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PROSPECTS FOR MINERAL METABOLIC DISORDERS CORRECTION IN CHILDREN WITH RECURRENT STATE OF URINARY TRACT INFECTION

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The purpose of the study was to establish the effectiveness of combined phyto-citrate compound in the treatment and prevention of recurrent urinary tract infections in children with saline dysmetabolism in the comparison groups. The study involved 33 children aged 6 to 18 years, patients with recurrent urinary tract infections in the acute exacerbation of the disease. According to the duration of combined phyto-citrate compound administration, children were divided into 2 groups: I (n=17) – received the drug in complex therapy of urinary tract infections for 1 month, II (n=16) – also received phyto-citrate compound in complex therapy for 1 month, but continued to take it to prevent urinary tract infections for the next 2 months in an intermittent mode for 10 days. The results of the study proved phyto-citrate effectiveness in the complex therapy of recurrent urinary tract infections in children on the background of saline dysmetabolism. Administration of this drug led to normalization of saline transport indicators in 82% (27/33) of patients ($p<0.05$) after the 1st month of treatment and reduced the risk of reinfection by 18 times: OR = 4.25±0.65 with 95% □□[1.18; 15.3] – b□f□r□tr□□tm□nt □nd OR = 0.235±0.65 [0.066; 0.846] – after the first month of treatment ($p<0.001$). Prolonged intermittent administration of the drug for the next 2 months reduced the risk of recurrent episodes of urinary tract □nf□t□□n b□ 3.5 t□m□s: OR = 1.88±0.9 [0.302; 11.73] – in case of choosing a 1-m□nth □□urs□ □f th□r□□□; □nd OR= 0.53±0.83 [0.085; 3.3], □<0.05 – as a result of preventive use of the combined phyto-citrate.

Key words: recurrent urinary tract infection, children, mineral dysmetabolism, combined phyto-citrate compound.

The work is a fragment of the research project "Study of the hyperuricemia treatment impact in patients with chronic kidney disease and justification of optimal therapy", state registration No. 0119U101718.

A comprehensive study of the factors contributing to the formation of recurrent urinary tract infections (UTIs) in children and analysis of their elimination effectiveness is undoubtedly one of the topical issues of clinical medicine [1].

Dysmetabolic nephropathy (DN) represents from 27% to 64% in the structure of the urinary system incidence in children, and in the daily practice of a pediatrician, the metabolic disorders syndrome in the

urine is observed in almost every third patient [6]. Some foreign studies also emphasize the increase in the incidence of recurrent UTIs combined with crystalluria [4]. Antibiotics can increase the risk of developing renal calculi, as found by American scientists [11]. Studies have shown that antibiotics can change the intestinal microflora by reducing the colonization of oxalate-degrading bacteria Oxalobacter formigenes [10]. This makes patients sensitive to the renal calculi formation. It is concluded that taking antibacterial drugs significantly reduces the frequency of Oxalobacter formigenes colonization, and the negative impact persists for at least 6 months [3].

Therefore, given the latest data, disorders of mineral metabolism are considered not only as a concomitant urological condition that contributes to the development and maintenance of urinary tract infections, but also as one that can be initiated and maintained by the infectious-inflammatory process in the urological tract [5, 9].

The purpose of our study was to establish the effectiveness of mineral dysmetabolism correction in children with recurrent UTIs and its impact on the course of the disease by including phyto-citrate compound in the complex therapy.

Materials and methods. During 2019, a randomized controlled clinical trial was carried out. 33 children aged 6 to 18 years with recurrent UTIs in combination with impaired mineral metabolism participated. The study was performed with the informed consent of parents, children and in accordance with the Declaration of Helsinki on Human Rights.

The study design of patients was observed in 2 comparison groups. In Group I (n = 17), children received basic standard treatment (antibiotic, antispasmodic drug, antipyretic agent, if required) enhanced by phyto-citrate (PC) compound (sodium citrate + potassium citrate + phytocomponents: powdered pericarp of French bean (Phaseolus vulgaris), dry extracts of Asian white birche (Betula platyphylla) leaves, Garden parsley (Petroselinum crispum) root, lingonberry (Vaccinium vitis-idaea) leaves, German chamomile (Matricaria chamomilla).

The duration of PC treatment at a dose of 1 capsule 2 times a day for children aged 6 to 11 years and 1 capsule 3 times a day for children aged 12 to 18 years for 1 month. In the second study group (n = 16), children also received PC as part of complex therapy in appropriate age-specific doses (as indicated above). The difference was in the PC term and administration schedule. The total duration of PC administration in this study group was 3 months. During the first month, administration schedule of PC was similar to Group I, and in the next 2 months –10-day administration of the drug alternated with a 10-day break (according to the recommendations of some authors in the case of prolonged courses of administration) under conditions of stable urine pH in the range of 6.2–6.8.

Patients were randomized using the STATISTICA application program package of the random number generator (even numbers corresponded to one group, odd numbers to another). Nonparametric statistical methods were used for analytical and mathematical processing. During testing of statistical hypotheses, the threshold value for the significance level was set at $p \leq 0.05$ [2].

Mathematical processing of the obtained data was performed using Microsoft Excel software (Microsoft Office 2013 Professional Plus, license agreement (EULAID: O15_RTM_VL. 1_RTM_RU) and STATISTICA 13.0 (StatSoftInc., serial No. ZZS9990000099100363DEMO-L).

Results of the study and their discussion. The study involved children aged 6 to 18 years, the mean age was 10.8±4.2. Among them were 76% girls (25/33) and 24% (8/33) boys. All patients at the time of involvement in the study had a clinical and laboratory manifestation of the disease. According to the nosology, there were 55% (18/33) of patients with chronic cystitis, with chronic pyelonephritis – 45% (15/33). The distribution of patients by age, sex, diagnosis and clinical and laboratory characteristics of the disease in the comparison groups is shown in table 1.

Therefore, patients were randomized, and no statistically significant discrepancy in these parameters in the comparison groups was found ($p > 0.05$).

Among this group, crystalluria was present in the vast majority of children in the form of oxaluria in 60% (20/33), urate accumulations occurred in 19% (6/33), a combination of urate accumulations with phosphaturia, or oxaluria in 21% (7/33) of patients.

Urinary response in most patients in both study groups at the beginning of treatment was alkaline, only in 19% (6/33) patients with persistent urate accumulations an acidic urine pH was determined. At the end of the 4th week of therapy, all patients had a stable fluctuation of urine pH in the range of 6.5–7.0. This fact was interpreted by us as an indirect sign of an increase in the level of urine citrate, which indicated an improvement in the lithogenic properties of urine. It is known that citrate is a dissociated anion of citric acid, an energy substrate of the TCA cycle that has a pronounced effect on purine metabolism [8]. It also has a direct inhibitory effect on the crystallization and precipitation of calcium salts, that is, it is an inhibitor

of renal calculi formation. And being one of the most important natural mechanisms of crystallization inhibition, citrate excretion in the urine depends on the state of acid-base homeostasis [14].

Table 1

Distribution of patients by main characteristics in comparison groups

Parameters		Group I, n=17	Group II, n=16	p
Age		10.3±5.2	10.9±3.6	p=0.88
Sex	Female	13/17	12/16	p=0.68
	Male	4/17	4/16	p=0.68
Body temperature °C,		37.4±0.27	37.5±0.63	p=0.48
Dysuria, n		13/17	14/16	p=0.84
Pain syndrome, n		9/17	7/16	p=0.72
Periorbital edema		8/17	8/16	p=0.84
Crystalluria		9/17	8/16	p=0.94
Bacteriuria		14/17	12/16	p=0.62
Leukocytosis, 10^9/l		5.2±1.4	5.6±1.23	p=0.86
CRP, mg/l		22.43±3.46	21±6.7	p=0.62
Leukocyturia, HPF		29.6±11.8	26±19.9	p=0.42
Haematuria, HPF		18.92±0.35	20.2±0.26	p=0.72
Proteinuria, g/per day		0.12±0.06	0.18±0.07	p=0.42
Accumulation of salts on the ultrasound		10/17	11/16	p=0.65
CP		7/17	8/16	p=0.79
CC		10/17	8/16	p=0.45

Notes: CP – chronic pyelonephritis, CC – chronic cystitis. p> 0.05 – an incredible indices discrepancy between the χ^2 criterion and the Yates's correction.

Leveling of clinical and laboratory signs of infectious and inflammatory process was detected at the end of 2 weeks of therapy in most (82%) of patients in both study groups (14/17 and 13/16, respectively). In them there was not found any dysuria, pain syndrome, normalization of body temperature (in all children), diuresis, CRP levels, leukocyturia, leukocytosis (table 2).

Table 2

Dynamics of clinical and laboratory signs of UTIs at the end of the 2nd week of treatment

Parameters	Group I, (n=17)		Group II, (n=16)		p
	before treatment, abs.	after 2 weeks of treatment	before treatment, abs.	after 2 weeks of treatment	
Clinical characteristics					
Abdominal/lower back pain	9/17	2/17	7/16	1/16	p=0.79
Dysuria	13/17	3/17	14/16	3/16	p=0.89
Periorbital edema in the morning	8/17	4/17	6/16	4/16	p=0.89
Loss of appetite	12/17	4/17	10/16	3/16	p=0.89
Sediment in a fresh portion of urine	10/17	15/17	9/16	14/16	p=0.79
Laboratory and instrumental data					
Urine output, l/day	1.0±0.04	1.4±0.03	0.9±0.04	1.2±0.04	p=0.79
urine pH	7.28±0.06	6.52±0.04	7.02±0.05	5.58±0.06	p=0.69
White blood cells, HPF	25.31±0.4	5.67±0.6	24.89±0.4	6.87±0.7	p=0.79
Red blood cells, HPF	18.92±0.35	4.32±0.3	16.85±0.41	5.84±0.4	p=0.79
Protein, g/per day	0.12±0.06	0.034±0.04	0.091±0.05	0.062±0.06	p=0.46
Bacteriuria	14/17	5/17	14/16	3/16	p=0.64
Accumulation of salts on the ultrasound	9/17	4/17	9/16	5/16	p=0.79

Note. p> 0.05 – an incredible indices discrepancy between the χ^2 criterion and the Yates's correction after 2 weeks of treatment in experimental groups.

Increased saluresis at the 2nd week of follow-up in an average of 88% (in 15 of 17 patients in Group I and in 14 of 16 patients in Group II) was interpreted as a positive crystallic and lithokinetic effect of complex phyto-citrate therapy. Moreover, due to the antispasmodic and anti-inflammatory action of PC, litholysis was not accompanied by increased dysuria, the presence of pain and did not lead to urinary tract obstruction.

Average values of mineral metabolism according to the results of saline transport corresponded to the norm in 82% of patients (14/17 and 13/16), p<0.05 at the end of the 1st month of therapy (fig. 1). Regression of the urinary syndrome in the form of a decrease in the levels of proteinuria and haematuria to the "micro" level became probable also after the 1st month of therapy (fig. 2).

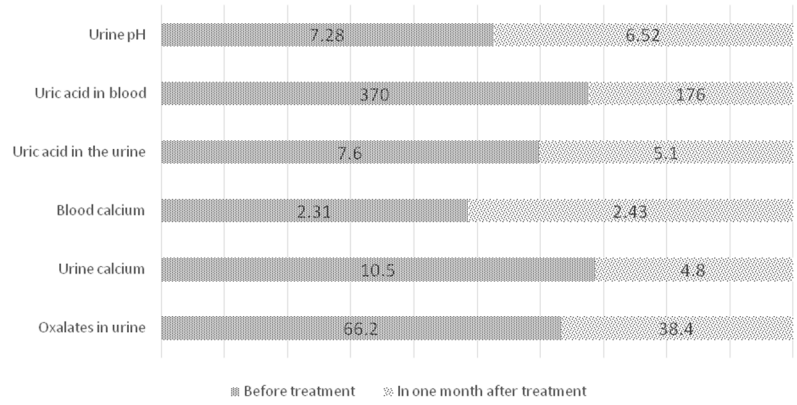

Fig. 1. Dynamics of changes in mineral metabolism in terms of saline transport at the end of the 1st month of therapy in Group I.

Note. p> 0.05 – an incredible indices discrepancy between the χ^2 criterion and the Yates's correction in comparison with Group II.

As can be seen from fig. 1, at the end of the 1st month of phyto-citrate therapy, there was a relevant decrease in patients of the mean values of oxalates excretion in the urine by 1.7 times, hyperuricemia level by 2.1 times, hyperuricosuria by 1.5 times, urinary calcium excretion by 2.2 times (p <0.05). The obtained results fully correspond to modern ideas about the proven effect of citrate alkalinization, which increases the dissociation of uric acid salts and reduces the tendency to renal calculi formation; affects the metabolism of purines in the organism by blocking aminogenesis, causes a decrease in the content of ammonia and purine derivatives in blood plasma, which contributes to hypouricemia [12].

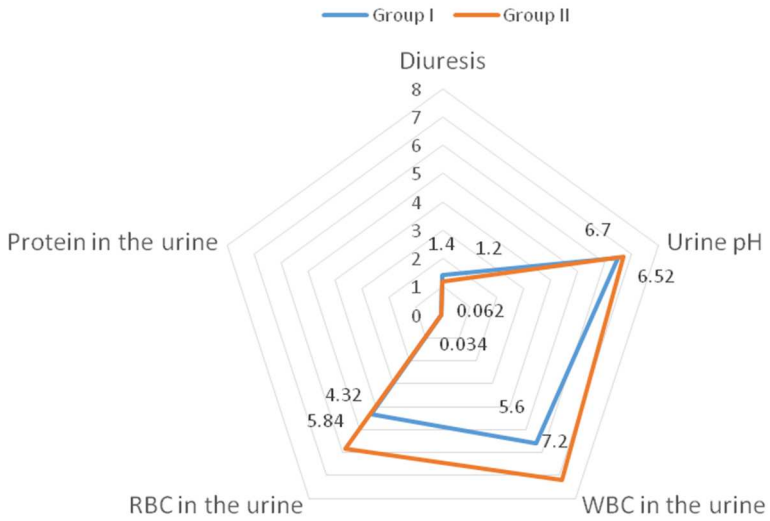

Fig. 2. Comparative dynamics of regression of urinary syndrome at the end of the 1st month of therapy in experimental groups

Note. p> 0.05 – an incredible indices discrepancy between the χ^2 criterion and the Yates's correction between experimental groups.

Haematuria, crystalluria, salt inclusions according to ultrasound examination had the most likely regression at the end of the 1st month of therapy, which probably contributed to the capillary-protective effect of lingonberry leaf extract (Vaccinium vitis-idaea) lingonberry and pericarp of beans (Phaseolus vulgaris) in combination with the litholytic action of parsley root extract (Petroselinum crispum) and the crystallic-disintegrating action of potassium – sodium citrate component. An interesting fact was the regression of microproteinuria (p<0.05) due to the action of phyto-citrate compound. This effect may have been provided by the action of birch leaf extract (Betula platyphylla), which is able to reduce albuminuria by improving microcirculation in the renal parenchyma and regulation of reabsorption in the tubules.

Patients in both groups at the end of the one month-long course of therapy remained comparable in terms of basic clinical and laboratory parameters. Analysis of the odds ratio (OR) showed an 18-fold higher probability (p <0.001) of the UTIs development before complex treatment (antibacterial therapy + complex phyto-citrate) in Groups I and II. Thus, the OR index before therapy was OR=4.25±0.65 at 95% CI [1.18; 15.3], after therapy-OR=0.235±0.65 [0.066; 0.846].

Subsequently, for 2 months, group I underwent clinical follow-up for repeated episodes of UTIs without medication. The second group of patients continued therapy with PC complex, when 10-day administration of the drug alternated with a 10-day break for the next 2 months.

According to the literature analysis, the minimum course of citrate therapy can be carried out for 1-2 months, extended to at least 6 months, with cystine formations – even up to 12 months. A number of scientists believe that to maintain normal values of mineral metabolism, constant administration of citrate mixtures is not required. Instead, after a stable establishment of favorable trends in urine chemistry (urine pH at the level of 6.2– 6.8), it is possible to perform 10-day administration of the drug alternated with a 10-day break for the required period [13].

As a result of a further 2-month follow-up of patients, repeated episodes of UTIs were registered in 4 patients of Group I (23.5%) who did not receive prophylactic therapy, and in 2 patients of Group II (12.5%) who received complex phyto-citrate compound as prophylaxis. Therefore, the probability of

recurrence in the case of choosing the therapeutic approach of Group I was OR=1.88±0.9 [0,302; 11,73] at 95% CI, whereas in the case of choosing the therapy used in the second study group – OR = 0.53±0.83 [0.085; 3.3], ($p < 0.05$). That is, the risk of UTIs recurrence was 3.5 times lower if you adhere to prophylactic therapy with PC for the next 2 months after completion of the basic 1 month-long course of UTIs treatment.

The obtained results coincide with the literature data, which indicate the pathogenetic contribution of impaired mineral metabolism metabolites in maintaining the recurrent course of UTIs and indicate the relevance of its correction in order to increase the treatment effectiveness and disease prevention [7]. According to many authors, therapeutic measures in the combination of UTIs and mineral dysmetabolism should be aimed both at the eradication of microorganisms, and litholysis of calculi elimination [15]. A number of scientists have concluded that it is drugs with a combination of sodium citrate and potassium citrate provide colloidal crystals stability of urine in different types of kidney stone diseases. Since 2011, according to the recommendations of the European Association of Urologists, citrate drugs have become a mandatory component of therapy for patients with urolithiasis and other hypocitrate conditions [7, 12].

Conclusions

1. The complex of therapy (antibiotic + complex phyto-citrate) in children with recurrent UTIs in the phase of infectious exacerbation was effective and reduced the risk of reinfection by 18 times ($p<0.001$).

2. The inclusion of phyto-citrate in the treatment regimen of patients with combined UTIs and mineral dysmetabolism led to normalization of salt transport in 82% (27/33), $p < 0.05$ patients at the end of the 1st month of therapy.

3. Prophylactic administration of the complex phyto-citrate compound (in the regimen of alternating 10-day administration and 10-day break) for 2 months after the course of UTIs treatment, reduced the risk of recurrence by 3.5 times, $p < 0.05$.

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Реферати

ПЕРСПЕКТИВИ КОРЕКЦІЇ МІНЕРАЛЬНОГО ДИЗМЕТАБОЛІЗМУ В ДІТЕЙ ІЗ РЕКУРЕНТНИМ ПЕРЕБІГОМ ІНФЕКЦІЇ СЕЧОВОЇ СИСТЕМИ

Буднік Т.В., Квашніна Л.В.

Метою дослідження було вивчення ефективності застосування комбінованого фітоцитратного засобу в комплексній терапії та профілактиці рекурентної інфекції

ПЕРСПЕКТИВЫ КОРРЕКЦИИ МИНЕРАЛЬНОГО ДИЗМЕТАБОЛИЗМА У ДЕТЕЙ С РЕКУРРЕНТНЫМ ТЕЧЕНИЕМ ИНФЕКИИ МОЧЕВОЙ СИСТЕМЫ

Будник Т.В., Квашнина Л.В.

Целью исследования было изучение эффективности комбинированного фитоцитратного средства в комплексной терапии и профилактике

сечової системи у дітей на тлі сольового дизметаболізму в групах порівняння. В дослідженні прийняли участь 33 дитини віком від 6 до 18 рр., хворі на рекурентну інфекцію сечовою системи в стадію загострення. За тривалістю застосування комбінованого фітоцитрату дітей було поділено на 2 групи: I (n=17) – отримували засіб в комплексній терапії ІСС протягом 1 місяця, I (n=16) – також отримували фітоцитратний засіб в комплексній терапії протягом 1 місяця, але продовжили його прийом у цілях профілактики ІСС ще наступні 2 місяці у переривчастому режимі по 10 днів.

Результати дослідження довели ефективність застосування комбінованого фітоцитрату у комплексній терапії рекурентної ІСС у дітей на тлі сольового дизметаболізму. Застосування зазначеного засобу призводило до нормалізації показників транспорту солей у 82 % (27/33) пацієнтів ($p<0,05$) вже після 1-го місяця терапії й знижувало ризик реінфекції в 18 разів: OR = 4,25 ± 0,65 при 95% ДІ [1,18;15,3] – до терапії та OR = 0,235 ± 0,65 [0,066;0,846] - після першого місяця терапії, ($p<0,001$). Пролонгований переривчастий прийом препарату протягом наступних 2-х місяців зменшував ризик повторних епізодів інфекції сечової системи в 3,5 рази: OR = 1,88 ± 0,9 [0,302;11,73] - у разі вибору 1-місячного курсу терапії; та OR= 0,53 ± 0,83 [0,085;3,3], $p<0,05$ – у результаті профілактичного застосування комбінованого фітоцитрату.

Ключові слова: рекурентна інфекція сечової системи, діти, мінеральний дизметаболізм, комбінований фітоцитратний комплекс.

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рекуррентной инфекции мочевой системы у детей на фоне солевого дизметаболизму в группах сравнения. В исследовании приняли участие 33 ребенка в возрасте от 6 до 18 лет с рекуррентной инфекцией мочевой системы в стадию обострения. Пациенты I группы (n = 17) – получали комбинированный фитоцитрат в комплексной терапии в течение 1 месяца, II группы (n = 16) – также получали фитоцитратное средство с целью терапии в течение 1 месяца, но продолжили его прием в целях профилактики повторного эпизода еще 2 месяца в прерывистом режиме по 10 дней.

Применение указанного средства приводило к нормализации показателей транспорта солей в 82% (27/33) пациентов ($p <0,05$) уже после 1-го месяца терапии и снижало риск реинфекции в 18 раз: OR = 4,25 ± 0,65 при 95% ДИ [1,18; 15,3] – до терапии и OR = 0,235 ± 0,65 [0,066; 0,846] - после первого месяца терапии ($p<0,001$). Пролонгированный прерывистый прием препарата в течение следующих 2-х месяцев уменьшал риск повторных эпизодов в 3,5 раза: OR = 1,88 ± 0,9 [0,302; 11,73] - в случае выбора 1-месячного курса терапии и OR = 0,53 ± 0,83 [0,085; 3,3], $p <0,05$ - в результате профилактического применения комбинированного фитоцитрата.

Ключевые слова: рекуррентная инфекция мочевой системы, дети, минеральный дизметаболизм, комбинированный фитоцитратний комплекс.

Рецензент Похилько В.І.