Urol Res (2008) 36:313–317
DOI 10.1007/s00240-008-0152-6

ORIGINAL PAPER

Can lemon juice be an alternative to potassium citrate in the treatment of urinary calcium stones in patients with hypocitraturia? A prospective randomized study

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Received: 14 October 2007 / Accepted: 29 August 2008 / Published online: 23 October 2008

Abstract To investigate that lemon juice could be an alternative to potassium citrate in the treatment of urinary calcium stones in patients with hypocitraturia, 30 patients with hypocitraturic urinary calcium stones were enrolled into study. The patients were divided into three groups equally. Exactly 60 mEq/day fresh lemon juice (≈85 cc/day) and potassium citrate (60 mEq/day) were given to the patients of first and second group, respectively. Dietary recommendations were made for the third group. Blood and 24-h urine tests were performed before treatment and repeated 3 months later. The differences between demographic datas of groups were not significant. There was no significant difference between values of blood tests performed before and after treatment in all groups. Statistically significant differences were found between pre- and post-treatment urine values in each group. Although there was no significant difference between pre-treatment citrate levels of the groups. A significant difference was found between post-treatment citrate levels of the groups. There was 2.5-, 3.5- and 0.8-fold increase in urinary citrate level of lemon juice, potassium citrate and dietary recommendation groups, respectively. Urinary calcium level was decreased only in lemon juice and potassium citrate groups after treatment. While there was no significant difference between pre- and post-treatment urinary oxalate levels in all groups, a significant decrease in urinary uric acid levels was determined in all groups. We suggest that lemon juice can be an alternative in the treatment of urinary calcium stones in patients with hypocitraturia. Additionally, dietary recommendations can increase effectiveness of the treatment.

Keywords Lemon juice · Hypocitraturia · Potassium citrate · Calcium stones

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Introduction

In urinary system, citrate is an important inhibitory substance which forms soluble complexes with calcium. It reduces the saturation of calcium phosphate and calcium oxalate and inhibits crytallization and enlargement. As a result, it decreases the formation of calcium containing stones [1].

Hypocitraturia is a frequent etiologic factor in patients with recurrent urinary stones. The causes of hypocitraturia include chronic diarrhea, renal tubular acidosis, urinary system infections, hypokalemia due to the use of thiazide diuretics, hereditary and idiopathic since many patients do not have a cause identified. The incidence of hypocitraturia observed in patients with recurrent urinary stone disease is between 19 and 63% [2].

As the classical treatment of hypocitraturia, potassium citrate increases urinary citrate level and pH and decreases urinary calcium excretion. So, it causes a relative decrease in calcium oxalate saturation [3, 4]. Potassium citrate, given to patients with hypocitraturic calcium stones, results with a significantly lower rate of new stone formation, when compared with patients under standard dietary recommendations [5]. Increasing fluid intake and restriction of foods rich from sodium, oxalate and proteins are among standard dietary recommendations given to patients with hypocitraturic calcium oxalate stones. If hypocitraturia is determined, the treatment should be supported by potassium citrate. The

treatment dose of potassium citrate is 30–100 mEq/day and it has several gastrointestinal side effects (nausea, vomiting, abdominal ache and diarrhea) [6]. Excessive side effects of potassium citrate therapy and need for long-term use causes problems about patient compliance.

Citrus fruits (lemon, orange and grapefruit), pineapple and strawberry contain natural citrate and the highest citrate level exists in lemon [7]. There are several studies made using citrus fruits. In one of these studies, Seltzer et. al. [8] declared that intake of lemon juice (5.9 g citric acid/2 l) for 6 days has increased urinary citrate levels twofolds. In another study, Goldfarb and Aslin [9] reported that citrate and oxalate levels were increased in healthy subjects after intake of grapefruit juice (240 ml) for 7 days. On the other hand, Wabner and Pak have determined that orange juice caused increase in urinary citrate and also oxalate levels and decrease in urinary calcium excretion. But, they have reported that increase in citrate level was insufficient to compansate for increase in oxalate level [10].

As far as we now, there is no study comparing lemonade with potassium citrate and dietary recommendations. We aimed to investigate whether lemon juice could be an alternative to potassium citrate and dietary recommendations in the treatment of the patients with hypocitraturic urinary stones in a randomized and prospective study.

Materials and methods

A total of 30 patients with a mean age of 37.6 ± 2.8 years (range 20–55) having hypocitraturic urinary calcium stones were enrolled into the prospective randomized study. The patients with endocrinologic and gasrointestinal diseases that could cause urinary system stones and hypocitraturia and those with distal renal tubular acidosis, chronic diarrhea, hyperparathrodism, active peptic ulcus, chronic renal diseases, hyperpotassemia, urinary tract infections and urinary tract anomalies and those having intolerance and allergy to potassium citrate were excluded from the study.

The diagnosis of calcium stones was made by X-ray crystallography. The limit of hypocitraturia was accepted as 0.6 mmol/day (115 mg/day) in males and as 1.03 mmol/day (200 mg/day) in females [11].

The patients were divided into three groups equally ($n = 10$). Fresh lemon juice (85 cc; two middle sized lemons) per day (containing 60 mEq of citrate) and 60 mEq/day potassium citrate were given to the patients of first and second group, respectively. Water, calcium, NaCl and protein intakes of 3.0 l/day, 1,200 mg/day, 5 g/day, 1.0 g/(kg day), respectively, and limited carbohydrate, lipid and oxalate intakes were advised in the dietary recommendations group [12]. Additionally, the patients of other groups were also advised to increase their water intake to 3.0 l/day. The treatment was continued for a period of 3 months in all groups.

The patients of lemon juice group were taught how to prepare fresh lemon juice at home. For this purpose 85 cc of lemon juice (60 mEq ≈ 4.2 g citrate) was completed to 1,000 cc adding water. This amount was consumed daily by patients for a period of 3 months.

Blood calcium, potassium, albumin, creatinine and uric acid levels and urinary oxalate, calcium, citrate, uric acid and creatinin levels and urine volume were measured in 24-h urine and urinary pH specimen in all groups before treatment. All these tests were repeated after completion of treatment.

Urinary calcium and oxalate levels were measured after addition of hydrochloric acid (HCl 10 N) in order to prevent the precipitation of calcium and oxalate. Urinary citrate level was measured by citrate liase technique using Boehringer–Mannheim Kit® (Boehringer, Ingeleheim Ltd, Ridgefield, Connecticut) and urinary oxalate level was measured by enzyme method of Sigma-Diagnostics® (Sigma Diagnostics, St. Louis).

Statistical Package for Social Sciences for Windows 10.0 program was used for statistical analysis. Mean and standart deviation tests were used as descriptive statistical methods. One-way Anova, Tukey HDS and Mann–Whitney U tests were used for comparison of quantitative parameters with normal distribution. Chi-square test was used for comparison of qualitative data. A $P < 0.05$ was considered to be statistically significant.

Results

When the demographic data of three groups were compared, there was no significant difference between them ($P > 0.05$). Mean age of lemon juice, potassium citrate and dietary recommmendations groups were 36.80 ± 14.28, 39.60 ± 14.67, 38.70 ± 12.01 years, respectively. There was no statistically significant difference in all groups, when comparison of pre- and post-treatmet blood chemistry tests was performed ($P > 0.05$). Pre- and post-treatment biochemical results of 24-h urine of the three groups are given in Table 1. There was no statistically significant difference between pre-treatment urinary citrate, oxalate, urate, creatinine and calcium levels and urine volume and pH of three groups.

Although no statistically significant difference was found between pre-treatment urinary citrate levels of the groups ($P > 0.05$), the post-treatment urinary citrate levels of the groups showed significant difference ($P < 0.05$). While there was a statistically significant difference between post-treatment urinary citrate levels of lemon juice and dietary recommendations groups ($P < 0.05$) and those of potassium

Table 1 Results of urinary chemical investigations and volume of the groups (in pre- and post-treatment 24-h urine)

	Lemon group (mean ± SD)			Potassium citrate group (mean ± SD)			Diet group (mean ± SD)		
	BT	AT	*P**	BT	AT	*P**	BT	AT	*P**
Citrate level (mg/day)	122.6 ± 64.69	302.7 ± 75.14	0.003	85.50 ± 44.21	324,70 ± 114,15	0.001	102.70 ± 22.62	186.5 ± 68.92	0.001
Oxalate level (mg/day)	24.80 ± 28.71	26.45 ± 19.98	0.794	26.90 ± 2.84	34.90 ± 13.21	0.079	21.70 ± 7.04	22.60 ± 12.43	0.862
Urate level (mg/day)	359.50 ± 180,03	311.00 ± 156.67	0.381	373.60 ± 191.52	327.00 ± 218.30	0.232	496.10 ± 161.11	427.20 ± 194.69	0.358
Creatine level (mg/day)	840.10 ± 544.32	944.60 ± 612.56	0.353	932.30 ± 644.45	1123.20 ± 547.75	0.418	1355.70 ± 539.44	1701.00 ± 783.53	0.264
Urine volume (cc/day)	1455.00 ± 903.83	2014.00 ± 944.49	0.032	1345.00 ± 486.76	1997.00 ± 790.33	0.035	1641.00 ± 487.59	2118.00 ± 588.68	0.047
Calcium level (mg/day)	186.60 ± 89.06	118.30 ± 86.16	0.406	270.70 ± 284.07	151.70 ± 118.75	0.204	195.10 ± 83.90	185.60 ± 61.63	0.059
pH	5.8 (±0.4)	6.0 (±0.3)	0.650	5.9 (±0.2)	6.5 (±0.3)	0.04	5.7 (±0.2)	5.8 (±0.3)	0.721

BT before treatment, *AT* after treatment

* Paired samples test

citrate and dietary recommendations groups ($P < 0.01$), no significant difference was found between post-treatment urinary citrate levels of lemon juice and potassium citrate groups ($P > 0.05$). When pre- and post-treatment urinary citrate levels were compared, a 2.5-, 3.5- and 0.8-fold increase was found in lemon juice, potassium citrate and dietary modifications groups, respectively. While urinary calcium levels have decreased in lemon juice and potassium citrate groups ($P < 0.05$), the urinary calcium levels did not change in dietary recommendations group ($P > 0.05$). Although urinary oxalate levels have increased in lemon juice group, the increment was statistically insignificant ($P > 0.05$). The urinary oxalate levels of the other two groups did also show no statistically significant difference ($P > 0.05$). The post-treatment uric acid levels of all three groups have decreased ($P < 0.05$). As the post-treatment urinary pH was increased in potassium citrate group ($P < 0.05$), the other groups showed no significant change ($P > 0.05$).

Gastric and oropharengeal discomforts, that did not require discontinuation of the drug, were observed in two patients of potassium citrate group. There was no problem about the continuation of treatment in the other two groups. The urinary output showed a significant increase in all groups ($P < 0.05$).

Discussion

It is difficult to define how the diet components play role on stone formation in urinary tract [13]. As far as we know, diet has several potential effects that increase or decrease the risks of stone formation. As low liquid and calcium intakes might cause stone formation in urinary tract, high protein, salt and oxalate intakes could also result in stone formation [13–15]. It is known that citrate is a natural substance which inhibits the formation of urinary calcium stones. Decreased urinary excretion of citrate is frequently related to urinary stone disease [16]. There are several studies claiming that most patients with kidney stones have decreased urinary citrate levels [1, 2].

It has been shown in adult studies that management of hypocitraturia resulted in decreased rate of stone recurrences [17, 18]. Oral potassium citrate is effective in increasing urinary citrate and pH. As a result of this effect, in conjunction with significantly decreased excretion of urinary calcium, potassium citrate decreases crystallization of uric acid and calcium oxalate [3]. For this reason, potassium citrate has been used successfully to prevent urinary stone formation in patients with hypocitraturic calcium urolithiasis [19]. It has been observed, in vivo studies performed with urine like syntethic solutions, that when urinary citrate levels was increased, the formation of calcium oxalate was decreased significantly [19].

Potassium citrate therapy requires ingestion of many tablets daily in order to provide a sufficient therapeutic dose. This regimen does dramatically decrease patient compliance and can impose a financial burden on the patient.

Citrus fruits can be used as an alternative to potassium citrate in the treatment of hypocitraturic urolithiasis [10, 20]. Citrus fruits are rich sources of natural citrate and they can supply enough citrate levels equal to routine potassium citrate treatment. When the most consumed citrus fruits were compared with each other, it has been found that lemon contains the highest level of citrate concentration which was approximately fivefolds of the concentration in orange [7]. A half glass of lemon juice can supply a daily citrate intake which is comparable to pharmacologic

treatment. Wabner et al. have evaluated biochemical effects of dietary citrate in patients with calcium stones using citrus fruits. They have demonstrated that mean daily urinary citrate level was increased from 571 to 952 mg in 11 patients after 1.2 l orange juice (containing 60 mEq potassium and 190 mEq citrate per day) intake. It has been found that this increase was in proximity with that obtained with potassium citrate treatment in the same 11 patients [10]. In another study, Honow et al. have given orange, grapefruit and apple juices mixture to nine healthy female subjects for 2 days and investigated their effects on urinary metabolic profile. It was observed that all three juices caused increase in urinary citrate excretion and urinary pH. Additionally, it was observed that only grapefruit juice provided a relative decrease in supersaturation of calcium oxalate crystallization [21].

Recently, Kang et al. in a retrospective study, have evaluated the effects of lemon juice and potassium citrate on urinary parameters. After a mean treatment period of months urinary citrate level increased to 383 and 482 mg/day in lemon juice and potassium citrate groups, respectively. They concluded that due to its significant citraturic effect, lemonade therapy has appeared to be a reasonable alternative for patients with mild hypocitraturia who could not tolerate first line therapy [20].

On the other hand, Koff et al. [22] have shown that lemonade did not provide improvements in urinary citrate or pH levels but did assist patients in mantaining urine output compared with potassium citrate therapy. Also Odvina et al., in a short-term randomized study, have found that orange juice but not lemonade provided alkali as evidenced by higher net gastrointestinal alkali absorption and higher urinary pH and citrate compared with control. Urinary calcium was not significantly different, but urinary oxalate was higher during the orange juice phase. The calculated supersaturation of calcium oxalate was lower in the orange juice phase compared with control. The calculated supersaturation of brushite was also significantly higher in the orange juice phase compared with both control and lemonade phases. Despite comparable citrate content, this study showed that orange juice has greater alkalinizing and citraturic effects than lemonade [23]. Alkali load enhances urinary citrate excretion by reducing renal tubular reabsorption and metabolism of citrate [23, 24]. The lack of alkalinizing and attenuated citraturic effects of lemonade probably is due to its accompanying proton, which could have neutralized the effect of citrate. Citraturia, however, could also develop through an alternative mechanism, unrelated to changes in acid–base status. A small fraction of administered citrate may escape in vivo metabolism and appear directly in the urine [25]. The mechanism may be responsible, in part, for the observed rise in urinary citrate in hypocitraturic calcium stone formers after consuming 2 l/day lemonade for 1 week [8]. Alternatively, dietary compositions may have influenced the response to lemonade administration.

In our study, patients with severe hypocitraturia were evaluated prospectively. Citrate was given as lemon juice to ten patients. Adaptation to and tolerance of lemon juice was favorable in all patients. There was also a statistically insignificant increase of urinary oxalate level in this group. Daily lemon juice consumption (as lemonade) has resulted in a more than 2.5-fold increase of urinary citrate level. The urinary citrate levels of the potassium citrate group and the dietary recommendation group were 3.5- and 0.8-fold of the pre-treatment levels. No significant change was observed in urinary calcium and oxalate levels.

Some of the studies as we mentioned above which have and some of which have not shown increases in citrate, it could be because of possible differences between the doses taken as a possible factor causing differences in urine chemistry results.

Wabner et al. have detected a statistically significant increase of urinary oxalate levels in patients under orange juice intake. This result could be attributed to ascorbic acid, a precursor of oxalate, which was found in higher concentration in orange juice compared to lemon juice [10]. It has been reported in literature that the rate of gastrointestinal intolerance to potassium citrate treatment was between 17 and 45% [6, 17]. In our study, intolerance to potassium citrate treatment was observed in two patients (20%). The potassium citrate treatment was discontinued for a period of 10 days in these patients and then started again.

Dietary recommendations for patients with hypocitraturic calcium urolithiasis include sodium restriction, decreased protein intake and increased fluid intake in order to decrease urinary-specific gravity below 1,010 and/or to guarantee a daily urine output above 2 l [13]. There is no need to define the dietary changes that should be made to decrease stone recurrence rates of the patients. So, the patients can play an active role in their treatment without social restriction imposed by pharmacologic treatment. This dietary regimen helps them to be harmonious during a potentially whole life treatment.

Our results have shown that lemonade treatment had a role in hypocitraturic patients. But, the patients receiving potassium citrate treatment had a higher increase of urinary pH in comparison to those receiving lemonade treatment. It has been known that citraturic effect of potassium citrate was due to net alkaline load produced by its oxidation to bicarbonate and its renal excretion [20, 24]. In spite of this, lemonade treatment has not caused urinary alkaline load due to low pH of lemon juice. The citraturic response in lemonade treatment was thought to be due to only renal excretion of unmetabolised citrate [25]. This fact might be the reason that lemonade did not increase urinary pH.

We suggest that lemon juice can be recommended in the treatment of patients with hypocitraturic urinary calcium stones. We think that the effectiveness of treatment and the patient compliance will increase, when dietary recommendations are also made in addition to this alternative treatment.

Two middle sized lemons is approximately contains daily dosages and priced nearly $0.5, daily dosage potassium citrate tablets cost nearly $3.9 in Turkey and $3.2 in Europe. This treatment also seems to be more cost-effective according to pharmacologic treatment.

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