The Tolerability of Potassium Citrate Tablet in Patients With Intolerance to Potassium Citrate Powder

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Purpose: To assess the tolerability of Potassium Citrate (KCit) tablets in patients with kidney stones that were not able to use the powder form of this drug due to unfavorable salty taste and /or gastrointestinal complications.

Materials and Methods: Twenty-three stone formers, with intolerance to potassium citrate powder form, which had referred to Labbafinejad stone preventive clinic in 2015, were included in this study. All of the patients took two potassium citrate tablets (10 meq), three times a day for two weeks. Spot urine samples and the 24-hour urine collections were performed before and after KCit therapy. In addition, a visual analog taste scale was completed to gauge the taste and palatability of the KCit tablets in comparison with the powder form.

Results: All of the patients claimed that they consumed the tablets as prescribed. The urine pH (5.7 ± 0.6 to 6.1 ± 0.8, $p = 0.006$), 24-hour citrate (235.8 ± 190.2 to 482.5 ± 323.2, $p = 0.0002$) and potassium (45.25 ± 22.5 to 75.27 ± 37, $p = 0.002$) were significantly higher after the treatment. In addition, the mean visual analog scale score was significantly improved in KCit therapy with tablet form versus to powder form of the drug (good vs. terrible score).

Conclusion: Oral tolerance of KCit therapy is improved with the use of Potassium Citrate tablet, with beneficial effects on 24-hour urine citrate, potassium, and pH.

Keywords: potassium citrate; tolerance; taste; gastrointestinal side-effects.

INTRODUCTION

Kidney stones remain a public health problem around the world and have a high rate of recurrence even with treatment[1]. The urine profile is one of the deciding indicators of urine stone formation as well as recurrence[2]. Consequently, clinical efforts should be focused on correcting the underlying abnormalities. One of these correctable abnormalities is hypocitraturia that is described as an isolated abnormality in up to 10% of calcium stone formers. Furthermore, it is also associated with additional abnormalities in 20% to 60% of stone formers[3-5].

The alkali citrate treatment has two major effects. At first, it increases urinary citrate levels in patients with calcium nephrolithiasis. Moreover, it provides an overall alkalization which is advantageous for patients with uric acid[6] and cystine stones[7]. The numerous benefits of the alkali citrate treatment, promotes its usage in a wide range of urinary system stones treatments.

In 1985, the Food and Drug Administration (FDA) approved potassium citrate (KCit) for the treatment of a wide variety of disorders that cause stone formation [8]. KCit is available in three forms in global pharmaceutical market: extended- release tablets, powder for dilution, and oral solution. Between these three forms, however the gastrointestinal (GI) side effects of the liquid preparations have been shown to be more than tablets (33% vs 9.3%)[9], but its effectiveness is better in patients with short intestinal transit such as chronic diarrheal syndromes[10].

Despite its widespread use, compliance to long term treatment with KCit is low, mainly due to its inappropriate salty taste suspected side effects[11] and inconvenience of bid (two times a day) or tid (three times a day) dosing specially with powder form that is necessary to be prepared. Considering the inconvenient use of the powder formulation and improvement of its tablet taste as declared by the manufacturer, we decided to evaluate the palatability and efficacy of simple form of KCit tablet (Urocitra) in groups of kidney stone forming patients with intolerance to powder form of this drug due to the unfavorable taste and upper GI side effects.

MATERIALS AND METHODS

This study was conducted as a quasi-controlled trial in stone formers referred to Labbafinejad stone clinic in 2015. Enrollment criteria included recurrent calcium stone formers whom only urinary metabolic risk factor was hypocitraturia (24-hour urinary citrate less than 320 mg/24 h) and were treated with potassium citrate powder, and were unable to tolerate this drug due to unfavorable salty taste and gastrointestinal complications. The patients were included only after at least one month of therapeutic interventions. Participants were excluded if they had renal failure (creatinine clearance < 60 mL/min), were taking on treatment that altering potassium metabolism (angiotensin-converting enzyme inhibitors, beta-blockers, potassium-sparing diuretics),

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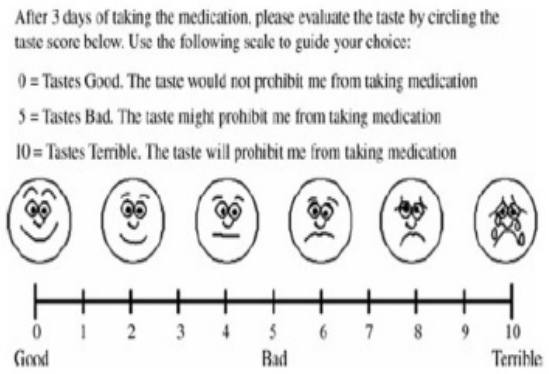

Figure 1. Visual Analogue Taste Scale for assessment the patient's satisfaction[30].

or consumed any kinds of citrate supplement within the last four weeks. Women were also excluded if they were in pregnancy or lactation. The institutional review board of the Urology and Nephrology Research Center (UNRC) approved the study protocols.

Twenty-three patients who met the mentioned criteria were enrolled in the study. Informed consent was taken from patients before participating in the study. Demographic information and initial questionnaires for all individuals were filled. Serum sample, fast urine and 24-hour urine were collected at baseline. To assess the drug influence on kidney function, serum potassium and creatinine were checked. Twenty-four hour urine was measured for volume, potassium, citrate and creatinine. Urinary pH was immediately determined on post-voiding spot urine sample using a pH electrode. Then, patients underwent treatment with potassium citrate tablets with the dosage of 6 tablets per day (2 tablets every 8 hours, each tablet contains 5 mili-equivalent citrate) for two weeks. At the end of the study, the analysis of serum metabolites, spot urine sample and 24-hour urine metabolites were repeated. The visual analog taste scale (VATS) (**Figure 1**) was used to assess patients' satisfaction. Furthermore, the amount of remained KCit tablet and measurement of 24-h urinary potassium were used as another criteria to evaluate patients' compliance [12]. It is noteworthy that all of our patients in this study have been advised to general dietary recommendation of preventive stone clinic protocol, at least three months before treatment with potassium citrate tablet.

Table 1. Demographic data of the patients and the prevalence of gastro-intestinal complications with powder form of potassium citrate (KCit).

	Mean ± SD[1] Number (percent)[2]
Age (years)	51.14 ± 9.89
Sex	
Male	16 (70%)
Female	7 (30)
Duration of initiation of stone disease (Years)	12.71 ± 9.74
History of stone intervention	
ESWL (yes)	8 (42%)
Surgery (Yes)	14 (74%)
Duration of KCit powder consumption before the study (months)	3.77 ± 4.43
Causes of intolerance to KCit powder	
Inappropriate salty taste	8 (35%)
Epigastric pain	7 (30%)
Nausea	6 (26%)
Heartburn	2 (9%)

1. SD: Standard Deviation. 2. Number for quantitative variables and percent for qualitative variables. 3. The collection of the dispersed time of consuming the powder form of Potassium citrate.

Method of analyzing serum and urine parameters: Serum creatinine were measured using a Jaffe kinetic method with BS-480 chemistry fully automated analyzer. Urine creatinine were measured using a Jaffe kinetic method with BT-4000 full-automated chemistry analyzer. Urinary citrate was determined by an enzymatic procedure using reagents from Darman Faraz Kave using Eppendorf Biophotometer. Serum and urine potassium were measured with the Eppendorf flame photometer and EasyLyte electrolyte analyzer, respectively. Urinary pH was measured with a pH electrode in urine samples immediately post-voiding using Bante 220 Portable pH Meter.

Statistical analysis was performed by SPSS 19. The normal distribution of the data was investigated through the Kolmogrov-smirnov test. As all variables were normally distributed, changes in patients' urinary metabolic profile and serum parameters before and after treatment with KCit tablet were identified by the paired t test. Significant changes were defined as p value < .05.

RESULTS

All the patients completed the study and their average age was 51.14 ± 9.89 (16 males and 7 females). The urinary metabolic profile and serum parameters of the studied population before and after KCit therapy were compared and the results are shown in **Table 1**. The patients' urinary pH increased significantly from 5.7 ± 0.6 to 6.1 ± 0.8 after treatment with KCit tablets (P = .006). Urinary citrate also showed a significant increase from 235.8 ± 190.2 to 482.5 ± 323.2 (P = .0002). In addition, mean urinary potassium showed significant increase (P = .002) as expected which indicates patients' compliance. No remarkable changes were observed in serum creatinine and potassium (**Table 2**).

All the individuals claimed that they consumed the tablets as prescribed. Only two patients, who had the history of gastrointestinal problems following food intake and most medications, experienced a little heartburn after consumption of KCit tablets, though it was tolerable for them with meals and they finished the delivered tablets.

The VATS score at baseline to assess the patients' satisfaction about KCit powder, was 8.35 ± 0.77 which represents "terrible" and after treatment changed to 2 ± 0.14, which accounts for "good" in this scale (P = .0001). As it is obvious from the results, patients' satisfaction significantly increased after intake of KCit tablets.

DISCUSSION

Kidney stone removal has been significantly facilitated by using the recently emerging non-invasive treatments[5]. Although these therapies- namely percutaneous nephrolithotomy and extracorporal shockwave lithotripsy- provide satisfactory results with associated acceptable rate of complications, they do not alter the underlying metabolic abnormality. Furthermore, stone recurrence is typically found post-treatment, even in

Table 2. The results of serum and urine analysis.

		Before KCit	After KCit	*p* value
	Total volume (ml)	1690 ± 473*	2050 ± 760	0.03
	pH 5.7±0.6	6.1 ± 0.8	0.006	
urine	Potassium (mg/day)	45.25 ± 22.5	75.27±37	0.002
	Citrate (mg/day)	235.8 ± 190.2	482.5±323.2	0.0002
	Creatinine (mg/day)	1.2 ± 0.5	1.1 ± 0.4	0.23
Serum	Potassium (mEq/L)	4.19 ± 0.4	4.15±0.4	0.81
	Creatinine (mg/dL)	1.18 ± 0.17	1.16±0.15	0.55

mEq: milliequivalent. ml: mili-litre. mg: mili-gram. KCit: Potassium Citrate.

those with a stone-free post-therapy status. In addition, following those therapies, the retained stone particles may aggregate or constitute a nucleus for new stone formation, thereby causing an elevated rate of stone growth. Based on the stone recursion frequency, the development of a medical prophylactic program to prevent recurrences is of utmost importance[5]. In addition, patient's compliance to medical recommendations of kidney stone clinic is another important factor, which affects the treatment outcomes. Our study revealed that the compliance of our patients to the tablet form of potassium citrate was satisfactory.

Potassium citrate has been used as a medical therapy of urolithiasis for more than two decades. Its effectiveness in treatment of urinary system stones has been reported in several studies[1,12]. Citrate is a known inhibitor of stone formation. In renal tubules citrate complexes with calcium, reduces the availability of ionic calcium to interact with oxalate or phosphate[13,14]. Moreover, citrate helps the inhibitory effects of macromolecular modulators of calcium oxalate crystallization processes, partly by interaction with Tamm-Horsfall protein[15]. In addition, citrate prevents crystal agglomeration and growth through its ability to bind to the crystal's surface, and it may prevent adhesion of calcium oxalate to renal epithelial cells[16]. Low urinary potassium is related to hypocitraturia[17], therefore one of the advantages of potassium preparations is either prevention or correction of hypokalemia. Also simultaneous administration of citrate with thiazide agents can be more effective in lowering urinary calcium excretion[18]. Lastly, potassium citrate is a meaningful treatment for uric acid and cystine nephrolithiasis, as it provides an alkali load which increases urinary pH, one of the principal determinants of uric acid and cystine solubility[5]. Also with considering the effect of KCit in delaying of the urease-induced crystallization, it may be useful in urinary infection stones[19].

Several authors supported the benefit of alkaline citrates in patients with renal calculi. A meta-analysis conducted by Phillip et al.[1], including seven randomized controlled trials with a total of 477 participants in preventing stone recurrence through the long-term administration of citrate preparations (at least six months), have been shown that KCit not only reduced the stone size, but also reduced new stone formation significantly, and increased citrate levels. In another review, Mattle et al.[20] on a short-term therapy (between 1 to 12 weeks) with alkali citrate[21-28] showed that after taking potassium citrate, urine pH increased by 1- 14% comparing to pretreatment values. The same was true for urinary citrate, which increased by between 27%- 94%.

Despite the significant therapeutic effects of alkali citrate, the main limitation of its widespread usage is the relatively low GI tolerability of available alkali citrate preparations. In one study, only 62% of patients consumed low doses of potassium citrate in long term [11]. In a review by Mattle et al., overall, 17% of subjects on placebo and 33% of treated patients with alkali citrate, in order to prevent stone recurrence, prematurely left the randomized trials due to drug side effects. Adverse effects that reduce treatment compliance included upper gastrointestinal disturbances (epigastric pain, heartburn, and nausea), loose stools and rash[1]. The problems with compliance are poorly reported in the literature, but some reasons cited are high cost, bad taste, and the inconvenience of bid or tid dosing [29,30]. Thus, the development of more tolerable alkali citrate preparations remains an important issue in the treatment of urinary stones. In this study, comparing the price of these two forms of potassium citrate shows that the cost of taking the tablet form is about 30% higher than powder (1.09 $ vs. 0.83 $); however, considering the better tolerability of tablet form and reported unused powder form of this drug, it is obvious that this amount of higher cost of tablet form is acceptable.

Whereas in middle Europe there is a preference for potassium sodium citrate, in North America (US, Canada) KCit is the favored preparation. The result of the criticism levelled against potassium sodium citrate by US authors, is that sodium moiety causes increased calciuria. More specifically, sodium may abolish the decrease in calciuria, one of the beneficial effects possibly exhibited by potassium citrate[29]. In our country, currently the only available preparation of KCit is the powder form, which some patients cannot tolerate it, especially due to its unappealing salty taste. The results of this study showed that the transformation of powder formulation into KCit tablets, improves the taste of KCit, facilitates taking the drug, and reduces gastrointestinal complications. There is no other study for comparison, the results of this study illustrate that the compliance for KCit tablets was satisfactory with regard to the subjects who took the tablet forms, and completed the study[30]. In some countries, there are also other forms of the medication such as the slow-release preparation, which is better tolerated. Other researchers have added an artificial sweetener (Splenda) to the powder form to enhance the taste property and compliance[30]. Our study confirms that changing the powder form to KCit tablet results in more tolerability, however, the question that whether this effect is truly durable in long term has remained unanswered, since if these changes sustain over time, there will be a significant reduction in kidney stone recurrence rate.

The small sample size and short follow-up time could be considered as shortcomings and limitations of the study. Therefore, a long-term study using higher doses of this easily tolerable medication is suggested to test and challenge our study results.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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