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ORIGINAL PAPER

EFFECTIVENESS OF COMBINED THERAPY IN UROLITHIASIS

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Abstract

Introduction. Urinary lithiasis is an important health issue, with an estimated prevalence of 2-3% in the general population and about 70% of recurrence rate.
The objective of the study. To evaluate the efficacy of combined medication (potassium and magnesium tribasic citrate and pyridoxine) versus traditional general recommendations, in removing the remaining stone fragments after extracorporeal shock wave lithotripsy, ureteroscopy and percutaneous nephrolithotomy.
Material and methods. The study enrolled 60 patients after kidney or ureteral stones treatment performed by extracorporeal shock wave lithotripsy (ESWL), with signs of calculus disintegration, ureteroscopy (URS) with contact lithotripsy, and after percutaneous nephrolithotomy (PNL). The patients were randomly divided into 2 groups. Patients from Group I (n=30) were administered potassium citrate tribasic 2.7 gr, magnesium citrate tribasic 376 mg, pyridoxine 25 mg in sachet, twice daily for two months. The control group (Group II), initially consisting of 30 patients, was prescribed only general recommendations.
Results. The increase in daily diuresis was statistically significant compared to the control group (2275±257 mL vs 1580 ± 321 mL, p <0.05). The urine pH in the

Résumé

L'efficacité de la thérapie combinée dans la lithiase urinaire

Introduction. La lithiase urinaire est un problème de santé significatif, avec une prévalence rapportée à la population générale estimée à 2-3% et un taux de récidive d'environ 70% tout au long de la vie.
L'objectif de l'étude. Évaluer l'efficacité des médicaments combinés (citrate tribasique de potassium et de magnésium et pyridoxine) par rapport aux recommandations générales traditionnelles, pour éliminer les fragments des calculi restants après la lithotripsie extracorporelle par ondes de choc, urétéroscopie et néphrolithotomie percutanée.
Matériel et méthodes. Dans l'étude, 60 patients ont été inscrits juste après le traitement des calculi rénaux ou urétéraux effectué par lithotripsie extracorporelle par ondes de choc (ESWL), avec des signes de désintégration du calcul, de l'urétéroscopie (URS) avec lithotripsie de contact et après néphrolithotomie percutanée (PNL). Les patients ont été répartis au hasard en 2 groupes de recherche. Les patients du groupe I (n = 30) ont reçu du citrate de potassium tribasique 2.7 gr, du citrate de magnésium tribasique 376 mg, de la

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study group was statistically significant higher (7.1±0.3) compared to the control group (6.2±0.9), p <0.01. The renal colic during the expulsion period of disintegrated calculus fragments was present in 1.8±0.3 cases (study group) compared with 6.7±0.8 (control group), p> 0.001. The „stone-free" rate was the basic index of the study. The rate of spontaneous removal of disintegrated stone fragments was 90.0% in the study group compared with 71.4% in the control group (p <0.05). The visual analogue scale (VAS) score was 4 points in the study group and 7 points in the control group.

Conclusions. The addition of combined therapy in the postoperative treatment of urinary calculi reduces the expulsion time of disintegrated calculus fragments, the number of attacks of renal colic and possibly the need for analgesic administration.

Keywords: urolithiasis, combined therapy, extracorporeal shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy.

Abbreviations:
ESWL – extracorporeal shock wave lithotripsy
URS – ureteroscopy
PNL – percutaneous nephrolithotomy
VAS – visual analogue scale

pyridoxine 25 mg en sachet deux fois par jour pendant deux mois. Le groupe témoin (groupe II), composé initialement de 30 patients), s'est vu prescrire quelques recommandations générales.

Résultats. L'augmentation de la diurèse quotidienne a été statistiquement significative par rapport au groupe témoin (2275±257 mL vs 1580±321 mL, p<0,05). L'étude du pH urinaire joue également un rôle central, étant du point de vue statistique significativement plus grand pour le lot de base: 7,1±0,3 contre 6,2±0,9 (p<0,01) pour le groupe de contrôle. La présence de la colique néphrétique dans la période d'expulsion des fragments désintégrés a présenté les résultats suivants : dans 1,8±0,3 des cas (le lot soumis à l'étude) contre 6,7±0,8 (le groupe témoin), p>0,001. Cela démontre la récurrence plus accentuée des troubles rénaux parmi les patients auxquels on n'a pas administré un traitement combiné**.** L'indice de référence de l'étude a été le taux de „stone-free". Le taux d'élimination spontanée des fragments désintégrés a atteint 90% dans le lot d'étude, contre 71,4% dans le groupe de contrôle (p<0,05). Le score de l'échelle visuelle analogue d'évaluation de la douleur enregistrée: 4 points dans le lot d'étude et 7 points dans le groupe témoin.

Conclusions. L'application du traitement combiné en post-opératoire des calculi rénaux réduit la durée d'expulsion des fragments désintégrés, le nombre d'accès de la colique néphrétique et éventuellement la nécessité d'administration des antalgiques. L'administration de médicaments a démontré le manque d'effets indésirables significatifs, s'étant avérée une option de traitement sûr et efficace.

Mots-clés: urolithiase, traitement combiné, lithotripsie extracorporelle (par ondes de choc), urétéroscopie, néphrolithotomie percutanée.

Introduction

The incidence of urolithiasis has dramatically increased over the last 30 years, probably because of the environmental changes[1-2]. It is one of the most common diseases of the kidneys and urinary tract. The probability of urolithiasis occurrence before 70 years is 12.5%[3]. While most people with renal lithiasis have only one episode, 35% of patients have two or more relapses[2,4]. Renal lithiasis is considered a chronic disease, as the cumulative recurrence rate increases progressively from the onset of urolithiasis and reaches 70% over 10 years[2]. Calculi can form anywhere in the urinary tract, but most commonly they are placed in the kidneys and ureters (92%), bladder (7%), urethra (1.4%)[2].

There are three groups of calculi: group I, calcium calculi (salts of calcium oxalate, calcium phosphate and calcium carbonate) – 65-75%; group II, mixed calculi containing magnesium, ammonium and calcium phosphates (struvite) – 5-15%; group III, uric acid calculi – 5-15%[1,2].

The deficiency of vitamin B6 has an important role in the occurrence of oxalate renal lithiasis. It is known that the treatment of endogenous hyper oxalemia with pyridoxine reduces the level of oxalic acid in the blood and urine[7-9].

Magnesium is a known inhibitor of calcium oxalate crystal formation in the urine. The effect of magnesium on calciuria was first described in 1909 by Mendel and Benedict. Thus, it is known that magnesium is capable of forming complexes with oxalates in the intestinal lumen and urine, in order to inhibit

the formation of calcium oxalate crystals in vitro and to increase citrate excretion with urine, in the case of magnesium in the form of citrate salts[10,11].

The value of the urine pH plays an important role in the formation of uric acid and phosphate stones. Epidemiological studies revealed that a decrease in the urine pH below 6.5 is the main factor in the pathogenesis of urate stone formation, while the pH level higher than 7.0 results in phosphate stone formation[12,13].

In recent years, extracorporeal and endourological methods are often used to remove reno-ureteral stones. The incomplete destruction of stones and the presence of residual fragments is a big problem in preventing the disease recurrence. Given the high frequency and recurrence of urolithiasis, long-term pharmacological treatment is necessary to reduce the risk of calculus formation in this category of patients.

Potassium magnesium tribasic citrate is a dietary supplement administered for the treatment of metabolic disorders predisposing to kidney stones. After administration, potassium magnesium tribasic contributes to rapid and painless elimination of kidney stones or stone fragments following the last intervention of stone disintegration, preventing their occurrence, as well as increasing the solubility of kidney stones to be eliminated with urine. Also, long-term administration of potassium and magnesium tribasic allows maintaining an optimal urine pH, necessary to prevent the occurrence of kidney stones in patients prone to renal calculi formation.

Citrate mixtures combined with pyridoxine and magnesium are recommended by the European Association of Urology Urolithiasis Guidelines (2018) in the prevention and treatment of reno-ureteral lithiasis[14].

The objective of the study was to evaluate the efficacy of combined medication (potassium and magnesium tribasic citrate and pyridoxine) versus traditional general recommendations, in removing the remaining stone fragments after extracorporeal shock wave lithotripsy, ureteroscopy and percutaneous nephrolithotomy.

Material and methods

The prospective study was performed in the Republican Clinical Hospital „Timofei Mosneaga", Department of Urology and Surgical Nephrology,

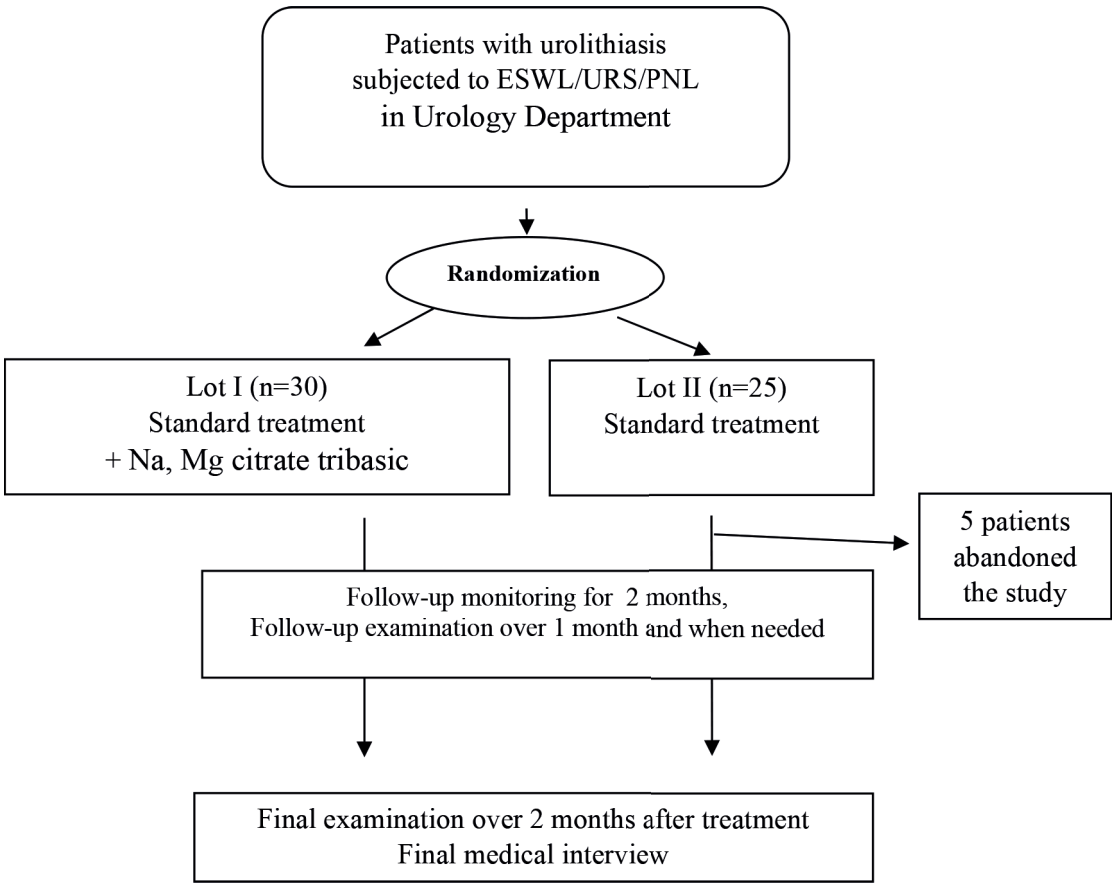

Fig. 1. Study design

Table 1. Demographic data of the patients included in the study.

Indices	*Study lot n=30*	*Control lot (n=25)*	*P*
Men, n (%)	19 (63.33%)	15 (60%)	>0.05
Women, n (%	11 (36.67%)	10 (40%)	
Urban, n (%)	18 (60%)	16 (64%)	>0.05
Rural, n (%)	12 (40%)	9 (36%)	
Age /years/ (Mean±SD)	47.17±7.2	48.19±7.6	>0.05
<30: n (%)	2 (6.67%)	2 (8%)	>0.05
30-55: n (%)	6 (20%)	4 (16%)	
>55: n (%)	22 (73.33%)	19 (76%)	
BMI (kg/m^2)			
Normal weight 18.50-24.99, n (%)	13 (43.33%)	12 (48%)	>0.05
Overweight 25.00-29.99, n (%)	11 (36.67%)	8 (32%)	
Class I obesity 30.00-34.99, n (%)	5 (16.67%)	4 (16%)	
Class II obesity 35.00-39.99, n (%)	2 (6.67%)	1 (4%)	
Treatment method of urinary calculi			
ESWL	14 (46.67%)	10 (40%)	>0.05
URS	11 (36.67%)	10 (40%)	
URS+ESWL	2 (6.67%)	5 (20%)	
URS+stent	1 (3.33%)	0 (0%)	
PNL	2 (6.67%)	0 (0%)	
Location of calculi			
Renal calculus	16 (53.33%)	10 (40%)	>0.05
Ureteral calculus	14 (46.67%)	15 (60%)	
Calculus on the left	17 (56.67%)	13 (52%)	>0.05
Calculus on the right	13 (43.33%)	12 (48%)	

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The study enrolled 60 patients immediately after kidney or ureteral stones treatment performed by extracorporeal shock wave lithotripsy (ESWL), with signs of calculus disintegration, ureteroscopy (URS) with contact lithotripsy, and after percutaneous nephrolithotomy (PNL). After obtaining the informed consent, the patients were randomly divided into 2 research groups. The study design is shown in Figure 1. Patients from group I (n=30) were administered potassium citrate tribasic 2.7 gr, magnesium citrate tribasic 376 mg, pyridoxine 25 mg in sachet twice daily for two months. The control group (group II), initially consisting of 30 patients (5 patients lost without reason mentioning), was prescribed only general recommendations (e.g. adequate hydration with 2-2.5 L of liquids per 24 hours, medicinal herbal teas or diuretic teas, diet without irritants (pungent, peppery and sour food, alcohol, caffeine, etc).

Evaluation criteria:

- Number of kidney colic.
- Need for analgesic medication (+ administered doses).
- Residual stone fragments over 1 month and 2 months.
- Stein-Strasse, the need for repeated ESWL or URS, additional invasive treatment.
- Follow-up monitoring of leukocyturia, hematuria, proteinuria, bacteriuria, urine pH; urine culture – to confirm the presence of leukocyturia and urinary tract infection.
- Follow-up monitoring of urine ionogram.

Exclusion criteria:

- Any disease or condition compromising the hematopoietic, renal, endocrine, pulmonary, central nervous, cardiovascular, immunological, dermatological, gastrointestinal or other systems.
- History of allergic conditions – asthma, urticaria, eczema.

Table 2. Results of general urine analysis with nycthemeral biochemical urine testing.

Indices	*Reference values*	*Study lot n=30 (mean±SD)*		*Control lot n=25 (mean±SD)*		*P*
		I analysis	*II analysis*	*I analysis*	*II analysis*	
Quantity	>2000 mL	1238±179	2275±257	1610±237	1580±321	<0.05
Acidity /pH	4.5 – 8.0	6.2±0.8	7.1±0.3	6.1±0.7	6.2±0.9	<0.05
Density	1 015 – 1 035	1027±6	1017±8	1030±6	1025±9	<0.05
Potassium /mmol/L	1.0 – 500.0	402±159	396±158	303.31±142	304.12±143	>0.05
Calcium /mmol/24h	2.5 – 7.5	6.25±3.37	6.26±3.38	5.02±2.6	5.03±2.61	>0.05
Magnesium /mmol/24h	3.0 – 5.0	3.1±1.57	4.9±2.2	3.67±1.61	3.74±1.62	<0.05
Sodium /mmol/L	25.0 – 1000.0	823±356	826±357	972±412	934±401	>0.05
Phosphorus /mmol/24h	12.9 – 42.0	31.14±15	32.12±17	32.10±15	32.16±16	>0.05
Uric acid /µmol/day	1500 – 4500	3005±1298	3010±1299	3026±1310	3054±1321	>0.05

Note: p – difference between initial and final data (at the end of the study).

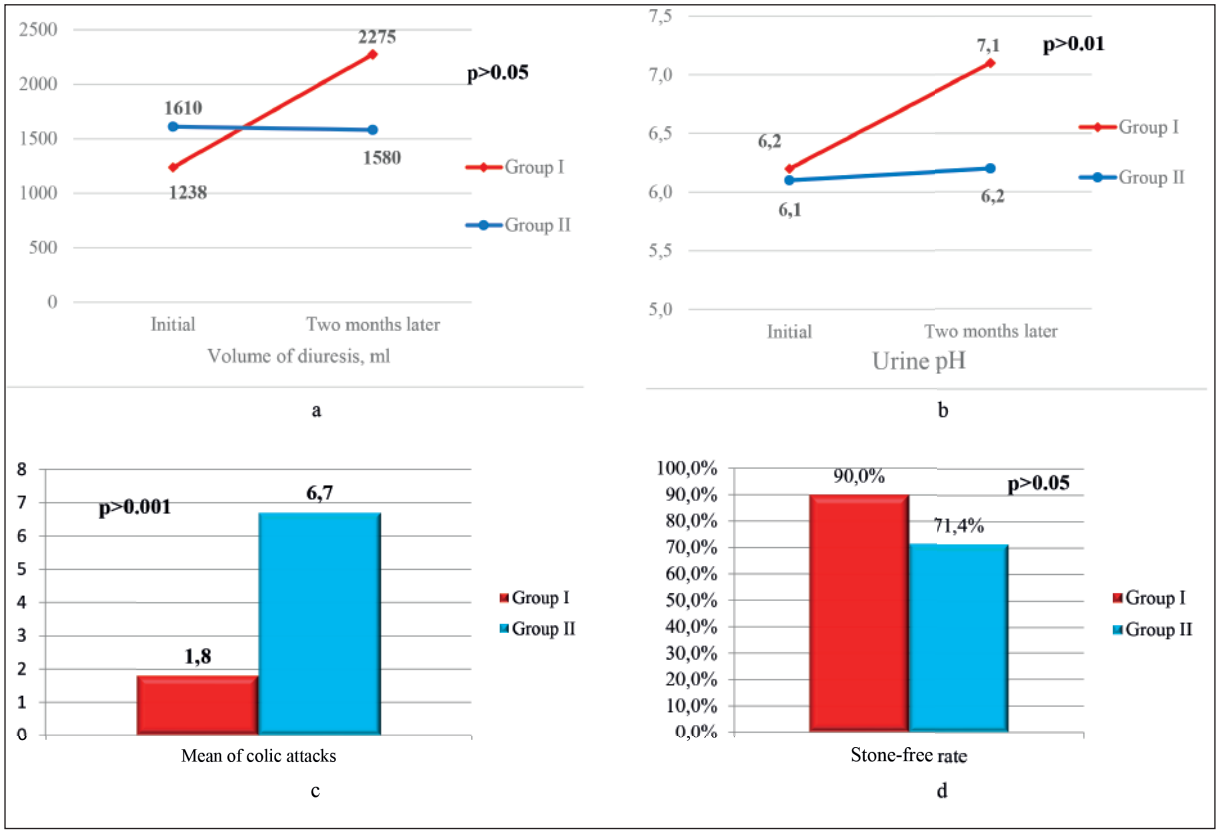

Fig. 2. Comparative results of (a) diuresis volume, (b) urine pH, (c) mean renal colic attacks and (d) stone-free rate of the patients in the studied groups.

Patients were subject to the following tests: urine analysis with urine sediment examination, assessment of potassium, calcium, magnesium, sodium, phosphorus, uric acid in 24 hours urine. The analyzes were performed according to standard procedures.

Statistical processing of the obtained results was performed by means of the MS Excel 2013 software and the SPSS 20 program (StatSoft). Descriptive and percentage statistics, t-Student and $\chi 2$ tests were used. The significance threshold for comparisons was set at 5% (p <0.05).

Results

The demographic data of the patients included in the study are presented in Table 1. The distribution by sex was: men – 34 (61.8%), women – 21 (38.2%). The mean age of the patients in the study group was 47.17±14 years (ranged from 24 to 67 years). The

analysis of the patients enrolled in the study found that the majority of the patients had a normal body mass – 13 pts (43.33%), 11 pts (36.67%) were overweight, 5 pts (16.67%) had class I obesity, 2 pts (6.67%) class II obesity. The difference between the study group and the control group was not statistically significant.

The data of urine examination with 24-hours biochemical urine testing are presented in Table 2. The results show that, after the administration of potassium and magnesium tribasic citrate with pyridoxine in Group I, the level of urine pH increased: the indices recorded before the medication administration were 6.2±0.8, and after the preparation administration 7.1±0.3, statistically significant ($p<0.05$). At the same time, increased magnesium level in the 24-hours urine was observed: before drug administration 3.1±1.57 mmoL/24h, after drug administration 4.9±2.2 mmoL/24h, a significant increase being noticed ($p <0.05$).

The data obtained in the study show that the increase in daily diuresis was statistically significant compared to the control group (2275±257 mL vs 1580±321 mL, $p <0.05$). The urine pH analysis has a special role, which in the study group (7.1±0.3) was statistically significant higher compared to the control group, 6.2±0.9 ($p <0.01$). The presence of renal colic during the expulsion period of disintegrated renal stone fragments showed the following results: 1.8±0.3 cases (study group) compared with 6.7±0.8 (control group), $p> 0.001$. This suggests the fact that renal disorders are more common in patients in whom potassium and magnesium tribasic was not administered. The basic study index was the „stone-free" rate. The rate of spontaneous removal of disintegrated calculus fragments was 90.0% in the study group (27/30), compared with 71.4% (20/28) in the control group ($p <0.05$), thus proving the drug effectiveness. The visual analogue scale (VAS) score was 4 points in the study group and 7 points in the control group. The comparative results of the studied indices are shown in Figure 2.

Discussion

Citrate is well known as a potent inhibitor of the crystallization of calcium salts. The combined therapy with citrate salts is commonly prescribed in clinical practice, in order to increase the urinary citrate and to reduce stone formation. Up to now, citrate was not studied alone, but only in combination with other drugs[4]. In our patients, the potassium and magnesium citrate significantly increased the urinary pH. There are no studies regarding the influence of potassium and magnesium citrate on urinary stone passage. It is known that urinary pH can influence ureteral peristalsis. In an animal model, Smith et al showed that intracellular alkalinity inhibited the amplitude of the action potential, therefore decreased the excitability of the cell[15]. While potassium citrate solution might lower the recurrence rate of calcium oxalate stones, the same effects were not seen with magnesium salts[14,16,17]. Therefore, administering magnesium salts alone has not been recommended[17]. Tiselius et al revealed an increased amount of urine calcium and no changes in urinary excretion of magnesium and oxalate in 12 months consumption of magnesium oxide[17]. Therefore, our results support unselective use of citrate for preventing calcium oxalate lithiasis. Miller and Kane noticed that 95% of stones ≤4 mm pass within 40 days[18]. Pricop et al recommended to invite patients after 4 weeks, for evaluation of the clinical status and general analysis of urine[19]. Clinicians should be aware that potassium salts can irritate the gastrointestinal tract[20]. During this period, pain, gastrointestinal intolerance, or signs of urinary infection (fever, leukocytes in urine), should be monitored[17,18]. In our study, we have decided to recall patients for hospital visits after 8 weeks, if no events occurred (intense pain, fever that would justify the change of the therapeutic strategy). EAU Guidelines on urolithiasis sustain that drug administration of combined therapy in urolithiasis has shown the lack of significant side effects, being a safe and effective treatment option[14]. Ceban et al recommended to not use active combined therapy in patients with active urinary tract infection with either urea-splitting or other organisms, in association with either calcium or struvite stones[7,8]. In our study, we demonstrated that the combined drugs administration increased the daily diuresis statistically significant, increasing the excretion of uric acid. The action of potassium and magnesium tribasic on urine pH leads to urine alkalinity, increasing the rate of spontaneous elimination of calculi pieces after different methods of stone fragmentation (ESWL, URS, PNL)[21,22].

The presented study had several limitations. The number of patients was too small to allow a definitive decision of drug effectiveness for each type of urinary metabolic abnormality and stone removal type. The study observed no treatment failures to analyze reasons for failure. Similarly, we cannot provide evidence to show whether the new combination has better tolerability or effectiveness. A big number of patients would be required to have enough power to determine whether these similar drugs have clinical differences. Further studies are needed to determine the role of an alkaline urinary pH on ureteral peristalsis and whether the association of the studied expelling agents with each other or with a non-steroidal anti-inflammatory agent can accelerate the process of eliminating the residual fragments of stones.

Conclusions

The drug administration increased the daily diuresis statistically significant, increasing the excretion of uric acid. The action of potassium and magnesium tribasic on urine pH leads to urine alkalinity, increasing the rate of spontaneous elimination of calculi pieces after fragmentation.

The administration of potassium and magnesium tribasic increases the excretion of ionized oxalate, as a result the crystallization formation is blocked. The addition of potassium and magnesium tribasic in the postoperative treatment (ESWL, URS, PNL) of urinary calculi reduces the expulsion time of disintegrated calculi fragments, the number of attacks of renal colic and possibly the need for analgesic medication. The drug administration has shown the lack of significant side effects, being a safe and effective treatment option.

Author Contributions:

Conceptualization, A.B. and P.B.; methodology, P.B. and E.C.; software, P.B.; validation, E.C.; formal analysis, A.B.; investigation, A.B and P.B; resources, A.B. and E.C.; data curation, P.B. and A.B.; writing–original draft preparation, A.B.; writing–review and editing, A.B, P.B, E.C.; visualization, P.B.; supervision, E.C. and P.B.; project administration, E.C. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."

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