

A LONG-TERM STUDY ON THE EFFICACY OF A HERBAL PLANT, *ORTHOSIPHON GRANDIFLORUS*, AND SODIUM POTASSIUM CITRATE IN RENAL CALCULI TREATMENT

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Abstract. The study was performed to compare the efficacy of a herbal plant, *Orthosiphon grandiflorus* (OG), and the drug sodium potassium citrate (SPC) in treatment of renal calculi. Forty-eight rural stone formers identified by ultrasonography were recruited and randomly assigned to two treatment groups (G1 and G2). For a period up to 18 months, subjects in G1 received 2 cups of OG tea daily, each tea cup made from an OG tea bag (contained 2.5 g dry wt), and G2 received 5-10 g of granular SPC in solution divided into three times a day. Once every 5 to 7 weeks, subjects were interviewed, given an additional drug supply, administered a kidney ultrasound and had spot urine samples collected for relevant biochemical analysis. From the recorded ultrasound images, rates of stone size reduction per year (ROSRPY) were calculated. The mean ROSRPY was 28.6±16.0% and 33.8±23.6% for G1 and G2, respectively. These two means were not significantly different. ROSRPY values of G1 and G2 were combined and divided into three levels: Level A (ROSRPY > mean + 0.5 SD), Level M (ROSRPY = mean ± 0.5 SD) and Level B (ROSRPY < mean - 0.5 SD). Dissolution of stones was least in Level B which was related to higher excretions of Ca and uric acid in the urine. After treatment, 90% of the initial clinical symptoms (*ie* back pain, headaches and joint pain) were relieved. Fatigue and loss of appetite were observed in 26.3% of G2 subjects. Our study indicates that treatment of renal calculi with OG tea is an alternative means of management. Further investigation is needed to improve dissolution of stones with a low ROSRPY.

INTRODUCTION

Nephrolithiasis is a common health problem in the Northeast Thailand (Sriboonlue *et al*, 1992; Premgamone *et al* 1995; Yanakawa *et al*, 1997). The reported prevalence of stones varies from 0.38% in the whole population as determined by a community survey (Sriboonlue *et al*, 1992) to 16% of a specific adult male group as determined by ultrasound examination (Yanakawa *et al*, 1997). Despite surgical removal of stones, the disease frequently recurs (Borwornpadungkitti *et al*, 1992).

Stone formers in rural Northeast Thai communities usually seek an herbal cure. The most commonly cited curative is a herbal plant, *Orthosiphon grandiflorus* (OG), a tropical bush of about 1 m in height. Nirdnoy and Muangman (1991) observed that drinking an infusion (tea)

made from OG caused an increase in urinary pH and the tendency of increased excretions of both K and citrate. Since one of the primary metabolic abnormality among renal stone formers in this region is marked K-depletion (Sriboonlue *et al*, 1991), we wanted to test whether consuming OG tea corrected the defect and aided in the dissolution of stones. We compared the herb tea with sodium potassium citrate (SPC), a drug widely used for the management of uric acid nephrolithiasis because it causes an increase in urinary pH and coincidental excretions of both K and citrate (Pak *et al*, 1986; Cicerello *et al*, 1994).

MATERIALS AND METHODS

Study protocol

Our study protocol was approved by the

Ethics Committee, Faculty of Medicine, Khon Kaen University. Prior to joining the study, written informed consent was obtained from each subject. During the study, subjects remained at home in their rural villages performing their regular daily activities.

The first visit: We visited cases of nephrolithiasis in Nam Phong and Muang districts previously identified during a community survey done by our Mobile Ultrasound Unit (Premgamone *et al*, 1995). We explained the purpose of our study, repeated the ultrasound examination and, if they met our inclusion criteria, asked them to join the trial treatment program. Included were subjects who had at least one stone with a diameter of 10 mm or more, a serum creatinine ≤ 4 mg/dl and no heart disease.

Subsequent visits: On the second and subsequent visits, the subjects were invited to visit the research team at a private clinic in downtown Nam Phong. The visits were scheduled every 5 to 7 weeks for a period of 18 months. At each visit, besides giving the routine interview and the additional drug supply, an ultrasound of the kidneys and stones was performed and videotaped. Urinalysis on spot samples (for white blood cells, red blood cells and protein) by a Urilux unit (Boehringer Mannheim Ltd, Mannheim, Germany) was done every visit. Blood tests (for creatinine) were performed at the beginning, and at the 8th and 15th months using a Reflotron, (Boehringer Mannheim Ltd, Mannheim, Germany).

Subjects

There were 48 subjects who met our inclusion criteria and who agreed to join the study. They comprised 23 males and 25 females and were 20 to 60 years old. These participants were randomly allocated into two groups according to the types of treatment: G1 was treated with OG (n = 24) and G2 with SPC (n = 24).

Treatments

The G1 subjects were assigned to take 250 ml (a cup) of OG tea in the morning and

in the late afternoon. The sun-dried OG plant was ground into a powder and 2.5 g packed in a standard tea bag. The tea was made by immersion of the bag in a cup of boiling water. It was drunk when sufficiently cooled.

Each of the G2 subjects was prescribed 5 to 10 g of SPC granules per day dissolved in water and taken after each meal. The subjects were trained to adjust the dose of SPC to keep their urinary pH between 6.2 and 6.8.

Patients who had significant numbers of white blood cells (WBC) in their urine ($\geq +1$), were given a two-month course of antibiotics. If a positive WBC persisted, they were given a suppressive dose of antibiotics.

Laboratory assessment

Each spot urine sample brought to the laboratory was analyzed for creatinine (by Jaffee's reaction), Ca (by atomic absorption spectrophotometer), K and Na (by flame photometry), uric acid (by uricase method) and oxalate (as described by Sriboonlue *et al*, 1998).

Calculation of the percentage of stone dissolution

The size of stones was measured from the ultrasound images by three different physicians (one being a professional radiologist) who were unaware of the patient groupings. Significant differences in stone sizes between G1 and G2 were evaluated by Wilcoxon's test. All continuous values were given as the mean \pm SD. The χ^2 and Fisher exact tests were used to test the significance of the categorical variables between groups. The rate of size reduction per year (ROSRPY) of a stone was calculated using the following formula:

$$\text{ROSRPY (\%)} = \frac{52 \times 100 \times (\text{size wk 0} - \text{size wk N})}{N \times \text{size wk 0}}$$

Where: N = the duration (in weeks) of treatments

Size wk 0 = the diameter of stone (in mm) at the beginning

Size wk N = the diameter of stone (in mm) at the Nth week

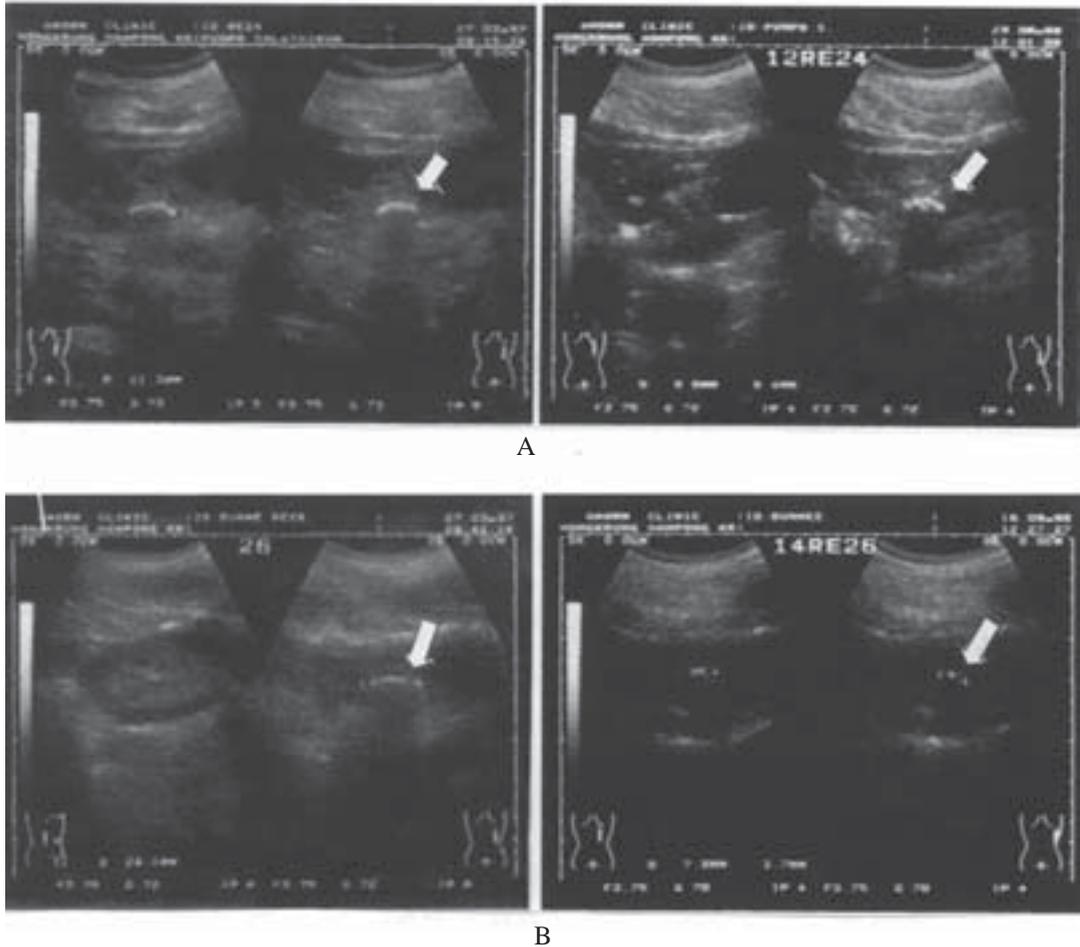


Fig 1—Ultrasound images of 2 renal stones (arrows) at the beginning and at 18th month of treatment with *Orthosiphon grandiflorus* (A) and sodium potassium citrate (B).

RESULTS

Drop outs

Seven subjects dropped out during the trial: two from G1 because they lost interest and five from G2 because they were experiencing fatigue and loss of appetite ostensibly from the SPC. Finally, we have 22 subjects with 33 stones in G1 and 19 subjects with 25 stones in G2.

Clinical symptoms change after treatment

Besides having kidney stones, 95% of the subjects also presented with some other clinical symptoms; primarily back pain (70.7%),

joint pain (68.3%), fatigue (60.9%), dyspepsia (51.2%), headaches (43.9%), paresthesia at the frank (36.6%), abdominal pain (34.1%), fever (24.4%) and myofascial pain (41.5%). After receiving treatment in the study, more than 90% of the subjects from both groups reported an easing of these symptoms. They claimed that they had better quality of life and an increased working capacity (90.2%). None of the subjects in G1 had any adverse effects from the OG whereas 26.3% of G2 subjects reported feeling fatigued or a loss of appetite. Were we to include the five subjects who dropped out, adversely affected G2 patients would have represented more than a third (34.78%) of the group.

Table 1

Rate of size reduction per year (ROSRPY) of stones at different periods of treatments.

Duration of treatment, months	2	5	7	10	13	18
Number of stones	33	33	33	33	33	24
%ROSRPY of G1, mean±SD	5.1±16.8	13.3±17.5	23.8±20.3	29.8±26.4	35.3±25.9	40.9±23.2
median	9.3	17.5	26.0	32.5	35.3	47.8
Number of stones	25	25	25	25	25	20
%ROSRPY of G2, mean±SD	12.1±16.7	21.5±19.6	33.8±17.3	41.2±22.1	46.1±27.0	38.5±26.8
median	14.3	23.1	39.0	46.2	50.2	45.8
p-value	NS	NS	NS	NS	NS	NS

Table 2

Percent of stone size changing per year.

Type of treatment	Unchanged or increased 0-3.65%	Rate of size reduction per year (ROSRPY) of stones						Mean±SD%	Median
		1-15 %	16-25%	26-35%	36-45%	46-55%	56-100%		
Number of stones Treated with OG tea (G1)	1 3.0%	6 18.2%	6 18.2%	6 18.2%	8 24.2%	6 18.2%	0 -	28.6±16.0%	36.7%
Number of stones Treated with SPC (G2)	3 12.0%	1 4.0%	3 12.0%	8 32.0%	3 12.0%	5 20.0%	2 8.0%	33.8±23.6%	35.1%

Table 3

Urinary parameters in each level of stone size reduction per year (not concerning the types of treatment). Rates of size reduction per year (ROSRPY) of stones were divided into 3 main levels; A = above mean, (> mean + 0.5 SD), M = medium (mean ± 0.5 SD) and B = below mean (< mean - 0.5 SD).

Urinary parameter		Level of ROSRPY			Significant
		A	M	B	
Creatinine, g/l	mean±SD	0.95±0.46	0.84±0.46	0.77±0.45	none
	median	0.86	0.82	0.70	
K, mg/gCr	mean±SD	1.65±1.10	2.42±2.30	2.42±2.05	none
	median	1.37	1.84	1.69	
Na, mg/gCr	mean±SD	2.09±1.90	3.52±3.90	2.60±2.20	none
	median	1.83	2.25	1.86	
Oxalate, µg/g Cr	mean±SD	10.38±8.50	14.84±13.50	12.12±9.70	none
	median	8.28	10.37	9.82	
Ca, mg/g Cr	mean±SD	62.09±52.60	54.71±33.80	79.22±46.50	Yes (AvsB)
	median	48.0	4.0	65.0	
Uric acid, mg/g Cr	mean±SD	348.9±219.5	421.0±269.7	535.1±341.3	Yes (AvsB)
	median	339.5	406.4	541.4	

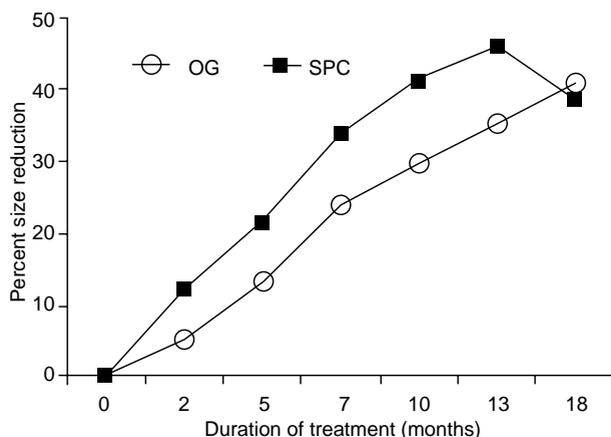


Fig 2—Rate of size reduction per year (ROSRPY) of stones as calculated from the ultrasound images at different periods of treatments with *Orthosiphon grandiflorus* (OG) and sodium potassium citrate (SPC).

Stone size reduction

The ROSRPY from pre-treatment through the 18th month are presented in Table 1 and Fig 1. As treatment progressed, the percentage of reduction linearly increased in both groups. Though the degree of reduction appeared greater in G2 than G1, the difference was not statistically significant. In Fig 1, the degree of reduction decreased in the 18th month in G2 because we did not include the subject who experienced 100% ROSRPY and quit the project early.

Two examples of the studied ultrasound imagery, stones at two different stages of treatment, are shown in Fig 2. The ROSRPY of studied stones was divided into seven levels (including the unchanged or increase in stone sizes) as shown in Table 2. Any stone with a ROSRPY of less than 15% was defined as an unresponsive stone. In G1 one stone were unchanged and 6 stones had 1-15% ROSRPY; in G2 three stones were unchanged or enlarged and one stone had 1-15% ROSRPY. Combining the two groups yielded 11(18.9%) unresponsive stones.

Urinary composition according to the ROSRPY

If the ROSRPY of all the subjects were

combined, regardless of treatments, they could be described as three levels (Table 3): Level A (above mean, ROSRPY > mean + 0.5 SD), Level M (medium or average, ROSRPY = mean + 0.5 SD) and Level B (below average, ROSRPY < mean - 0.5 SD). From various parameters determined, there were statistically significant differences between Levels A, M and B in urinary excretions of Ca and uric acid, which were least in Level A – the level with the highest ROSRPY.

DISCUSSION

The solubility of uric acid in an acid solution is very low; solubility at pH 5.5 is only about one sixth of a solution of pH 6.5 (10). This suggest that if a stone has uric acid as a main component it could be dissolved successfully by the increase in urinary pH. An increase in urinary pH after taking SPC is well documented, due to the alkali-load-effect of the ingested citrate, where 1 mol of citrate yields 3 mol of bicarbonate (Simpson,1983; Pak *et al*, 1986; Ettinger, 1989). Therefore, uric acid stones are effectively treated with SPC (Pak *et al*, 1986; Cicerello *et al*, 1994). Though the urinary pH had not been assessed in the present trial, in a 24-h-follow-up study, Nirdnoy and Muangman (1991) observed that 6 hours after drinking OG tea the urinary pH of six healthy volunteers increased significantly. This, however, is a temporary phenomenon because the urinary pH did return to normal levels within the 24-h period. The tendency of greater efficacy in reducing stone size of SPC over OG tea is probably due to a more persistent in alkali load caused by SPC.

Although most stones in Northeast Thailand are reported to be calcium type, their actual components are mixed and do include uric acid (Prasongwatana *et al*,1983; Sriboonlue *et al*,1993). Ettinger (1989) reported that patients with mixed calculi resemble patients with uric acid stones, they are usually elderly, are often Asian and they tend to excrete acidic urine. This fits the characterization of our subjects. If a stone is small and has uric acid as one

of components, theoretically, it could be dissolved by an increase in urinary pH though dissolution would take longer than a purely uric acid stone. The difference in the reduction rate of stone size observed in our study reflects the chemical composition of the stones: the more rapid the reduction, the higher the uric acid content. Since we did not exclude patients with urinary tract infections, unresponsive cases may represent struvite stones, which are not solubilized by a mere increase in urinary pH (Griffith, 1982). Other underlying metabolic abnormalities, such as hyperuricosuria, hypercalciuria, hyperoxaluria and hypocitraturia, may also directly contribute to the efficacy of dissolving stones.

Level B, the lowest ROSRPY, had significantly higher urinary excretions of both Ca and uric acid than the Level A. Further investigation, particularly by analyzing a 24-h urine sample, would help to determine which of these subjects were hypercalciuric and hyperuricosuric, respectively. However, about 70% of our subjects had frequent joint pain, which is closely related to abnormal uric acid metabolism. These symptoms were improved in 90% of the subjects in both groups after the treatment given in our trial probably because of an improvement in the uric acid balance of the body - a decrease in production, an increase in its excretion, or both.

Allopurinol is commonly used in reducing uric acid production, it has also been shown that the drug can be used to reduce the recurrence of calcium stones associated with hyperuricosuria (hyperuricosuric calcium oxalate nephrolithiasis) (Coe and Raisin, 1973). Consequently, allopurinol used in combination with either OG tea or SPC, should improve the rate of stone size reduction in Level B subjects.

Another important metabolic irregularity among stone formers in Northeast Thailand is that they show marked hypocitraturia (Sriboonlue *et al*, 1991). Since urinary citrate is an important stone inhibitor, low levels of urinary citrate should increase the precipitation of various Ca salts. Though we did not assess for

urinary citrate, Level B exhibited significantly higher urinary excretion of calcium than the other groups. The tendency to hypercalciuria of Level B, if concomitant with hypocitraturia, would seriously limit the efficacy of both OG and SPC. Perhaps, in case of stone patients with hypercalciuria, an additional use of anti-hypercalciuric drug, for instance, cellulose phosphate and thiazide (Yendt *et al*, 1966) should help to accelerate the ROSRPY.

Clinicians should be aware that patients who present with multiple clinical symptoms such as chronic dyspepsia, back pain, joint pain, fatigue, headaches and myalgia should also be screened for the stone disease and urinary infection. In fact, most of these symptoms are the common presentations seen in outpatient department of community hospitals in the Northeast. Although the ROSRPY after taking OG tea in G1 was lower than in G2, it did improve the clinical symptoms and had the added benefit of not causing any adverse effects. Since *Orthosiphon grandiflorus* grows easily in Thailand, and since the prevalence and the recurrence of nephrolithiasis in this region are high, regular use of the herb is recommended as a prophylactic and/or a therapy.

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