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

JEYARAMAN*, SR PRASAD**, SK MITRA†

*Consultant Urologist, Professor and Head, Department of Urology, Madras Medical College, Chennai.
**Medical Advisor,
†Executive Director, R&D Center, The Himalaya Drug Company, Bangalore.
Address for correspondence: Dr SR Prasad, Medical advisor, R & D Center, The Himalaya Drug Company, Bangalore. E-mail: dr.prasad@himalayahealthcare.com

After 28-day treatment with Cystone syrup, disappearance of calculi was noted in 12 patients. A significant symptomatic relief from abdominal pain and dysuria was reported by patients.

Abstract

The present study was planned to evaluate the efficacy and safety of Cystone syrup, a polyherbal formulation, in lower ureteric calculi. The prevalence of urinary calculi is estimated to be 5% in the general population, with an annual incidence of as much as 1%.

This 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, marked hydronephrosis, acute renal failure, multiple ureteral stones, pregnant or lactating women, women with childbearing potential without adequate contraception, and those with hepatic or renal or cardiac disease were excluded from the study.

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

Twenty-five patients were enrolled in the study and all the subjects completed the study. On starting Cystone syrup therapy, a significant (p < 0.0001) symptomatic relief from abdominal pain and dysuria was reported by patients. There was a significant (p < 0.0001) reduction in the mean number of pain episodes from 4.520 ± 0.451 to 1.320 ± 0.298 per day at the end of the therapy. A significant reduction (p < 0.0001) in the daytime and night-time urinary frequency, and tenderness in KUB area was observed at the end of treatment. Disappearance of stones was noted in 12 (48%; p < 0.001) patients at the end of the 28-day study period. Therefore, it may be concluded that Cystone syrup is clinically safe and
effective in the management of lower ureteric calculi.

Introduction

The prevalence of urinary calculi is estimated to be 5% in the general population, with an annual incidence of as much as 1%. Men are twice as likely as women to develop calculi, with the first episode occurring at an average age of 30 years. Women have a bimodal age of onset, with episodes peaking at 35 and 55 years. Without preventive treatment, the recurrence rate of calcium oxalate calculi increases with time and reaches 50% at 10 years.

Renal calculi are crystalline mineral deposits that form in the kidney. They develop from microscopic crystals in the loop of Henle, the distal tubule, or the collecting duct, and they can enlarge to form visible fragments. The process of stone formation depends on urinary volume; concentrations of calcium, phosphate, oxalate, sodium and uric acid ions; concentrations of natural calculi inhibitors (e.g., citrate, magnesium, Tamm-Horsfall mucoproteins, bikunin); and urinary pH.

Calculi are classified into five categories based on their composition: calcium oxalate (70%), calcium phosphate (5-10%), uric acid (10%), struvite (15-20%) and cystine (1%).

With hydration and pain control, calculi smaller than 5 mm will pass spontaneously in approximately 90% of patients. The rate of passage decreases as stone size increases; a 1 cm stone has a <10% chance of passing without surgical intervention. Recent studies have suggested that the use of the α1-adrenergic blocker, tamsulosin, can increase the chance of spontaneous passage of ureteric calculi.

Surgical options include extracorporeal shock wave lithotripsy, ureteroscopic stone extraction and percutaneous nephrolithotomy. Ureteric calculi is a significant health problem. Although, surgical management has become increasingly tolerable, medical prevention of recurrent calculi is feasible, easily obtained and greatly desirable.

Study procedure

The study was an open, non-randomized and non-comparative, prospective, phase III clinical trial, conducted at B.R. Speciality Hospital and Research Centre, T. Nagar, Chennai, Tamil Nadu, India between March 2007 to June 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 and Tamil) were submitted to the institutional ethics committee and were approved by the same.

Twenty-five patients were enrolled in the study and all the subjects completed the study. The present study was designed to evaluate the efficacy and safety of Cystone syrup, a polyherbal formulation, in the management of lower ureteric calculi. Cystone syrup comprises of extracts of Tribulus terrestris, Boerhaavia diffusa, Saxifraga ligulata, Cyperus rotundus, Asparagus racemosus, Dolichos biflorus, Vetiveria zizanioides, Curcuma zedoaria and Trikatu and powders of Suvarchika, Narasara, Yuvakshara and Saindhava.

Patients and methods

Inclusion criteria

Patients above 18 years of age, of either sex, and diagnosed with ultrasonographically or radiologically, with visible distal ureteric calculi of 5-10 mm size, below the common iliac vessels were included in the study.

Exclusion criteria

Patients with any complication like severe pain, hematuria or obstruction requiring immediate surgery, marked hydronephrosis, acute renal failure, pregnant or lactating women, women with childbearing potential without adequate contraception, those with hepatic or renal or cardiac disease, and those unwilling to give informed consent were excluded from the study.
of Cystone syrup, twice a day after meals for 28 days.

All patients were reviewed 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 (either reported or observed).

All patients were investigated before and after treatment for complete urine analysis with culture and sensitivity, blood urea, serum creatinine, sodium, potassium, calcium and bicarbonate, and uric acid levels. Patients also underwent abdominal radio imaging and ultrasound examination at baseline and at the end of the therapy.

Primary and secondary end-points

The predefined primary end-points were the effects on change in the number and size of stones, and spontaneous passage of stone. The predefined secondary end-points were symptom score reduction, short- and long-term safety, and overall compliance to the drug treatment.

Adverse events

All adverse events, reported or observed by patients, were recorded with information about severity, date of onset, duration and action taken regarding the study drug. Relation of adverse events to study medication were predefined as “unrelated” (a reaction that does not follow a reasonable temporal sequence from the administration of the drug), “possible” (follows a known response pattern to the suspected drug, but could have been produced by the patient’s clinical state or other modes of therapy administered to the patient) and “probable” (follows a known response pattern to the suspected drug that could not be reasonably explained by the known characteristics of the patient’s clinical state).

Patients were allowed to voluntarily withdraw from the study if they experienced serious discomfort during the study or sustained serious clinical events requiring specific treatment. For patients withdrawing from the study, efforts were made to ascertain the reason for dropout. Non-compliance (defined as failure to take <80% of the medication) was not regarded as treatment failure, and reasons for non-compliance were noted.

### Statistical analysis

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
<th>Statistics and significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>3.053 ± 0.143</td>
<td>2.684 ± 0.110</td>
<td>1.211 ± 0.211*</td>
<td>1.053 ± 0.248*</td>
<td>0.474 ± 0.221*</td>
<td>FS: −179.5; p&lt;0.0001, significant</td>
</tr>
<tr>
<td>Dysuria</td>
<td>2.080 ± 0.163</td>
<td>2.000 ± 0.173</td>
<td>1.680 ± 0.160</td>
<td>1.480 ± 0.201</td>
<td>0.800 ± 0.216*</td>
<td>FS: 33.84; p&lt;0.0001, significant</td>
</tr>
<tr>
<td>No. of pain episodes</td>
<td>4.520 ± 0.451</td>
<td>3.240 ± 0.226*</td>
<td>2.800 ± 0.192*</td>
<td>2.240 ± 0.240*</td>
<td>1.320 ± 0.298*</td>
<td>R² = 0.3576; FS = 4.888; p&lt;0.0001, significant</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>1.960 ± 0.227</td>
<td>1.920 ± 0.223</td>
<td>1.760 ± 0.210</td>
<td>1.600 ± 0.208</td>
<td>0.880 ± 0.226*</td>
<td>R² = 0.6694; FS = 12.61; p&lt;0.0001, significant</td>
</tr>
<tr>
<td>Tenderness in KUB area</td>
<td>2.160 ± 0.180</td>
<td>2.040 ± 0.187</td>
<td>1.760 ± 0.145</td>
<td>1.440 ± 0.183</td>
<td>0.840 ± 0.214*</td>
<td>FS: 44.44; p&lt;0.0001, significant</td>
</tr>
</tbody>
</table>

Statistical analysis was carried out using repeated ANOVA test and Friedman test, followed by Dunnet’s Multiple Comparison test.

* p<0.01 and ** p<0.001 as compared with day 0 value.

Abbreviation: FS: Friedman statistic value
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 (19 males and six 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 (Table 1; Figs. 1 and 2). There was a significant ($p<0.0001$) reduction in the mean number of pain episodes from 4.520 ± 0.451 to 1.320 ± 0.298 at the end of the therapy (Table 1 and Fig. 3). A significant reduction ($p<0.0001$) in the daytime and night time urinary frequency, and tenderness in KUB area was observed at the end of treatment (Table 1; Figs. 4 and 5). The reduction in the symptoms started appearing from the day 7 of therapy itself.

Disappearance of calculi (dissolution or spontaneous passage) was noted in 12 (48%; $p<0.0001$) patients at the end of the 28-day study period, as confirmed by X-ray KUB and ultrasound examination (Table 2 and Fig. 6). The size of expelled stones varied between 5-8 mm, the average size being $6.08 \pm 0.2865$ mm. There was a significant decrease ($p<0.001$) in the mean size of the calculi from 7.204 ± 0.341 mm to 4.040 ± 0.821 mm after 28 days of treatment with Cystone syrup (Table 3 and Fig. 7).

| Table 2. Reduction in number of patients with calculi following Cystone syrup treatment |
|---------------------------------|-----------------|-----------------|
| **No. of patients** | **Present** | **Absent** |
| Before treatment | 25 | 0 |
| After treatment | 13 | 12* |

Statistical analysis was carried out using repeated ANOVA test, followed by Fisher’s exact test. *$p<0.001$ as compared with day 0 value.

| Table 3. Reduction in mean calculi size before and after treatment with Cystone syrup (mean ± SEM) |
|---------------------------------|-----------------|-----------------|
| **Parameter** | **Before treatment** | **After treatment** |
| Calculi size (mm) | 7.204 ± 0.341 | 4.040 ± 0.821* |

Statistical analysis was carried out using repeated ANOVA test, followed by Paired "t" test. *$p<0.001$ as compared with day 0 value.
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

The majority of individuals with nephrolithiasis have small ureteral stones that pass spontaneously. However, patients may experience severe pain during this process, which significantly alters their quality-of-life and may limit their vocational responsibilities. Therefore, measures to facilitate stone passage are uniformly embraced.

The rate of spontaneous passage with no medical intervention for a stone of 5 mm or smaller in the proximal ureter is estimated to be 29-98%, and in the distal ureter, 71-98%. The most important factors in predicting the likelihood of spontaneous stone passage are stone location and stone size.

Recently, medical expulsion therapy has been investigated as a supplement to observation in an effort to improve spontaneous stone passage rates, 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 medical expulsion
therapy are calcium channel blockers, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and alpha-1-adrenergic receptor antagonists. A recent meta-analysis was performed, looking at studies that compared stone passage rates in patients who were given calcium channel blockers or alpha-1-adrenergic receptor antagonists versus controls who did not receive these medications. The analysis demonstrated a 65% greater chance of passing a ureteral stone in patients who received either medication.

In the present study, disappearance of calculi (dissolution or spontaneous passage) was noted in 12 patients at the end of the 28-day study period. Other stones could not be passed out as they were more than 10 mm in size. A significant symptomatic relief from abdominal pain and dysuria was reported by patients. There was a 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, and tenderness in KUB area was observed at the end of treatment. The reduction in symptoms started appearing from the Day 7 of therapy itself.

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

In an investigation, a methanol extract obtained from roots of Boerhavia diffusa exhibited a significant spasmolytic activity in the guinea pig ileum, probably through a direct effect on the smooth muscle. The hexane extracts of Cyperus rotundus showed potent treatment of dysuria.

In Ayurveda, Asparagus 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 Asparagus racemosus showed inhibitory potential on lithiasis (stone formation) and this plant extract inhibits stone formation.

The chemical constituents of the essential oil of Curcuma zedoaria (Berg.) Rosc. were...
analyzed by gas chromatography-mass spectrometry (GC-MS). The essential oil was evaluated for potential antimicrobial activity against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Vibrio parahaemolyticus, Salmonella typhimurium* and *Bacillus cereus. V. parahaemolyticus*. The oil was sensitive to the presence of *B. cereus, V. parahaemolyticus, Staphylococcus aureus,* and *Escherichia coli, Pseudomonas aeruginosa,* and *Vibrio parahaemolyticus*. The potential antimicrobial activity of the essential oil was evaluated for *Salmonella typhimurium* and *Staphylococcus aureus*. The essential oil was sensitive to the presence of *B. cereus, V. parahaemolyticus, Staphylococcus aureus,* and *Escherichia coli, Pseudomonas aeruginosa,* and *Vibrio parahaemolyticus*. The overall compliance of Cystone syrup was good. No clinically significant adverse reactions were reported or observed during the entire study period.

**Conclusion**

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

This study indicates Cystone syrup to be an effective and safe treatment in lower ureteric calculi as it expels the stones and brings about significant reduction of symptoms associated with calculi.

References