Management of Renal Colic in Primary Care and When to Refer the Patient to a Urologist

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Prevalence of Renal Calculi: Global Scenario

Renal stone disease has been known as a very common disorder for centuries, and is increasingly prevalent even in recent times.[1,2] Indeed, renal stone formation has become a global problem, which spares no geographical, cultural, or racial groups.[3] Stone disease affect 5-15% of the population worldwide and are the third most common disorder of the urinary tract, preceded only by the urinary tract infections and prostate diseases. In India, almost 5-7 million individuals suffer from stone disease and at least 1/1000 of Indian population requires hospitalization due to renal calculi.[1-4]

Renal calculi are more common in adults compared to the elderly, and are the least common in pediatric population; the age of peak incidence ranges from 20 to 40 years. It is two to three times more common in men than in women, with a lifetime risk of about 12% in men and 6% in women.[1,2,5] Lately, the male predominance of stone disease seems declining, and a new trend seems to be the increased incidence of stone formation in women. Renal calculi continue to be more common in men; however, the incidence rate ratio of men to women with urinary tract calculi has narrowed from 3.4 to 1.3.[2,6,7]

One of the major problems with renal calculi is the high rate of recurrence, which ranges from 40% to 60%. In absence of appropriate treatment, there is a 50% chance of forming a second stone within 7 years of an initial stone.[8] Thus, with a prevalence of more than 10% and an expected recurrence rate of almost 50%, renal calculi are considered a medical challenge and have a remarkable effect on the healthcare system.[4,5,9]

Risk Factors for Renal Calculi

A definite causative factor is not identified in most cases of renal calculi. However, risk of renal calculi is increased by various factors, such as family history of kidney stones, insulin resistance, a history of hypertension, primary hyperparathyroidism, a history of gout, chronic metabolic acidosis, and surgical menopause.[10]

Reduced fluid intake and ensuing urine concentration are among the most crucial risk factors influencing stone formation. Individuals producing < 1 L of urine per day are reported to be at the highest risk of stone formation, whereas producing 2 L of urine per day considerably lessens the risk. Besides, increased consumption of oxalate as well as caffeinated, high-sugar content beverages has also been demonstrated to contribute to calculi formation. Further, the incidence of stones is more in warmer climates, due to a combination of dehydration and sun exposure. Various epidemiologic studies in the developed countries have revealed that regions with higher average temperatures have the highest stone rates (Box 1).[1,2,6,11,12]

Obesity is another risk factor, with several studies demonstrating both high body mass index and weight as independent risk factors for stone formation. The interplay of obesity and other components of the metabolic syndrome have been associated with calculi formation through various pathophysiological aspects, including increased urinary oxalate excretion, increased uric acid production and impaired ammoniogenesis. Obesity has also been linked to decreased urinary pH and associated renal calculi. Previous stone formation is also a risk factor,

Box 1: Risk factors for urinary stone formation

- Reduced fluid intake
- Less than 1 litre of urine production per day
- Warmer climate
- Obesity
- Previous stone formation
- Family history of urinary stones
- Abnormality of urinary tract
- Insulin resistance
- History of hypertension
- Primary hyperparathyroidism
- History of gout
- Chronic metabolic acidosis
- Surgical menopause

with a 30-40% recurrence rates within five years of the initial episode. In addition, the risk of experiencing urinary stones is almost three times higher if a patient has a family history of stone disease.[1,2,6,12]

Symptoms of Renal Colic

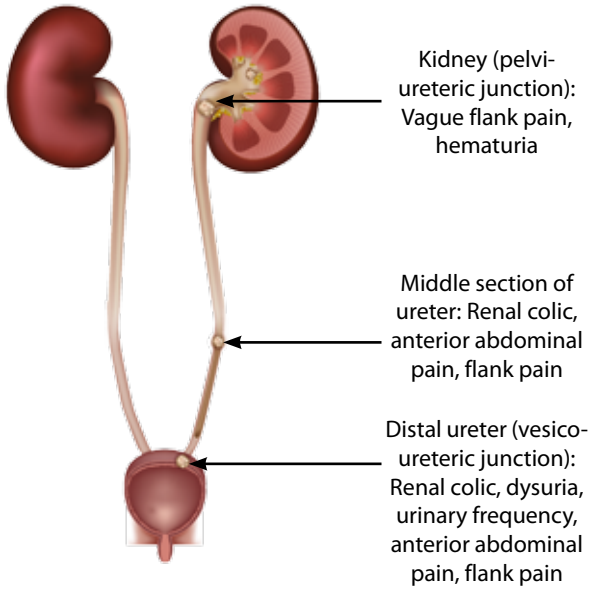
The classic presentation of renal colic is the sudden onset of excruciating loin pain in the costovertebral angle, lateral to the sacrospinus muscle, and beneath the 12th rib.[12] In majority of patients (almost 85%), it is accompanied by microscopic hematuria. Dysuria or frequency, nausea, vomiting, and occasionally ileus are commonly observed.[13]

Depending on the obstruction site, the pain may radiate to the flank, groin, and testes or labia majora. As the stone descends down the ureter, the pain tends to migrate caudally and medially.[12] Importantly, the pain is a colic, and therefore occurs in waves of changing intensity.[1,2] Anatomically, the three narrowest parts of the ureter are at the pelvi-ureteric junction (PUJ), in the mid ureter where the ureter crosses the iliac vessels, and at the vesico-ureteric junction (VUJ). The most common site at presentation by far is at the VUJ, accounting for the presence of more than 60% of stones in this location.[1] If a stone approaches the VUJ, the patient may usually complain of, in addition to pain, urinary urgency, frequency and dysuria, caused by irritation of the detrusor muscle from the stone (Figure 1).[1,2,12]

Etiological Basis of Renal Colic

Urinary stones are large crystal aggregates being embedded in a non-crystalline protein matrix. These

Figure 1: Relationship between stone location and symptoms



crystals pack together forming a stone and on attaining a certain size they start moving. During their transit through the ureter, they frequently cause colic symptoms. Importantly, about 12% of the population is likely to suffer from renal colic sometime in their lifetime, with recurrence rates approaching almost 50%.[1,14]

Renal colic is most frequently caused by the transit of calculi through the urinary tract. The pain is caused by obstruction of the urinary flow by a urinary stone, leading to increased pressure on the urinary tract wall. The rising pressure stimulates release of prostaglandins that cause vasodilatation. This in turn leads to diuresis and thus further increases the intrapelvic pressure. Prostaglandins also lead to smooth muscle spasms of the ureter around the stone that further adds to pain. Severity of pain is also increased by edema and inflammation near the stone, increase in peristalsis, and pressure of the proximal stone.[2,14,15]

Urinary calculi are the most common cause; however, the term 'renal colic' may refer to an assortment of symptoms attributed to the kidney and ureter. There exist other intrinsic, or in some cases extrinsic factors such as lymphadenopathy. Of note, extrinsic factors usually lead to milder and more chronic distress. Usually, the intrinsic

Table 1: Important factors to be considered in patient's history for diagnosis of renal colic

Presence of systemic illness	Anatomical features	History of kidney disease	Drugs that affect calculi formation
• Primary hyperparathyroidism • Renal tubular acidosis • Cystinuria • Gout • Diabetes mellitus • Renal insufficiency • Medullary sponge kidney	• Horseshoe kidney • Previous urinary diversion • Obstruction of the ureteropelvic junction • Solitary kidney • Previous renal or ureteral surgery	• History of urinary tract infection or pyelonephritis, or both • Family history of urolithiasis • Detailed history of previous stone events » Treatment » Stone analysis	• Carbonic anhydrase inhibitors • Ephedrine • Guaifenesin • Calcium with vitamin D • Triamterene • Indinavir or sulfadiazine

factors are blood clots (from upper tract bleeding) or sloughed renal papilla (in sickle cell disease, diabetes, or chronic use of certain medications).[1]

Diagnosis of Renal Colic

Initial evaluation of the patient with renal colic should include a detailed case history, including past or family history of calculi with previous treatments and stone analysis, duration and evolution of symptoms, and any anatomical abnormalities or surgery of the urinary tract. It should be followed by physical examination that is important to rule out nonurologic causes. Comorbidities should also be identified; particularly any systemic disorder that might increase the risk of renal calculi formation or that might influence the clinical course of the disease (Table 1). All patients with suspected renal calculi should undergo urinalysis, to detect typical microhematuria, urine pH and the presence of crystals, which may help to identify the stone composition.[12,16]

Diagnostic Imaging

History and physical examination may help suspect renal colic, but diagnostic imaging is important to confirm or exclude the presence of urinary stones.[12] The diagnostic imaging techniques used for patients with suspected renal colic include plain abdominal radiography, ultrasound imaging, intravenous urography and computed tomography.[17] Computed tomography is considered the best diagnostic tool owing to its excellent accuracy in detecting ureteral calculi. Nonetheless, ultrasound imaging can achieve a high sensitivity and specificity for the depiction of ureteral calculi and acute obstruction; besides, it has numerous advantages including its reproducibility, availability, lower cost and absence of radiation. Therefore, ultrasound imaging may be considered the primary imaging technique in patients with renal colic.[18] The varied presentations of renal colic and its broad etiologic basis necessitate a systematic diagnostic approach (Figure 2).

Management of Patient with Renal Colic

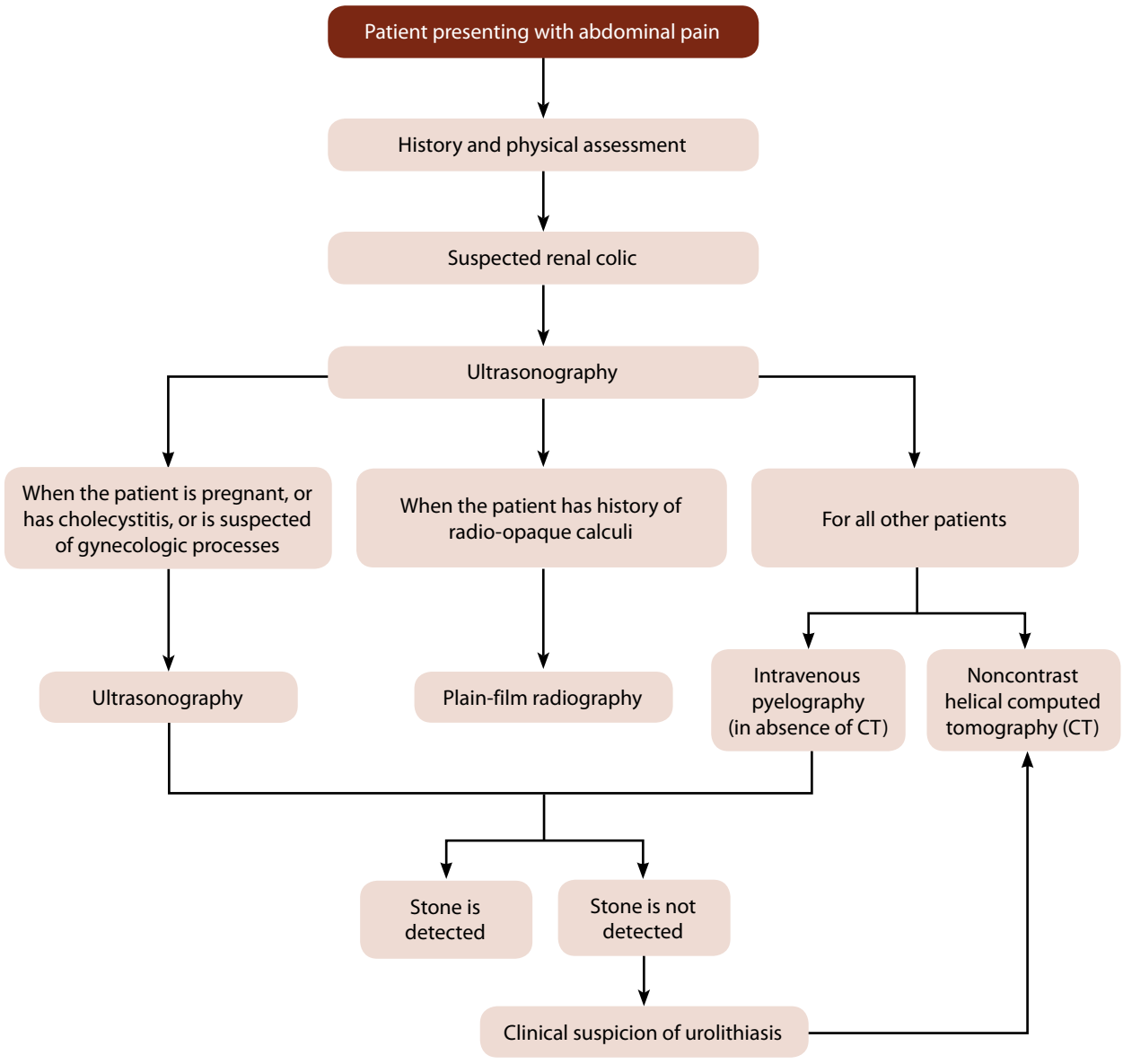
Renal colic pain is often expressed as the worst pain the patient has ever gone through. Therefore, in such conditions, the priority should be to relieve the excruciating pain and spasm, or at least lessen the intensity. The use of effective analgesics like; non steroidal anti-inflammatory drugs (NSAIDs), and opioids, or a combination of medications (anti-inflammatory and spasmolytic agents such as drotaverine), play crucial roles in the treatment of these patients.[2,19]

Pain Management: Use of Antispasmodics

Spasmolytics are traditionally used for relief of smooth muscle spasm in conditions such as renal colic, biliary colic, or dysmenorrhoea.[14] Drotaverine is an effective spasmolytic agent, which inhibits phosphodiesterase type IV (PDE4) in the smooth muscle cells that hydrolyses cyclic adenosine monophosphate (cAMP). This leads to increase in cAMP concentration, which decreases uptake of calcium (exerting mild Ca-channel blocking effect) and alters its distribution among the cells. Drotaverine is shown to relieve smooth muscle spasm in all organs where PDE4 is present, including smooth muscles of the kidney or ureter. Importantly, it has no anticholinergic effect. It is effectively being used in various countries for treating renal colic. In routine practice it is usually used in combination with an analgesic, thus augmenting the spasmolytic effect.[19,20]

With an aim to explore the role of drotaverine in acute renal colic, a group of researchers conducted a randomized, single-blind study[21] that evaluated drotaverine hydrochloride against diclofenac sodium on 100 patients (50 in each group) with renal colic. The primary outcome

Figure 2: A systematic diagnostic approach to suspected renal colic



of the study was reduction in pain intensity as recorded on visual analog scale (VAS), at baseline and 30 and 60 minutes post-drug administration. The drug efficacy was defined as ≥50% reduction in pain intensity 60 minutes post-administration, without exacerbation during the next 2 hours. A remarkable decrease in VAS was observed, with drotaverine (52.4%) compared to diclofenac (49%) at 30 minutes. Further, at 60 minutes, the mean changes in VAS were 61.3% for drotaverine compared to 60.4% for diclofenac (Figure 3). The therapy was found effective by 90% patients in the drotaverine group and 88% patients in the diclofenac group. The results corroborated the efficacy and safety of drotaverine as analgesic in renal colic, and were suggestive of its use as an alternative or add-on therapy to currently available options.

Figure 3: Reduction in pain intensity, as assessed by visual analogue scale, with drotaverine versus diclofenac

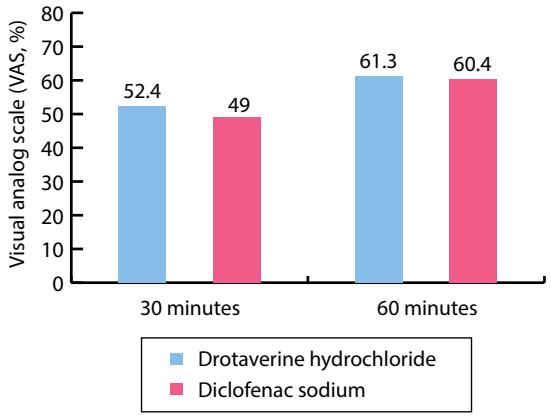
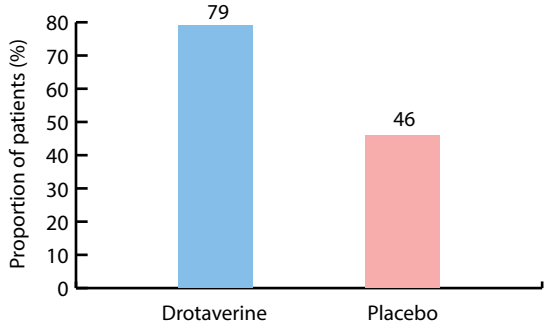


Figure 4: Relief in acute colicky pain of renal and ureteric stones by drotaverine versus placebo



In another study[19] involving patients with colicky pain caused by renal and ureteric stones, drotaverine was found to be effective in 79% of patients compared to placebo group (46%). It was observed that pain intensity was reduced in more than two-thirds of patients receiving drotaverine (Figure 4).

Drotaverine is also shown to be more effective compared to its counterparts. Palea et al in their review on the effects of drotaverine relaxation on the human ureteral muscle ring reported that the effect of drotaverine in relaxing muscles of the human ureter was almost six times stronger than papaverine; therefore, the ureteral muscle relaxant advantage can be employed in the treatment of patients affected with renal colic.[2]

These studies thus substantiate that for renal colic caused by renal and ureteric stones, drotaverine is an effective treatment option, with no serious adverse effects. Of note, the efficacy can be augmented with the concomitant administration of NSAIDs.[19]

Both NSAIDs and drotaverine hydrochloride are frequently used medication for acute renal colic.[17,22] Given that spasmolytic agents relieve the pain associated with smooth muscle spasm, the combination of NSAIDs with spasmolytics is likely to be synergistic.[14] In a study conducted by Pareek and colleagues,[23] addition of drotaverine to aceclofenac was found to provide considerable therapeutic benefit as compared to monotherapy with aceclofenac. Besides, fixed dose combinations of spasmolytics such as drotaverine with analgesics, including mefenamic acid and aceclofenac have been shown to be highly effective in pain relief associated with acute spasms.[14]

Medical Expulsive Therapy

Medical expulsive therapy (MET) has emerged as a promising option for the management of renal calculi. It refers to the treatment of stone disease by combining drugs of various classes, which help in spontaneous passage of renal calculi. MET comprises combination of drugs such as alpha adrenoreceptor blockers, calcium channel blockers, corticosteroid, analgesics, and hydration.[24]

Role of Tamsulosin in Stone Expulsion

Smooth muscles of lower ureter are densely populated with alpha-adrenergic receptors. The bladder outlet, prostate, and proximal urethra are predominated by the alpha-1a receptors, whereas alpha-1d-receptors are found in lower ureter and detrusor muscle of bladder. Drugs that exert inhibitory effect on these receptors result in smooth muscle relaxation, cause peristalsis to cease, and relieve spasm. Tamsulosin, an alpha adrenoceptor blocker, is one such drug, which is a potential agent of MET as it increases the passage rate and lowers the passage time for stones up to 10 mm.[24]

Tamsulosin is effective in hastening the passage of ureteral stones and decreasing both the severity and duration of renal colic. Tamsulosin exerts a stimulatory action on α-adrenergic receptors present in the ureter. Stimulation of these receptors causes an increase in

both, the force of ureteral contraction and the frequency of ureteral peristalsis. This leads to an increase in the intraureteral pressure gradient around the stone, which raises the urine bolus above the stone (increased intraureteral pressure above the stone). At the same time, peristalsis below the ureter (and consequently intraureteral pressure below the stone) decreases along with fall in basal and micturition pressure even at the bladder neck. Consequently, the urge to expel the stone gets intensified. A large slew of studies has substantiated the efficacy of tamsulosin in the management of ureteral stones.[25-30]

Though meta-analyses of previous randomised controlled trials concluded that the smooth muscle relaxant drugs tamsulosin and nifedipine assisted stone passage for people managed expectantly for ureteric colic, but emphasised the need for high-quality trials with wide inclusion criteria.

Role of Urinary Alkalinization

Urine pH is a crucial factor in the formation of renal calculi. Uric acid, cystine, and calcium oxalate stones tend to form in acidic urine; therefore, prevention of stone formation necessitates urinary alkalinization either by consuming a diet high in fruits and vegetables, drinking alkaline mineral water, or taking supplemental or prescription citrate.[31]

Potassium citrate and sodium bicarbonate are commonly used for urine alkalization. Natural sources of dietary citrate include citrus fruits and juices, such as lemon juice, orange juice, and fresh tomato juice, which is found to have the highest citrate and low oxalate content.[24,32] Nonetheless, dietary replacement with potassium citrate therapy has yielded better outcomes. The same was revealed in a study conducted by Kang and coworkers,[32] wherein 11 patients with hypocitraturic nephrolithiasis taking potassium citrate therapy were compared with 11 matched patients on lemonade therapy. It was found that although both the therapies increased the urinary citrate levels, the effect with potassium citrate (mean increase +482 mg per day) was remarkably better than the lemonade (mean increase +383 mg per day). Potassium citrate therapy offers various advantages including chemodissolution of stones, increased urinary pH, increased urinary citrate, and reduced stone recurrence rate (Box 2). Indeed, potassium citrate is a preferred alkalinizing agent than sodium bicarbonate, because of the avoidance of a high sodium load.[33-35]

Box 2: Advantages of citrate therapy

- Chemodissolution of stones
- Increased urinary pH
- Increased urinary citrate
- Reduced stone recurrence rate
- Effective in medically compromised patients

Need for Urology Referral

Decisions regarding a trial of conservative medical therapy or referral for urologic intervention are mostly guided by stone size and its location in the urinary tract. Drug therapy is highly effective in stone expulsion; however, it is imperative that an appropriate urology referral be made in certain cases such as patients with a stone greater than 5 mm in size, or patients receiving medical expulsion therapy who do not pass their stones within 2-3 weeks.[12] Patients who are systemically unwell with renal calculi are more prone to have an infected and obstructed urinary tract system that needs emergency urological consultation for imaging and possible drainage.36 Besides, surgical intervention is required in patients with persistent obstruction, failure of stone progression, sepsis, or persistent or increasing pain.[37]

Conclusion

Urinary stone disease is a common disorder with increasing prevalence, particularly among men. Renal colic is generally caused by the passage of calculi through the urinary tract and obstructing the flow of urine. Renal colic pain is one of the most painful experiences in a person's life. The classic presentation of renal colic is the sudden onset of excruciating loin pain in the costovertebral angle, lateral to the sacrospinus muscle, and beneath the 12th rib. NSAIDs are the most effective frequently used analgesics for treating renal colic. Drotaverine represents an effective alternative or add-on analgesic to currently available options for renal colic. For renal colic caused by renal and ureteric stones, drotaverine is shown to be effective in more than two-thirds of patients, with no serious adverse events. Concomitant administration of NSAIDs is likely to augment the efficacy. Therefore, fixed dose combination of drotaverine with aceclofenac or mefenamic acid provides highly effective therapy in relief of acute spasmodic pain including renal colic pain. Besides, medical expulsive therapy and urinary alkalinization are also effective approaches for the management of renal colic.

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