined with a NSAID, such as Aceclofenac, to provide comprehensive coverage of pain related or unrelated to secondary spasm where several inflammatory mediators are involved. Aceclofenac is a novel, long-acting, well-tolerated NSAID with fewer incidences of side effects and established safety profile. It provides sustained pain relief by preferentially blocking cyclo-oxygenase II enzyme, which makes it an ideal NSAID for combining with fast acting drotaverine, for effective pain relief. Vinod and Ashish, in a prospective randomized clinical trial, demonstrated that drotaverine plus aceclofenac is more effective than aceclofenac alone for pain relief. Patients receiving Drotaverine (80 mg) and Aceclofenac (100 mg) combination showed statistically significant reduction in pain scores at day 1, 3 and 5, postoperatively. The combination of Drotaverine and Aceclofenac thus helps to break the vicious circle of pain, spasm and inflammation, leading to better efficacy. Drotaverine and Aceclofenac can be given in cases of renal colic, ureteric colic, post-lithotripsy and in cases of post surgical spasm. This is to ensure fast onset of pain relief in pain due to renal and ureteric stones.[16]

Potassium Citrate: Place in Therapy

Citrate salts reportedly prevent new stone formation, significantly reduce stone size, and result in stone size stability in patients with predominantly oxalate-containing stones. The need for retreatment for stone removal was also seen to be significantly less with citrate therapy.[17] Among alkali citrates, potassium citrate is the most commonly studied and used agent, with dosage ranging from 30-60 mEq in divided doses daily.[18] 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 CaOx, cystine, and uric acid stones.[19]

Box 1: 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: 03/03/2020.

Potassium citrate is preferred over sodium citrate for urinary alkalinisation due to several reasons. It attenuates calciuria and, therefore, is likely to be more effective in preventing calcium stones, while reducing urinary calcium excretion. Sodium citrate, on the other hand, tends to increase urinary calcium and the risk of calcium stones.[18,20,21] It enhances urinary cystine excretion as well.[20] The NICE recommendations on use of potassium citrate for preventing stone recurrence is enumerated in box 1.[22]

Uric acid stones

The primary intervention for preventing uric acid stones is alkali therapy to raise urine pH above solubility.[23] Herein, a target pH of 6-6.5 can effectively prevent and dissolve uric acid stones, which is readily achievable with bicarbonate or citrate salts (preferably potassium citrate) supplementation.[20,24]

Calcium based stones

Potassium citrate corrects hypocitraturia, which occurs alone or in combination with other abnormalities in about 10-60% of calcium stone formers.[20] A study conducted to this effect demonstrated patients receiving 40 mEq of oral potassium citrate daily for one year to have a significantly reduced stone recurrence rate of 1.72%, as compared to 25.86% seen in no-treatment subgroup. Both the groups were duly encouraged to high fluid intake with low salt, low oxalate diet. Furthermore, potassium citrate therapy was seen to have a good expulsive effect on residual stone fragments as well.[25]

Non-calcium based stones

Potassium citrate, titrated to achieve the target pH, is first-line therapy for uric acid stone formers, with sodium bicarbonate reserved for those unable to tolerate potassium citrate or for whom renal dysfunction or hyperkalemia precludes its use.[22] Evidence had revealed that potassium citrate supplementation in recurrent renal stone formers beneficially altered the urinary risk profile by increasing anti-lithogenic factors. Importantly, fasting glucose, glycated hemoglobin, cholesterol levels and body mass index remained unaffected post 3 months of potassium citrate therapy, suggesting it to be safe and devoid of unfavourable metabolic adverse effects.[26]

Surgical Intervention

Extracorporeal shock wave lithotripsy

Extracorporeal shock wave lithotripsy (ESWL) uses high–energy shock waves to fragment the stone; the patients subsequently pass out the fragments.[27]

Mini Percutaneous Nephrolithotripsy

Mini-PCNL can be the first-line treatment for renal stones with a diameter larger than 2 cm in children, and general indications for mini-PCNL in adults may include renal stones less than 2 or 2.5 cm in size with previous failure of ESWL.[28]

Laser Lithotripsy Using Holmium

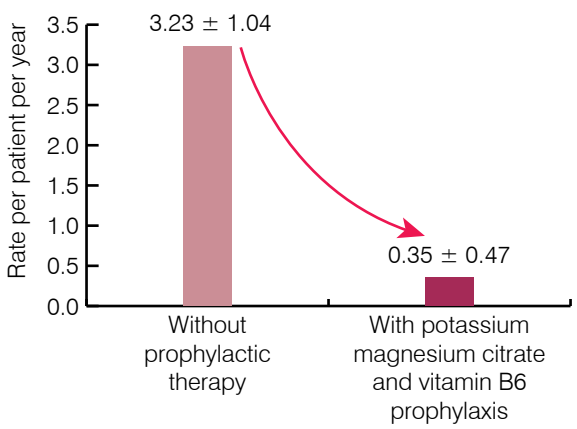
YAG laser has become the standard for stone lithotripsy due to its efficacy and safety. The holmium laser is effective for any composition of stones. Stones are ablated via a photothermal effect, the laser radiation being absorbed by residual water in the stone, creating a vapour pressure that breaks the stone.[29]

Prevention of Recurrent urolithiasis

Available data had shown that recurrence rate after formation of an initial stone was as high as 50% at 5 yr and 80–90% at 10 yr. People who form stones are more prone to develop urinary metabolic abnormalities compared to a healthy population, while patients who form recurrent stones tend to have more significant metabolic abnormalities than those with a single stone episode.[30] Potassium Citrate reduces the stone recurrence rates in calcium stone formers.[23]

A study was conducted to study the effects of long-term treatment with potassium magnesium citrate and vitamin B-6 prophylaxis. Potassium magnesium citrate prophylaxis was seen to produce 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, while urinary pH concomitantly rose significantly from 5.62 ± 0.2 to 6.87 ± 0.01, and remained maintained at 6.87 ± 0.01. Notably, the stone recurrence rate declined from 3.23 ± 1.04 per patient per year to 0.35 ± 0.47 per patient per year, as seen in figure 4. Clinical efficacy of the therapy after spontaneous passage or compelled procedural clearance of symptomatic stones was also seen to be better in treated patients as compared to

Figure 4: 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.

controls who underwent similar procedures for their stones, thus lending credence to this therapeutic combination.[31]

Conclusion

Urolithiasis has gradually become a universal problem as it is known to affect patients across geographical, cultural, and racial boundaries. With the increasing prevalence of uroliathiasis, utilization of imaging for diagnosis, treatment planning, and posttreatment follow-up has markedly increased. Imaging has a critical role in the initial diagnosis, treatment planning and post-treatment surveillance of patients with urolithiasis. Acute flank pain is the most common symptom associated with urolithiasis which is often relieved with the passage of the stone. Stone location, size, and composition along with patient symptoms are the factors that impact the decisions regarding urologic intervention. The first-line treatment for ureteral stones is medical expulsive therapy (α-blockers or calcium channel blockers with or without steroids and nonsteroidal anti-inflammatory medications), as well as hydration and analgesia. Tamsulosin is effective in expulsion therapy and increases the passage rate for stones up to 10 mm. Furthermore, Drotaverine a directly acting, smooth muscle antispasmodic agent brings about quick and effective pain relief in cases of renal and ureteral colic. Lastly, citrate salts prevent new stone formation, significantly reduce stone size, and result in stone size stability in patients with predominantly oxalate-containing stones; therefore, potassium citrate is preferred over sodium citrate for urinary alkalinisation. It is also effective in reducing the recurrence of calcium oxalate and phosphate urolithiasis.

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