An Analysis of the Post-interventional Stone-Free rate for patients undergoing Citrates and Pyridoxine Administration

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ABSTRACT

Multiple fragments of kidney stones must be treated adjuvantly following flexible ureteroscopy and Holmium laser lithotripsy to achieve stone-free status. The purpose of this study was to evaluate the effectiveness of citrate and pyridoxine therapy in preventing lithiasis recurrence.

Patients receiving endoscopic treatment for kidney stones were assessed. Our study involved 149 patients with kidney stones up to 2 cm in diameter who received Holmium laser lithotripsy and digital flexible ureteroscopy. After that, a predominantly low-protein diet was followed along with 2-3 liters of water a day - approximately 400 ml every four hours. There were two groups of them. The patients in Group B received only general treatment, while the patients in Group A received a combination of 975 mg potassium citrate, 60 mg magnesium citrate, and 25 mg pyridoxine per sachet in addition to general treatment.

After 90 days, Group A had a higher stone-free rate (84%) than Group B (70.2%) ($p<0.05$). Group A had a higher expulsion rate than Group B (33.33% versus 18.91%, $p<0.05$) and a better reduction in mean residual stone size (2.34mm versus 1.54mm, $p<0.05$).

The use of potassium citrate, magnesium citrate, and pyridoxine provided favorable results following digital flexible ureteroscopy with Holmium laser lithotripsy.

Keywords: kidney stones, pyridoxine, citrates, stone-free rate

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Introduction

The prevalence of kidney stones worldwide is between 5-15%, with no apparent pattern of distribution, with an increasing trend in the last 25 years [1,2]. Approximately 85% of kidney stones contain calcium oxalate (monohydrate or dihydrate) or calcium phosphate. A stone can also be made up of uric acid, urates, cystine, or ammonia-magnesium phosphate [3,4].

As ureteroscopy has become the main treatment modality to target upper urinary pathologies in recent years, semi-rigid and flexible ureteroscopy has become more common for kidney stones [5-7]. It is now possible to perform flexible ureteroscopy to treat kidney stones, reducing surgical trauma as well as complications caused by surgery [8-9]. Its widespread adoption has been attributed to the Holmium laser as a fundamental premise. Stones in the kidney calyx system can be effectively treated with this laser regardless of their composition or location [10]. The pelvicalyceal system is scattered with multiple lithiasis fragments after flexible ureteroscopy and Holmium laser lithotripsy are performed to remove kidney stones. There are always differences in intraoperative complications, and some small fragments of lithiasis remain to be naturally eliminated after surgery because each case is unique [11]. It is usually necessary to undergo adjuvant treatment in order to achieve stone-free status.

There is evidence in the literature that potassium citrate prevents nephrolithiasis by inhibiting stone formation [12-16]. Our study aimed to investigate the effect of potassium citrate, magnesium citrate, and pyridoxine administration on stone-free rates following flexible ureteroscopy and Holmium laser lithotripsy.

Materials and Methods

A total number of 49 patients with kidney stones up to 2 cm in size were enrolled in a prospective, double-blind, randomized trial between January 2018 and November 2020. The instrument used was the 8.4 Fr URF-V3 2001982 (Olympus, Hamburg, Germany). The Holmium laser lithotripsy was performed using a 10.7/12 Fr ureteral sheath (Flexor, COOK medical, Bloomington, Indiana, USA). The laser lithotripsy within the renal pelvis was performed with high power settings - energies of 1-2J and frequencies of 30-60Hz. These settings have been found to be safe and effective for active endourological treatment of renal stones [17].

The following day, a radiologist performed ultrasounds on every patient to assess the remaining fragments. After surgery, X-ray diffraction or infrared spectroscopy were mandatory crystallographic examinations. There was a general treatment regimen consisting of drinking 400ml of water every four hours, supplemented with low-protein foods, such as fruits, vegetables, and fibers.

There were two groups of patients: Group A had 75 patients receiving general treatment along with 2703 mg potassium citrate, 376 mg magnesium citrate, and 25 mg pyridoxine per sachet. Usually, this dose was taken twice daily, at 8am and 8pm. Only general treatment was provided to 74 patients in Group B. A radiologist performed a check-up after 90 days of treatment. According to the lectures [18], ultrasound was performed in all cases. In the event that stones were identified during this examination, low-dose computed tomography (CT scan) was used to determine how many stones were present, their size, and their location in the body.

Patients with oxalate and/or calcium phosphate, uric acid or a combination of these conditions were included in this study, as well as adults who consented, who did not have a urinary tract infection, no cancer pathology, no concurrent or previous cytostatic therapy, or had no endocrinological pathology. The study excluded pregnant women with lithiasis, those with allergies to previous citrate treatments, and those with pathologies contraindicating citrate administration (severe hepatic and renal dysfunction). This study examined the potential of citrate and pyridoxine therapy to prevent lithiasis recurrence in patients with kidney stones following flexible digital ureteroscopy with Holmium laser lithotripsy.

SPSS 20.0 (SPSS Inc., 2012) was used for statistical analyses. The study's main endpoint was the stone-

free rate after endourological therapy. To investigate the primary endpoint for two independent samples, two-sided chi-square tests were used. The variables studied were also analyzed descriptively. In both groups, the secondary endpoint was stone expulsion capacity after 90 days of conservative treatment. The two-sided (chi-square) test was used to determine BMI, stone composition, and this. After 90 days after endourological treatment, residual stone size was another endpoint to be evaluated. To evaluate the differences between the groups at baseline, after surgery, and 90 days after treatment, we used Wilcoxon Rank Sum test and two-way factorial ANOVA (analysis of variance). A natural logarithmic transformation was applied if the outcome variable's distribution was too skewed to the right. Inferential tests were considered significant if the P-value was below 0.05.

The Helsinki Declaration, revised in 2013, was followed in this study. Emergency Clinical Hospital "St. John" Bucharest approved the procedure. Patients participating in the study signed informed consent forms.

Results

In Group A, there are 53.34% male patients, compared to 46.66% female patients, whereas in Group B, there are 51.35% female patients, compared to 48.65% male patients. Statistically, there was no significant difference between the groups, with a p-value of 0.567.

There are many similarities between the two groups in terms of age distribution. In Group A, the mean value was 49.61, while in Group B, it was 47.93. Based on the p-value of 0.494, 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, 25.33 % of patients were in Group A and 32.43% of patients were in Group B. 53.33% for Group A and 51.35% for Group B patients had a BMI from 18.5 to < 25. Regarding BMI from 25 to < 30 we had 16% patients for Group A and 12.16% for Group B. The last category, BMI from 30 to < 35 we had 5.34% patients for Group A and 4.06% for Group B. At the $\chi 2$ test, the p-value was 0.754. 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 and middle calix, and inferior calix. The first category accounted for 70.67% of patients in Group A, while the second category accounted for 29.33%. In Group B, there were 64.86% residual stones in the superior and middle calix, and 35.14% in the inferior calix. As a result of the $\chi 2$ test, the p-value was 0.999. 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 (68% in Group A and 79.73% in Group B). Calculi made of uric acid were reported at 13.3% for Group A and 10.81% for Group B. In only 9.46% of cases mixed composition calculations were identified for group B, compared to group A, where the percentage of those was considerably higher, respectively 18.7%. 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 0.866 was found for no significant differences between the groups.

Table 1. Demographics

	Group A (N=75)	Group B (N=74)	P-value
Age			**0.494**
Mean (SD)	49.61 (15.3)	47.93 (14.6)	
Median [Min, Max]	48.0 [23.0, 84.0]	47.0 [20.0, 79.0]	
Sex			**0.567**
F	35 (46.66%)	38 (51.35%)	
M	40 (53.34%)	36 (48.65%)	
BMI			**0.754**
<18.5	19 (25.33%)	24 (32.43%)	
18.5 to <25	40 (53.33%)	38 (51.35%)	
25 to <30	12 (16%)	9 (12.16%)	
30 to <35 (Class 1)	4 (5.34%)	3 (4.06%)	
Residual stone position			**0.999**
Superior and Middle Calix	53 (70.67%)	48 (64.86%)	
Inferior Calix	22 (29.33%)	26 (35.14%)	
Stone composition			**0.209**
Uric acid	10 (13.3%)	8 (10.81%)	
Calcium Oxalate/ Phosphate	51 (68%)	59 (79.73%)	

	Group A (N=75)	Group B (N=74)	P-value
●*Calcium Oxalate*	*24 (32%)*	*27 (36.49%)*	
●*Calcium Phosphate*	*6 (8%)*	*9 (12.16%)*	
●*Calcium Oxalate and Phosphate*	*21 (28%)*	*23 (31.08%)*	
Mixt	14 (18.7%)	7 (9.46%)	

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

There was a total stone-free rate of 77.2% after 90 days of treatment. Group A had an 84% stone-free rate, while Group B had a 70.3% stone-free rate [Table 2]. The $\chi 2$ test shows a p-value of 0.046, 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	12 (16%)	63 (84%)
Group B	22 (29.7%)	52 (70.3%)
Total	34 (22.8%)	115(77.2%)

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

We found that Group A had a 33.33% stone expulsion capacity at three months, while Group B had an 18.91% stone expulsion capacity [Table 3]. The results were considered statistically significant (the $\chi 2$ test shows a p-value of 0.045) and revealed that patients treated with a combination of citrates had a better stone expulsion rate [Table 4].

Table 2. Stone-free rate at 90 days

	Expulsion	No expulsion
Group A	25 (33.33%)	50 (66.67%)
Group B	14 (18.91%)	60 (81.09%)
Total	39 (26.17%)	110 (73.83%)

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

A descriptive statistical analysis of the variables, Initial Mean after ureteroscopy and 90-days Mean after treatment, was used to investigate the last endpoint [Figure 1]. The only patients considered here were those who still had residual stones after 90 days of treatment. At three months, Group A showed a reduction in mean residual stone size, which was 2.34 mm. Wilcoxon Rank Sum test results were statistically significant (p 0.002). We also found a reduction in the mean residual stone size in Group B, respectively 1.54 mm, which was statistically significant in the Wilcoxon Rank Sum test (p = 0.000). Results of the two-way factorial ANOVA (analysis of variance) were statistically significant, p=0.032. Based on Levene's test, the variance between groups was homogeneous (greater than 0.05). Citrate treatment significantly reduced residual stones size according to the results obtained (F A, B = 4.804, 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

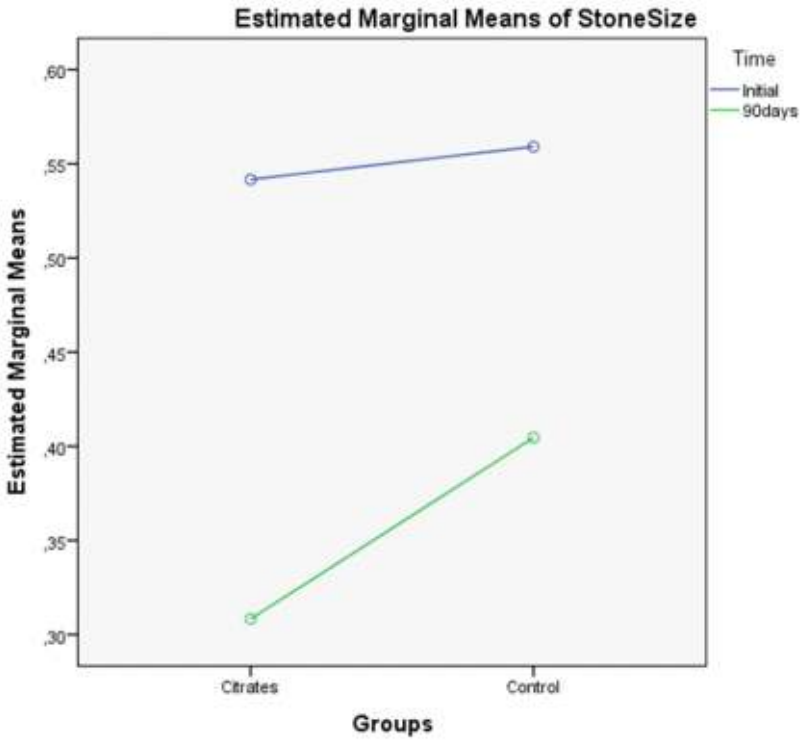


Fig. 1 Mean residual stone size

Discussions

A meta-analysis published in Urolithiasis in 2018 concluded that flexible ureteroscopy has become a minimally invasive surgical method used worldwide over the past 20 years. This surgery is considered the gold standard of treatments for kidney stones less than 2 cm in diameter because of its low morbidity and favorable operative results [47]. For stone lithotripsy during flexible ureteroscopy, the Holmium: yttrium-aluminum-garnet (Ho: YAG) laser and laser fiber have become the standard because of their safety and effectiveness [19].

The optimal size of a stone for conservative treatment is less than 5 mm. According to Coll et al., stones with a size of less than 5 mm have a 75% chance of being eliminated regardless of their location. Segura et al. noted that stones located at the distal ureter less than 5 mm would be eliminated between 71 and 98% [20, 21]. This inclusion criterion was used in compiling the study group. Small calculi, however, do not guarantee their spontaneous elimination. Miller et al. conducted a study about the passage of ureteral calculi. At 2 mm, 5% of patients require endourological intervention; at 2 to 4 mm, the percentage reaches 17% [38].

There is evidence that residual lithiasis fragments form crystallization nuclei for future urinary stones. According to Skolarikos et al. [22], recurrence from a residual fragment is likely to occur between 21 and 59% over the next 25 years. Consequently, obtaining a stone-free status became a benchmark. Conte et al. studied the effects of potassium citrate on a group of patients at high risk of kidney stones for 15 days and compared the results with those obtained by two other groups of patients at high risk for kidney stones (one group received placebo therapy, while the other received an additional diet enriched in phytates). In citrate therapy, 52% of patients were at minimal risk of developing kidney stones, which was the highest rate of elimination of lithiasis risk [23].

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.
Based on a group of 35 patients treated with an average dose of 45.40 ± 15.20 mEq / day, Spivacow et al. reported a remission rate of 91%, higher than that of our study, respectively 77.2% as total stone-free rate [26]. This study had an average follow-up period of 31.60 ± 14.30 months, much longer than our study (which had a follow-up period of only 3 months).

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. A relatively small number of cases and a short follow-up period are limitations of this study. Despite the fact that it is a single-center study, we do not consider these limitations to affect the study's quality.

Conclusion

When combined with magnesium citrate, potassium citrate, and pyridoxine, a favorable effect was found regarding the stone-free rate among patients previously treated with digital flexible

ureteroscopy and Holmium laser lithotripsy. This also led to an increase in stone expulsion rates and a reduction in mean residual stone sizes. A larger study group and a longer follow-up period are needed to determine the utility and efficacy of this therapy and if it can be applied in time.

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