ORIGINAL RESEARCH

24-Hour Urinary Citrate Determination Among Filipino Urinary Stone Formers After Potassium Citrate Therapy: a Prospective, Cohort Study

Harris L. Lim, MD and David T. Bolong, MD, FPUA

Section of Urology, Department of Surgery, University of Santo Tomas Hospital

Objective: Urolithiasis, a common problem in medicine, poses a significant burden with prevalence of 1-15%. Potassium citrate therapy has become one of the cornerstones of medical stone management with hypocitraturia being the most common metabolic problem in stone formers. The authors determined the effects of potassium citrate on urinary metabolic profiles and its impact on stone burden among Filipino stone formers.

Patients and Methods: This is a prospective, cohort study in patients seen at the UST Hospital between 2016 and 2018. Twenty-four hour urine citrate levels, stone sizes and urine pH pre-therapy and post-therapy were analyzed.

Results: Significant changes in urinary citrate, pH and stone sizes were noted as soon as 3 months after the onset of therapy. These changes included increase in urinary pH (6.1 to 6.7; p=0.001), increase in urinary citrate (109.1 to 253.4mg/day; p<0.001) and decrease in stone size (0.56 to 0.37cm; p=0.037). The changes in the urine citrate and the changes in the stone size were not correlated using the Pearson correlation scatter plot.

Conclusion: Potassium citrate therapy provides a significant alkali and citraturic treatment among Filipino stone formers. However, there is no significant correlation between changes in stone size and changes in urine citrate level.

Keywords: Potassium citrate therapy, urolithiasis

Introduction

Stone disease, with a lifetime prevalence of 1% to 15%, is a global phenomenon. With recent data, the incidence increase worldwide nearly doubled from 1994 to 2010.[1] Although usually asymptomatic, this may cause renal colic, urinary tract obstruction, infection, procedure-related morbidity and renal failure. Despite the availability of various procedures, medical management is still important.[2] Hence, a safe and effective medical therapy in preventing urolithiasis must always be considered. Citrate, a major inhibitor of stone formation by a variety of actions, must be well-studied. Well-known actions that inhibit stone formation include forming a complex with calcium reducing its availability to act with oxalate or phosphate and the prevention of calcium oxalate precipitation and nucleation.[1] It is known that hypocitraturia has been involved as a causative factor in 19-63% of urolithiasis.[3]

Hypocitraturia, common among stone formers, is an important and correctible abnormality. It exists as an isolated abnormality in 10% of calcium stone formers and with other abnormalities in 20-60% of stone formers.[7] Several

studies have proven that low urinary citrate level is frequent in recurrent stone formers and potassium citrate prevents the formation of stones. Hypocitraturia, according to some studies, has been defined as urinary citrate levels of less than 300mg/day[4,5] and effect of potassium citrate therapy in increasing urinary citrate level among Caucasians has been established in some studies.[15,16] However, Filipinos, compared with Caucasians have different diet, genetic makeup and environment that could contribute to urinary formation of stones and reaction with potassium citrate therapy. Its effect on urine citrate level among Filipino stone formers has not been established. Hence, a more extensive evaluation should be conducted in these after initiation of potassium citrate therapy. According to the European Association of Urology, the high risk stone former requires specific metabolic evaluation and subsequent stone-specific recurrence prevention.[8] However, currently, metabolic evaluation, such as 24-hour urinary citrate levels is not routinely requested especially after initiation of potassium citrate therapy. Arguments still continue for indications of metabolic evaluation and no standardized urine citrate level has been established for Filipino stone formers on potassium citrate therapy.

With different medical and surgical treatment of urolithiasis, recurrence rate remains as high as 50% in 10 years. Citrate is a normal component of urine and several studies showed that low levels of this substance is a factor for stone formation and recurrence.[6] Hence, medical treatment such as potassium citrate is important and will help prevent formation and recurrence of stones. Potassium citrate should be given at doses 30-60meq/ day in two to three divided doses. With studies done by Song, et al. and Unno, et al. 30-60 meq/day of potassium citrate was used to determine its effect on the urine citrate level among stone formers.[15,16] This study aims to determine the 24-hour urinary citrate levels among Filipino stone formers after initiation of potassium citrate therapy. With this goal, providing a urine citrate level among Filipino recurrent stone formers on potassium citrate therapy, will guide the physician on the indications and dose of potassium citrate to be prescribed in relation to the 24 hour urinary citrate level that can be a basis of the follow-up of patients with urinary stones while on medical management.

Patients and Methods

In this study, Variable of Interest included mean 24 hour urinary citrate level before and after 2nd, 6th and 12th month of potassium citrate therapy.

Patient Selection

The study employed a prospective cohort design. Between June 2017 and August 2018, patients of UST Hospital were selected as subjects. Written informed consent was obtained from each patient and details of procedure were explained.

Inclusion criteria included adult Filipino, age 20-70 years old, history of recurrent stone formation, with either radiologic or ultrasound findings of urolithiasis, history of spontaneous passage of stone, and previous surgical intervention.

Exclusion criteria included patients with renal insufficiency, urinary tract infection, with current medications taken such as diuretics, potassium citrate, herbal medications that may affect citrate level.

Patients were recruited from a single Urologist at private Urology clinic at the hospital. All patients had a detailed history taken and physical examination performed. They underwent urine dipstick test to confirm the presence or absence of UTI. They had KUB ultrasound or CT stonogram done to confirm the presence or absence of urinary tract stones at the time of the study.

Intervention

Baseline characteristics were measured including presence of stones, urine pH and 24-hr urinary citrate level.

The primary outcome measured was a 24-hour urinary citrate level that was obtained on the day of the study. The study was done in the Urology clinic and laboratory of the university hospital.

Potassium citrate therapy (30meq /day) was initiated and after 2 months, 6 months and 12 months of potassium citrate therapy, 24-hour urine citrate level was measured. Each study participant received clear instructions from the Urology nurse about the collection of a 24 hour urine sample, proper handling of urine and was provided with a special container. Subjects were instructed to collect the urine sample while on their usual diet and to avoid any medical therapy other than potassium citrate that may alter the urinary citrate levels. Twenty four hour urine samples were collected in appropriate containers placed at temperature 4-6°C. Twenty four - hour urinary citrate excretion was measured by enzymatic citrate lyase technique (Bergmeyer method) with spectrophotometer (Spectronic Genesis 20) at the University of Santo Tomas Laboratory department. All the collected data were analyzed and descriptive analysis was used to calculate mean and standard deviation.

Statistical Analysis

Means and standard deviation summarized the age, urine pH and urine citrate of patients, and stone size while counts and percentages summarized the gender and the number of patients with normal urine citrate before and after treatment. Paired t-test was used to determine if there are significant changes in the urine citrate and stone size before and after treatment. Pearson correlation was used to determine if change in urine citrate and stone size is correlated.

P-values less than 0.05 indicate significant increase. Statistical tests were performed using Stata ver 13.0.

Results

A total of 26 patients included in the study had a mean age of 54.8 years (range, 32 to 79), composed of 14 (53.8%) males and 12 (46.2%) females (Table 1)

The urine pH of patients significantly increased (p=0.001) after a two-month treatment. Before the treatment, the patients had a mean urine citrate of 109.1 (range, 8.8 to 273.0). After the treatment, the patients had a mean urine citrate of 253.4 (range, 61 to 706). The treatment significantly increased (p<0.001) the urine citrate of the patients at an average of 144.3 mg [95% CI: 74.9 to 213.6].

Moreover, there is a significant increase (p=0.008) in the number of patients who had normal urine citrate, from 0% to 30.8%. (Table 2)

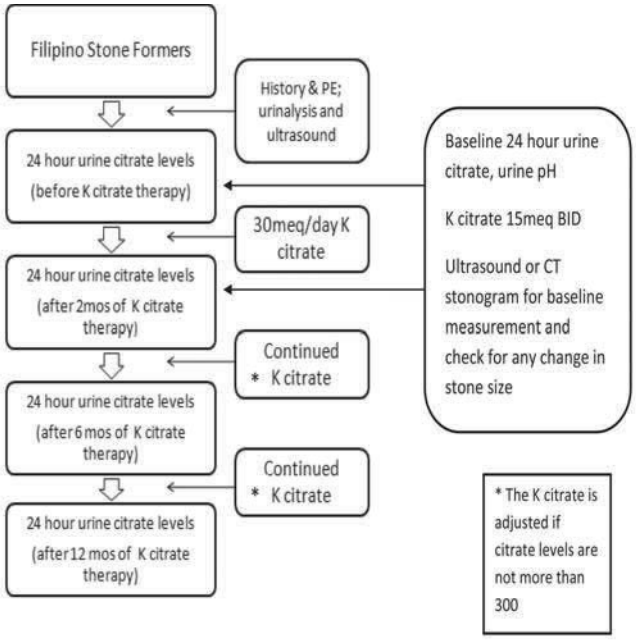


Figure 1. Flowchart

Table 1. Demographic profile of patients

Demographics	Summary
Number of Patients	26
Age (years)	54.8 ± 13.5
Gender: Male	14 (53.8%)

Values expressed as mean ± SD, or counts (%).

Table 2. Urine characteristics before and after two-month treatment

Urine pH and	Pre-Tx	Post-Tx	p-value
Citrate			
Urine pH	6.1 ± 0.6	6.7 ± 0.9	0.001
Urine citrate (mg)	109.1 ± 75.6	253.4 ± 176.2	<0.001
Normal (urine citrate >300 mg)	0 (0%)	8 (30.8%)	0.008

The mean urine citrate of the 10 patients after 6 months significantly increased (p=0.016). This shows that after 6 months of treatment, their urine citrate increased, at an average, by 168.6mg [95% CI: 40 to 297.2]. But the proportion/number of patients with normal urine citrate did not increase significantly (p=0.500). (Table 3)

The mean urine citrate of the 4 patients after 12 months did not significantly increase (p=0.069). Additionally, the proportion/number of patients with normal urine citrate did not increase significantly (p=0.250). (Table 4)

Table 3. Urine citrate after 6 months.

		6-month		
	n	Pre-Tx	Post-Tx	p-value
Urine citrate (mg)	10	93.6 ± 73.8	262.2 ± 190.3	0.016
Normal		0 (0%)	2 (20%)	0.500

Table 4. Urine citrate after 12 months.

	n	Pre-Tx	Post-Tx	p-value
Urine citrate (mg)	4	74.6 ± 61.7	269.9 ± 169.2	0.069
Normal		0 (0%)	3 (75%)	0.250

Power and Sample Size

Results showed that there was an increase of 144.3 mg (the standard deviation of the increase is 171.72). Power analysis for a paired-means test and standard of the differences were used and gain the power of 0.9844 which shows that the sample size of 26 is enough to conclude that the treatment, indeed, increased the urine citrate. (Figure 2)

A total of 19 patients were included in the analysis of the stone size. The seven excluded patients had calcinosis (3) or had unavailable information on their stone size (4). The mean stone size of the 19 patients before and after the treatment was 0.55 cm (range, 0.2 to 0.9) and 0.37 (range, 0 to 1.00), respectively. This is sufficient

```
. power pairedmeans, sddiff(171.716) altdiff(144.25385) n(26)

Estimated power for a two-sample paired-means test
Paired t test
Ho: d = d0  versus  Ha: d != d0

Study parameters:

        alpha =    0.0500
            N =        26
        delta =    0.8401
           d0 =    0.0000
           da =  144.2538
         sd_d =  171.7160

Estimated power:

        power =    0.9844
```

Figure 2. Computation of power and sample size.

Table 5. Stone size.

	Pre-Tx	Post-Tx	p-value
Stone size (cm)	0.55 ± 0.23	0.37 ± 0.37	0.037

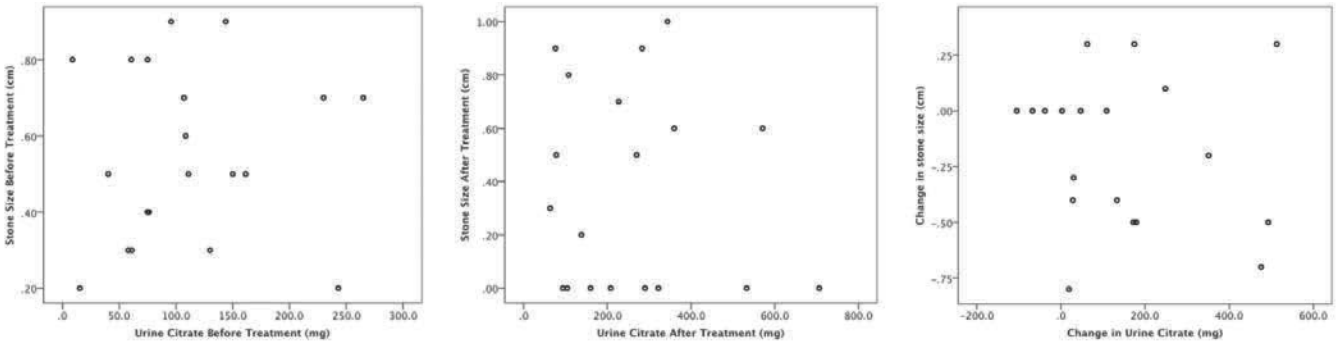
evidence that there was a significant decrease (p=0.037) in the mean stone size of patients after the 2-month treatment, which indicates that, at an average, the stone size decreases by 0.18 cm [95% CI: 0.01 to 0.34]. (Table 5)

A total of nine (47.4%) patients had decreased stone size, six (31.5%) patients had no change in the stone size, and four (21.1%) patients had increased stone size after the treatment.

It was not evident that the urine citrate and stone size are correlated before (r = 0.055, p=0.817) and after (r = - 0.103, p = 0.674) the treatment. Moreover, the changes in the urine citrate and the changes in the stone size are not correlated (r = 0.151, p = 0.537). (Figure 3)

Discussion

Nephrolithiasis, a common problem encountered in medicine poses a significant burden. Medical therapy for prevention of stone recurrence is more effective than conservative measures. According to Suarez, et al. medically-treated patients had a significantly greater remission rate than untreated patients.[9]



(a) (b) (c)

Scatterplots of the urine citrate and stone size (a) before, (b) after treatment, and (c) their changes

Figure 3. Correlation of stone size and urine citrate.

Approximately, 75% of patients with nephrolithiasis have calcium stones which may have multiple metabolic abnormalities including hypocitraturia. Among Filipino patients with nephrolithiasis, a study by Arcinas, et al. concluded that mixed hypocitraturia was the most common abnormality followed by pure hypocitraturia.[3]

In the clinical setting, potassium citrate remains the mainstay of medical treatment for nephrolithiasis by acting as an inhibitor of crystallization of stone forming salts such as calcium oxalate, calcium phosphate and uric acid. According to American Urological Association guidelines, clinicians should offer potassium citrate therapy to patients with recurrent stones and all patients with hypocitraturic nephrolithiasis of any etiology.[10] In a study by Arcinas, et al., alkali citrate as medical therapy in the prevention and dissolution of calcium nephrolithiasis showed a reduced risk of stone recurrence and effectiveness in dissolving existing stones.[2]

Renal stone formation involves different phases, urinary inhibitors and promoters. Known inhibitors are citrates, magnesium, pyrophosphate, Tamm-Horsfall proteins, glycosaminoglycans and high urine volume.[1] Hypocitraturia, a correctible abnormality is found in 15-63% of patients with nephrolithiasis. Potassium citrate therapy demonstrated to be the best option for management of calcium nephrolithiasis in hypocitraturic stone former. It is safe and effective. It also plays a significant role in the medical management of urolithiasis by inhibiting stone formation by increasing its solubility through forming salts. It is known that this medication increases urine pH and urine citrates, and decreases stone recurrence in recent studies. A study by Leitao, et al. noted 68% remission rate and 93% decrease in stone formation among stone formers who received potassium citrate for a mean duration of 41 months.[11] It is necessary to monitor urinary factors such as citrate level in individuals with calcium oxalate stones while on medical therapy. However, there is still no established 24-hour urine citrate level that should be maintained, among Filipino stone formers, especially with patients taking potassium citrate. A comparative study of urinary citrate level by Halili, et al. among Filipino stone formers vs non-stone formers, the 24-hour urine citrate level of 40 patients showed significant difference.[12] Another study done by Catipay, et al. done in 1997 with 32 patients, showed that the stone former group has significantly lower urinary citrate levels than the non-stone former group.[6] With these local studies, they established urine citrate level among Filipino stone formers. However, recent data, among Filipino stone formers regarding the effect of potassium citrate therapy in terms of 24-hour urine citrate level, is still lacking and not well-established. Among Filipino stone formers, with different metabolic function, a question has been raised as to whether this effect is truly effective and significant.

The authors noted a significant increase in the urinary pH and urine citrates in patients treated with potassium citrate on the 3rd ,6th and 12th month therapy among Filipino stone formers. As urinary pH and urine citrate level increase, it increases the activity of citrate to decrease calcium-based and uric acid calculi. With the result, there was significant decrease in the mean stone size after potassium citrate therapy. However, changes in the urine citrate and stone size are not correlated.

In this study, even with sufficient sample size to determine the effect of potassium citrate in urine pH and urine citrate, the effect on the stone size cannot be statistically concluded. A larger population is recommended for future studies.

References

1. Campbell -Walsh Urology 11th edition
2. Bolong DT, Arcinas RP, et al. The effect of alkali citrate as medical therapy in the prevention and dissolution of calcium nephrolithiasis: A meta-analysis of randomized control trials. University of Santo Tomas Hospital, Section of Urology, 2009-2013
3. Bolong DT, Arcinas RP, et al. Metabolic workup of Filipino patients with nephrolithiasis seen at a tertiary hospital. University of Santo Tomas Hospital, Section of Urology, 2009-2013
4. Anjum, Muhammad Rafique et al. 24-hour urinary citrate levels in recurrent renal stone formers and healthy controls. Nishtar Med J 2009; 1:1
5. Mithani, Shoaib, et al. Comparison of 24-hour urinary citrate levels in urolithiasis patients and healthy controls. Saudi J Kidney Dis Transpl 2012; 23: 1227-31.
6. Catipay R, et al. Urinary citrate determination in Filipino urinary stone formers and normal controls: an Initial report. University of Santo Tomas Hospital, Section of Urology, 1997
7. Ahmed Bilal, et al. 24-hour urinary citrate levels and frequency of hypocitraturia among patients with recurrent nephrolithiasis. Pakistan J Med Health Sc 2016; 10: 3.
8. European Association of Urology Urolithiasis Guidelines, 2015
9. Suarez M, et al. Potassium citrate: Treatment and prevention of recurrent calcium nephrolithiasis. Jscimedcentral, 2015
10. American Urologic Association Urolithiasis Guidelines 2014
11. Leitao R, et al. Impact of long term potassium citrate therapy in urinary profiles and recurrent stone formation. J Urol 2009; 181(3): 1145-50.
12. Halili E, et al. Comparative study on the urinary citrate levels in Filipino stone formers vs non-stone formers. Phil J Urol 2009; 19(2): 172-7.
13. Curhan G, et al. 24-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int 2001; 59(6): 2290-8.
14. Schubert, Strohm, et al. Urinary stone formers with hypocitraturia and normal urinary pH are at high risk of recurrence. Urol Int 2012; 88(3): 294-7.
15. Unno R, et al. Potassium citrate prevents the development of renal microcalculi into symptomatic stones in calcium stone forming patients. Int J Urol 2017; 24(1): 75-81.
16. Song Y, et al. Potassium citrate decreases urine calcium excretion in patients with hypocitraturic calcium oxalate nephrolithiasis. J Urol 2016; 44(2): 145-8.
17. Lojanapiwat B, et al. Alkaline citrate reduces stone recurrence and regrowth after shockwave lithotripsy and percutaneous nephrolithotomy. Int Braz J Urol 2011; 37(5): 611-6.
18. Robinson Leitao, et al. Impact of long-term potassium citrate therapy on urinary profiles and recurrent stone formation. J Urol 2009; 181(3): 1145-50.