https://doi.org/10.31925/farmacia.2023.3.16 **ORIGINAL ARTICLE**

STONE FREE-RATE EXPERIENCE IN POST-INTERVENTIONAL PATIENTS UNDERGOING CITRATES AND PYRIDOXINE ADMINISTRATION

MIHAI ANDREI ENE [1#], VIOREL JINGA [2,3], PETRIŞOR AURELIAN GEAVLETE [1,2], COSMIN VICTOR ENE [1,2], CĂTĂLIN ANDREI BULAI [1,2], CRENGUTA SORINA SERBOIU [2#], BOGDAN FLORIN 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*
[3] *"Prof. Dr. Theodor Burghele" Clinical Hospital, Bucharest, Romania*

**corresponding author: bogdan_geavlete@yahoo.com*
[#]Authors with equal contribution.

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Abstract

In order to achieve stone-free status following flexible ureteroscopy and Holmium laser lithotripsy of kidney stones, multiple remaining fragments require adjuvant treatment. This study aimed to evaluate the effectiveness of citrate and pyridoxine therapy in preventing lithiasis recurrence. Patients with kidney stones who have undergone endourological treatment were examined. We conducted a prospective, randomized trial study on 182 patients who had kidney stones up to 2 cm in diameter and received digital flexible ureteroscopy with Holmium laser lithotripsy. Afterwards, the general treatment consisted of 2 - 3 L of water *per* day - approximately 400 mL every four hours - and a predominantly low-protein diet. We divided them into 2 groups. Group B received only general treatment, while in Group A (92 patients), a combination of 2703 mg potassium citrate, 376 mg magnesium citrate, and 25 mg pyridoxine *per* sachet was added. At 90 days, the stone-free rate was higher (84.78%) in Group A compared to Group B (70.2%) ($p < 0.05$). It was also found that Group A had a higher expulsion rate than Group B (34.78% *versus* 20%, $p < 0.05$) and a better reduction in mean residual stone size (2.36 mm *versus* 1.66 mm, $p < 0.05$). Administration of potassium citrate, magnesium citrate, and pyridoxine provided favourable results for obtaining stone-free status after digital flexible ureteroscopy with Holmium laser lithotripsy.

Rezumat

Pentru a obține statusul *stone-free* secundar ureteroscopiei flexibile cu litotriție laser Holmium pentru litiaza renală, fragmentele restante necesită tratament adjuvant. Acest studiu are ca scop evaluarea eficacității tratamentului cu citrați și piridoxină în prevenția recurențelor litiazice. Au fost studiați pacienți care au beneficiat de tratament endourologic pentru litiaza renală. Am efectuat un studiu prospectiv, randomizat pe 182 de pacienți cu litiază renală până în 2 cm diametru, care au beneficiat de ureteroscopie flexibilă digitală cu litotriție laser Holmium. Apoi un tratament general care constând în doi-trei litri de apă pe zi - aproximativ 400 mL la fiecare 4 ore - și o dietă săracă în proteine a fost instituit. Am împărțit pacienții în 2 grupuri. Grupul B a primit doar tratament general în timp ce Grupul A a beneficiat de o adăugare a unei combinații de 2703 mg citrat de potasiu, 376 mg citrat de magneziu și 25 de mg piridoxină la acesta. La 90 de zile rata *stone-free* a fost mai mare în Grupul A (84,78%) comparativ cu Grupul B (70%) ($p < 0,05$). De asemenea Grupul A a avut o rată de expulzie mai mare comparativ cu Grupul B (34,78% *versus* 20%, $p < 0,05$) și rezultate mai bune în reducerea dimensiunii medii a litiazei reziduale (2,36 mm *versus* 1,66 mm, $p < 0,05$). Administrarea citratului de potasiu, citratului de magneziu și piridoxinei a oferit rezultate favorabile în obținerea statusului *stone-free* secundar ureteroscopie flexibile digitale cu litotriție laser Holmium.

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

Introduction

Globally, kidney stones are found in about 5 - 15% of the population, without a clear pattern, and are more common among males with an increasing trend in the last 25 years [1, 2]. Kidney stones are usually calcium oxalate (monohydrate or dihydrate), calcium phosphate or a combination of both (about 85% contain calcium). Other stones can be made of uric acid, urates, cystine, or ammonia-magnesium phosphates [3, 4].

In recent years, there has been a growing trend of frequent use of semi-rigid or flexible ureteroscopy for kidney stones, so it has become the main treatment modality to target upper urinary pathologies [5-7] and the minimally invasive surgery of choice for this disease in North America [8, 9]. These minimally invasive techniques have also become widely available in many other parts of the world, allowing flexible ureteroscopy for kidney stones to reduce surgical trauma and complications [10, 11]. A fundamental premise that has led to its widespread adoption is the Holmium laser. This laser is highly effective regardless of the composition or location of the stones in the renal calyx system [12].

Following the practice of flexible ureteroscopy and Holmium laser lithotripsy of kidney stones detected in the kidney, multiple lithiasis fragments are scattered throughout the pelvicalyceal system. Because each case is different, the intraoperative difficulties also differ, with some small lithiasis fragments remaining to be naturally eliminated [13]. Usually, to achieve a stone-free status, adjuvant treatment is required. Some countries use phytotherapy, particularly those without a modern medical system to meet their needs [10, 14]. As major pharmaceutical companies have grown and industrialization has taken place in all fields, pharmaceuticals have developed in recent years [15]. The effectiveness of potassium citrate in the prevention of nephrolithiasis is mentioned in the literature [16], as it is a strong inhibitor of the lithogenesis process [17-20], its widespread use brings economic benefits [21, 22] by avoiding hospitalization and indirect costs. Potassium citrate is easily metabolized in the body. By increasing the excretion of free bicarbonate ions, an increase in urinary pH occurs. Due to a high urinary pH value, the solubility of uric acid will increase, thus allowing it to effectively dissolve the stones of this composition [23]. The mechanism of action of citrates for the inhibitory effect on calcium oxalate crystallization is a reduction of calcium oxalate supersaturation by forming complexes with calcium and direct inhibition of crystal growth and aggregation. The metabolism of absorbed potassium citrate produces an alkaline load, which increases urinary pH and also urinary citrate concentration as a result of enhanced citrate clearance. This reduces the activity of calcium ions by increasing dissociated calcium anions, simultaneously decreasing urine saturation in oxalate or calcium phosphate [24].

The aim of the study was to investigate the effect of administration of the combination of potassium citrate, magnesium citrate, and pyridoxine on the stone-free rate in patients who benefited from flexible ureteroscopy and Holmium laser lithotripsy of kidney stones.

Materials and Methods

Study design

Between January 2018 and November 2021, we conducted a prospective, double-blind, randomized trial on 182 patients with kidney stones up to 2 cm in size who benefited from flexible digital ureteroscopy with Holmium laser lithotripsy. This was performed using the 8.4 Fr URF-V3 2001982 (Olympus, Hamburg, Germany). We used a 10.7/12 Fr ureteral sheath (Flexor, COOK medical, Bloomington, Indiana, USA) during the entire surgery when we performed Holmium laser lithotripsy. In order to perform laser lithotripsy within the renal pelvis, high power settings were used with an energy between 1-2J and a frequency between 30 Hz and 60 Hz. Active endourological treatment of renal stones was found to be safe and effective in these settings [25].

Taking out the fragments at the end of the procedure was accomplished with a Dormia 2.2 Fr (Colopast, Humlebaek, Denmark) basket. The next day a radiologist performed an ultrasound on every patient to evaluate the remaining fragments. Following surgery, crystallographic examinations by infrared spectroscopy or X-ray diffraction were mandatory. Fluid intake may prevent the formation of stones by diluting urine components and decreasing urine acidity, which is well known and recommended as the first step in preventing urolithiasis [26, 27]. A general treatment regimen consisted of drinking approximately 400 mL of water every four hours and eating primarily low-protein foods, including fruits, vegetables, and fibre. According to the literature, those have an influential role in preventing the recurrence of renal stones because their alkaline content increases urinary pH [28-31].

Patients were randomized into two groups: Group A consisted of 92 patients who received general treatment and a combination of citrates - 2703 mg potassium citrate (975 mg potassium), 376 mg magnesium citrate (60 mg magnesium) and 25 mg pyridoxine *per* sachet. This dose was taken 2 times a day, at 8 am and 8 pm usually. Group B consisted of 90 patients who received only general treatment. After 90 days of treatment, a check-up was made by a radiologist (who did not have access to the study data). In all cases, ultrasound was performed as suggested in the lectures [32]. When stones were identified during this examination, a low dose computed tomography (CT scan) was used to determine the exact number, stone size and localization.

Inclusion criteria

For this study, the inclusion criteria were oxalate and/or calcium phosphate, uric acid or a combination of oxalate and/or calcium phosphate and uric acid patients, adults with consent for inclusion, no urinary tract infection, no cancer pathology and no concurrent or previous cytostatic therapy, and no endocrinological pathology.

Exclusion criteria

The study excluded patients who had previously exhibited allergies to citrate treatments, those with pathologies that contraindicated citrate administration (such as severe hepatic or renal impairment), and pregnant women with lithiasis. The aim of the study was to determine whether citrate and pyridoxine therapy could prevent lithiasis recurrence in patients with kidney stones who had undergone flexible digital ureteroscopy with Holmium laser lithotripsy.

Ethics

The present investigation adhered to the tenets of the Helsinki Declaration, which underwent revision in 2013. The institutional Ethical Commission of the Emergency Clinical Hospital "St. John" Bucharest has granted approval. An informed consent form was signed by each patient participating in the study.

Statistical analysis

Statistical analyses were performed using SPSS v. 20.0 (SPSS Inc., 2012). The study's main endpoint was the stone-free rate 90 days after endourological therapy. A two-sided $\chi2$ (chi-square) test was used to investigate the primary endpoint for two independent samples. This test was used because the outcome is a binary categorical variable with more than five cases in each category (the outcome is the stone-free rate after 90 days). A descriptive statistical analysis of the variables used in the study was also performed. The secondary endpoint was stone expulsion capacity in both groups after 90 days of conservative treatment. The stone expulsion meant that the patients recovered a stone during miction. It should be noted that this does not mean that the stone-free status has been implicitly achieved, since there have been patients who had multiple stones and successfully expelled one or more of them, but did not achieve a stone-free status. The two-sided $\chi2$ (chi-square) test was used to investigate this, the BMI and the stone composition in each group. Another endpoint was the effect of residual stone size 90 days after endourological therapy. We used the Wilcoxon Rank Sum test for each group and a two-way factorial ANOVA (analysis of variance) to evaluate the groups differences at baseline, after surgery and the effects of treatment, after 90 days. If the distribution of the outcome variable was too skewed to the right, the variable was transformed with a log transformation based on the natural logarithm. p-values below 0.05 obtained in the inferential tests were considered statistically significant.

Results and Discussion

Regarding gender distribution, in Group A the percentage of male patients is 53.26% compared to female patients 46.74%, while in Group B it can be found 51.11% female patients, compared to 48.89% male patients. There were no statistically significant differences between the groups, with the p-value being 0.555.

The similarities between the two groups can be noticed in terms of age distribution. The mean for Group A is 49.3, while for Group B the value is 47.86. The p-value was 0.514, so we did not find any statistical differences.

In terms of BMI, we had no patients who were classified as Class 2 or Class 3 obese. For BMI < 18.5, we had 25% of patients in Group A and 30% of patients in Group B. 52.17% for Group A and 50% for Group B patients had a BMI from 18.5 to < 25. Regarding BMI from 25 to < 30 we had 15.22% of patients in Group A and 12.22% in Group B. The last category, BMI from 30 to < 35 we had 7.61% of patients in Group A and 7.78% in Group B. At the $\chi2$ test, the p-value was 0.86. There were no differences of statistical significance between the groups.

All residual stones were less than 6 mm in diameter. Considering their position, we classified them into two categories: superior and middle calix, and inferior calix. In Group A, 71.74% of patients were in the first category and 28.26% in the second. In Group B, there was a prevalence of 68.89% of residual stones in the superior and middle calix, and 31.11% in the inferior calix. At the $\chi2$ test, the p-value was 0.674. There were no statistically significant differences between the groups.

Following the postoperative crystallographic analysis, it was found that calcium oxalate/phosphate was the most common composition for both groups (69.56% for Group A and 80% for Group B, respectively). Calculi made of uric acid were reported as a percentage of 13.04% for Group A and 12.12% for Group B. In only 8.88% of cases mixed composition calculations were identified for group B, compared to group A, where the percentage of those was considerably higher, at 17.4%. In the $\chi2$ test, the p-value was 0.192, so there were no differences of statistical significance between the groups (Table I). The same $\chi2$ test was previously used for the calcium oxalate and/or phosphate stones composition and no differences of statistical significance were found between the groups, with a p-value of 0.964.

After 90 days of treatment, a total stone-free rate of 77.47% was found. In Group A, the stone-free rate was 84.78%, and in Group B, the stone-free rate was 70% (Table II). The $\chi2$ test shows a p-value of 0.017, equivalent to the fact that the results obtained are statistically significant (Table IV).

Investigating the secondary endpoint of the study, the stone expulsion capacity at three months for the entire lot, we found a 34.78% rate for Group A and a 20% rate for Group B (Table III). The results were considered statistically significant (the $\chi2$ test shows a p-value of 0.026) and revealed that patients treated with a combination of citrates had a better stone expulsion rate (Table IV).

In order to investigate the last endpoint of the study (Figure 1), we utilized a descriptive statistical analysis of the variables, initial mean after ureteroscopy and 90-day mean after treatment. These were taken into account only for patients who still had residual stones after 90 days of treatment. In Group A we found a reduction at three months in the mean residual stone size, of 2.36 mm. The results were statistically significant in the Wilcoxon Rank Sum test (p = 0.001). In Group B we also found a reduction in the mean residual stone size at three months, respectively of 1.66 mm, a value that was statistically significant at the Wilcoxon Rank Sum test (p = 0.000). The outcome of comparing the groups using a two-way factorial ANOVA (analysis of variance) revealed statistically significant results, p = 0.034. Levene's test indicated a value of 0.374 (greater than 0.05) which meant that we had homogeneous variances between groups. Citrate treatment significantly reduced residual stones according to the results obtained ($F_{A,B} = 4.667$, $p < 0.05$) (Table IV).

Table I

Demographics

	Group A (N = 92)	Group B (N = 90)	p-value
Age			**0.514**
Mean (SD)	49.3 (15.1)	47.86 (14.7)	
Median [Min, Max]	48.0 [21.0, 84.0]	47.0 [20.0, 82.0]	
Sex			**0.555**
F	43 (46.74%)	46 (51.11%)	
M	49 (53.26%)	44 (48.89%)	
BMI			**0.86**
< 18.5	23 (25%)	27 (30%)	
18.5 to < 25	48 (52.17%)	45 (50%)	
25 to < 30	14 (15.22%)	11 (12.22%)	
30 to < 35	7 (7.61%)	7 (7.78%)	
(Class 1)			
Residual stone position			**0.674**
Superior and Middle Calix	66 (71.74%)	62 (68.89%)	
Inferior Calix	26 (28.26%)	28 (31.11%)	
Stone composition			**0.192**
Uric acid	12 (13.04%)	10 (12.12%)	
Calcium Oxalate/Phosphate	64 (69.56%)	72 (80%)	
*Calcium Oxalate	37 (40.22%)	42 (46,67%)	
*Calcium Phosphate	9 (9.78%)	11 (12.22%)	
*Calcium Oxalate and Phosphate	18 (19.56%)	19 (21.11%)	
Mixt	16 (17.4%)	8 (8.88%)	

Table II

Stone-free rate at 90 days

	Residual stone	Stone-free
Group A	14 (15.22%)	78 (84.78%)
Group B	27 (30%)	63 (70%)
Total	41 (22.53%)	141 (77.47%)

Group A (Treatment); Group B (Control)

Table III

Expulsion rate

	Expulsion	No expulsion
Group A	32 (34.78%)	60 (65.22%)
Group B	18 (20%)	72 (80%)
Total	50 (27.47%)	132 (72.53%)

Group A (Treatment); Group B (Control)

Table IV

p-value

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

p-values were calculated via the $\chi2$ test for stone-free rate and expulsion rate, respectively *via* two-way factorial ANOVA for mean residual stone size

With the help of electron microscopy (TEM), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), transmission electron microscopy (TEM) and the nanoparticle size analyser, it was revealed that calcium phosphate, uric acid and magnesium ammonium phosphate particles coexist in lithiasis formed from calcium oxalate. As a confirmation, almost all of them showed sharp corners with sizes varying from a few nanometers to a certain number of microns. The tendency to aggregate was identified, thus realizing the premises of the lithogenesis potential [33].

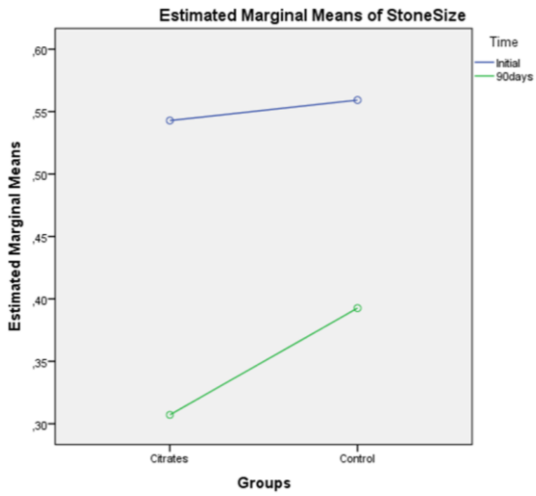

Figure 1.

Mean residual stone size

According to the latest guidelines [34], all first-time kidney stone patients should undergo stone analysis. The analytical procedures most commonly used are infrared spectroscopy (IRS) or X-ray diffraction (XRD) [35-37].

There are several limitations to this study, including a relatively small number of cases and a short follow-up period. In view of the strict inclusion criteria, even though it is a single-centre study, we do not consider these limitations to affect the quality of the study.

Nowadays, a stone size of less than 5 mm is considered optimal for initiating conservative treatment. Using computed tomography, Coll *et al*. showed that the chances of eliminating a stone with a size of less than 5 mm are 75% regardless of its location. At the same time, Segura *et al*. noted that the chances of eliminating a stone located at the distal ureter less than 5 mm are between 71% and 98% [38, 39], an inclusion criterion that we relied on in compiling the study group. However, the small size of the calculus is not equivalent to a guarantee of its spontaneous elimination. Miller *et al*. conducted a study about the passage of ureteral calculi. Even at a size of 2 mm, 5% of patients required endourological interventions while, in the case of those with stones between 2 mm and 4 mm in size, the percentage can reach 17% [40].

The residual lithiasis fragments have been shown to form crystallization nuclei for future urinary stones. The chance of their recurrence starting from a residual fragment is between 21% and 59% over the next 25 years of evolution according to a study by Skolarikos *et al*. [41]. The stakes of obtaining stone-free status became a benchmark in these cases. Conte *et al*. followed for 15 days the effect of treatment with potassium citrate in a group of patients at high risk of developing kidney stones and compared the results obtained with those of two other groups of patients at high risk of kidney stones (in one group placebo therapy was used, while the other group was given an additional diet rich in phytates). Patients receiving citrate therapy had the highest rate of elimination of the risk of developing lithiasis, with 52% of patients at minimal risk of developing kidney stones [42].

An 89-case study by Pak *et al*. also indicates the role of citrate deficiency in the etiopathogenesis of calcium lithiasis and the efficacy of citrate treatment in kidney stones. In some cases, this condition has been linked to other metabolic disorders, including hypercalciuria and hyperuricosuria, both of which are correlated with urinary stone formation. Also, a therapeutic regimen with 20 mEq citrate 3 times a day, for a period that was between 1 and 4.33 years, caused a 97.80% decrease in the formation of new stones and once again remission was obtained at 79.80% [43]. However, potassium citrate supplements vary widely in their cost and citrate content. Supplements offer satisfactory alkali citrate and can be utilized in alkalinization regimens [44]. In this context, the outcomes of our study show a good stone-free rate – 84.78%, but it should be noted that other therapeutic regimens were used (2703 mg of potassium citrate, 376 mg of magnesium citrate and 25 mg of pyridoxine *per* sachet), as well as a much shorter follow-up period of only 90 days.

Spivacow *et al*. followed the remission rate of kidney stones in a group of 35 patients treated with an average dose of 45.40 ± 15.20 mEq/day, and the result was a remission rate of 91%, higher than that of our study, respectively 77.2% as total stone-free rate [45]. And in this study, the average follow-up period was 31.60 ± 14.30 months, much higher than in our study (which was only 3 months).

Due to the lack of important studies on the utility of citrates after flexible ureteroscopy with laser lithotripsy, we had to compare our outcomes to other surgical technique studies for kidney stones. The study of Elbaset *et al*. is a controlled clinical trial, on a sample of 150 patients, randomized into 3 groups: in the first group only oral citrate treatment was administered, in the second group shock wave lithotripsy (SWL) treatment was used, and in the third group the therapy administered was the combination of SWL and oral citrate therapy. The main focus of the study was Stone-Free-Rate (SFR) 3 months (90 days) after the start of therapy. The best results were obtained in patients who underwent SWL and were given oral citrate therapy [46]. This is an aspect compared to that in our study, in which general treatment with drug-associated therapy after surgery had the best outcome.

The study of Lojanapiwat *et al*., a randomized controlled trial, on a sample of 76 patients treated with extra-corporeal shock wave litho-tripsy (ESWL) and per-cutaneous nephrolithotomy (PCNL) who had residual stones less than 4mm or were stone-free, divided into two groups: one group (study group) received oral therapy with citrate, while the other group received a placebo treatment, found that the 12-month SFR for the residual stone group was higher in patients receiving citrate treatment (30.8%) than in placebo-treated patients (9.1%), which leads to a similarity to the results obtained in our study [47].

According to Rosa *et al*., the utility of using various citrate preparations (sodium-potassium citrate, potassium citrate, potassium magnesium citrate, potassium bi-carbonate and sodium bicarbonate) is known to reduce the risk in stone-former patients. As such, citrate supplementation could play an important role in expulsion therapy after SWL. Our outcomes are similar to those, with the stone expulsion capacity being improved for patients treated with a combination of citrates after flexible ureteroscopy with laser Holmium lithotripsy [48].

In a meta-analysis published in 2018 in Urolithiasis, Doizi *et al*. concluded that flexible ureteroscopy has become a minimally invasive surgical method used worldwide for the past 20 years. Low morbidity and favourable operative results were the starting points for this surgery to be considered the gold-standard of treatment for kidney stones below 2 cm [49]. Because of its safety and excellent results, using Holmium: yttrium-aluminum-garnet (Ho:YAG) laser and laser fibre has become the standard for stone lithotripsy during the fURS procedure [50].

As a result of a Cochrane review of seven randomized controlled trials involving 477 participants, Phillips *et al*. found citrate therapy increased the likelihood of stone size reduction to less than 5 mm (relative risk [RR] = 2.35; 95% confidence interval [CI], 1.36 to 4.05) [51]. In line with this, our results also showed that the mean reduction of residual stone size was greater in the group that received treatment with a combination of citrates (2.36 mm compared to 1.66 mm).

Conclusions

The administration of the combination of potassium citrate, magnesium citrate, and pyridoxine emphasized a favourable impact concerning the stone-free rate in patients previously benefiting from digital flexible ureteroscopy and Holmium laser lithotripsy for renal calculi. Moreover, this therapeutic approach helped increase the stone expulsion rate and the reduction in mean residual stone size, but more studies need to be conducted with larger study groups and longer follow-up periods.

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Conflict of interest

The authors declare no conflict of interest.

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