Post-interventional stone-free rates for patients treated with citrates and pyridoxine

A. ENE [1], P. GEAVLETE [1,2], R. MIRON [1], R. MULTESCU [1,2], B. GEAVLETE [1,2]

[1] "Saint John" Emergency Clinical Hospital, Urology Department, Bucharest, Romania
[2] "Carol Davila" University of Medicine and Pharmacy, Faculty of Medicine, Bucharest, Romania

ABSTRACT

Introduction

For stone-free status, it is necessary to treat multiple fragments of kidney stones adjuvantly following a PCNL (percutaneous nephrolitotomy) procedure. The aim of this review is to evaluate the validity of citrate and pyridoxine therapy as a means of preventing recurrence of lithiasis.

Materials and Methods

We examined kidney stone patients who had undergone endourological treatment. Our study involved 68 patients with kidney stones between 2 and 3 cm diameter who underwent a percutaneous nephrolitotomy (PCNL). Following that, a predominantly low-protein diet was followed along with 2-3 liters of water each day. There were two groups of them. The patients in Group A received a combination of 975 mg potassium citrate, 60 mg magnesium citrate, and 25 mg pyridoxine per sachet. In contrast, the patients in Group B received placebo treatment.

Results

Group A had a higher stone-free rate (83.84%) than Group B (59.38%) after 90 days ($p<0.05$). In Group A, there was an overall higher expulsion rate (38.88% versus 12.5%) and a greater reduction in residual stone size (2.83mm versus 1.61mm, $p<0.05$).

Conclusions

Potassium citrate, magnesium citrate, and pyridoxine were found to be effective after percutaneous nephrolithotripsy.

Keywords: stone-free rate, percutaneous nephrolithotripsy, citrates, pyridoxine

Correspondence to: Dr. Andrei Ene, M. D.
"Saint John" Emergency Clinical Hospital, Department of Urology
13 Vitan-Barzesti St., District 4, code 042122, Bucharest, Romania
Tel: +40724094901; Fax: +40213345970
e-mail: ene.mihai_andrei@yahoo.com

Introduction

In the last 25 years, kidney stones have been increasing in prevalence worldwide from 5-15%, widely distributed [1, 2]. Most kidney stones contain calcium oxalate (monohydrate or dihydrate) or calcium phosphate. There are also stones made of uric acid, urates, cystine, or ammonia-magnesium phosphate These stones form when substances in the urine become highly concentrated and crystallize. Factors such as dehydration, diet, and certain medical conditions can increase stone formation risk [3, 4].

Urolithiasis can be treated with extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, and percutaneous nephrolithotomy (PNL) [5]. In accordance with the guidelines established by the American Urological Association for the surgical treatment of urolithiasis, PNL has the highest clearance rate for stones in the surgical treatment of urolithiasis [6, 7].

A PCNL is the standard treatment for the treatment of large stones in the kidney (more than 2 cm) and are also considered as treatment options for large stones that do not respond well to shock waves [8]. It is important to note that standard PCNL is an invasive procedure which carries a considerable risk of complications and post-procedure morbidity [1, 9]. As a result of surgery, there is a possibility of postoperative complications, such as bleeding (8%), the need for blood transfusions (3% to 6%), and postoperative sepsis (2%) [10-12].

It is common for recurrences of stones to be found after the procedure. After this therapy, stone fragments that have been retained may reaggregate or form a nucleus for the formation of new stones, causing a rapid growth rate of new stones after this therapy [13]. It is always possible that there will be variations in intraoperative complications, and some small fragments of lithiasis may remain in the body after surgery as a result of the uniqueness of each case —[14]. It is usually necessary to undergo adjuvant treatment to achieve stone-free status. Achieving stone-free status is beneficial as it reduces the risk of recurrent kidney stones and associated complications. It can also alleviate pain and discomfort, improving the patient's overall quality of life.

A number of studies have shown that potassium citrate prevents nephrolithiasis from occurring by inhibiting the lithogenesis process Potassium citrate is essential in maintaining kidney health as it helps to neutralize urinary acidity, reducing the risk of stone formation. By increasing urinary citrate levels, it binds with calcium and prevents the formation of calcium oxalate stones. This makes potassium citrate a vital supplement for individuals predisposed to kidney stones [15-19]. The purpose of our study was to investigate the effect of potassium citrate, magnesium citrate, and pyridoxine administration on stone-free rates following percutaneous nephrolithotripsy.

Materials and Methods

This study involved 68 patients with kidney stones of diameters ranging from 2 to 3 cm in size who underwent percutaneous nephrolithotomies between January 2022 and November 2024 as part of a prospective, double-blind, randomized study. During the procedure, a standard nephroscopy was performed (26-Fr StorzTM nephroscope under fluoroscopic guidance) as well as a pneumatic lithotripsy.

In order to confirm the presence of any remaining fragments, a radiologist performed ultrasounds on all patients the next morning. A crystallographic examination was mandatory after surgery, such as X-ray diffraction or infrared spectroscopy. As a general treatment regimen, it was recommended that patients should drink 2-3 liters of water daily, as well as consuming low-protein foods, such as fruits, vegetables, and foods high in fiber.

Two groups of patients were studied: Group A consisted of 36 patients receiving general treatment along with 975 mg potassium citrate, 60 mg magnesium citrate, and 25 mg pyridoxine per sachet. In general, this dose was taken twice a day at 8am and 8pm. A placebo treatment was administered to 32 patients in Group B. A 90-day follow-up was conducted by a radiologist. In all

cases, ultrasound was performed, according to the lectures [20]. The CT scan was used to determine how many stones were present, their size, and their exact location if stones were detected during this examination.

The study included patients with oxalate, calcium phosphate, uric acid or a combination of these conditions, as well as adults who consented and did not have a urinary tract infection, neoplasy pathology, concurrent or previous cytostatic therapy, or endocrinological conditions. Pregnant women with lithiasis, allergic reactions to prior citrate treatments, and those with pathologies contraindicating the administration of citrate (severe hepatic and renal impairments) were excluded. In this study, citrate and pyridoxine therapy were examined for their potential to prevent lithiasis recurrence after percutaneous nephrolithotomy.

For statistical analysis, SPSS 20.0 (SPSS Inc., 2012) was used. Stone-free rates after endourological therapy were the study's primary endpoint. Two-sided chi-square tests were used to examine the primary endpoint for two independent samples. A descriptive analysis was also conducted on the variables studied. Both groups were evaluated on stone expulsion capacity after 90 days of conservative treatment. A two-sided (chi-square) test was used to determine this secondary endpoint, as well as BMI and stone composition. Another endpoint to be evaluated after endourological treatment was residual stone size after 90 days. The Wilcoxon Rank Sum test and two-way factorial ANOVA (analysis of variance) were used to compare the groups at baseline, after surgery, and 90 days after treatment. If the outcome variable's distribution was too skewed to the right, a natural logarithmic transformation was applied. A significant inferential test was defined as one with a P-value less than 0.05. The study was conducted in accordance with the revised Helsinki Declaration of 2013. The procedure was approved by the Emergency Clinical Hospital "St. John" Bucharest. Informed consent was obtained from all participants in the study.

Results

In Group A, there are 36.11% male patients, compared to 63.89% female patients, whereas in Group B, there are 46.88% female patients, compared to 53.12% male patients. Statistically, there was no significant difference between the groups, with a p-value of 0.158.

There are many similarities between the two groups in terms of age distribution. In Group A, the mean value was 47.39, while in Group B, it was 49.84. Based on the p-value of 0.474, there was no statistically significant difference between the two groups.
There were no patients classified as Class 2 and Class 3 obese based on their BMI. For BMI < 18.5, 19.44 % of patients were in Group A and 28.12 % of patients were in Group B. 47.22% for Group A and 40.62% for Group B patients had a BMI from 18.5 to < 25. Regarding BMI from 25 to < 30 we had 22.22% patients for Group A and 21.85% for Group B. The last category, BMI from 30 to < 35 we had 11.11% patients for Group A and 9.37% for Group B. At the $\chi 2$ test, the p-value was 0.859. Statistically, there was no difference between the groups.

There were no residual stones larger than 6 mm in diameter. Our classification was based on their position: superior calix and middle+inferior calix. The first category accounted for 77.77% of patients in Group A, while the second category accounted for 22.23%. In Group B, there were 78.12% residual stones in the superior calix, and 21.88% in the middle+inferior calix. As a result of the $\chi 2$ test, the p-value was 0.973. A statistically significant difference did not exist between the groups.

Both Groups A and B had a significant proportion of calcium oxalate/phosphate in their postoperative crystallographic analyses (63.88% in Group A and 68.75% in Group B). Calculi made of uric acid were reported at 16.66% for Group A and 18.75% for Group B. In only 19.44% of cases mixed composition calculations were identified for group A, compared to group B, where the percentage of those was lower, respectively 12.5%. In the $\chi 2$ test, the p-value was 0.209, so there weren't any statistical differences between the groups [Table 1]. The same $\chi 2$ test was used previously to determine calcium oxalate and/or

phosphate stone composition, and a p-value of 0.738 was found for no significant differences between the groups.

Table 1. Demographics

	Group A (N=36)	Group B (N=32)	P-value
Age			**0.474**
Mean (SD)	47.39 (15.3)	49.84 (12.3)	
Sex			**0.158**
F	23 (63.89%)	15 (46.88%)	
M	13 (36.11%)	17 (53.12%)	
BMI			**0.859**
<18.5	7 (19.44%)	9 (28.12%)	
18.5 to <25	17 (47.22%)	13(40.62%)	
25 to <30	8 (22.22%)	7 (21.85%)	
30 to <35 (Class 1)	4 (11.11%)	3 (9.37%)	
Residual stone position			**0.973**
Superior Calix	28 (77.77%)	25 (78.12%)	
Middle+Inferior Calix	8 (22.23%)	7 (21.88%)	
Stone composition			**0.209**
Uric acid	6 (16.66%)	6 (18.75%)	
Calcium Oxalate/ Phosphate	23 (63.88%)	22 (68.75%)	
Mixt	7 (19.44%)	4 (12.5%)	

***Group A (Treatment); Group B (Placebo)**

There was a total stone-free rate of 72.06% after 90 days of treatment. Group A had an 83.84% stone-free rate, while Group B had a 59.38% stone-free rate [Table 2]. The χ2 test shows a p-value of 0.034, equivalent to the fact that the results obtained are statistically significant [Table 4].

Table 2. Stone-free rate at 90 days

	Residual stone	Stone-free
Group A	6 (16.66%)	30 (83.34%)
Group B	13 (40.62%)	19 (59.38%)
Total	19 (27.94%)	49 (72.06%)

***Group A (Treatment); Group B (Placebo)**

We found that Group A had a 38.88% stone expulsion capacity at three months, while Group B had an 12.5% stone expulsion capacity [Table 3].

The results were considered statistically significant (the χ2 test shows a p-value of 0.014) and revealed that patients treated with a combination of citrates had a better stone expulsion rate [Table 3].

Table 3. Stone-free rate at 90 days

	Expulsion	No expulsion
Group A	14 (38.88%)	22 (61.12%)
Group B	4 (12.5%)	28 (87.5%)
Total	18 (26.47%)	50 (73.53%)

***Group A (Treatment); Group B (Placebo)**

Figure 1 shows a descriptive statistical analysis of the variables, Initial Mean after ureteroscopy and 90-day Mean after treatment. In this study, only patients with residual stones after 90 days of treatment were considered. Three months after treatment, Group A showed a reduction in mean residual stone size of 2.83 mm. Results of the Wilcoxon Rank Sum test were statistically significant (p 0.027). Statistically significant reductions were also found in Group B, respectively 1.61 mm, in the Wilcoxon Rank Sum test ($p = 0.001$).

A two-way factorial ANOVA (analysis of variance) revealed statistically significant results, p=0.039. Levene's test indicated homogeneity of variance between groups (greater than 0.05). Based on the results obtained, citrate treatment significantly reduced residual stones size ($p<0.05$) [Table 4].

Table 4. P-value

Stone-free rate	<0.05
Expulsion rate	<0.05
Mean residual stone size	<0.05

P-values were calculated via the χ2 test for stone-free rate and expulsion rate, respectively via two-way factorial ANOVA for mean residual stone size

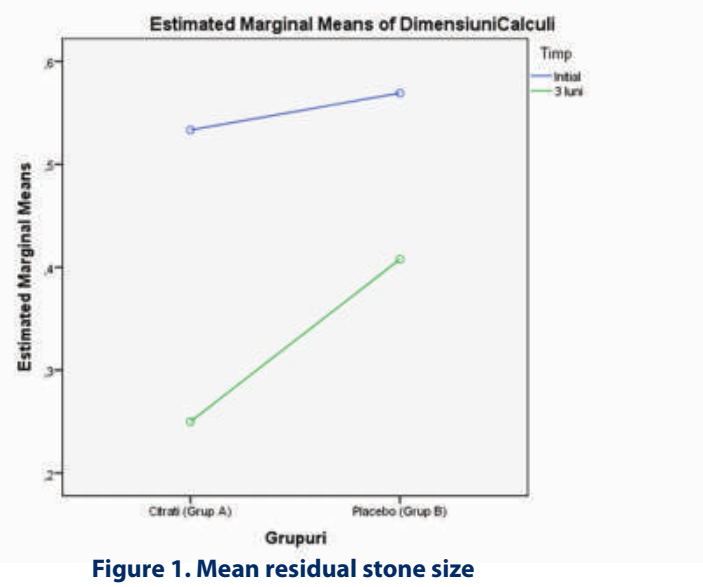


Figure 1. Mean residual stone size

Discussions

For conservative treatment, a stone should be less than 5 mm in size. It is estimated that 75% of stones under 5 mm in size can be eliminated regardless of their location, based on Coll et al.'s study. In one study, Segura et al. reported that 71 to 98% of distal ureter stones less than 5 mm would be eliminated [21, 22]. The study group was compiled using this inclusion criterion. However, small calculi are not guaranteed to disappear spontaneously. A study by Miller et al. examined ureteral calculi passage. When the diameter reaches 2 mm, 5% of patients require endourological intervention, while when it reaches 2 to 4 mm, 17% do[23].

Residual lithiasis fragments may form crystallization nuclei for future urinary stones. Skolarikos et al. estimate that between 21 and 59% of residual fragments will recur over the next 25 years[24].

Therefore, obtaining a stone-free status became a benchmark. During a 15-day study, Conte et al. evaluated the effects of potassium citrate on patients at high risk of kidney stones and compared them to the results obtained by two other groups of patients at high risk (one receiving placebo therapy, the other receiving an additional diet enriched with phytates). According to citrate therapy, 52% of patients had minimal risk of developing kidney stones, which was the highest rate of elimination of lithiasis risk[25].

Pak et al. also report that citrate deficiency contributes to the etiopathogenesis of calcium lithiasis and that citrate treatment is effective in treating kidney stones. A number of metabolic disorders have been linked to urinary stone formation, including hypercalciuria and

hyperuricosuria. Furthermore, a therapeutic regimen involving 20mEq citrate 3 times a day for a period of between 1 and 4.33 years decreased new stone formation by 97.80%, again resulting in 79.80% remission [24]. There is a wide variation in the cost and the amount of citrate in potassium citrate supplements. A supplement that contains alkali citrate can provide satisfactory alkalinization [25]. The results of our study in this context show an 84% stone-free rate, but it is important to note that we used other therapeutic regimens (975 mg of potassium citrate, 60 mg of magnesium citrate, and 25 mg of pyridoxine per sachet), and we had a much shorter follow-up period of only 90 days.

Citrate deficiency also contributes to calcium lithiasis etiopathogenesis, and citrate treatment is effective in treating kidney stones, according to Pak et al. Hypercalciuria and hyperuricosuria are two metabolic disorders associated with urinary stone formation. Moreover, in a treatment regimen consisting of 20mEq citrate taken 3 times a day for 1 to 4.33 years, new stones formed were decreased by 97.80%, again resulting in 79.80% remission [26]. In potassium citrate supplements, the cost and amount of citrate vary widely. Supplements containing alkali citrate can provide satisfactory alkalinization [27]. We found 72.06% of our study participants were stone-free, but it is important to note that we used other therapeutic regimens (975 mg of potassium citrate, 60 mg of magnesium citrate, and 25 mg of pyridoxine per sachet), and our follow-up period was much shorter.

According to Phillips et al., seven randomized controlled trials involving 477 participants were reviewed by Cochrane. A study of citrate therapy found a reduction in stone size of less than 5 millimeters was more likely (relative risk [RR] = 2.35; 95% confidence interval [CI], 1.36 to 4.05) [27]. Additionally, we found that treatment with a combination of citrates significantly reduced residual stone size (2.34 mm compared to 1.54 mm) with a greater mean reduction of residual stone size. In a review conducted by Cochrane, Phillips et al. found seven randomized controlled trials involving 477 participants. Accord to a study conducted on citrate therapy, a reduction in the stone size of less than 5 millimeters was more likely to occur (relative risk [RR] = 2.35; 95% confidence interval [CI], 1.36 to 4.05) [28]. We also found that treatment with a combination of citrates reduced residual stone size by a greater average (2.83 mm over 1.61 mm) than treatment alone.

The study has limitations due to a relatively small number of cases and a short follow-up period. We consider this study to be of high quality despite its single-center limitation.

Conclusion

It was found that pyridoxine, magnesium citrate, and potassium citrate were beneficial when combined with percutaneous nephrolitothripy to improve stone-free rates. This also resulted in higher stone expulsion rates and smaller residual stones. This therapy must be studied with a larger group of participants and be followed up for a longer period of time to determine its efficacy and utility.

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