Original Article

Litholytic Property of Kulattha (Dolichous Biflorus) vs Potassium Citrate in Renal Calculus Disease : A Comparative Study

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Abstract

Objective: Renal calculus disease is associated with recurrence after its surgical removal in large number of cases. Kulattha is acclaimed to have litholytic property in ayurvedic literature. We decided to compare the litholytic property of Kulattha with potassium citrate, an agent used to reduce stone recurrence in modern medicine.

Methods: Forty seven patients with diagnosis of calcium oxalate renal calculi were taken in study. Twenty four patients received Kulattha (Group I) and 23 patients were given potassium citrate(Group II) for a period of 6 months. The size of renal calculi was studied by periodic ultrasound assessment in both groups.

Results: Mean size of stone in group I at 0 month and at 6 month were 5.42±1.55 mm and 4.26±1.2 mm. mean size of stone in group II at 0 month and at 6 month was 6.46±3.08 mm and 4.64±1.40 mm.

Statistical analysis showed that P value of less than 0.05 was seen in the first group from 0 to 6 month. There was no significant difference in the stone size within group II when the 3rd month and 6th month visit was compared with initial visit.

Conclusion: Kulattha can be used to reduce the recurrence of calcium oxalate stone and it is shown to have a better result than the use of conventional potassium citrate in such patients.

Introduction

It is estimated that at least 10% of the population in the industrialized part of the world is afflicted by urinary tract stone disease. Kidney stones are common in industrialized nations with an annual incidence of 0.5% to 1.9%.[1,2] In India upper and lower urinary tract stones occur frequently but the incidence shows wide regional variation.[3] The incidence of renal calculi is comparatively low in the southern part of country compared to other parts.[4] The prevalence of urolithiasis is as high as 7.6% in Satpura part of Maharashtra.[5] Pendse et al had reported a high and progressively increasing incidence of urolithiasis in Udaipur and some other parts of Rajasthan in the western part of India.[6] With its multifactorial etiology and high rate of recurrences, urinary tract stone disease provides a medical challenge. Calcium oxalate (CaOx) urolithiasis accounts for approximately 75% of urinary stone disease in the United States.[7] Many studies from India have also documented that calcium oxalate forms the major constituent of renal calculi disease in India.[4,8] Such high incidence of calcium oxalate stones have been attributed to major consumption of cereals like millet, which are high in calcium and phosphate, beside factors like lack of animal proteins and increased consumption of oxalate rich vegetables.[4,9] For a patient unfortunate enough to form a stone, the chance of recurrence is high (30% in next 10 years for calcium stone former).[10] Medical management has improved over the years and a strategy of metabolic evaluation and treatment has been shown to be highly effective and leads to a significant cost savings. Surgical advancement has mainly focused on removal of stones and usually small stones are left as such.

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Renal stone was well known in olden times in Ayurveda. Ashmari was correlated to urolithiasis. Sushruta, the father of surgery, has elaborately described the etiopathogenesis, symptomatology, and management of ashmari by drugs, paramedical therapy and surgery. Kulattha, Varun, and Sighru are among the drugs which was used by ancient and recent practitioners in ayurvedic medicine. Researchers and Ayurvedic practitioners have proposed that these ayurvedic preparations have litholytic and lithopreventive properties. This prospective study was undertaken to study the efficacy of Kulattha in patients having renal calculus disease and to compare its efficacy with potassium citrate as a litholytic agent.

Material and Method

The study was conducted in the Department of Nephrology. Patients who attended the OPD or were admitted in the ward from May 2005 to May 2006 with diagnosis of renal calculus disease were included in the study. Informed consent was taken. The institutional review board at the Banaras Hindu University approved the study. Total of 47 cases who fulfilled the following inclusion criteria were included in the study:

1. Patient with renal calculus proved on X-ray KUB or USG and urine showing calcium oxalate crystalluria.
2. Serum creatinine < 2 mg%
3. Patient not taking any other lithotriptic agent
4. Stone size < 5 mm

Patients with serum creatinine > 2mg%, stone size > 5mm or with radiological evidence of hydronephrosis (grade 3 or above) were excluded from study. Patients were randomly divided into two groups, group I to receive Kulattha (Dose: 1 to 2 gm/day in three equally divided doses) and group II to receive potassium citrate (Dose: 10 to 15 ml six hourly). A total of 24 cases were in group I and 23 cases in group II.

Table 1 : Serum level of various substances at 0, 3, and 6 month of follow up between the two groups

	Group I (Kulattha)			Group II (Potassium citrate)		
	0 month	3 month	6 month	0 month	3 month	6 month
Creatinine (mg%)	1.31±0.74	0.87±0.65	0.91±0.75	0.93±0.66	0.74±0.41	0.75±0.29
Urea (mg%)	39.2±22.2	28.75±17.05	29.7±19.73	30.6±19.7	25±6.06	25.17±3.31
Calcium (mg%)	9.15±0.57	9.23±0.4	9.35±0.36	9.15±0.515	9.32±0.42	9.4±0.39
Phosphorous (mg%)	3.9±1.13	4.4±1.04	4.4±0.78	3.87±0.5	3.98±0.58	4.33±0.72
Uric acid (mg%)	4.52±0.67	4.5±0.59	4.5±0.42	4.56±0.45	4.48±0.64	4.58±0.52
Hemoglobin (gm%)	10.7±1.88	10.55±1.71	10.76±1.67	10.26±2.22	9.98±1.96	10.36±1.8
Albumin (gm%)	3.31±0.77	3.2±0.59	3.15±0.51	3.6±0.45	3.58±0.49	3.5±0.37
FBS (mg%)	95.24±23.59	91.7±22.05	90.54±17.9	96.22±16.64	88.87±18.59	88.13±12.9
PTH (ng/l)	38.87±8.4	41.2±8.42	36.62±6.6	37.13±8.02	35.47±4.98	37.86±7.06

Table 2 : Urinary excretion on various substances at 0, 3 and 6 months of follow up between the two groups

	Group I (Kulattha)			Group II (Potassium citrate)		
	0 month	3 month	6 month	0 month	3 month	6 month
Urinary protein excretion (gm/day)	0.589± 0.51	0.58±0.63	0.53±0.51	0.42±0.26	0.402±0.25	0.40±0.12
Urinary creatinine excretion (gm/day)	0.68± 0.27	0.69±0.22	0.64±0.17	0.67±0.33	0.70±0.18	0.70±0.07
Urinary calcium excretion (gm/day)	208.6± 51.6	234.1± 48.06	221.87± 59.9	176.2± 51.6	174.7± 49.3	187.65± 31.17
Urinary phosphate excretion (mg/day)	681.58± 103.58	695.83± 77.2	707.87± 117.59	810.13± 97.99	811.17± 72.18	829.4± 80.9
Urinary uric acid excretion (mg/day)	489.79± 114.6	516.3 ± 78.6	532.5± 87.16	607.17± 46.012	623.22± 58.96	636.1± 50.1
Urinary oxalate excretion (mg/day)	38.6±5.96	36.95±5.23	38.95±6.02	43.6±8.27	44.2±6.28	47.6±5.4

Table 3 : Ultrasound estimated stone size at 0, 3, and 6 month of follow up in both groups

Groups	Stone size in mm(mean ± SD)			Within the group comparison paired "t" test	
	0 month	3 month	6 month	0 vs 3	0 vs 6
Group I	5.42± 1.55	4.84± 1.00	4.26± 1.2	t = 1.61 p ≥ 0.05	t = 4.19 p ≤ 0.05
Group II	6.46± 3.08	5.2± 2.73	4.64± 1.40	T =2.26 P ≥ 0.05	t = 2.07 p ≥ 0.05

All the patients were thoroughly examined. All of them were subjected to base line urine, hematological, biochemical and radiological investigation. Patients were followed up for a period of six months. The allocated drug was started and every month they were reassessed for any improvement or deterioration of symptom. All investigation except USG was done once a month. USG was done at enrollment into study and then at 3rd and 6th month. Clinical improvement with radiological evidence of reduction in size of calculus or history of passage of stone in urine was taken as criteria for improvement. Patients who developed any side effects or had deterioration of renal function were taken off the study protocol.

Result

Analysis of data obtained was done at end of study period. The age of patients ranged from 25 to 40 years. Mean age in both groups was well matched and no statistical difference was noted. In group I male to female ratio was 5:1 and in group II ratio was 3:1. Most common presenting feature was the subjective feeling of pain abdomen in 95-100% of patients in both groups. Other common symptoms were nausea, vomiting, dysuria and hematuria.

In group I (Kulattha) pain abdomen was present in 100%, hematuria in 54.16% and dysuria in 4.2% of patients at presentation. After 6 months of therapy, dysuria improved in all (100%), hematuria improved in 84.6% of cases and pain abdomen improved in 58.3%. In group II pain abdomen was present in 95.6%, hematuria in 26.04% and dysuria in 13.04% at presentation. After 6 month of therapy with potassium citrate, dysuria and hematuria improved in all (100%) while pain abdomen improved in 86.36%.

Mean serum creatinine at the start of therapy in group I was 1.31±0.74 mg% and 0.93±0.66mg% in group II. There was statistically significant difference in the value of serum creatinine within the group I when third and sixth month visit was compared with initial visit. There was no significant difference in the value of serum creatinine within the group II when third and sixth month values were compared with initial visit. Mean serum urea at the starting of drug in group I was 39.2±22.2mg% and 30.6±19.7 mg% in group II. No significant difference in the value of serum urea and creatinine was noted among the two groups when third and sixth month visit was compared with initial visit (Table 1).

The serum concentration of calcium, phosphorous and uric acid was looked at in both the groups, as the serum levels of these substances are known to influence stone formation. The serum level of calcium , phosphorous and uric acid was 9.15 ±0.57mg%, 3.9±1.13mg%,4.52 ± 0.67mg% respectively in group I and 9.15± 0.57mg%, 3.87±0.5mg%, 4.56±0.458mg% respectively in group II. There was no significant difference in the value of serum calcium, phosphorous and serum uric acid level among the two groups when third and sixth month visit was compared with initial visit values (Table 1).

Serum PTH level was estimated in both the groups. Mean serum PTH at the starting of the drug was 38.87±8.4 ng/l in group I and 37.13± 8.02 ng/l in group II. After six month of treatment serum PTH level were 36.62±6.6 and 37.86±7.06 in group I and II, respectively. There was no significant difference in the value of serum PTH within the group I and II when 3rd and 6th month values were compared with values at initial visit. Also there was no significant difference in the serum PTH level among the groups at initial visit and then at sixth month visit.

Fig. 1 : Dolichous Bifiorus (Plant)

The urinary excretion of various substances which have a possible effect on stone formation, growth and recurrence was also studied in both the group (Table 2). However there was no significant difference in the value of urinary protein excretion and urinary creatinine excretion among the groups at initial visit and then at sixth month visit.

Ultrasound was done routinely according to study protocol to analyze the stone size in both the groups. Mean size of stone in group I at 0 month and at 6 month were 5.42±1.55 mm and 4.26±1.2 mm. mean size of stone in group II at 0 month and at 6 month was 6.46±3.08 mm and 4.64±1.40 mm (Table 3).

Hence it was obvious that there was a significant reduction in the stone size in group I from 0 to 6 month. Statistical analysis showed that P value of less than 0.05 was seen in the first group from 0 to 6 month. It is of interest to note here that a significant reduction in stone size was not noted till about 3 months of follow up (p value greater than 0.05). This would mean that a longer follow up is required for this drug to show its favorable effect. There was no significant difference in the stone size within group II when the 3rd month and 6th month visit was compared with initial visit.

Mean hemoglobin at the starting of the drug in group I was 10.7±1.88gm% and in group II was 10.26±2.22 gm%. No significant change in hemoglobin was noted between the two groups during follow up. Similarly serum albumin level was comparable between the groups at the beginning and during follow up. Mean fasting blood glucose level at initial visit was 95.24±23.59 in group I and 96.22±16.6 in group II. The fasting blood glucose level fell in both groups during the study period.

Discussion

Modern medical science is currently in the throes of a revolution which is likely to have a dramatic impact on both the theory of medicine and the way it is practiced. Another participant in this exciting climate of change and ferment is Ayurveda, India's ancient medical system. Around 1,250 plants are currently used in various Ayurvedic preparations.[18] The first significant contribution from Ayurvedic materia medica came with the isolation of the hypertensive alkaloid from the sarpagandha plant (Rouwolfia serpentina),[19] valued in Ayurveda for the treatment of hypertension, insomnia, and insanity. This was the first important ancient-modern concordance in Ayurvedic plants. With the gradual coming of age of chemistry and biology, disciplines central to the study of biologic activities of natural products, many Ayurvedic plants have been reinvestigated. Ashmari or urolithiasis is as old a problem as ayurveda itself. Modern medical fraternity has been able to decipher the etiology, precipitating factors associated with renal stone formation. However lacunae are still present in the complete understanding of this complex process of stone formation. With the recent advances in the knowledge of pathogenesis of urolithiasis, the medical management is not only restricted to increased fluid intake, but to determine the cause of urolithiasis by a battery of investigation, the use of a particular drug to prevent urolithiasis if required and then to check the effectiveness of the drug by the application of investigations. Although great advances in the field of stone removal have been made in the last two decade, surgical treatment of the urinary tract stone is an incomplete procedure. The goal of the surgical treatment is the removal of existing stones while that of the medical treatment is prevention of recurrent stone formation.

In India, Ayurvedic and Unani medicines had discovered the treatment for dissolving stones or renal calculi in the kidney or ureter. Dolichus biflorous, commonly known as Kulattha, was administered to colic patients who have stones formed due to deposits of calcium phosphates or oxalates. Kulattha was also used by Indian physicians in the 16th century for allergic conditions such as urticaria, chronic rhinitis, asthma, bronchitis and for treating flatulence and adiposity. In unani medicine, the concentrated water extract of kulthi seed and shalgram (Brassica rapa) seeds is given for destroying stones in the kidney. The medical management of urolithiasis has undergone a great change in the modern era. In the present time the management of urolithiasis is not only stone removal but also to prevent its recurrence. Hypocitraturia is associated with recurrent calcium nephrolithiasis.[13] Potassium citrate has been used in stone clinic to prevent recurrence of renal stones.[12,14] Potassium citrate taken orally is absorbed mostly under normal circumstances. Substantial in vitro evidence has suggested that urinary citrate reduces the growth rate of CaOx crystals.[15,16] The citrate after absorption is metabolized to bicarbonate. In absence of a deficit of bicarbonate in plasma, the bicarbonate ions are excreted in urine that is rendered alkaline. The small amount of absorbed citrate that escapes oxidation in the urine contributes in a minor way to the citraturic action of potassium citrate. In the presence of hypokalemia, the potassium ion augments citrate excretion by correcting intracellular acidosis. During long-term treatment, potassium citrate has been shown to cause a sustained rise in urinary citrate and pH. This alkalinized urine also promotes solubility of uric acid, cystine, and urease-induced crystals.[17] Potassium citrate has a hypocalciuric effect because of enhanced renal calcium absorption and is usually transient. Since both kulattha and potassium citrate were known to be helpful in renal calculi patients, we decided to compare both the drugs in this study.

Kulattha has been long been used to treat renal stone. Although the composition of it is well known now, the pathophysiology of prevention of recurrence of stone is still unexplained. We used kulattha in 24 patients having CaOx stones for a period of 6 months and potassium citrate in 23 patients. In our study males constituted 78% of the patients (37/47). The male predominance is just a reflection of male dominance of our society rather than the so high recurrence of stone disease in male in this study. A male member would seek treatment for any medical problem much earlier and more frequently than a female. No patient was lost to follow up. Compliance of patient to both the medication was good and no patient discontinued their medication. We looked at the parameters known to influence the

Fig. 2 : Kulattha (Seeds)

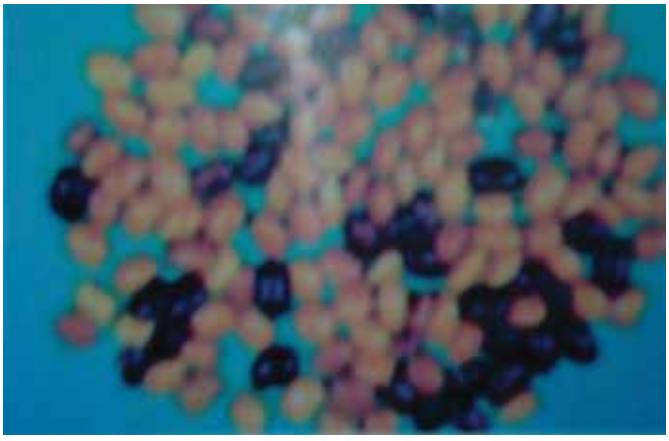

Fig. 3 : Kulattha (seeds)

stone formation and recurrence, in both the groups. Serum level of calcium, phosphorus, uric and were not markedly affected in both groups with treatment. Similarly urinary excretion of calcium, phosphorous, uric acid, oxalate, creatinine and protein were not significantly affected by treatment in both groups. However, the USG assessment of renal calculi at 6 month, in patients on kulattha showed a significant decrease in size of calculi from 5.42 ±1.55mm to 4.26±1.2mm ($p \leq 0.05$). This significant reduction in size of calculi was not seen at 3 month of follow up, suggesting that Kulattha required a prolonged use to show favorable effect. Of interest was the fact that although the recurrence of stone decreased the known factors which influence the stone formation like serum calcium, phosphorous, uric acid and urinary excretion of calcium, phosphorous, uric acid were not different in both groups. This lets us to believe that still unexplained parameters exists which probably are influenced favorably by Kulattha and prevent stone recurrence.

Kulattha is a branched or trailing annual, with small trifoliate leaves, and very wide climbing, slender stem(Figure I).[20] When it matures, it gives narrow, flat, curved pods. The pods contain 5-6 flattened ellipsoid seeds, 1/8" -1/4" long (Figure II, Figure III). Analysis of the Kulattha seed gave the following values : moisture 11.8%, crude protein 22.0%, fat 0.5%, mineral matter 3.1%, fibre 5.3%, carbohydrate 57.35%, calcium 0.28% and phosphorous 0.39%; iron 7.6mg, nicotinic acid 1.5 mg, carotene 119 (international vitamin unit A unit) per 100 g. The seed are rich in various enzymes.[11,20] Presence of Urease was first documented by Masteer and Marshall in 1916.[11] It was found that the germinated seeds gave higher urease activity than the ungerminated seeds, which, indicated that germination merely increases the solubility of enzyme. Other chemical constituent present are: streptogenin, beta-sitosterol, a phyto-haemagglutinin, beta-N-acetylglucosaminidase, alpha and beta galactosidases, alpha mannosides and beta –glucosides. During clinical trials, the aqueous extract of the seed on patients with various disorders was noted to increase the urine output. These various constituents of Kulattha probably help in changing the micro and macro environment of CaOx stones, leading to decreased recurrence of calculi.

Further prolonged prospective studies would be required to look at litholytic properties of these drugs. And a combined approach using surgery to remove larger stones along with conventional medicines which is supported by drugs like Kulattha to prevent further recurrence of stones would alleviate the suffering caused by age old problem of nephrolithiasis in near future.

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