RESEARCH ARTICLE

LONG-TERM EFFECTS OF POTASSIUM CITRATE THERAPY ON HYPOCITRATURIC CALCIUM STONES: A PROSPECTIVE RANDOMIZED STUDY

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ARTICLE INFO

ABSTRACT

Background: Potassium citrate effectively reduces recurrence of hypocitraturic calcium nephrolithiasis.
Objective: To evaluate the impact of long-term potassium citrate therapy on urinary metabolic parameters and stone recurrence rates in patients with hypocitraturic calcium stones.
Design, Setting, Participants: This prospectively randomized controlled trial was conducted from January 2003 to December 2012. Patients aged over 40 years old, with a history of hypocitraturic calcium stones were eligible: of 347 patients, 101 were in the control group, and 102 patients were in the potassium citrate group. Baseline examinations and patient recruitment occurred in 2001.
Intervention: Potassium citrate therapy consisted of Urocit®-K 60 mEq. per day. All patients met with a dietitian and were instructed to maintain a diet restricted to 2 g of sodium and 65 g of protein. The patients were asked to consume sufficient fluid to urinate ≥ 2 L daily.
Main Outcome Measure: The primary outcome was mean change in urinary citrate level, measured throughout the entire follow-up period at an outpatient clinic for up to 10 years.
Results: The final analysis included 101 (control) and 102 (Potassium citrate) patients. In the Potassium citrate group, mean urinary citrate levels increased from 197.8 (baseline) to 523.7 mg/day (9th year), with a response rate of 67.65% (P<0.001 vs. control). The stone recurrence rate ranged from 6.90% (1st year) to 68.32% (9th year) in the control group and from 2.94% (1st year) to 28.43% (9th year) in the potassium citrate group (P<0.001).
Limitations: Enrolled patients was diagnosed complete stone free. The study cannot elucidate the role of residual fragments in the recurrent stones.
Conclusions: Potassium citrate provides a significant alkali and citraturic response during long term therapy with a sustained change in urinary parameters. Moreover, long term potassium citrate therapy significantly decreases the stone formation rate, confirming usefulness in patients with hypocitraturic calcium stones.

INTRODUCTION

Management of recurrent urinary stones requires both diet/lifestyle modification and medical therapy. One of the important elements of medical therapy is the administration of potassium alkali, such as potassium citrate, which decreases stone formation rate in patients with idiopathic hypocitraturic calcium nephrolithiasis (Barcelo *et al*., 1993; Pak *et al*., 1986) and hyperuricosuria (Pak and Peterson, 1986) and in thiazide-unresponsive patients. (Pak *et al*., 1985) Potassium citrate (KCit) is an oral alkalinizing agent that has been used for more than 30 years in patients with hypocitraturic nephrolithiasis.

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The beneficial effect of potassium citrate is believed to arise from its citraturic and urinary alkalinizing actions. The increase in urinary citrate retards spontaneous nucleation and agglomeration of calcium oxalate crystals. (Pak, 1991) Moreover, by increasing urinary pH and decreasing urinary content of undissociated uric acid, potassium citrate treatment also prevents the formation of uric acid stones. (Pak *et al*., 1986) Therefore, potassium citrate has become widely accepted as first-line therapy for the treatment of idiopathic hypocitraturic nephrolithiasis. (Pak and Fuller, 1986; Spivacow *et al*., 2010) While previous studies, including randomized, controlled trials, have confirmed the effectiveness of this medication, there are sparse data on the impact of KCit during a prolonged duration of treatment. This paper describes

a prospectively randomized trial undertaken to evaluate the effect of long-term KCit therapy on metabolic parameters in patients with hypocitraturic calcium stones. In this study, we concurrently compared the stone recurrence rate in patients who received KCit therapy with that of control patients who received no medical prophylaxis.

MATERIALS AND METHODS

Study Design

The study was approved (STM No. 03B-006) by the Institutional Review Board of St. Martin De Porres Hospital in Chia-Yi city, where the work was undertaken. All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committee and in compliance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was designed as a prospectively randomized controlled trial and carried out from January 2003 to December 2012.

Study Population

We assessed the eligibility of all patients who had a history of surgical stone removal at our hospital and confirmation of calcium stones by chemical analysis and thin section petrographic analysis. The patients, aged over 40 years old, were recruited from a urological outpatient clinic; all patients who were diagnosed with hypocitraturic calcium stones (defined as less than 320 mg citrate in a 24-hour urine collection)[9] were eligible. Stone-free status was confirmed using nonenhanced computed tomography during the baseline study period. Exclusion criteria included: medullary spongy kidney, solitary kidney, chronic kidney disease, infectious stones, active stone disease with pain, hematuria, obstruction, taking thiazide-type diuretics, primary hyperparathyroidism, hyperkalemia, any diseases or medications that potentially could affect acid-base status, hyperuricosuria, gastrointestinal disease, chronic diarrhea, or pregnancy or nursing. Patients with hypercalcemia, struvite, and uric acid stones were also excluded. All patients signed an informed consent form before participating. All patients were well self-motivated and had adequate family support for the study.

Study Interventions

All patients met with a dietitian and were instructed to maintain a diet restricted to 2 g of sodium and 65 g of protein. The patients were asked to consume sufficient fluid to urinate at least 2 L daily. This could be any noncaffeinated fluid. All vitamins and dietary supplements were stopped. KCit therapy consisted of Urocit®-K 20 mEq. orally 3 times daily (Urocit®-K 10 mEq. Paladin Labs, Mission Pharmacal, Canada), and consumed 2 L water throughout each day. All patients were followed in an outpatient setting every 3 months. The healthcare team visited quarterly with each subject by telephone. The visit contents included whether the content of the diet was in accordance with intake instructions, whether water intake was sufficient, whether there was any discomfort. Reminders were also provided at the clinic during annual

follow-up, when other matters were also addressed. A baseline study included three consecutive-day 24-hour urine samples, followed by fasting venous blood sample collected the following morning. Collected urine was refrigerated for sanitary and odor control. Each participant was given a urine collection set and instructed to collect 24-hour urine output. On each micturition, the participant was instructed to divide the urine in two equal aliquots using two graduated cylinders and to pour them into two separate vessels. The first vessel, containing 10 mL HCl 37%, was used to measure calcium, oxalate, magnesium, phosphorus, and creatinine (the aliquot used to measure oxalate was subsequently diluted in boric acid); the second, containing chlorexidine 20%, was used to measure pH, sodium, chloride, potassium, citrate and uric acid. The patients were studied annually for at least 9 years of follow-up in an outpatient setting, at which time nonenhanced abdominal/pelvic computed tomography, three consecutive-day 24- hour urine samples, and venous blood were obtained for the same tests as baseline study.

Randomization

A total of 347 patients were eligible, and 295 were prospectively randomized (using a random numbers table) into two groups before they were enrolled in the study. A total of 140 patients in the control group and 155 patients in the KCit group were available for consideration. Among them, 13 patients in the control group and 15 patients in the KCit group, who were unwilling to be randomized, were not allocated to the trial. The remaining 127 patients were allocated to the control group and received ordinary hydration. Of these, 14 patients missing the primary outcome and 12 patients withdrawing informed consent were eliminated from the analysis. Another 140 patients were allocated to the KCit group. Of these, 16 patients missing the primary outcome and 14 patients withdrawing informed consent were eliminated from the analysis. An additional 8 patients in the KCit group could not tolerate KCit therapy due to gastrointestinal distress and were eliminated. Thus, the final analysis was conducted with 101 (control) and 102 (KCit therapy) patients as the denominator in each randomization arm (Fig. 1).

Study Outcomes

The primary outcome measure was the mean change in urinary citrate level. The secondary outcomes were citrate response rate and stone recurrence rate. The citrate response rate was defined by determining the number of patients with urinary citrate level above 320 mg/day and dividing by the total number of patients. The effect of KCit on stone recurrence was assessed by review of pre-therapy and post-therapy nonenhanced abdominal/pelvic computed tomography for each patient by the same radiologists. Reviewers were blinded to the dates of the imaging studies. Stone recurrence was determined for each patient and defined as any newly formed stone, passage of a stone that had not been preexisting, increase in the residual stone size to greater than 2 mm compared to previous images during follow-up periods, and surgical removal. The stone recurrence rates were based on the patient history by determining the number of stone formers and dividing by the total number of patients. The stone burden (mm^2) of each stone

was determined by multiplying the maximum length and width of each fragment. Overall stone burden was determined by summing the stone burden of the individual fragments.

Sample Size and Statistical Analysis

Detection of a 40% difference in the mean urinary citrate level in the treatment groups at a significance level of 0.05 and a power of 80% required a sample size of 100 patients per group. All analyses were conducted using SPSS® version 14.0.1. The differences in mean urinary citrate increases between the KCit and control groups were determined using the Mann-Whitney U test. Kaplan-Meier analysis for stone-free duration was applied between the KCit and control groups. The demographics were assessed with the Mann-Whitney U test and chi-square test. Mean changes in the urinary parameters and stone burden between groups were examined and compared using the Mann-Whitney U test. Changes in stone burden and metabolic parameters within both groups were analyzed using Cochran's Q test and Friedman's test.

RESULTS

A total of 203 patients completed the study protocol: 101 patients in the control group and 102 patients in the KCit group. No significant statistical difference was observed in patient age, gender distribution, body mass index, stone composition, stone laterality, previous intervention modalities, and co-morbidities (Table 1).

Table 1. Patients Demographics and Stone Characteristics

Characteristic	Control group	Lemon juice group	*P* value
	N=96	N=93	
Age(yr) [a]			
Mean	50.52±2.84	50.77±2.97	0.6
Range	45-55	45-55	
Gender [b]			0.6
Male	74(77.1%)	69(74.2%)	
Female	22(22.9%)	24(25.8%)	
Body mass index [a]	24.73±2.85	24.87±2.69	0.7
Male [a]	24.60±2.96	25.03±2.83	0.3
Female [a]	25.18±2.46	24.41±2.22	0.2
Co-morbidities [b]			1.0
Diabetes mellitus	17 (17.70%)	19 (20.43%)	
Cardiovascular disease	9 (9.38%)	8 (8.60%)	
LUTS	5 (5.21%)	6 (6.45%)	
Hypertension	16 (16.67%)	15 (16.13%)	
Stone composition [b]			0.8
Calcium oxalate	38(39.58%)	34(36.56%)	
Calcium phosphate	14(14.58%)	13((13.98%)	
Mixed	44(45.83)	46(49.46%)	

Values are presented as mean±standard deviation or number (%).
[a] Mann-Whitney U test
[b] Chi-square test
LUTS: Lower urinary tract symptom

In the KCit group after therapy, the mean urinary citrate level increased from 197.8 (baseline) to 523.7 mg/day (9th year), with a response rate of 67.65% (P<0.001 vs. control group) (Table 2). The stone recurrence rate ranged from 6.90% (1st year) to 68.32% (9th year) in the control group and from 2.94% (1st year) to 28.43% (9th year) in the KCit group, respectively, and the difference was statistically significant (P<0.001). In the Kaplan-Meier analysis, the log-rank statistic for differences

between curves was significantly different (P<0.001) (Fig. 2). The stone burden (mm^2) significantly increased over time in both groups (P<0.001) (Fig. 3). The mean baseline and post-therapy 24-hour urinary metabolic parameters are shown in the Table 2. Total urine volume, pH value and potassium were significantly different between the two groups (P<0.001) (Figs. 4 and 5). Baseline urinary citrate did not differ between the two groups (Table 2). Pronounced increases in urinary citrate were observed for the KCit group after therapy, with sustained increases during follow-up when compared with the control group. No statistically significant changes were observed in CCr (mL/min), calcium, sodium, magnesium, uric acid, and oxalate between the two groups. Significant differences were observed for pH value, total urine volume, citrate level, and stone burden rate within each group (P<0.001). During the 9 years follow-up, 8 patients experienced severe gastrointestinal distress to dropout the study. Minor complaints are few reported, including diarrhea, nausea, fullness, fatigue and inconvenience (Table 1).

DISCUSSION

The most common composition of kidney stones is calcium-based, which is up to 80% of all types of stones (Pattaras and Moore, 1999). The purposes of stone management are complete stone clearance, prevention of new stone formation and regrowth, preservation of renal function, control of urinary tract infections and, whenever the case, correction of abnormal anatomy and underlying metabolic abnormality. Metabolic abnormalities were also detected in the majority of patients with recurrent calcium nephrolithiasis. The common metabolic abnormalities are hypocitraturia followed by hypercalciuria and low urine output, which is the same as the previous study (Stitchantrakul *et al*., 2007). The primary goal of treating hypocitraturic calcium stone is to increase the 24-hour urinary citrate excretion to greater than 320 mg (Pak, 1994). Patients frequently ask how they can alter their diets to help prevent recurrent urinary stones. Routine dietary modifications for hypocitraturic calcium stones have included sodium restriction, decreased overall protein intake, and increased fluid ingestion to maintain a urinary specific gravity of less than 1.010 or to achieve a daily urine output of greater than 2 L. (Preminger *et al*., 1985) Identification of dietary modifications continues to be needed to help patients decrease stone recurrence rates, as these modifications allow patients to become actively involved in their own treatment without the social stigma of prescribed pharmacological therapies. The KCit has been a cornerstone of medical stone management for more than 30 years. To our knowledge, ours is the first prospectively randomized controlled study to evaluate the long-term effects of KCit therapy on 24-hour urinary metabolic parameters, stone burden, and stone recurrence rates. Numerous retrospective studies have demonstrated the biochemical benefit of oral potassium citrate supplementation in elevating urinary citrate levels (Stitchantrakul *et al*., 2007; Preminger *et al*., 1985).

Our results confirm the usefulness of KCit therapy in patients with hypocitraturic calcium stones, increasing urinary citrate excretion to normal levels. The first studies that assessed the long-term effects of KCit therapy was the study by Pak *et al*. (1985).

Table 2. 24-Hours Urine Biochemistry and stone recurrent status

	Baseline	1 year	2 year	3 year	4 year	5 year	6 year	7 year	8 year	9 year	P value
pH value [a]											
Control	6.35	6.41	6.43	6.46	6.28	6.37	6.50	6.37	6.60	6.51	<0.001[d]
(SD)	(0.31)	(0.65)	(0.32)	(0.38)	(0.36)	(0.33)	0.31	(0.29)	(0.39)	(0.36)	
Lemon juice	6.35	6.50	6.44	6.35	6.56	6.46	6.62	6.54	6.56	6.63	<0.001[d]
(SD)	(0.30)	(0.37)	(0.34)	(0.30)	(0.37)	(0.36)	(0.35)	(0.27)	(0.30)	(0.34)	
P value[a]	0.9	0.6	0.9	0.4	<0.001	0.1	0.2	<0.001	0.6	0.1	
Uric acid (mg/day) [a]											
Control	507.65	512.65	517.29	515.71	514.64	517.10	511.62	513.55	513.97	514.94	>0.5[d]
(SD)	(73.24)	(68.40)	(47.33)	(46.10)	(51.46)	(65.61)	(71.57)	(72.84)	(69.84)	(73.47)	
Lemon juice	507.2	527.5	524.1	536.9	530.1	536.3	524.7	537.3	527.5	535.1	<0.001[d]
(SD)	(72.6)	(58.7)	(65.9)	(65.1)	(69.6)	(68.3)	(63.3)	(64.9)	(64.3)	(77.2)	
P value[a]	0.9	0.2	0.3	0.9	0.9	0.6	0.2	0.3	0.3	0.2	
Oxalate (mg/day) [a]											
Control	27.07	28.06	27.93	28.41	27.25	27.93	27.51	27.92	26.80	27.85	0.8[d]
(SD)	(1.53)	(2.77)	(2.40)	(2.70)	(1.84)	(2.53)	(1.95)	(2.43)	(1.57)	(2.25)	
Lemon juice	27.25	28.25	27.38	27.69	26.73	28.37	27.74	28.61	27.54	28.07	>0.5[d]
(SD)	(1.58)	(2.33)	(1.37)	(1.28)	(1.81)	(1.72)	(1.55)	(1.60)	(1.96)	(1.94)	
P value[a]	0.1	0.4	0.4	0.7	0.2	0.4	0.5	0.6	0.8	0.3	
Total urine volume (mL/day) [a]		< 0.05		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	
Control	1926.0	1986.06	2004.02	1933.47	1891.6	1949.68	1989.03	1920.04	2001.67	1957.62	<0.001[d]
(SD)	(95.24)	(128.92)	(150.35)	(114.76)	(142.7)	(144.56)	(108.58)	(111.28)	(145.25)	(137.01)	
Lemon juice	1961.95	2022.41	1994.43	2052.99	1997.81	2095.58	2068.29	2003.12	2072.48	2015.89	<0.001[d]
(SD)	(129.46)	(124.72)	(111.37)	(111.18)	(106.74)	(134.13)	(116.54)	(141.67)	(85.18)	(130.44)	
P value[a]	0.1	0.02	0.8	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
CCr (mL/min) [a]											
Control	92.31	92.54	92.31	91.92	92.52	93.08	92.69	93.21	91.27	91.78	>0.5[d]
(SD)	(5.12)	(5.20)	(5.12)	(5.01)	(5.13)	(5.70)	(5.30)	(5.25)	(4.74)	(4.79)	
Lemon juice	92.50	92.55	92.58	92.85	92.36	91.57	93.0	92.55	92.43	93.09	>0.5[d]
(SD)	(5.79)	(5.33)	(5.53)	(5.36)	(5.25)	(5.64)	(5.24)	(4.90)	(5.57)	(5.97)	
P value[a]	0.7	1.0	0.7	0.2	0.9	0.8	0.5	0.5	0.3	0.9	
Creatinine (mg/day)[a]											
Control	1429.26	1434.54	1428.26	1386.88	1395.28	1440.35	1397.66	1442.22	1414.29	1421.63	>0.5d
(SD)	(73.73)	(74.32)	(72.76)	(72.14)	(73.87)	(82..08)	(76.32)	(75.60)	(68.25)	(68.98)	
Lemon juice	1438.21	1440.31.	1433.15	1453.46	1430.42	1418.61	1434.74	1432.72	1430.10	1440.50	>0.5d
(SD)	(81.06)	(79.42)	(77.42)	(77.18)	(75.74)	(81.21)	(75.31)	(70.56)	(80.35)	(85.97)	
P value[a]	0.6	0.5	0.2	0.5	0.7	0.7	0.2	0.6	0.6	0.5	
Sodium (mEq/day) [a]											
Control	140.52	140.38	142.01	141.29	141.23	140.56	140.42	140.60	140.71	139.83	>0.5[d]
(SD)	(4.09)	(3.84)	(4.13)	(4.37)	(4.32)	(4.14)	(4.04)	(4.01)	(4.09)	(4.23)	
Lemon juice	140.88	139.90	140.56	141.13	140.56	143.11	141.91	141.76	142.31	143.34	>0.5[d]
(SD)	(3.77)	(3.86)	(3.67)	(4.20)	(3.67)	(6.58)	(4.10)	(6.67)	(4.88)	(5.66)	
P value[a]	0.4	0.5	0.2	1.0	0.4	0.3	0.8	0.3	0.3	0.6	
Citrate (mg/day) [a]		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	
Control	199.13	187.45	192.04	197.92	187.67	198.44	188.13	200.52	191.24	196.25	>0.5[d]
(SD)	(33.58)	(39.16)	(49.17)	(30.09)	(28.16)	(34.74)	(29.20)	(36.82)	(33.33)	(32.71)	
Lemon juice	197.41	360.46	375.16	383.75	372.18	368.46	386.97	371.08	386.08	404.18	<0.001[d]
(SD)	(34.46)	(106.02)	(130.40)	(137.53)	(128.73)	(127.85)	(139.91)	(130.06)	(136.18)	(131.94)	
P value[a]	0.7	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
Response rate		60.21%	60.21%	60.21%	60.21%	60.21%	60.21%	60.21%	60.21%	60.21%	<0.001[c]
Potassium (mEq/day) [a]											
Control	47.81	51.38	49.07	47.63	45.56	50.25	47.52	50.25	49.33	47.09	>0.5[d]
(SD)	(5.51)	(7.30)	(7.79)	(5.46)	(6.01)	(7.74)	(5.60)	(8.97)	(4.81)	(4.86)	
Lemon juice	47.99	52.33	47.83	50.56	51.80	48.32	52.61	48.15	52.47	47.86	>0.5[d]
(SD)	(4.67)	(7.54)	(4.40)	(5.84)	(7.31)	(4.66)	(7.01)	(4.94)	(8.29)	(6.82)	
P value[a]	0.8	0.4	0.1	0.3	0.6	0.2	0.7	0.12	0.9	0.3	
Calcium (mg/day) [a]		< 0.001		< 0.001	< 0.001	< 0.001	< 0.001				
Control	180.44	185.18	181.81	177.55	181.21	176.31	182.22	180.35	185.23	179.50	>0.5[d]
(SD)	(4.14)	(9.40)	(4.19)	(7.73)	(4.95)	(8.41)	(5.69)	(4.17)	(8.68)	(5.60)	
Lemon juice	180.37	177.95	185.13	188.74	175.24	184.18	188.76	181.89	186.61	179.68	>0.5[d]
(SD)	(4.01)	(5.62)	(8.81)	(11.42)	(8.50)	(5.60)	(12.66)	(6.94)	(12.45)	(7.68)	
P value[a]	0.8	<0.001	0 .06	<0.001	<0.001	<0.001	<0.001	0.08	0.8	0.9	
Magnesium (mg/day) [a]											
Control	84.17	85.19	87.79	84.44	86.35	84.25	85.27	84.42	83.85	84.73	>0.5[d]
(SD)	(8.92)	(9.42)	(12.78)	(9.04)	(9.72)	(9.63)	(8.77)	(9.76)	(9.00)	(9.12)	
Lemon juice	84.10	85.27	84.24	84.48	84.24	86.26	85.66	83.95	84.88	84.83	>0.5[d]
(SD)	(9.20)	(9.51)	(9.01)	(7.44)	(9.01)	(7.08)	(8.36)	(9.85)	(7.83)	(8.22)	
P value[a]	1.0	1.0	0.8	0.7	0.2	0.1	0.7	1.0	0.5	0.9	

[a] Mann-Whitney U test: comparison between control and lemon juice group
[c] Cochran's Q test: for citrate response rate
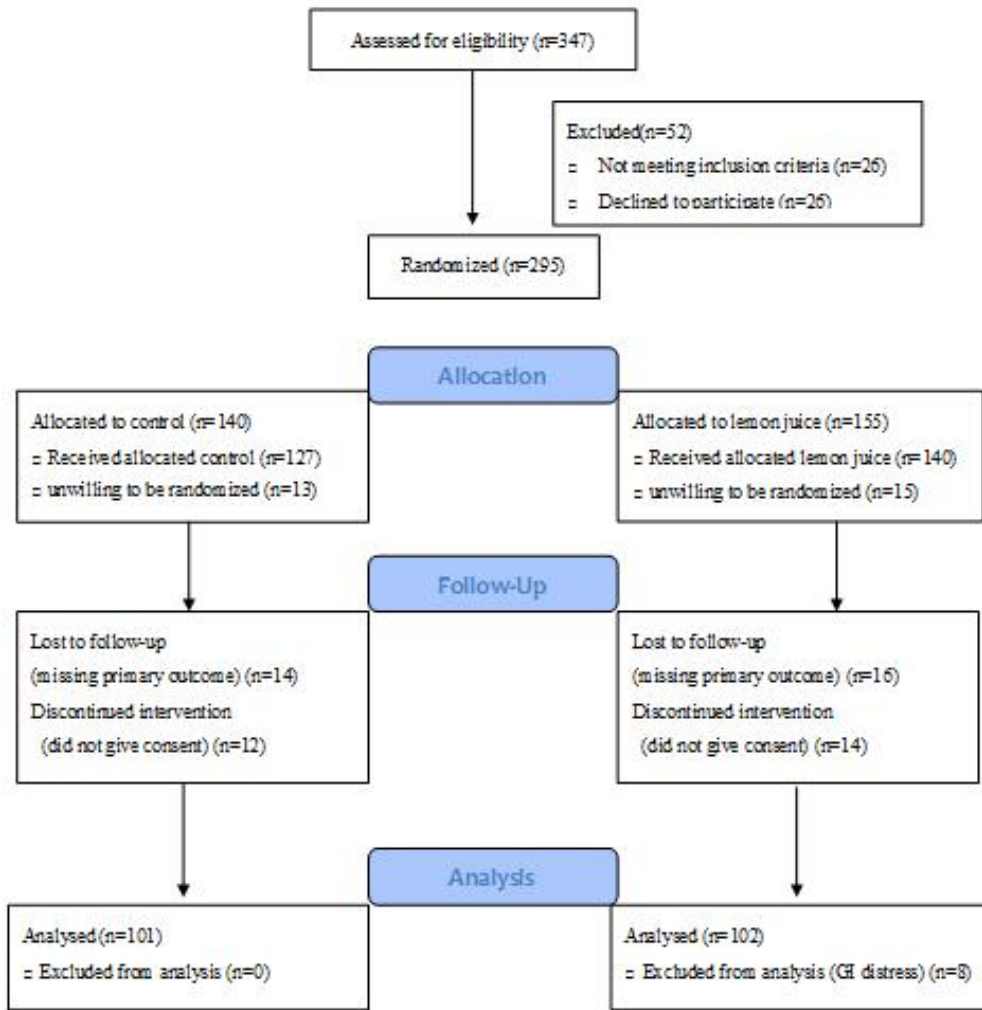[d] Friedman's test: comparison within each group

Fig. 1. Summary of study disposition numbers of participants declining further follow-up or not responding are cumulative in direction of participant flow
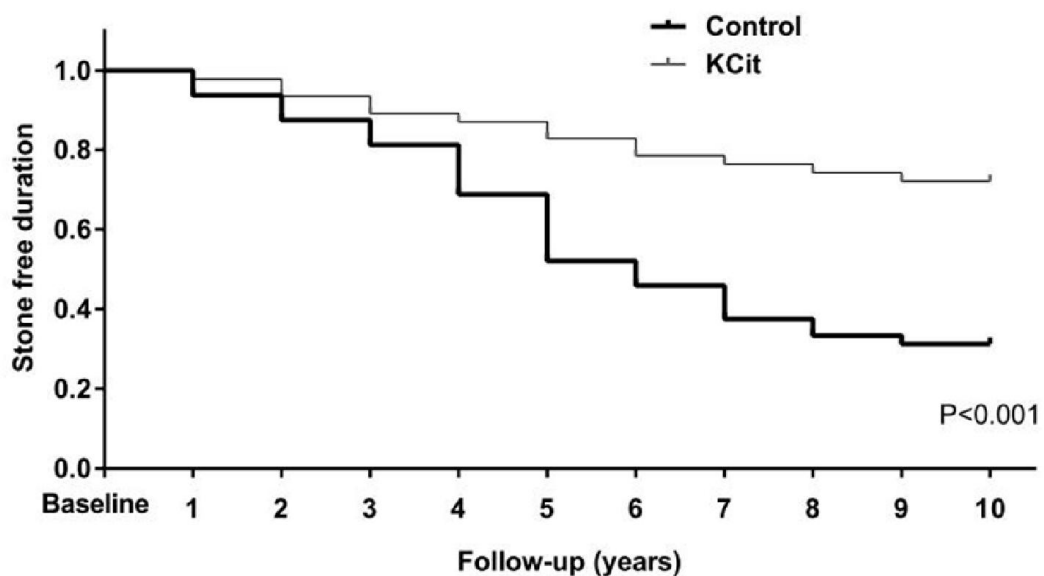

Fig. 2

Effect of long term KCit therapy on stone free duration. Kaplan-Meier curve for stone free duration in lemon juice group and control group. Log-rank statistic for differences between curves (p<0.001)
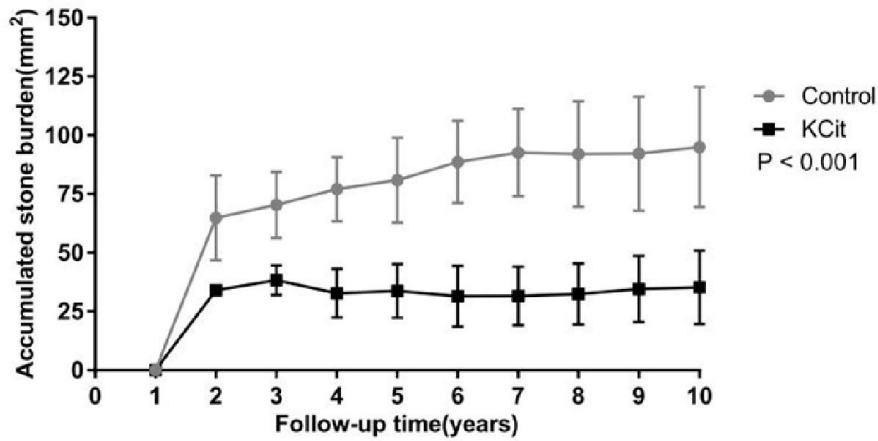
Fig.3
Effect of long term KCit therapy on accumulated stone burden (nm^2) Bars indicate mean±standard errors (p<0.001)
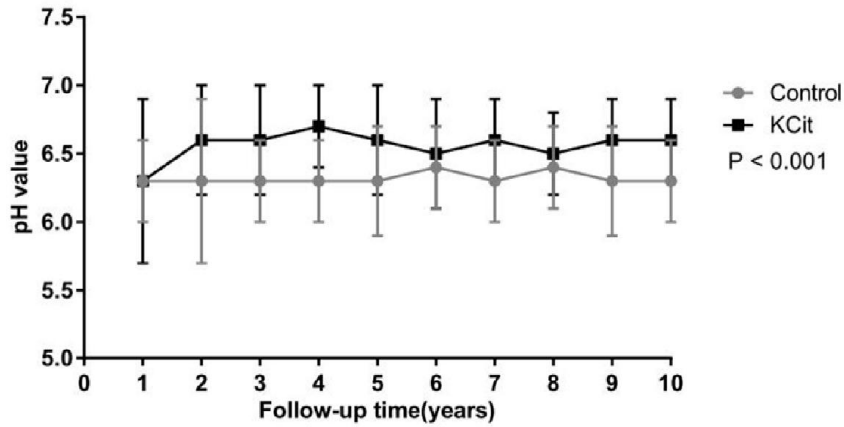

Fig. 4
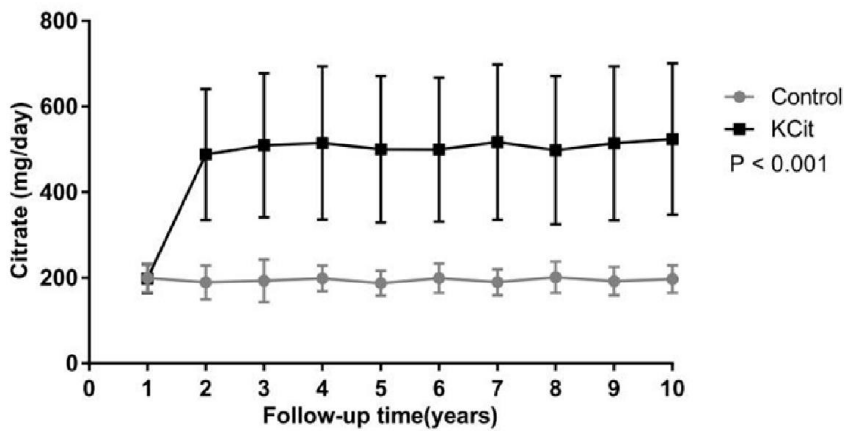**Effect if kibg term KCit thearpy on urinary pH. Bars indicate mean±standard erros (p<0.001)**

Fig.5
Effect of long term KCit thearpy on total urine volume (mL/day). Bars indicate mean±standard erros (p<0.001)

Abbreviations and Acrinyms
KCit = potassium citrate
CCr= Creatinine clearance rate

The investigators used KCit 20 mEq.3 times daily for 1-4 years in 89 patients with calcium nephrolithiasis. The KCit therapy caused a sustained increase in urinary pH and potassium and restored urinary citrate to normal levels (Pak *et al*., 1985). Among the groups assessed by Pak *et al*, those with hypocitraturia were very similar to our patients. Urinary citrate rose from an average of 162 to 410 mg/d at 8 months of treatment, which is quite similar to what was found in our study in 102 patients with hypocitraturic calcium stones, in which the increase was from 197.9 to 487.7 mg/d after the first year of treatment. Similar results were also reported by Spivacow *et al* and Ronbison *et al*. (2010, 2009).

However, the question has been raised as to whether this effect is truly durable in the long term or whether there is a potential decrease in effectiveness of this therapy with time, as has been seen for thiazide diuretics (Preminger and Pak, 1987). We noted a durable response up to 9 years after the initiation of KCit therapy for hypocitraturic calcium stones. There was no degradation of the effect of KCit, as has been seen with thiazides, which can be associated with a certain degree of tolerance with long term treatment (Preminger and Pak, 1987). There was a statistically significant correlation between the increases in urinary citrate and urinary pH in the entire study population. Previously groups have reported a similar long term but in significantly smaller study populations (Spivacow *et al*., 2010; Robinson *et al*., 2009; Barcelo *et al*., 1993; Whalley *et al*., 1996; Lee *et al*., 1999). As urinary pH increases, there is enhanced renal citrate production and increased tubular reabsorption of citrate, thereby increasing the inhibitor activity of citrate to decrease calcium based stones. Moreover, these changes were sustained over time and produced an important reduction in kidney stone recurrence. The KCit regimen described here could aid in increasing patient compliance with and acceptance of potentially lifelong therapy. Patients receiving pharmacological KCit supplementation are required to maintain a rigorous schedule of numerous tablets or liquid supplements taken routinely 3 to 4 times daily. Patient compliance is known to show significant decreases when medications must be administered more than once daily. (Pak *et al*., 1987) Dropout rates attributable to the inconvenience of multi-tablet KCit administration have surpassed 25% in long-term studies with 3 months to 3 years of followup. (Cramer *et al*., 1989; Schwille *et al*., 1992) In our long term study, 8 patients cannot comply the regimens and discontinue KCit therapy, not as other previous study. KCit supplementation has also been associated with gastrointestinal intolerance in 17 to 45% of patients on long-term therapy, resulting in decreased compliance and cessation of therapy (Barcelo *et al*., 1993; Cramer *et al*., 1989; Schwille *et al*., 1992; Hofbauer *et al*., 1994). However, slow release KCit formulations in our studymay increase the compliance of our patients during the long term therapy, resulting in better durability. Our results showed statistically significant decreases in stone burden (64.9 mm^2 1st year for the control vs. 34.0 mm^2 1st year for the KCit group) and in stone recurrence rates (68.32% 9th year in the control group vs. 28.43% 9th year in the KCI group). The stone recurrent rates are slightly lower than in other reported studies (Preminger *et al*., 1985; Barcelo *et al*., 1993; Whalley *et al*., 1996). Uribarri *et al* stated that six large retrospective studies show the "natural cumulative recurrence

rate of renal stones" to be 14% at 1 year, 35% at 5 years, and 52% at 10 years (Uribarri *et al*., 1989). This finding may reflect the fact dehydration and low urinary volume are widely accepted risk factors for urinary stone disease. Besides, the current study confirms that long term KCit therapy can effectively decrease the stone recurrence rate. Our study has an important limitation; namely, the absence of residual fragments in the baseline imaging study as standard group for comparison. The study cannot elucidate the crucial factor of residual stones for recurrence in the KCit therapy.

Conclusion

The slow-release KCit therapy provides a significant alkali and citraturic response during long term therapy with a sustained change in urinary parameters. Moreover, long term KCit therapy significantly decreases the stone formation rate, confirming usefulness in patients with hypocitraturic calcium stones.

REFERENCES

Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CYC. 1993. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol*., 150: 1761–1764.

Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CYC. 1993. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol*., 150:1761-1764.

Cramer JA, Mattson RH, Prevey ML, ScheyerRD, OuelleteVL. 1989. How often is medication taken as prescribed? A novel assessment technique. *JAMA*, 261: 3273-3277.

Hofbauer J, Hobarth K, Szabo N, Marberger M. 1994. Alkali citrate prophylaxis in idiopathic recurrent calcium oxalate urolithiasis-a prospective randomized study. *Brit J Urol*., 73: 362-365.

Lee YH, Huang WC, Tsai JY and Huang JK. 1999. The efficacy of potassium citrate based medical prophylaxis for preventing upper urinary tract calculi: a midterm followup study. *J Urol*., 161: 1453-1457.

Pak CYC and Fuller C. 1986. Idiopathic hypocitraturic calcium oxalate nephrolithiasis successfully treated with potassium citrate. *Ann Intern Med*., 104: 33–37.

Pak CYC, Fuller C, Sakhaee K, *et al*. 1985. Long-term treatment of calcium nephrolithiasis with potassium citrate. *J Urol*., 134:11-19.

Pak CYC, Peterson R, Sakhaee K, Fuller C, Preminger G, Reisch J. 1985. Correction of hypocitraturia and prevention of stone formation by combined thiazide and potassium citrate therapy in thiazide-unresponsive hypercalciuric nephrolithiasis. *Am J Med*., 79: 284–288.

Pak CYC, Sakhaee K, Fuller C. 1986. Successful management of uric acid nephrolithiasis with potassium citrate. *Kidney Int*., 30: 422–428.

Pak CYC. 1987. Citrate and renal calculi. *Mineral Electrolyte Metab*., 13: 257-266.

Pak CYC. 1991. Citrate and renal calculi. New sights and future directions. *Am J Kidney Dis*., 17: 420–425.

Pak CYC. 1994. Citrate and renal calculi: an update. Miner Electrolyte. *Metab*., 20: 371–377.

Pak CYC. and C Fuller. 1986. Idiopathic hypocitraturic

calcium oxalate nephrolithiasis successfully treated with potassium citrate. *Ann intern Med.*, 104:33-37.

Pak CYC. and Peterson R. 1986. Successful treatment of hyperuricosuric calcium oxalate nephrolithiasis with potassium citrate. *Arch Intern Med.*, 146: 863–867.

Pattaras JG, Moore RG. 1999. Citrate in the management of urolithiasis. *J Endourol.*, 13: 687-92.

Preminger GM and Pak CYC. 1987. Eventual attenuation of hypocalciuric response to hydrochlorothiazide in absorptive hypercalciuria. *J Urol.*, 137: 1104.

Preminger GM, Harvey JA, Pak CYC. Comparative efficacy of "specific" potassium citrate therapy versus conservative management in nephrolithiasis of mild to moderate severity. *J Urol.*, 1985;134: 658-661.

Robinson MR, Leitao VA, Haleblian GE, Scales CD Jr., Chandrashekar A, Pierre SA, Preminger GM. 2009. Impact of long-term potassium citrate therapy on urinary profiles and recurrent stone formation. *J Urol.*, 181:1145-1150.

Schwille PO, Herrmann U, Wolf C, Berger I, Meister R. 1992. Citrate and recurrent idiopathic calcium urolithiasis. A longitudinal pilot study on the metabolic effects of oral potassium citrate administered over the short-, medium- and long-term medication of male stone patients. *Urol Res.*, 20: 145-155.

Spivacow FR, Negri AL, Polonsky A, Del Valle EE. 2010. Long-term treatment of renal lithiasis with potassium citrate. *Urology*, 76:1346-1349.

Stitchantrakul W, Kochakarn W, Ruangraksa C, Domrongkitchaiporn S. 2007. Urinary risk factors for recurrent calcium stone formation in Thai stone formers. *J Med Assoc Thai.*, 90: 688-98.

Uribarri J,Oh MO, Carroll HJ. 1989. The First Kidney Stone. *Ann Intern Med.*, 111(12):1006-1009.

Whalley NA, Meyers AM, Martins M and Margolius LP. 1996. Long-term effects of potassium citrate therapy on the formation of new stones in groups of recurrent stone formers with hypocitraturia. *BJU Int.*, 78: 10-17.

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