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Lime juice as a dietary alternative to mist potassium citrate for urine alkalinisation: A prospective, cross-over clinical trial

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Abstract

Introduction: Urinary citrate is a potent inhibitor of urinary crystallization that is freely filtered in the proximal tubule of the kidney. We aimed to investigate the effect of citrate supplementation with fresh lime juice on the urinary pH and calcium excretion level among healthy individuals compared with that of mist potassium citrate.

Methods: In this prospective, cross-over single-centre study, 50 healthy medical student volunteers were randomly allocated to two treatment arms. One arm was prescribed with potassium citrate, while the other arm received citrate supplementation with a home preparation of fresh lime juice. The urinary pH and calcium-to-creatinine ratio (uCa/uCr) were measured at baseline and after 7 days of treatment. This was followed by a washout period of 2 weeks, after which each participant crossed over to the other treatment arm, and the urinary measurements were repeated.

Results: Potassium citrate significantly increased the urinary pH among all participants, while fresh lime juice did not. Both fresh lime juice and potassium citrate reduced the uCa/uCr, although this effect was not significant.

Conclusion: Fresh lime juice is not as effective as potassium citrate in improving the urinary pH and calcium excretion level of healthy individuals. Therefore, it should be used as an adjunct rather than an alternative to potassium citrate.

Introduction

Urinary tract stone disease is a major health concern worldwide, and a recurrence rate of up to 75% makes it a substantial economic burden.[1] Correctable metabolic abnormalities are important causes of recurrent urinary tract stone formation. Hypocitraturia together with other metabolic abnormalities contributes to 15–63% of recurrent stone formations.[2] The urinary pH also affects the supersaturation of solutes, leading to stone formation. In particular, an acidic urinary pH promotes the formation of uric acid and cysteine stones, while an alkaline urinary pH causes crystallisation of calcium and phosphate.[3]

Urinary citrate is a potent and naturally occurring inhibitor of urinary crystallisation that is freely filtered in the proximal tubule of the kidney.[2] Citrate binds to the calcium oxalate crystal surface, inhibiting crystal growth and aggregation.[4]

Mist potassium citrate is the currently recommended prophylaxis for secondary prevention of urolithiasis.[2,5] Absorbed citrate is metabolised to bicarbonate to enable systemic alkali loading, decrease bone resorption and increase renal calcium reabsorption.[2] Potassium citrate increases the urinary pH and citrate level and decreases urinary calcium excretion to an extent that the probability of stone relapse is reduced.[6] A treatment dose of potassium citrate of 30–100 mEq/L per day can cause gastrointestinal side effects such as nausea, vomiting, abdominal ache and diarrhoea.[6] Up to 48% of alkali citrate-treated patients have withdrawn prematurely from studies because of intolerable side effects[5] causing problems with patient compliance.

An alternative treatment is the use of citrus fruits rich in citric acid, which may have fewer gastrointestinal side effects. Dietary citrate may be used as an adjunct to standard pharmacotherapy or as a primary therapy for patients who cannot tolerate potassium citrate or are non-compliant.[7] A study that quantitatively assessed the citric acid load among different fruit juices has shown that

lemon and lime have the highest citrate load among commercially available fruit juices.[8] An increased urinary excretion of citrate after lemonade consumption has been demonstrated in patients with urolithiasis.[9] Although the citrate load of lime is comparable with that of lemon, no study has yet compared the efficacy of citrate-rich tropical fruits such as lime with that of potassium citrate.

Lime (*Citrus aurantifolia*), an originally wild species from the *Rutaceae* family, is a common plant in Southeast Asia. It is rich in citrate and antioxidants such as ascorbic acid, polyphenols and flavonoids.[10] The addition of lime juice in water consumed throughout the day could add to the overall fluid intake, resulting in increased urine output and reduced urine supersaturation.[11]

We aimed to investigate the effect of citrate supplementation with fresh lime juice on the urinary pH and calcium excretion level of healthy individuals compared with that of potassium citrate to determine whether lime juice could be a dietary alternative to potassium citrate.

Methods

This prospective, randomised, non-blinded, cross-over clinical trial was conducted among healthy volunteers from Universiti Kebangsaan Malaysia Medical Centre (UKMMC) from September 2019 to August 2020. The research protocol (ID: JEP-2019-078) was approved by the Medical Ethics Board of UKMMC.

The study sample size was determined on the basis of a previous study[12] that demonstrated the ability of an oral lime-based regimen to significantly increase the urinary pH. The Power and Sample Size Calculator was used to determine the sample size that could achieve a study power of 0.9 and a significance level of 0.05. With an anticipated 10% drop-out rate, the estimated sample size was 50.

A presentation on the prevalence and socioeconomic burden of urinary tract stone disease and details of the study proposal was conducted at UKMMC to inform potential study participants about the clinical trial. Individuals who were interested in participating in the study were provided with detailed patient information sheets on the main and side effects of lime juice and potassium citrate as well as dietary caution during the study period. A total of 50 healthy medical student volunteers were recruited for this study. Individuals who were pregnant, those with comorbidity (e.g. cardiac or renal disease needing fluid restriction), those with pre-existing urinary tract disease, those who were on medication or dietary supplementation and those with allergy or intolerance to potassium citrate were excluded from the study. By including healthy participants, we were able to minimise the effects of comorbidity on the absorption, metabolism and urinary excretion of medications. Informed consent was obtained from all participants, and they were free to withdraw from the study at any point.

For each participant, first morning spot urine samples were collected to establish the baseline urinary pH and calcium level. Urinalysis was performed in our laboratory using the Abbott c8000 (Abbott Laboratories (M) Sdn Bhd, Petaling Jaya, Selangor Darul Ehsan, Malaysia) and Cobas u601 (Roche Services (Asia Pacific) Sdn Bhd, Subang Jaya, Selangor, Malaysia) urine chemistry systems. The urinary calcium level was quantified using the urinary calcium-to-creatinine ratio (uCa/uCr).

Simple random sampling was used to assign each participant to one of two treatment arms. Group A was prescribed with the standard treatment regimen of 14 mL potassium citrate three times daily for 7 days. The potassium citrate preparation contained 200 mg anhydrous citric acid in 5 mL solution, amounting to 560 mg citric acid in 14 mL potassium citrate solution. On day 8, first morning spot urine samples were collected from each participant to determine the post-treatment urinary pH and uCa/uCr.

Group B was shown how to make a home preparation of fresh lime juice. Penniston et al.[8] quantitatively assessed citric acid from different tropical fruits and showed that the juice of freshly squeezed lime contains 45.8 g/L concentration of citric acid. In this study, we first determined the amount of juice that could be extracted from each lime fruit and found that two full-sized lime fruits produced an average of 10 mL (range: 8–13 mL) of juice. To ensure consistency and compliance, we instructed each participant to consume a home preparation of 10 mL fresh lime juice extracted from two full-sized limes, containing 460 mg citric acid, mixed with 250 mL water three times daily for the next 7 days. On day 8, first morning spot urine samples were collected to

determine the post-treatment urinary pH and uCa/uCr.

All participants were provided with a medication adherence sheet that they must use during the study period. They were required to mark off the appropriate column after consumption of the citrate preparation. This sheet was reviewed, and the degree of compliance with treatment was recorded. At the end of the first treatment period, all participants underwent a washout period of 2 weeks to clear any effects potassium citrate and lime juice might have had on the urinary parameters.

After the washout period, each participant crossed over to the other treatment arm. First morning spot urine samples were collected to determine the baseline urinary pH and uCa/uCr. Thereafter, group A consumed the same home preparation of fresh lime juice, while group B consumed 14 mL of potassium citrate three times daily for 7 days. On day 8, first morning spot urine samples were recollected to determine the post-treatment urinary pH and uCa/uCr.

All baseline and outcome data were tabulated using Microsoft Excel. As the study was a cross-over trial, each patient served as his/her own control. Statistical analysis was performed using the Statistical Package for the Social Sciences version 22.0. Means and standard deviations were used for continuous variables with a normal distribution. The outcomes between the two treatment arms were assessed using an independent samples t test, with a P value of <0.05 considered as statistically significant.

Results

A total of 50 healthy medical student volunteers, comprising 25 men and 25 women, were enrolled in the study. The mean age of the participants was 23.5 years (range: 22.0–25.0 years). **Table 1** summarises the demographic characteristics of the study population. Three male participants opted to withdraw from the study, as they were unable to tolerate the taste of potassium citrate. Forty-seven participants completed the study and were included in the final analysis. Medication adherence was evaluated using a self-report medication adherence sheet. The compliance rate for potassium citrate was 94%, while that for lime juice was 100%.

Table 1. Demographic characteristics of the participants.

Characteristics	n=47 (%)
Age (year)	
20–22	31 (65.9)
23–25	16 (34.1)
Sex	
Male	22 (46.8)
Female	25 (53.2)

Table 2 shows the mean urinary pH at baseline and after 7 days of oral consumption of potassium citrate and home preparation of fresh lime juice. The mean urinary pH at baseline and after oral consumption of potassium citrate was 6.2±0.8 and 6.7±1.0, respectively. The independent samples t test showed that the mean urinary pH significantly increased (P=0.025) after oral consumption of potassium citrate. The mean urinary pH after oral consumption of the home preparation of fresh lime juice was 5.9±0.8. The independent samples t test revealed that the mean urinary pH did not significantly change (P=0.148) after oral consumption of lime juice. Figure 1 shows the mean urinary pH at baseline and after treatment in both treatment arms.

Table 2. Urinary pH and uCa/uCr at baseline and after 7 days of oral consumption of potassium citrate and home preparation of fresh lime juice (n=47).

	Potassium citrate				P-value	Lime juice				P-value
	Pre-treatment		Post-treatment			Pre-treatment		Post-treatment		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Urine pH	6.200	0.800	6.700	1.000	0.025	6.100	0.800	5.900	0.800	0.148
uCa/uCr	0.211	0.125	0.180	0.115	0.214	0.259	0.215	0.212	0.114	0.187

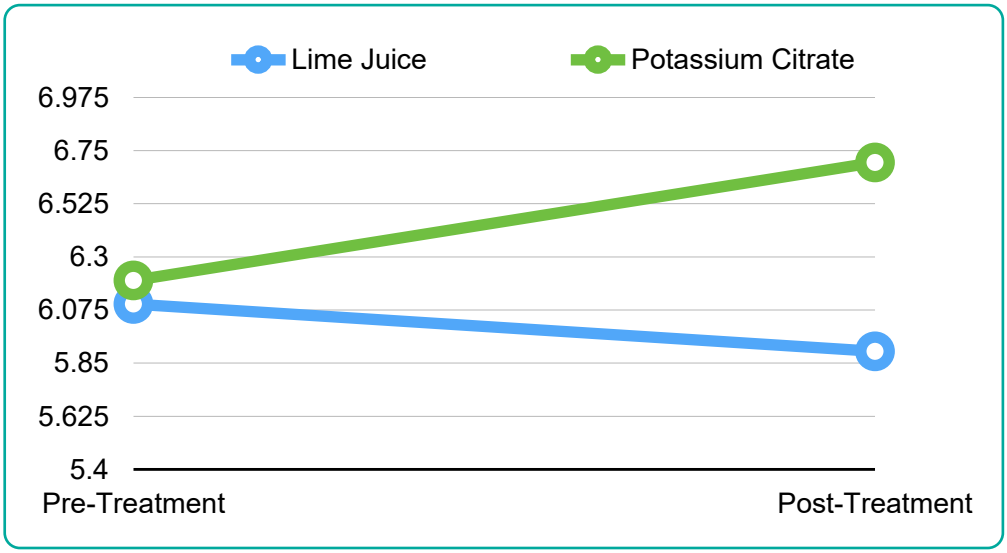

Figure 1. Mean urinary pH at baseline and after 7 days of oral consumption of potassium citrate and home preparation of fresh lime juice (n=47).

Table 2 also shows the mean uCa/uCr at baseline and after 7 days of oral consumption of potassium citrate and home preparation of fresh lime juice. The normal uCa/uCr is <0.14, and values exceeding 0.20 are often found in patients with hypercalciuria. The baseline mean uCa/uCr among the healthy young volunteers was >0.20.

The mean uCa/uCr after oral consumption of potassium citrate and home preparation of fresh lime juice was 0.18±0.12 (P=0.214) and 0.21±0.11 (P=0.187), respectively. Although there was a reduction in the mean uCa/uCr in both treatment arms, the result was not significant in the independent samples t test.

Figure 2 shows the changes in the mean uCa/uCr before and after treatment in both treatment arms. Cohen's d was used to calculate the effect size, which was 0.258 for the potassium citrate treatment arm and 0.273 for the fresh lime juice treatment arm.

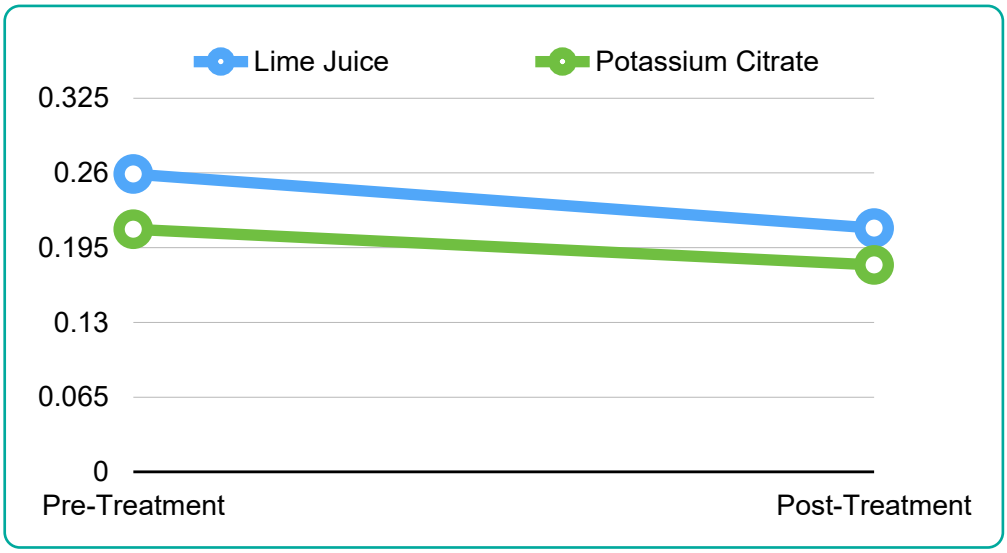

Figure 2. Mean uCa/uCr at baseline and after 7 days of oral consumption of potassium citrate and home preparation of fresh lime juice (n=47).

Discussion

Non-surgical factors that prevent urinary tract stone formation include increased fluid intake to produce a urine output of at least 2 L; reduced urinary calcium, oxalate and uric acid excretion; increased urinary citrate excretion; and an alkaline urinary pH.[13] Herein, we aimed to investigate the effects of fresh juice from lime, which is a common plant in Southeast Asia, to determine whether it could be a dietary alternative to potassium citrate.

In our study, there was no significant difference between the mean urinary pH at baseline and after fresh lime juice consumption for 7 days. In comparison, the mean urinary pH significantly increased from 6.2±0.8 to 6.7±1.0 after the standard treatment with potassium citrate for 7 days. Our findings are similar to other reports on a smaller number of patients with urinary tract stones and hypocitraturia showing that lemonade therapy increased the urinary volume but did not induce urinary alkalinisation.[13] Other studies have investigated the effects of citrus and non-citrus fruit juices on urinary parameters with widely variable results.[12,14]

The differences between the effects of fresh lime juice and potassium citrate on the urinary pH could be explained as follows. First, while the content of citric acid in fruit juices can be standardised, systemic alkalinisation depends on the metabolisation of citric acid to bicarbonate, and there is a wide variation in the absorption and metabolisation of citrate in fruit juices. Tosukhowong et al.[12] demonstrated that the urinary pH increased after lime consumption because a lime powder concentrate added with pharmaceutical-grade potassium was used instead of fresh lime juice. Second, the efficacy of mist potassium citrate in urinary alkalinisation could also be attributed to the presence of potassium.[15] Wabner et al.[16] and Odvina[17] showed that orange juice consumption increased the net gastrointestinal alkali absorption, urinary pH and urinary citrate level, yielding an alkali load similar to that of potassium citrate. This is because citrate in orange and grapefruit juices is complexed mainly by potassium,[17] while that in lime and lemon juices is ingested as citric acid. These indicate that the accompanying cation plays an important role, and if the bicarbonate formed in the liver is neutralised by a proton, there is no net alkalinisation effect.[18] Third, although patients who experience gastrointestinal side effects may be unwilling to continue with potassium citrate treatment, pharmacologically manufactured mist potassium citrate and potassium-fortified lime powder provide a more accurate and consistent dose of potassium and citrate, which is difficult to match with freshly squeezed lime juice, as there is a variation in the age of the fruit and dilution of the home preparation.

The uCa/uCr has been generally used as a surrogate marker for 24-hour urinary calcium excretion. Paccaud et al.[19] showed that first morning and evening spot urine samples showed the greatest correlation with 24-hour urinary calcium excretion in healthy individuals aged 6 to 16 years. In our study, we found that the mean random uCa/uCr decreased from 0.26±0.22 to 0.21±0.11 after fresh lime juice consumption for 7 days. Similarly, the mean uCa/uCr decreased from 0.21±0.12 to 0.18±0.12 after the standard treatment with potassium citrate for 7 days. However, the reduction in the mean uCa/uCr in both treatment arms was not significant in the independent samples t test. This finding is similar to that of Tosukhowong et al.[12] who demonstrated a reduction in urinary excretion of calcium and oxalate after consumption of potassium-fortified lime powder, but which was not significant, and the findings of other studies using citrus and non-citrus fruit juices.[14] In our study population, Cohen's d for evaluating the effect size of the change in the mean uCa/uCr was 0.2, indicating a small effect. The treatment duration might not have been sufficient; a significant change could be obtained with a longer test period. In addition, urinary calcium excretion is dependent on dietary variations in animal protein and sodium intake, which we were unable to control for in an actual clinical setting.

Incidentally, we found that the mean baseline uCa/uCr among the healthy young volunteers was >0.20. As the normal value for the uCa/uCr is <0.14, and values exceeding 0.20 are often found in patients with hypercalciuria, this finding indicates an unusually high prevalence of hypercalciuria among our study population. Such finding could be related to a diet composed of fast-food rich in animal protein and salt intake common among medical students, long working hours with reduced physical activity, the effect of movement control orders owing to the coronavirus disease pandemic enforced during a part of the study period on the dietary habits and physical activity of the participants or the composition of the local water supply. Hussein et al.[20] investigated

the 24-hour urinary parameters among patients with urinary tract stones from northeast Peninsular Malaysia and found that 14.5% of 96 patients had hypercalciuria. In our study population, the prevalence of hypercalciuria was 40.4%. Gul et al.[21] found that the prevalence of hypercalciuria among school-aged children in the northern region of Turkey was 4.7% and was higher among populations living in rural areas and those with obesity. They concluded that urinary calcium excretion varies among different geographical regions and not merely countries. This warrants further investigation of the prevalence of hypercalciuria among healthy populations, especially since Malaysia is located within the Afro-Asian stone-forming belt.[22]

The compliance with fresh lime juice treatment was better than that with mist potassium citrate treatment among our study population. Fresh lime juice also increased the overall fluid intake compared with potassium citrate and had fewer added calories than other fruit juices. It may be a useful dietary alternative in patients with calcium phosphate stones who do not require urinary alkalinisation.

The strength of our study lies in the number of participants recruited, which exceeded that in previous studies. Both treatment arms were well matched for age and sex, and as this was a cross-over trial, each participant served as his/her own control, obviating other confounding factors such as body mass index. Furthermore, the study was conducted among healthy individuals to determine whether lime juice could be a primary preventive alternative in tropical countries with a high prevalence of urinary tract stone disease. In contrast, the weakness of the study was the difficulty in providing an equivalent dosage of citrate to the study participants, as an increase in the volume of lime juice would result in poor compliance. There were also variations in fluid intake, dietary animal protein and salt ingestion and urine output volume. We did not enforce a consistent fluid intake or metabolic diet, as we wanted to conduct our study in an actual clinical setting.

Conclusion

Fresh lime juice is not as effective as mist potassium citrate in urinary alkalinisation. Both lime juice and potassium citrate minimally reduce urinary calcium excretion, although this reduction is not significant. Lime juice is generally well tolerated with no gastrointestinal side effects. As it increases overall fluid consumption with fewer added calories, it may be a useful dietary adjunct in the primary prevention of urinary tract stones.

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Author contributions

KS and PN conceived and designed the study. AA contributed to the implementation of the study and obtained funding. KS, MMM and UA carried out the investigation and collected data. KS and AA performed the data analysis. KS and PN wrote the manuscript.

Ethical approval

The research protocol (ID: JEP-2019-078) was approved by the Medical Ethics Board of Universiti Kebangsaan Malaysia Medical Centre.

Conflicts of interest

All authors declare no conflicts of interest.

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Data sharing statement

Raw data will be available upon request.

How does this paper make a difference in general practice?

- This paper highlights the benefits of lime juice, including a minimal reduction of urinary calcium excretion and better patient compliance, making it a useful dietary adjunct.
- The findings provide useful information for counselling patients on primary and secondary prevention of urinary tract stones.
- There is a lack of efficacy of dietary supplements compared with that of pharmacologically manufactured preparations that provide a more accurate and consistent dose of citrate.

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