Original Article

Oral dissolution therapy for renal radiolucent stones, outcome, and factors affecting response: A prospective study

Shady Mohammed Salem, Mohammed Farag Sultan, Atef Badawy

Department of Urology, Faculty of Midicine, Menoufia University, Shibin Elkom, Egypt

Abstract

Background: Urolithiasis is a widespread problem, that affects up to 10% of population. Uric acid stones come second to calcium stones in prevalence (around 10% of urolithiasis). Potassium citrate is currently the treatment of choice for urine alkalization with minimal side effects and high tolerability.

Aims and Objectives: This study is trying to present the outcome of oral dissolution therapy (ODT) for treating radiolucent renal stones and evaluating factors affecting its success in a prospective manner.

Materials and Methods: Between 2015 and 2018, 147 patients with solitary radiolucent renal stones were offered ODT using potassium sodium hydrogen citrate (K citrate). The study included patients diagnosed by noncontrast computed tomography (NCCT) with stone size of 5–30 mm in the longest dimension and attenuation less than 600 Hounsfield units (HU) . Patient compliance, blood pressure, creatinine level, K level, and tolerance to side effects were followed up at days 3, 7, and 15 and then monthly for 3 months. Follow-up renal ultrasound at 6-week intervals and a final NCCT at the end of treatment. Successful dissolution was defined as complete stone dissolution or residual that measures up to 2 mm in maximum length. Data were collected, tabulated, and analyzed using Stata 12.0 software (Stata Corporation, College Station, TX, USA).

Results: One hundred and thirty-nine patients were included in the analyses. The age was 45.1 ± 10.5 years. DJ stent was used in 47 (33.8%) patients. Overall response rate was 64.8%. The stone location within the kidney (pelvic or calyceal) showed no difference between responders and non-responders. Stone longest diameter was smaller in responders (17 ± 5.7 mm) versus 19.2 ± 6.1 mm in nonresponders (P value = 0.039). The mean stone attenuation value (HU) was also lower in responders(347.4 ± 68.5 HU) versus (428.9 ± 84.0 HU) in nonresponders with $P < 0.001$. DJ insertions seemed to have marginal effect on stone dissolution on univariate analysis but found insignificant in multivariate analysis.

Conclusion: ODT is safe and effective in the treatment of radiolucent renal stones. The efficacy was affected by stone density and stone size with more tendencies to failure with bigger stones and denser stones. Double J stent insertion may facilitate dissolution rate. There was no effect of the baseline urinarypH, hyperuricemia, or stone location on the dissolution rate of the stones.

Keywords: ODT, radiolucent, uric acid, urolithiasis

Address for correspondence: Dr. Mohammed Farag Sultan, Hala Eisa Binladen Hospital, Ibrahim Adham Street, Alhamra, Jeddah, KSA.
E-mail: mfsultan2005@yahoo.com
Received: 09.02.2019, **Accepted:** 01.07.2019

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/UA.UA_20_19

How to cite this article: Salem SM, Sultan MF, Badawy A. Oral dissolution therapy for renal radiolucent stones, outcome, and factors affecting response: A prospective study. Urol Ann 2019;11:369-73.

INTRODUCTION

Urolithiasis is a widespread problem, and it is estimated to affect between 5% and 10% of population per lifetime. Urolithiasis incidence shows a progressive rise over the past two decades, which may be attributed to global warming, obesity, and dietary changes.[1] Uric acid stones come second to calcium stones in prevalence and compromise around 10% of all stone diseases.[2] Uric acid stone incidence varies widely among different countries with least in India and highest in the Middle East, with a range of 5%–40%. This difference can be related to climate, genetics, and dietary habits.[2,3]

Uric acid stone formation is a complex process with several contributing factors including uric acid output, urinary pH, urine volume, genetic predisposition, and metabolic syndrome.

Acidic urinary pH appears to be the most common risk factors identified in patients with uric acid stones. Uric acid solubility decreases drastically from 200 mg/dl in pH of 7 to 7–15 mg/dl in pH of 5.[4] In a study of metabolic characters of 342 uric acid stone formers, the mean urinary pH was 5.4 with almost all the patients with urinary pH below 6.[5]

Hyperuricosuria can be identified in one-third of uric acid stone formers. Uric acid is a metabolite of purine; the higher levels of uric acid in urine are associated with high protein diet, catabolic state during chemotherapy, or uricosuric drugs used in the treatment of gouty arthritis.[6]

Several studies linked uric acid stone formation to insulin resistance; stone formers with diabetes are six folds more likely to form uric acid stones than nondiabetic stone formers. Urinary pH was inversely related to insulin sensitivity and body weight.[7,8]

As uric acid stones can be dissolved in urinary pH over 6.5,[9] several alkali therapies were tried. Historically, Na citrate was tried; however, it was associated with higher adverse effect due to excessive sodium load which increased blood pressure and caused higher urinary calcium predisposing for calcium stones.[10]

Potassium citrate is currently the treatment of choice for urine alkalization with minimal side effects and high tolerability.[9,11]

Aim of work

This study is trying to present the outcome of oral dissolution therapy (ODT) for treating radiolucent renal stones and evaluating factors affecting its success in a prospective manner.

METHODS

Between January 2015 and January 2018, 147 patients with solitary radiolucent renal stones were offered ODT using potassium sodium hydrogen citrate (K citrate).

The study was prospectively designed and approved by the hospital ethical committee.

The study included patients diagnosed with solitary renal stones by noncontrast computed tomography (NCCT) with stone size of 5–30 mm in the longest dimension and attenuation less than 600 Hounsfield units (HU) and X-ray of the kidney, ureter, and bladder showing no radiopaque stones. Only patients with normal creatinine and two urine analyses with acidic pH were included. We excluded bilateral cases and cases with congenital anomalies with the kidney or the pelvicalyceal system.

The drug used was UrolytU® (Meda Meda Egypt and KSA). The drug is supplied in granule form, active ingredient is potassium sodium hydrogen citrate (ratio is 6:6:3:5). The drug is accompanied by dipstick pH indicators. Patients were instructed to take the drug in three times daily regimen, with evening dose doubled. The urine pH was adjusted dose by dose to 6.2–6.8 using the pH-sensitive strips.

Patient compliance, blood pressure, creatinine level, K level, and tolerance to side effects were followed up at days 3, 7, and 15 and then monthly treatment. The treatment offered for 3 months with follow-up renal ultrasound at 6-week intervals and a final NCCT at the end of treatment. We adopt the 3-month treatment period to be an average period of the drug to cause a reasonable effect, especially for larger stones. If at any point of the scheduled follow-up, the patient NCCT or ultrasound showed clearance of stone, the treatment is then discontinued and only prophylaxis regimen was started.

Successful dissolution was defined as complete stone dissolution or residual that measures up to 2 mm in maximum length.

Patients with increasing blood pressure, rising creatinine, or K level or those noncompliant or not tolerating the drug were removed from the analysis.

Data were collected, tabulated, and analyzed using Stata 12.0 software (Stata Corporation, College Station, TX, USA).

For univariate analysis, we used Chi-square test and Mann–Whitney test when appropriate. We used $P < 0.05$ as statistically significant results. We used multivariate

logistic regression model combining factors that were statistically significant in univariate analysis and reported 95% confidence interval.

Of 147 patients included in the study, 18 patients were not able to continue the study; 11 patients did not tolerate drug taste and/or had gastric upset, 5 patients developed hypertension, and 2 patients had potassium level higher than 5.5 mg/dl. One hundred and thirty-nine patients were available for the statistical analysis.

Besides the demographics of the study group, we evaluated the effect of stone density (HU), maximum diameter, site within the kidney, hyperuricemia, and the presence of Double J (DJ) stent on the stone dissolution.

RESULTS

One hundred and thirty-nine patients were included in the analyses. The age of cohort ranged from 22 to 70 years, with a mean of 45.1 ± 10.5.

DJ stent was used in 47 (33.8%) patients. The causes for DJ insertion were: residual stones after percutaneous nephrolithotomy (PCNL) in 18, migrated stone after ureteroscopy (URS) in 13, pyelonephritis in 9, and impacted stone at pelviureteral junction (PUJ) causing persistent pain or high creatinine in 7.

Overall response rate was 64.8% (90 patients), and response rate was not affected by age or gender. Both responders and nonresponders had baseline acidic urinary pH with insignificant difference. The responders' mean urine pH was 5.17 ± 0.11 versus 5.21 ± 0.22 in nonresponders (P = 0.901). In this cohort, 13 patients were hyperuricemic – 8 (8.8%) among responders and 5 (10.2%) nonresponders with P = 0.799 (insignificant difference). The stone location within the kidney (pelvic or calyceal) also showed no difference between the two groups.

Stone longest diameter was smaller in responders, with a mean stone size of 17 ± 5.7 mm versus 19.2 ± 6.1 mm in nonresponders with P = 0.039. The mean stone attenuation value (HU) was also lower in responders, with a mean stone density of 347.4 ± 68.5 HU versus 428.9 ± 84.0 HU in nonresponders with $P < 0.001$ (highly significant). DJ insertions seemed to have marginal effect on stone dissolution, with 31 responders (34.4%) with DJ versus 16 non-responders (32.7%) with DJ stents [Table 1]. On multivariate analysis, there was no significant effect of DJ insertion [Table 2].

Further analysis was done using logistic regression with stone size, density, and presence of DJ. Stone density was highly predictive of stone dissolution with 95% confidence interval of −0.023 to −0.010 and $P < 0.001$, followed by stone size with 95% confidence interval of −0.188 to −0.034 and P value = 0.005. The presence of DJ stent was not predictive with P value = 0.832 [Table 2].

DISCUSSION

Stone disease treatment has undergone great improvement over the past decades; shock wave lithotripsy (SWL), retrograde intra-renal surgery, and PCNL have widely replaced open surgery. All those procedures were subject to large-scale well-designed studies that demonstrated their outcome and side effect profile.[12,13]

Oral dissolution of radiolucent renal stones (urine alkalization) has been used for over 50 years. Despite the

Table 1: Factors affecting stone dissolution (univariate analysis)

Variable	Responders (*n*=90)	Nonresponders (*n*=49)	*P*
Age (years), mean±SD	45.1±10.8	44.6±11.3	0.734
Sex			
Male	47 (52.2)	27 (55.1)	0.105
Female	43 (47.8)	22 (44.9)	
Urine pH, mean±SD	5.17±0.11	5.21±0.22	0.901
Hyperuricemia			
Yes	8 (8.8)	5 (10.2)	0.779
No	82 (91.1)	44 (89.8)	
Stone site			
Pelvic	32	22	0.369
Calyceal	58	27	
Stone longest dimension (mm), mean±SD	17±5.7	19.2±6.1	0.039
Stone density in HU units, mean±SD	347.3±68.5	428.9±84	<0.001
Presence of DJ			
Yes	31 (66)	16 (34)	0.045
No	59 (64.1)	33 (35.9)	

Univariate analysis of factors affecting stone dissolution. DJ: Double J, SD: Standard deviation

Table 2: Multivariate analysis of factors affecting stone dissolution

Variable	95% CI	*P*
Stone size	−0.188–−0.034	0.005
Stone density	−0.023–−0.010	<0.001
DJ	−0.974-0.784	0.832

Logistic regression for factors affecting stone dissolution. DJ: Double J, CI: Confidence interval

widespread use, it still lacks standardization when compared to other stone treatment options such as SWL, RIRS, and PCNL. This gap is intensified by the lack of high-volume prospective studies of that therapy. Yet, it is an option in the treatment of uric acid stones in both European and American guidelines.[14,15]

Radiolucent stones (mainly uric acid) pose a challenge as its localization cannot be done with standard X-ray. In SWL, Smith *et al*. reported equal results for ultrasound (48 patients) and fluoroscopy (49 patients) localization with stone-free rates of 60% and 45% subsequently. They reported that ultrasound localization required specifically trained operator and he used adjuvant fluoroscopy when needed, and X-ray exposure decreased from 2113 mGy/cm^2 in the fluoroscopy group to 103 in the ultrasound group.[16] In another study, Cimentepe *et al*. reported the use of ultrasound localization and fluoroscopy with intravenous contrast for radiolucent stones with 89% of stone-free rates.[17]

Kumar et al. in a randomized controlled study compared the results of SWL, RIRS, and mini PCNL, for the treatment of 1–2 cm lower calyceal radiolucent stones. They achieved stone free rates of 73.8%, 86.1%, and 95.1% respectively. Despite RIRS and mini PCNL surpassed SWL, however, cost, hospital stay, and associated morbidity were higher.[18]

Mokhless *et al*. reported results for combining SWL and ODT in the treatment of stones in 24 children (29 renal units), with a mean age of 6.3 and stone burden range of 12–65 mm. They reported 100% stone clearance rate.[19]

Moreover, ODT was shown to be as effective as SWL in the treatment of radiolucent stones in the pediatric population. In their studt, Elderwy *et al*. randomized 87 children with a median age of 2.5 years and radiolucent stone burden range of 7–24 mm into 39 underwent SWL and 48 received ODT. They found that the stone-free rates were 72.9% ODT and 82.1% SWL, and the difference was statistically insignificant ($P = 0.314$).[20]

In the current study, we tried to identify the results of ODT used in a standardized way in large cohort and characterize the factors affecting the outcome. We opted to employ ODT in larger stone burden up to 3 cm as several reports of good results with stone burden >2 cm.

The limitations of this study included the few number of the patients, lack of the usage of stone surface area, exclusion of complex burden, and bilateral cases.

CONCLUSION

ODT is safe and effective in the treatment of radiolucent renal stones. The efficacy was affected by stone density and stone size with more tendencies to failure with bigger stones and denser stones. Double J stent insertion may facilitate dissolution rate. There was no effect of the baseline urinary pH, hyperuricemia, or stone location on the dissolution rate of the stones.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Pearle MS, Calhoun EA, Curhan GC; Urologic Diseases of America Project. Urologic diseases in America project: Urolithiasis. J Urol 2005;173:848-57.
2. Sakhaee K. Epidemiology and clinical pathophysiology of uric acid kidney stones. J Nephrol 2014;27:241-5.
3. Rafique M, Bhutta RA, Rauf A, Chaudhry IA. Chemical composition of upper renal tract calculi in Multan. J Pak Med Assoc 2000;50:145-8.
4. Kenny JE, Goldfarb DS. Update on the pathophysiology and management of uric acid renal stones. Curr Rheumatol Rep 2010;12:125-9.
5. Pak CY, Sakhaee K, Peterson RD, Poindexter JR, Frawley WH. Biochemical profile of idiopathic uric acid nephrolithiasis. Kidney Int 2001;60:757-61.
6. Sakhaee K, Maalouf NM, Sinnott B. Clinical review. Kidney stones 2012: Pathogenesis, diagnosis, and management. J Clin Endocrinol Metab 2012;97:1847-60.
7. Daudon M, Traxer O, Conort P, Lacour B, Jungers P. Type 2 diabetes increases the risk for uric acid stones. J Am Soc Nephrol 2006;17:2026-33.
8. Abate N, Chandalia M, Cabo-Chan AV Jr., Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: Novel features of renal manifestation of insulin resistance. Kidney Int 2004;65:386-92.
9. Skolarikos A, Straub M, Knoll T, Sarica K, Seitz C, Petřík A, *et al*. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. Eur Urol 2015;67:750-63.
10. Singh SK, Agarwal MM, Sharma S. Medical therapy for calculus disease. BJU Int 2011;107:356-68.
11. Ngo TC, Assimos DG. Uric acid nephrolithiasis: Recent progress and future directions. Rev Urol 2007;9:17-27.
12. Donaldson JF, Lardas M, Scrimgeour D, Stewart F, MacLennan S, Lam TB, *et al*. Systematic review and meta-analysis of the clinical effectiveness of shock wave lithotripsy, retrograde intrarenal surgery, and percutaneous nephrolithotomy for lower-pole renal stones. Eur Urol 2015;67:612-6.
13. De S, Autorino R, Kim FJ, Zargar H, Laydner H, Balsamo R, *et al*. Percutaneous nephrolithotomy versus retrograde intrarenal surgery:

A systematic review and meta-analysis. Eur Urol 2015;67:125-37.
14. Pearle MS, Goldfarb DS, Assimos DG, Curhan G, Denu-Ciocca CJ, Matlaga BR, *et al*. Medical management of kidney stones: AUA guideline. J Urol 2014;192:316-24.
15. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, *et al*. EAU guidelines on diagnosis and conservative management of urolithiasis. Eur Urol 2016;69:468-74.
16. Smith HE, Bryant DA, KooNg J, Chapman RA, Lewis G. Extracorporeal shockwave lithotripsy without radiation: Ultrasound localization is as effective as fluoroscopy. Urol Ann 2016;8:454-7.
17. Cimentepe E, Unsal A, Saglam R, Balbay MD. Comparison of clinical outcome of extracorporeal shockwave lithotripsy in patients with radiopaque v radiolucent ureteral calculi. J Endourol 2003;17:863-5.
18. Kumar A, Kumar N, Vasudeva P, Kumar Jha S, Kumar R, Singh H. A prospective, randomized comparison of shock wave lithotripsy, retrograde intrarenal surgery and miniperc for treatment of 1 to 2 cm radiolucent lower calyceal renal calculi: A single center experience. J Urol 2015;193:160-4.
19. Mokhless IA, Sakr MA, Abdeldaeim HM, Hashad MM. Radiolucent renal stones in children: Combined use of shock wave lithotripsy and dissolution therapy. Urology 2009;73:772-5.
20. Elderwy AA, Kurkar A, Hussein A, Abozeid H, Hammodda HM, Ibraheim AF. Dissolution therapy versus shock wave lithotripsy for radiolucent renal stones in children: A prospective study. J Urol 2014;191:1491-5.