GENERAL UROLOGY
Original Article

Is it safe to prescribe ascorbic acid for urinary acidification in stone-forming patients with alkaline urine?

Alkalen idrarlı taş hastalarında idrarın asidifikasyonu için hastalara askorbik asit reçetelendirmek güvenli mi?

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ABSTRACT

Objective: To study the effect of ascorbic acid (AA) supplementation on urinary pH, metabolic stone work-up parameters, and development of *de novo* urolithiasis in stone-forming patients.

Material and methods: A retrospective review of the patients followed-up at a tertiary stone centre between September 2009 and October 2015 was performed. Patients with recurrent urolithiasis who received AA supplementation as a urinary acidifying agent were included in the study. Detailed metabolic stone work-up, including two 24-hour urine collections obtained pre- and post-AA supplementation were compared. In addition, imaging studies were reviewed to assess the development of *de novo* urolithiasis.

Results: Twenty-four patients were included in the study with a mean age of 60.6 years and a median daily AA dose of 1000 mg (range: 500-2000 mg). Median follow-up period was 22.6 months (range: 19.7-32.1). After AA supplementation, there was a significant decrease in urinary pH (7.6 vs. 6.9, p=0.02). Although there was no significant increase in the daily oxalate excretion, two patients (8.3%) had their AA dose reduced or discontinued due to *de novo* hyperoxaluria (342.9 vs 510.2 umol/day; p=0.75). Other serum and urinary parameters did not show any significant changes. Eight (33.3%) patients developed *de novo* urolithiasis with struvite and carbonate apatite being the major components.

Conclusion: AA supplementation resulted in significantly lower urinary pH in patients with recurrent urolithiasis and alkaline urine pH. Prospective studies are needed to assess whether this reduction in urinary pH is associated with lower stone recurrence rates.

Keywords: Ascorbic acid; dietary supplements; urolithiasis.

ÖZ

Amaç: Taş hastalarında askorbik asit (AA) eklenmesinin idrar pH'sı, metabolik taş oluşum parametreleri ve yeniden taş oluşumu üzerine etkisini araştırmaktır.

Gereç ve yöntemler: Eylül 2009 ile Ekim 2015 arasında üçüncü basamak taş tedavi merkezinde izlenen hastalar retrospektif yöntemle gözden geçirilmiştir. İdrarı asidifiye eden madde olarak AA katkısı alan nüks taş hastaları çalışmaya alınmıştır. AA katkısı vermeden önce ve verdikten sonra olmak üzere 2 kez alınan 24 saatlik idrar örneklerinde yapılan ayrıntılı metabolik taş analizleri birbirleriyle karşılaştırılmıştır. Ayrıca, yeniden taş oluşumunu değerlendirmek için görüntüleme çalışmaları gözden geçirilmiştir.

Bulgular: Yaş ortalaması 60,6 yıl ve günde ortalama 1000 mg (500-2000 mg) dozunda AA alan 24 hasta çalışmaya dahil edilmiştir. Hastalar ortalama 22,6 ay (19,7-32,1 ay) izlenmiştir. AA katkısı aldıktan sonra idrar pH'ında anlamlı bir azalma olmuştur (7,6'ya karşın 6,9, p=0,02). Günlük oksalat ekskresyonunda herhangi bir anlamlı artış olmamasına rağmen iki hastada (%8,3) *de novo* hiperoksalüri (342,9'e karşın 510,2 umol/gün; p=0,75) nedeniyle AA dozu azaltılmış veya kesilmiştir. Diğer serum ve idrar parametrelerinde anlamlı değişiklikler görülmemiştir. Sekiz hastada (%33,3) başlıca bileşenleri strüvit ve karbonat apatit olan de novo taş hastalığı gelişmiştir.

Sonuç: AA katkısı taş hastalığı yinelenmiş alkalen idrar pH'sı olan hastalarda idrar pH'sının anlamlı derecede azalmasına yol açmıştır. İdrar pH'sındaki bu azalmanın daha düşük taş nüksüyle ilişkili olup olmadığını değerlendirmek için prospektif çalışmalara gerek vardır.

Anahtar sözcükler: Askorbik asit; diyet katkıları; ürolityazis.

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Introduction

Struvite stones are made of magnesium ammonium phosphate and calcium carbonate apatite. They are formed in alkaline urine through the action of urea-splitting organisms such as *Proteus*, *Klebsiella* and *Pseudomonas*.[1,2] This process is facilitated by the action of urease enzyme that breaks down urea into ammonia and carbon dioxide, which both respectively hydrolyze into ammonia and bicarbonate, thus alkalinizing the urine. This milieu favours formation of struvite and carbonate apatite stones.[1,2] As a potent irreversible inhibitor of bacterial urease, acetohydroxamic acid (Lithostat, Mission Pharmacal, San Antonio, USA), was described in 1965.[3] In a randomized clinical trial, Williams et al.[4] found that 7 patients (36.8%) who received placebo developed *de novo* urolithiasis when compared with none of the 18 patients who received acetohydroxamic acid ($p<0.01$).[4] Thus, acetohydroxamic acid could be used as a prophylactic agent against formation of struvite stones. However, this medication is not available in Canada possibly due to its adverse effects such as tremulousness and phlebothrombosis.[4]

According to the latest Canadian Urological Association guidelines, struvite stones do not require a detailed metabolic evaluation since only scarce number of metabolic abnormalities can be identified.[5] However, close radiological and bacteriological monitoring are recommended for those patients.[5] In fact, little could be offered to these patients other than surgical extraction of all struvite stones and antibiotic prophylaxis.

Ascorbic acid (AA) has been studied in the literature regarding to its effects at lowering urinary pH in patients with recurrent urinary tract infections.[6] Results have been controversial. While some studies refuted its acidifying effects, others showed significant reductions in urinary pH after AA supplementation.[7-10] However, none of these studies have examined the acidifying effects of AA in recurrent urolithiasis patients with alkaline urine. The aim of the present study was to assess the effects of AA supplementation on urinary parameters in patients with recurrent urolithiasis and alkaline urine. The primary endpoint was to determine whether AA supplementation lowers urinary pH. Secondary endpoint was to assess its effects on serum and 24-hour urine collection parameters and to assess any changes in stone composition or formation of *de novo* urolithiasis. The hypothesis of this study was that AA supplementation would result in lower urinary pH and higher urinary oxalate excretion.

Material and methods

Study design

After a review of all patients followed at a tertiary stone clinic between September 2009 and October 2015, 43 patients who received AA supplementation were retrospectively identified and 24 of them met the inclusion criteria and were included in the present study (Figure 1).

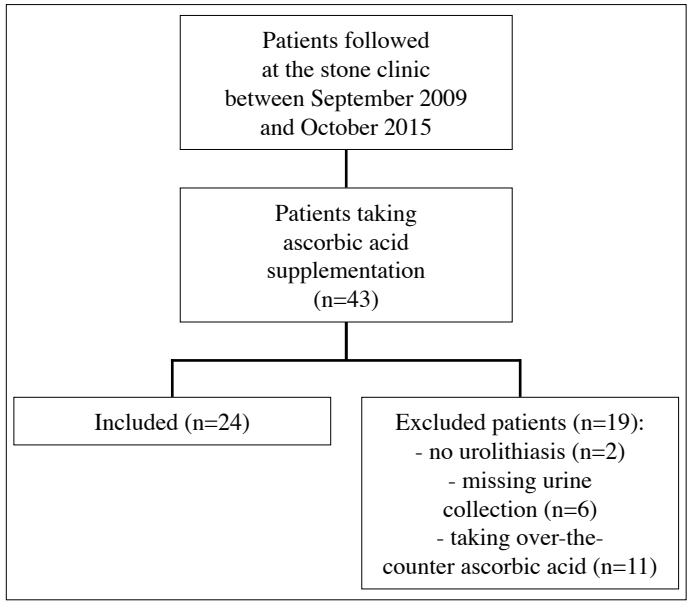

Figure 1. Study design and patient selection

Patients who were prescribed AA supplementation were included. Exclusion criteria consisted of over-the-counter use of AA without prescription, no history of urolithiasis and missing data about urine collection parameters pre- or post-AA supplementation. Clinical, and demographic about patients' age, gender, AA dosage and the concomitant use of mandelamine or prophylactic antibiotics were collected. Biochemical data about pre- and post-AA metabolic stone work-up including fasting morning urinalysis with pH, two 24-hour urine collections and stone analysis (if available) were collected. Twenty-four-hour urine collection parameters included urine volume, creatinine, calcium, sodium, oxalate, magnesium, phosphorus, potassium, urea nitrogen, uric acid and citrate. Since each metabolic work-up consisted of analysis of 24-hour urine collections obtained at two separate occasions, the worst value for each parameter was used for the present study. Serum parameters analyzed included intact parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH) VD], ionized normalized calcium, creatinine, potassium and uric acid. Patients were followed semi-annually with imaging studies (abdominal ultrasound, plain abdominal radiography or abdominal computed tomography) to assess for *de novo* urolithiasis, defined as progression of already existing urolithiasis or appearance of new urolithiasis.

Statistical analysis

Version 22 of IBM Statistical Package for the Social Sciences Statistics for Windows (IBM SPSS Statistics Armonk, NY, USA) was used to perform statistical analyses. Descriptive data are presented in terms of means and 95% confidence intervals (CI) of the means, or medians and ranges. The Wilcoxon Signed -Rank Test was used to compare the mean (± SD) values for pre- and post-AA supplementation urinary parameters such as pH, volume, creatinine, sodium, calcium, oxalate, magnesium, phosphorus, potassi-

Table 1. Metabolic stone work-up before, and after ascorbic acid supplementation

Variable [reference values]		Pre-ascorbic acid supplementation	Post-ascorbic acid supplementation	p
Urinalysis	Urine pH	7.6 (7.3-7.8)	6.9 (6.5-7.3)	0.02
24-hour				
Urinary parameters	Volume (mL/d)	1667 (1299-2035)	1290 (847-1733)	0.93
	Creatinine (mmol/d) [7.1-17.7]	8.92 (7.17-10.68)	7.70 (5.33-10.07)	0.16
	Sodium (mmol/d) [40-220]	128 (112-145)	138 (102-174)	0.14
	Calcium (mmol/d) [2.5-7.5]	3.62 (2.83-4.42)	3.55 (2.53-4.58)	0.05
	Oxalate(umol/d) [100-480]	342.9 (285-401)	510.2 (170-851)	0.75
	Magnesium (mmol/d) [3.0-5.0]	2.32 (1.71-2.93)	2.72 (1.55-3.88)	0.97
	Phosphorus (mmol/d) [12.9-42.0]	18.7 (15.7-21.7)	17.0 (13.1-20.8)	0.48
	Potassium (mmol/d) [26-77]	48.7 (40-57.3)	38.2 (29.4-46.9)	0.45
	Urea nitrogen (mmol/d) [430-710]	272 (230-314)	263 (206-321)	0.39
	Uric acid (mmol/d) [1.5-4.4]	2.43 (2.05-2.80)	2.08 (1.62-2.55)	0.59
	Citrate (mmol/d) [1.6-4.5]	1.69 (1.13-2.25)	1.23 (0.68-1.78)	0.67
Serum parameters	PTH intact (pmol/L) [1.60-6.90]	5.32 (3.90-6.75)	6.71 (4.54-8.88)	0.17
	25(OH) VD (nmol/L) [75-250]	60.4 (47.8-73.0)	60.0 (36.5-83.5)	0.80
	Ionized Normalized Calcium (mmol/L) [1.15-1.32]	1.19 (1.16-1.21)	1.21 (1.18-1.24)	0.50
	Creatinine (umol/L) [55-110]	82 (63-101)	70 (53-88)	0.18
	Potassium (mmol/L) [3.5-5.0]	4.4 (4.2-4.6)	4.3 (4.0-4.5)	0.13
	Uric acid (umol/L) [150-470]	325 (296-354)	321 (281-360)	0.42

Data are presented as means and 95% confidence interval. 25(OH) VD: 25-hydroxyvitamin D; AA: ascorbic acid; CI: confidence interval; PTH: parathyroid hormone; UTI: urinary tract infection

um, urea nitrogen, uric acid, and citrate. In addition, the Wilcoxon Signed- Rank Test was used to compare the mean (± SD) of pre- and post-AA supplementation values for serum parameters such as intact PTH, 25(OH) VD, ionized normalized calcium, potassium, and uric acid. A two-tailed p value of <0.05 was considered statistically significant.

Results

The mean patients' age was 60.6 years (95% CI: 52.7-68.5) including 11 (45.8%) females. All patients had recurrent urolithiasis and alkaline urine with mean baseline pH of 7.6. Patients were prescribed AA supplementation with a median daily dose of 1000 mg (range 500-2000 mg) to acidify urine. Fifteen patients (63%) were also on prophylactic antibiotics. In addition, 5 patients (21%) were also on mandelamine treatment. The median follow-up time was 22.6 months (range: 19.7-32.1 months). Two patients (8.3%) were not compliant with AA supplementation and another three patients (12.5%) had their total daily dose of AA decreased from the initial dosage to improve compliance. Two patients (8.3%) had their AA dose reduced or discontinued due to *de novo* hyperoxaluria.

There was a statistically significant reduction in mean urinary pH post-AA supplementation (7.6 vs. 6.9; p=0.02) (Figure 2). Furthermore, the 24-hour urinary oxalate excretion increased post-AA supplementation. However, this increase was not statistically significant (342.9 umol/d vs. 510.2 umol/d; p=0.75). In addition, there were no significant differences in other urinary parameters measured (Table 1). Similarly, there were no statistically significant differences between pre- and post-AA serum parameters in terms of intact PTH (p=0.17), 25(OH) VD (p=0.80), ionized normalized calcium (p=0.5), serum creatinine (p=0.18), serum potassium (p=0.13), and serum uric acid (p=0.42) (Table 1).

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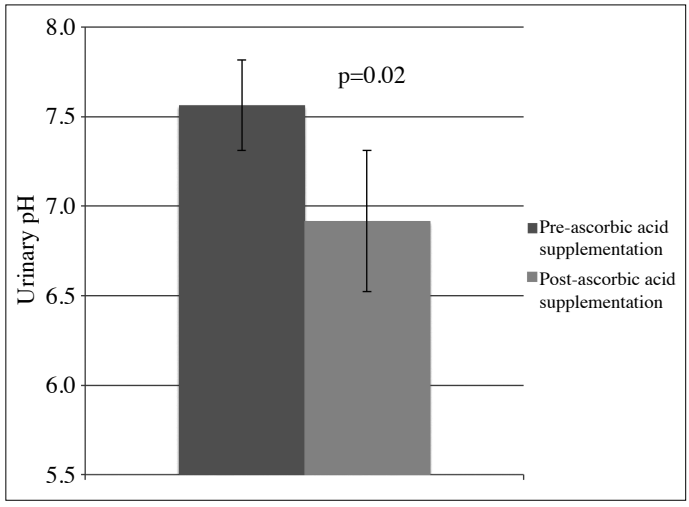

Figure 2. Urinary pH pre- and post-AA supplementation

Table 2. Stone composition before and after ascorbic acid supplementation

Stone composition	Pre-ascorbic acid supplementation (n=17)	Post-ascorbic acid supplementation (n=3)
Struvite	9 (53%)	2 (67%)
Carbonate apatite	6 (35%)	1 (33%)
Calcium oxalate	2 (12%)	0
Uric acid	0	0

Over a median follow-up of 22.6 months, eight out of 24 patients (33.3%) had *de novo* urolithiasis. Six (75%) of these patients with *de novo* urolithiasis were also taking mandelamine, prophylactic antibiotics or both. Pre-, and post-AA supplementation stone analyses were available for 17 and 3 patients, respectively (Table 2). Except for 2 patients who formed calcium oxalate stones, pre-AA supplementation stone analysis showed that most patients had struvite or carbonate apatite stones. Interestingly, none of the patients developed uric acid stones or pure calcium oxalate after AA supplementation. Post-AA supplementation stone analyses for the three patients showed the presence of struvite and carbonate apatite stones.

Discussion

Ascorbic acid supplementation has been studied in the past with regards to its urinary acidifying effects. However, there has been conflicting evidence regarding its efficiency. Furthermore, previous studies mostly focused on AA supplementation in healthy subjects, calcium stone-formers, or patients with recurrent urinary tract infections. However, no study has been performed in patients with struvite stones. In the current study, AA supplementation was used in patients with recurrent urolithiasis and alkaline urine and it resulted in a significant decrease in urinary pH. Similarly, McDonald and Murphy[11] found a significant decrease in urinary pH of twelve patients with indwelling catheter and chronic urinary tract infections (Table 3). Although post-AA urine pH was as low as 5.3, AA supplementation was used only for one day. Furthermore, Murphy et al.[6] studied patients complaining of chronic urinary tract infections associated with chronic indwelling catheters, chronic intermittent catheterization or without catheter. They showed that AA was an effective urinary acidifying agent only in patients with uninfected urine. In patients with infected urine, AA supplementation alone did not result in significant reduction in urinary pH. However, when AA supplementation was combined with antibacterial therapy such as nalidixic acid (negGram), mandelamine, or nitrofurantoin (furadantin), it resulted in significant reduction in urinary pH. This was attributed to the eradication of urease-producing bacteria by the antibacterial agent.[6] While the results of the study by Murphy et al.[6] are congruent with the current study, they did not assess *de novo* urolithiasis. In another study, 47 calcium stone-forming patients were recruited to receive either 1 or 2 g of AA supplementation per day. There was no significant change in pre- and post-AA supplementation urinary pH with oral intake of either 1 g or 2g amino acid.[7] However, one could argue that the patient population in that study were calcium stone-forming patients who had acidic urinary pH prior to receiving AA. These patients were different from patients in the present study who were stone-forming patients with alkaline urine with mostly struvite or carbonate apatite stones.

Travis et al.[12] analyzed the effect of AA supplementation in hospitalized sick children. They couldn't find any consistent decrease in urinary pH with high doses of AA (Table 3). However, they were particularly looking to obtain a pH less than 5.5 in order to optimize the effects of methanamine mandelate in the prophylaxis of urinary tract infections, since pH of 5.5 is recommended for optimal conversion of methanamine mandelate to formaldehyde, the active antiseptic moiety.[10,12] Similarly, they have not shown significant reduction in post-AA supplementation urinary pH (Table 3).[8-10,12,13] Similar to Baxmann et al.[7] all of these studies had baseline acidic urinary pH, which could explain lack of significant reduction in post-AA supplementation urinary pH. Unlike previously published papers, the present study has included stone-forming patients with alkaline urine. This could explain why this study showed a significant acidifying effect of AA supplementation.

Baxmann et al.[7] study found that AA supplementation in calcium-stone forming patients resulted in significant hyperoxaluria following both oral intake of 1 g/day and 2 g/day ascorbic acid. However, there was discrepancy in measuring urinary oxalate depending on the assay used**.** Therefore, urinary oxalate measurements may not have been accurate.[7] In another study, there was a significant increase in urinary oxalate. However, they used daily doses of 10 g AA whereas in the present study 2000 mg was the maximum dosage (Table 3).[14] In the current study, one patient had his AA supplementation discontinued due to *de novo* hyperoxaluria and another had his dose reduced for the same reason. However, there was no significant increase in mean 24-hour uri-

Table 3. Previous studies on ascorbic acid supplementation

Author	Year	# of patients	Dose of ascorbic acid	Patient population	Baseline urinary pH	Final urinary pH	p	Remarks
Murphy et al.[6]	1965	38	3-6 g/day	19 patients with chronic catheter, 8 patients with intermittent catheter, 11 patients without catheter	-	-	-	Significant decrease in urinary pH in in patients with uninfected urine. AA was more effective in patients with chronic UTI on prophylactic antibiotics
Baxmann et al.[7]	2003	47	1 g/day or 2 g/day, for 3 days	Calcium stone-forming patients	5.8	5.8	>0.05	AA resulted in increased in urinary oxalate excretion. However, this was not the same population as struvite and carbonate apatite stone-formers in the present study
Castello et al.[8]	1996	13	2 g/day	Spinal cord injury patients	5.93	-	0.96	Baseline pH was already acidic. This was randomized control trial
Barton et al.[9]	1981	7	2 g IV	Healthy subjects	5.93	6.39	<0.05	There was a significant rise in urinary pH. However, baseline pH was already acidic
Nahata et al.[10]	1977	10	4 g/day and 6 g/day	Healthy subjects	5.6 to 6.5	Decreased by 0.24	-	Baseline pH was already acidic
McDonald and Murphy[11]	1959	15	2.5 g/day for 1 day	Chronic Urinary Tract Infection UTI patients, chronic indwelling catheter patients	7.4	5.3	<0.1	-
Travis et al.[12]	1965	12	2-8 g/m^2/day	Pediatric hospitalized patients	6.0	>5.5	-	There was no consistent lowering of urinary pH unless given mandelamine as an adjunct. However, baseline pH was already acidic
Hetey et al.[13]	1980	20	4 g/day for 5 days	Spinal cord injury patients	5.4 to 6.03	Decreased by 0.58	-	Baseline pH was already acidic. This was randomized control trial
Schmidt et al.[14]	1981	4	10 g for 5 days	Healthy subjects	-	-	-	There was an increased urinary oxalate excretion from 555 to 966 umol/L/day
Takigushi et al.[15]	1966	30	1 g/day for 90 days or 2 g/day for 180 days or 2 g/day for 90 days	Healthy subjects	-	-	-	There was no significant increase in urinary oxalate excretion. Oral AA was mostly excreted in the urine as reduced AA
Present study	2017	24	500 mg-2000 mg/day	Stone-formers with alkaline urine	7.6	6.9	0.02	Patients were mainly struvite and carbonate apatite stone formers. There was no significant rise in urinary oxalate excretion

nary oxalate excretion. This is similar to what Takigushi et al.[15] found. Finally, Schmidt et al.[14] found that at least 25% of AA is excreted in the urine and most AA is excreted in the urine as reduced AA. Therefore, 24-hour urine collections could be used to monitor the development of hyperoxaluria in patients receiving AA supplementation.

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Recurrence rates of struvite stones have been reported to range from 30 to 85% within 6 months.[1,16] In this study, 8 (33.3%) patients had *de novo* stones after a median follow-up of 22.6 months. This is within the reported range of stone recurrence in patients with struvite stones.

Limitations of the present study include its small sample size as well as its retrospective design. Nonetheless, the present study is the first study to demonstrate significant reduction in urinary pH after AA supplementation in patients with recurrent urolithiasis and alkaline urine. In addition, there were no *de novo* pure calcium oxalate or uric acid stones.

In conclusion, AA supplementation resulted in significantly lower urinary pH in patients with recurrent urolithiasis and alkaline urine pH. Prospective studies are needed to assess whether this reduction in urinary pH is associated with lower stone recurrence rates.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of McGill University Health Center (MUHC) (Study Code: 15-532-MUHC).

Informed Consent: No informed consent was needed as this was retrospective chart review for quality control study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.A.N., A.S., N.F., S.A.; Supervision – Y.A.N., N.F., S.A.; Data Collection and/or Processing - Y.A.N., A.S.; Writing Manuscript - Y.A.N., A.N., N.F., S.A.; Critical Review - Y.A.N., A.N., N.F., S.A.

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Hasta Onamı: Bu bir kalite kontrol çalışması olduğu için hasta çizelgeleri retrospektif olarak gözden geçirilmiş, bu nedenle bilgilendirilmiş onam alınmasına gerek görülmemiştir.

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Yazar Katkıları: Fikir - Y.A.N., A.S., N.F., S.A.; Denetleme – Y.A.N., N.F., S.A.; Veri Toplanması ve/veya İşlemesi - Y.A.N., A.S.; Yazıyı Yazan - Y.A.N., A.N., N.F., S.A.; Eleştirel İnceleme - Y.A.N., A.N., N.F., S.A.

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