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Safety and Efficacy of an Ayurvedic Formulation Cystone in Management of Ureteric Calculi: A Prospective Randomized Placebo Controlled Study

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Abstract: Problem statement: Medical management of urolithiasis is still a challenge for modern medical practice. In the present study, Cystone tablet, an Ayurvedic formulation claimed to be useful in urolithiasis was evaluated for its safety and efficacy in reduction or expulsion of ureteric calculi and to assess the role of Cystone in relieving the clinical symptoms. **Approach:** This was a prospective randomized, double blind placebo-controlled trial amongst 52 patients with upper urinary tract calculi of 5-10 mm diameter. Patients were evaluated by plain abdominal film of the Kidneys, Ureter and Bladder (KUB) plus an ultrasound examination, for 6 months. Patients were equally divided into active treatment or placebo. The patients were advised to take Cystone or placebo in a dose of one tablet, thrice daily for 6 months. Patients kept a record of number of pain episodes; severity of pain was assessed by Visual Analogue Scale (VAS). In addition, other parameters such as fever, low backache and decrease in frequency of urine were evaluated to assess the relief of clinical symptoms. Urinary microscopy and hamatological parameters were also evaluated. **Results:** In active medication group, there was a significant reduction in the size of the calculi while there was an increase in the placebo arm. There was significant lower VAS score in the active medication arm as compared to placebo. On urine analysis, significant reduction in microscopic hematuria, pus cells (pyuria), bacteruia and crystalline sediments was seen. Significant disappearance of the calculi by both X-ray abdomen and ultrasonography and a significant reduction in the size of the stone was seen with Cystone treatment. There was no improvement in relief of clinical symptoms or investigations in the placebo treated subjects. **Conclusion:** This study suggested that the Ayurvedic formulation Cystone tablet had a therapeutic promise in the management of ureteric calculi. It probably helped in reducing the size of the calculi and facilitates in its passage and significantly relieves the symptoms with improvement in urine parameters. This formulation was well tolerated.

Key words: Urolithiasis, ayurvedic formulation, cystone

INTRODUCTION

Humankind is known to be suffering from urinary stone disease, which was first noticed by Egyptian mummies dated to 4800 BCE[1]. Hippocrates in the 4th century BCE noted renal stones together with a renal abscess and wrote in the Hippocratic oath "I will not cut the stone" (Clendening, 1960). Urolithiasis in its different forms is a frequently encountered urological condition. For many years it has been at the forefront of urology. This situation might have changed with the advent of new, less invasive approaches to the management of urinary calculi. Nevertheless, urinary stones continue to occupy an important place in everyday urological practice. Currently urinary stones affect 10-12% of the population with a peak incidence at 20-40 years of age (Wasserstein, 1998). It is one of the most common and painful urologic disorder of the urinary tract that affects more than 3 million people every year alone in the United States (Hollingsworth *et al*., 2006). The lifetime risk of developing urolithiasis ranges between 5 and 12% (Alok *et al*., 2008) and significantly affects the economy and public health as it has a high rate of recurrence (Hiatt *et al*., 1982).

Risk factors for developing urolithiasis include age, sex, diet, geographic location, genetic predisposition and urinary composition. Apart from these, the anatomy

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of the upper and the lower tract might be contributing factor in predisposing an individual to urinary tract infection or stasis (Gupta and Kesarwani, 2002). Small urinary calculi pass out of the body without any clinical intervention (Miller and Kane, 1999). In several studies, it has been reported that spontaneous passage rates of urinary stones ranges between 70-98% for small (≤5 mm) distal ureteric calculi (Healy and Ogan, 2005). However size and location of the calculi play an important role in predicting spontaneous passage. Typical symptoms of acute renal colic are intermittent colicky flank pain that may radiate to the lower abdomen or groin, often associated with nausea and vomiting (Eskelinen *et al*., 1998). Lower urinary tract symptoms such as dysuria, urgency and frequency may occur as the stone enters the ureter. Large calculi associated with unbearable pain can be treated with ureteroscopy, extracorporeal shock wave lithotripsy, percutaneous nephrostomy and surgery. Calcium channel blockers and adrenergic alpha antagonists and steroids are effective in enhancing the passage of urinary calculi. Phytotherapy with medicinal plants is widely used worldwide as an alternative primary healthcare. Regarding the treatment of urinary stone disease, several medicinal plants are available (Nirdnoy and Muangman, 1991; Yasui *et al*., 1999; Selvam *et al*., 2001; Premgamone *et al*., 2001; Freitas *et al*., 2002; Atmani *et al*., 2004). Since the plants are claimed to be non-toxic, low-cost, available in rural areas and culturally acceptable, their effectiveness in the treatment of urinary stones has been widely studied. Herbal medicines have been used to help in urolithiasis through anti-inflammatory, diuretic, litholytic, antimicrobial and antispasmodic actions, though many of these properties are speculative. Cystone tablets, one such an Ayurvedic formulation and has been claimed for its safety and efficacy in Urolithiasis. The principal herbs of Cystone tablets (Table 1) have undergone extensive studies and geographical source and harvest time for each of the herbal ingredients have been recorded. Good Agricultural and Collection Practice (GACP) was followed during the collection and manufacture of this Ayuurvedic formulation (Sing *et al*., 2007. Botanical identification and an Ayurvedic criteria for desired quality were in accordance with the guidelines of Pharmacopoeial Standards of an Ayurvedic formulations (Fong, 2002) and were carried out by a qualified chemist approved by the Food and Drug Administration. This formulation has been approved by regulatory authorities in India as an Ayurvedic formulation and is available for clinical practice for the past sixty years. This study was aimed to evaluate the efficacy and safety of Cystone tablets in subjects with urolithiasis.

Table 1: Principal herbs in Cystone tablet

Ingredients	Quantity (mg)
Didymocarpus pedicellata	130
Saxifraga ligulata	98
Rubia cordifolia	32
Cyperus scariosus	32
Achyranthes aspera	32
Onosma bracteatum	32
Vernonia cinerea	32
Shilajeet (Purified)	26
Hajrul yahood bhasma	32

MATERIALS AND METHODS

Study design: This was a randomized placebo-controlled double blind clinical trial carried out at the Department of Urology, Safdarjung Hospital, New Delhi, India between January 2008 and March 2009 in accordance to the ethical guidelines of Helsinki (Puri *et al*., 2009). Allocation was concealed. The sample size of 52, with 26 in each arm was calculated to have a power to detect a 25% reduction with urinary stones at 95% confidence limit.

Inclusion and exclusion criteria: Patients of either sex aged 18-65 years presenting clinically with characteristic loin pain, vomiting, fever and radiological or ultrasonographically diagnosed with ureteric calculi measuring between 5-10 mm in size and willing to sign the informed consent form and comply with the study procedures were included in the study. Those with larger urinary calculi, renal and or hepatic pathology and any systemic disorder requiring other medication or surgery were excluded from the study. Pregnant and lactating women were not included in the study.

Study procedure: This study was carried out in 52 consecutive eligible patients out of 81 patients who attended the Urology Clinic at Safdarjung Hospital, New Delhi, India. The study protocol, Case Report Forms (CRF), regulatory clearance documents, product related information and informed consent forms (in English and Hindi) were approved by the institutional ethics committee. The patients were informed about the study drug, its effects, duration of the trial and overall plan of the study and were included in the clinical study only after written informed consent was obtained from each of them. They were free to withdraw from the study if they so desired. Patients ate their *ad libitum* diets. Detailed clinical history was noted by interviewing the patients. Thorough clinical examination and symptomatic evaluation was carried out and the details were noted in the CRF. Urolithiasis was determined clinically, the diagnosis was confirmed by plain X-Ray of the abdomen followed by

ultrasonography. The X-Ray KUB and ultrasonography was used to calculate the surface area of each stone based on length and width. Largest diameter of a stone was considered instead of the surface area in ultrasonography evaluation. The cumulative diameter was calculated for subjects with multiple calculi. Patients were advised to take the Ayurvedic formulation Cystone or an identical placebo in a dose of one tablet thrice daily orally for six months. All patients were asked to maintain a record of number of pain episodes, while severity of pain was assessed on a visual analogue scale (Hollingsworth *et al*., 2006). Patients underwent clinical, hematological and radiological evaluation on entry, at 3 and 6 months. The clinical symptoms like fever and low backache were scored using numerical scale. They were allowed Diclofenac 50 mg tablet in case of severe abdominal pain.

Primary and secondary outcome measures: The predefined primary outcome measures were the effect on change in the number and size, spontaneous passage of stone and symptomatic relief. The predefined secondary outcome was incidence of adverse effects and patient compliance.

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 had 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 less than 80% of the medication) was not regarded as treatment failure and reasons for non-compliance were noted.

Statistical analysis: Statistical analysis was carried out using Fisher's Exact Test for presence or absence of various signs and symptoms. Repeated measures of ANOVA followed by Dunnett's Multiple Comparison Posthoc Test were used for analysis of haematological parameters. Pyuria was analyzed by repeated measures of ANOVA using Friedman test followed by Dunnett's Multiple Comparison Posthoc Test. Calculi size before and after treatment was analyzed using Paired Student's 't' test. Values are expressed as mean ± SD for haematological parameters, pyuria and calculi size and remaining parameters were evaluated by the incidence of symptoms. The minimum level of significance was fixed at $p<0.05$. Statistical analysis was carried out using GraphPad Prism Version 4.03 for Windows, GraphPad Prism Software, San Diego California USA.

RESULTS

The demographic data of the patients on entry (Table 2) indicated that thirty eight males and fourteen female patients with a mean age of 34.73±10.09 years were included in the study. Out of the 52 subjects, 26 subjects each received either Cystone tablets or placebo in a random fashion. With Cystone treatment, a significant ($p<0.0001$) symptomatic relief from intermittent abdominal pain (58%), fever (92%), low backache (54%) was observed (Table 3).

There was also an improvement in the frequency and flow of urine though it was not significant. Urine analysis, indicated significant ($p<0.0001$) improvement in microscopic hematuria, pus cells, bacteriruria and crystalline sediments (Table 4).

Disappearance of the calculi as seen by ultrasonography was noticed in 13 out of 26 patients (50%) treated with Cystone tablets ($p<0.0001$) and a decrease in the size of the stone in remaining subjects. In patients treated with placebo out of 26 patients, there was disappearance of stone in 2 patients. Disappearance of the calculi by plain X-ray abdomen and pelvis was seen in 15 patients out of 26 patients (58%) treated with Cystone tablets ($p<0.0001$) there was decrease in the size of the stone in another 11 subjects. In patients treated with placebo out of 26 patients, there was disappearance of stone in 2 patients (Table 5).

Table 2: Demographic data on patients on entry

Parameters	Cystone	Placebo
Mean age in years	34.00±10.09	34.00±8.60
Male: Female	20:6	18:8
Smokers	12	16
Alcoholics	10	12
Diet (Veg: Nonveg)	14:12	20:6
No. of sedentary workers	20	22
Previous history of constipation	16	18
Pain	26	26
Low back ache	26	24
Fever with rigors	13	14

Table 3: Effect of drug therapy on clinical symptoms of urolithiasis

		Cystone (n = 26)			Placebo (n = 26)		
Parameters		On entry	End of 3rd month	End of 6th month	On entry	End of 3rd month	End of 6th month
Pain	Present	26	23	11	26	20	19
	Absent	0	3	15[a,b]	0	6	7
Fever	Present	13	4	0	14	8	8
	Absent	13	22[c]	26[a]	12	18	18
Low back ache	Present	26	19	12	24	24	22
	Absent	0	7[d]	14[a]	2	2	4
Decrease in urinary frequency	Present	8	4	5	3	3	3
	Absent	18	22	21	23	23	23

p-value: [a]: p<0.0001 as compared to 'on entry' value; [b]: p<0.01 as compared to '3rd month' value; [c]: p<0.017 as compared to 'on entry' value; [d]: p<0.001 as compared to 'on entry' value

Table 4: Effect of drug therapy on urine analysis

		Cystone (n = 26)			Placebo (n = 26)		
Parameters		On entry	End of 3rd month	End of 6th month	On entry	End of 3rd month	End of 6th month
Microscopic hematuria	Present	20	17	0	20	18	14
	Absent	6	9	26[a,b]	6	8	12
Urinary infection (microscopy evidence)	Present	19	13	4	14	8	8
	Absent	7	13	22[a,c]	12	18	18
Bacteriruria	Present	22	14	6	22	24	22
	Absent	4	12[d]	20[a,e]	4	2	4
Crystalline substance in the sediment	Present	25	24	10	24	24	24
	Absent	1	2	16[a,f]	2	2	2

p-value: [a]: p<0.0001 as compared to 'on entry' value; [b]: p<0.0001 as compared to '3rd month' value; [c]: p<0.017 as compared to '3rd month' value; [d]: p<0.03 as compared to 'on entry' value; [e]: p<0.04 as compared to '3rd month' value; [f]: p<0.001 as compared to '3rd month' value

Table 5: Effect of drug therapy on radiological investigation

		Cystone (n = 26)			Placebo (n = 26)		
Parameters		On entry	End of 3rd month	End of 6th month	On entry	End of 3rd month	End of 6th month
X-ray abdomen showing renal calculi	Present	26	22	11	26	24	24
	Absent	0	4	15[a,b]	0	2	2
Renal ultrasonography showing renal calculi	Present	26	22	13	26	24	24
	Absent	0	4	13[a,c]	0	2	2

p-value: [a]: p<0.0001 as compared to 'on entry' value; [b]: p<0.0002 as compared to '3rd month' value; [c]: p<0.017 as compared to '3rd month' value

Table 6: Effect of the drug on pyuria

	Cystone (n = 26)			Placebo (n = 26)		
Parameter	On entry	End of3rd month	End of6th month	On entry	End of3rd month	End of6th month
Pyuria	1.39±0.85	0.58±0.70[a]	0.12±0.33[b]	1.44±1.2	1.23±2.4	1.06±1.8

p-value: [a]: p<0.01 as compared to 'on entry' value; [b]: p<0.001 as compared to '3rd month' value. The values for Pyuria is evaluated using 4 point scale: Occasional to Nil: 0; 1:≤5; 2:6-9; 3:≥10

Table 7: Effect of drug on calculi size

	On entry		End of 6th month	
Parameter	Cystone (n = 26)	Placebo (n = 26)	Cystone (n = 26)	Placebo (n = 26)
Calculi size in mm	10.56±3.28	10.22±4.1	4.51±6.30[a]	11.28±6.1

p-value: [a]: p<0.0001 as compared to 'on entry' value

There was significant (p<0.001) reduction in the pus cells (pyuria) at the end of treatment in Cystone group (Table 6) .The study showed significant reduction in the calculi size from 10.56±3.28-4.51±6.30 mm (57%) at the end of the treatment in Cystone group (p<0.0001) as compared to placebo (increase by 10.37%) (Table 7).

Table 8: Effect of drug on various haematological parameters

	Cystone			Placebo		
Parameter	On entry	End of 3rd month	End of 6th month	On entry	End of 3rd month	End of 6th month
Hemoglobin (g dL^{-1})	11.84±1.18	11.82±1.20	11.93±1.67	12.44±2.36	11.23±2.89	12.92±3.41
WBC (/cu.mm.)	7438.00±1552	7562.00±655	7365.00±582	8890.00±1864	8667.00±1456	8552.0±1224
Polymorphs (%)	62.73±6.08	62.38±4.01	62.04±3.63	64.84±9.67	69.84±10.54	66.45±9.12
Lymphocytes (%)	33.62±5.93	34.15±4.73	34.00±3.81	38.68±7.26	38.67±8.18	37.26±7.99
Eosinophils (%)	2.35±2.00	2.85±1.43	2.85±1.29	2.78±1.20	2.23±1.54	2.54±2.61
Monocytes (%)	1.00±2.00	1.00±1.10	1.12±1.56	1.22±1.86	1.59±1.99	1.34±1.57
ESR (mm)	22.88±11.27	19.62±8.88[a]	18.19±9.19[a]	20.45±13.38	21.09±12.16	22.52±10.88

p-value: [a]: $p<0.001$ as compared to 'on entry' value

There were no changes in haematological parameters except for a significant decrease in ESR (Table 8). There were no adverse effects either reported or observed during the study.

DISCUSSION

There are a number of options for treatment of urinary calculi, including surgery, endoscopic procedures such as ureteroscopy, percutaneous nephrolithiotomy and extracorporeal shockwave lithotripsy (Heilberg and Schor, 2006). Patients invariably prefer a medical therapy for the advantage of convenience. Medications like calcium channel blockers, alpha-adrenergic blockers, steroids are used but adverse effects compromise their long-term consumption. On the other hand, some herbal remedies have been used to treat urinary stone disease, although scientific principles have been lacking. With the understanding of many pathophysiological features underlying urinary stone disease and the mechanism of herbal remedies that can have a role in the formation and treatment of urinary stones; phytotherapy might be an alternative treatment with an effective, safe and acceptable options. Although some oral medications have positive effects, they are not effective in all patients. Oral citrate is one of the most widely used medical therapies for preventing urinary stone disease (Serhat and Kupeli, 2006). However, this drug is not tolerated by all patients and some patients are still active stone formers during this therapy (Mattle and Hess, 2005). Due to the adverse effects of these drugs, alternative treatment modalities composed of herbal remedies have been the mainstay of medical therapy for thousands of years, especially in Eastern civilizations (Serhat and Kupeli, 2006). Use of medicinal plants as a source of relief and cure from various illness is as old as humankind itself. Even today, medicinal plants provide a cheap source of drugs for majority of world's population. Plants have provided and will continue to provide not only directly usable drugs, but also a great variety of chemical compounds that can be used as starting points for the synthesis of new drugs with improved pharmacological properties (Potterat and Hostettmann, 1995). World Health Organization has also emphasized development and utilization of herbal drugs and traditional medicines for the benefit of the world population, in terms of cost effectiveness and side effects of the drugs. The organization has also estimated that about 80% of the population living in the developing countries relies on traditional medicine for their healthcare needs (World Health Organization, 2002).

Cystone is an Ayurvedic formulation, designed and developed for the management of urolithiasis or renal calculi. This product came into existence in 1943 and since then this product has been in use all over the world for the management of urolithiasis and UTI.

Herbs like *Didymocarpus pedicellata* has been shown to have diuretic activity (Chopra *et al*., 1996a). Another plant, *Saxifraga ligulata*, is reported to have active principles like afzelechin and bergenin. Afzelechin and bergenin are tannins and possess astringent properties, which make them effective anti-microbial agents. Bergenin is a known diuretic and is helpful in dissolving kidney stones (Asolkar *et al*., 1992; Chopra *et al*., 1996b). The roots of *Rubia cordifolia* contain ruberythic acid, which has been proved to dissolve oxalate stones present in the urinary tract, thereby facilitating their expulsion without recourse to surgery (Basu and Hazra, 2006; Tripathi and Sharma, 1999; Jisha and Nair, 2008). It also possesses astringent, antibacterial and anti-inflammatory actions. The oil from the roots of *Cyperus scariosus* has been found to exhibit anti-inflammatory properties (Khare, 2004; Chopra *et al*., 1996c). Studies conducted on the extracts of *Cyperus scariosus* were found to have potent antioxidant activity. *Achyranthes aspera* has potent anti-inflammatory, astringent, demulcent and diuretic activity (Chopra *et al*., 1996d). *Onosma bracteatum* is known to have diuretic action. It regulates urine output, acts as a demulcent and provides soothing action. It is useful in bladder irritation and is a spasmolytic (Khare, 2007). Hajrul Yahood bhasma is

useful as a diuretic and a lithotropic. It is given in retention of urine and in other diseases of the urinary tract. Shilajeet (purified) treats urinary disorders due to its tonic activity (Agarwal *et al*., 2007). It is probable that these ingredients may be producing an additive activity to bring about relief in Urolithiasis. Several of these herbs contain saponins which have antiuroliathiatic effect.

CONCLUSION

The present study indicates that Cystone tablet is an effective and safe alternate in the management of Urolithiasis. It brings about significant symptomatic relief and helps in expulsion of stones or reducing the size of the renal stones. No clinically significant adverse reactions were reported or observed during the study period. A further study in a larger population will be required to confirm the evidence seen in the present clinical study.

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