Evaluation of Efficacy and Safety of Cystone Syrup in Lower Ureteric Calculus

Abstract

The present study evaluated the efficacy and safety of Cystone syrup, a polyherbal formulation, in lower ureteric calculus. The incidence of urolithiasis is high in developing countries, and in the northern and north-western regions of India.

The study was an open, non-randomized, non-comparative, prospective clinical trial conducted as per the ethical guidelines of Declaration of Helsinki. Twenty-five patients having lower ureteric calculi were included in this study. Patients with any complication like severe pain, hematuria or obstruction requiring immediate surgery, hydronephrosis, acute renal failure, multiple ureteric stones, pregnant or lactating women, women with childbearing potential without adequate contraception, hepatic/renal/cardiac disease were excluded.

A thorough history and clinical examination was done before treatment and during follow-up visits every week till the end of treatment on day 28 along with recording of adverse events. All patients were investigated before and after the treatment for routine urine analysis with culture and sensitivity and blood urea, serum creatinine, sodium, potassium, calcium, bicarbonate and uric acid levels. All patients also underwent abdominal radio imaging and ultrasound examination at baseline and at the end of the therapy.

All 25 patients enrolled completed the study. On starting Cystone syrup therapy, a significant \( p < 0.0001 \) symptomatic relief of abdominal pain and dysuria was reported. There was a significant \( p < 0.0001 \) reduction in the mean number of pain episodes from 2.72 ± 1.339 to 0.92 ± 0.8622 per day at the end of the therapy. A significant reduction \( (p < 0.0001) \) in the daytime and night time urinary frequency was observed at the end of treatment. Disappearance of stones was noted in 11 (44%, \( p < 0.001 \)) patients at the end of the 28-day study period. It was concluded that Cystone syrup is clinically safe and effective in the management of lower ureteric calculus.

Introduction

Urolithiasis affects 1-5% of population. The incidence is higher in developing countries, including India. It has been hypothesized that the main source of dietary proteins being cereals, unlike meat in western countries, is an important etiological factor. The northern and north-western regions of India can be described as an endemic stone-forming belt due to a dietary pattern rich in cereals and pulses.

Urolithiasis is a consequence of complex physicochemical processes and the major contributory factors are urinary super saturation, crystallization, calculogenesis and matrix formation. The sequence of events in the formation of any urinary stone can be: Urinary saturation, super saturation, nucleation, crystal growth, crystal aggregation, crystal retention and stone formation.

Kidney stones smaller than 4 mm in diameter are most likely to be flushed out in urine without any medical intervention, except occasional analgesics and anti spasmodics that enable the patient to endure the episode, which may last several days. Kidney stones >5 mm in diameter are less likely to be flushed out in urine on their own. If the stone is larger than...
Prospective, phase III clinical trial, randomized and non-comparative, Procedure give informed consent.

Patients and methods

Inclusion criteria

Patients above 18 years, of either sex, diagnosed ultrasonographically or radiologically with visible distal ureteric calculi of 4 mm size or larger, below the common iliac vessels.

Exclusion criteria

Patients with severe pain, hematuria or obstruction requiring immediate surgery, marked hydronephrosis, acute renal failure, pregnant or lactating women, women with childbearing potential without adequate contraception, hepatic or renal or cardiac disease, and those unwilling to give informed consent.

Procedure

The study was an open, non-randomized and non-comparative, prospective, phase III clinical trial, conducted at Shree Sai Hospitals, Chennai, India from December 2006 to May 2007 as per the ethical guidelines of Declaration of Helsinki. The study protocol, case report forms (CRFs), regulatory clearance documents, product related information, and informed consent forms (in English, Hindi and Tamil) were approved by the institutional ethics committee and were approved by the same.

The OPD patients were informed about the study drug, its effects, duration of stay in the trial and overall plan of the study. A written informed consent was obtained. The history was noted by interviewing each patient. Thorough clinical examination and symptomatic evaluation was carried out and the details were noted down in the CRF. Patients were advised to take one teaspoonful of Cystone syrup, twice a day after meals for 28 days.

All patients were followed up every week till the end of treatment on day 28 and symptomatic evaluation and clinical examination was done, along with recording the occurrence of any adverse event/s (either reported or observed).

One Way ANOVA test followed by Dunnett’s multiple comparison test for evaluation of symptomatic scores, Fisher’s Exact test and Paired Student ‘t’ test for evaluation of reduction and passage of stones by comparing baseline values and end-of-the-treatment values were used.

Results

Twenty-five patients were enrolled in the study (8 males and 17 females)
and all the subjects completed the study. The mean age of the patients was 37.2 years. On starting Cystone syrup therapy, a significant \((p < 0.0001)\) symptomatic relief from abdominal pain and dysuria was reported by patients (Tables 1 and 2; Figs. 1 and 2). There was a significant \((p < 0.0001)\) reduction in the mean number of pain episodes from \(2.72 \pm 0.2678\) to \(0.92 \pm 0.1724\) at the end of the therapy (Table 3 and Fig. 3). A significant reduction \((p < 0.0001)\) in the daytime and night time urinary frequency was observed at the end of treatment (Tables 4 and 5; Figs. 4 and 5). The reduction in the symptoms started appearing right from the day 14 of therapy.

**Disappearance of calculi** (dissolution or spontaneous passage)
was noted in 11 (44%; p < 0.001) patients at the end of the 28-day study period, as confirmed by X-ray KUB and ultrasound examination (Table 6 and Figs. 6 and 7). The size of expelled stones varied between 5-12 mm, the average size being 7 mm. There was a significant decrease (p < 0.001) in the mean size of the calculus from 8.80 ± 0.55 mm to 6.08 ± 1.06 mm after 28 days of treatment with Cystone syrup (Table 7 and Fig. 8).

There was no change in the biochemical investigations of blood urea, serum creatinine, sodium, potassium, calcium and bicarbonate, and uric acid levels and urine analysis done between baseline and day 28 of the therapy.

There were no recurrences and clinically significant adverse events, either reported or observed, during the study period.

**Discussion**

Recent advances in endoscopic stone management have allowed kidney stones to be treated using minimally invasive techniques, which have increased success rates and decreased treatment-related morbidity. These advances include shock wave lithotripsy (SWL), ureteroscopy and percutaneous nephrostolithotomy. Although these approaches are less invasive than traditional open surgical approaches, they are expensive and have inherent risks.

Despite success has been shown with calcium channel blockers or with calcium channel blockers (MET) has been investigated as a supplement to observation in an effort to improve spontaneous stone passage, which can be unpredictable. Because ureteral edema and ureteral spasm have been postulated to affect stone passage, these effects have been targeted for pharmacologic intervention. Therefore, the primary agents that have been evaluated for MET are calcium channel blockers, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and α1-adrenergic receptor antagonists.

Although success has been shown with calcium channel blockers with or without steroids and/or NSAIDs, α-blockers, with their high success rates, excellent safety profile, low side effect profile, and ease of use, have become the leading candidate in MET.

In the present study, disappearance of calculi (dissolution or spontaneous passage) was noted in 11 patients at the end of the 28-day study period. A significant symptomatic relief from abdominal pain and dysuria was reported by patients.
significant reduction in the mean number of pain episodes from baseline to the end of the therapy. A significant reduction in the daytime and night time urinary frequency was observed at the end of treatment. The reduction in symptoms started appearing from the day 14 of therapy itself.

The beneficial actions of Cystone syrup might be due to the synergistic actions of its ingredients. T. terrestris has long been used empirically to propel urinary stones. The diuretic and contractile effects of T. terrestris indicate that it has the potential of propelling urinary stones. The steroidal saponin constituents obtained from T. terrestris were tested for their antimicrobial and cytotoxic effects.

In an investigation, a methanol extract obtained from roots of B. diffusa exhibited a significant spasmylytic effect. The beneficial actions of Cystone syrup might be due to the synergistic actions of its ingredients. T. terrestris has long been used empirically to propel urinary stones. The diuretic and contractile effects of T. terrestris indicate that it has the potential of propelling urinary stones. The steroidal saponin constituents obtained from T. terrestris were tested for their antimicrobial and cytotoxic effects.

Figure 7. Ultrasound images of patients with lower ureteral stones before and after treatment with Cystone syrup.
activity in the guinea pig ileum, probably through a direct effect on the smooth muscle.

The hexane extracts of C. rotundus showed potent treatment of dysuria.

In Ayurveda, A. racemosus has been described as a rasayana herb and has been used extensively as an adaptogen to increase the non-specific resistance of body against a variety of stresses. The ethanolic extract of A. racemosus showed inhibitory potential on lithiasis (stone formation) and this plant extract inhibits stone formation.

Methanol extract of the roots of A. racemosus showed considerable in vitro antibacterial efficacy against Escherichia coli, Shigella dysenteriae, Shigella sonnei, Shigella flexneri, Vibrio cholerae, Salmonella typhi, Salmonella typhimurium, Pseudomonas putida, Bacillus subtilis and Staphylococcus aureus.

The chemical compositions of the essential oil of C. zedoaria (Berg.) Rosc. were analyzed by gas chromatography-mass spectrometry (GC-MS). The essential oil was evaluated for potential antimicrobial activity against S. aureus, E. coli, Pseudomonas aeruginosa, Vibrio parahaemolyticus, S. typhimurium and Bacillus cereus. V. parahaemolyticus was sensitive to the presence of the essential oil.

The analgesic activity of C. zedoaria rhizomes was proven in a phytochemical analysis study.

Soxhlet extracts of seeds of D. biflorus and S. ligulata showed in vitro antilithiatic/anticalcificiation activity. An in vitro study has showed the effect of D. biflorus seeds on crystallization of calcium phosphate, a major constituent of kidney stone.

Therefore, the observed clinical benefits of Cystone syrup might be due to the synergistic actions of its ingredients.

Conclusion

Surgery or lithotripsy is the available option in urolithiasis and recurrence is the core issue in the clinical management of urolithiasis. A drug, which will inhibit calculogenesis, in addition to high success rates, excellent safety profile, low side effect profile, and ease of use, is ideal for management of urolithiasis.

This study indicates Cystone syrup to be an effective and safe treatment in lower ureteric calculus as it expels the stones and brings about significant reduction of symptoms associated with urolithiasis. The overall compliance of Cystone syrup was good. No clinically significant adverse reactions were reported or observed during the entire study period.

References