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THE USE OF TABLET FORM OF POLYOXIDONIUM® FOR IMMUNOCORRECTION IN CHILDREN WITH SECONDARY PYELONEPHRITIS

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Background. Some aspects of diagnostics and treatment of secondary pyelonephritis in children continue to be urgent tasks of pediatrics, especially with regard to immunological changes in this disease and the search for ways to optimally correct them. The purpose of the study: to study immunological disorders in children with VP and to determine the features of the use of the tablet preparation Polyoxidonium® for their correction.

Materials and methods. The study is an open controlled prospective comparative single-center study, including two groups: observation and control. The observation group consisted of 40 children aged 5–15 years (*Me* = 10; Q_1 = 6; Q_3 = 14) with secondary pyelonephritis, realized against the background of congenital urological pathology. The control group consisted of 100 practically healthy children (health groups 1 and 2) aged 5 to 17 years (*Me* = 10; Q_1 = 7; Q_3 = 14). The patients underwent a standard examination, including in-depth immunological examination. The revealed violations of immunological resistance justified the inclusion of the domestic drug Polyoxidonium in the complex therapy of patients.

Results. 3 months after the treatment with the Polyoxidonium immunomodulator, an increase in the level of immunoglobulin A, the total number of lymphocytes, B cells, normalization of the number of CD19 lymphocytes, a decrease in the number of T lymphocytes and CD4 cells, an increase in phagocytosis and natural killers was noted.

Conclusion. Thus, complex therapeutic tactics for children with secondary pyelonephritis should be determined taking into account individual immunological shifts, namely: a reduced number of CD19 lymphocytes and the level of immunoglobulin A, an excessively high content of helper cells, to increase phagocytosis and the number of NK lymphocytes.

Keywords: secondary pyelonephritis; immunocorrection; Polyoxidonium®; children.

ПРИМЕНЕНИЕ ТАБЛЕТИРОВАННОЙ ФОРМЫ ПРЕПАРАТА «ПОЛИОКСИДОНИЙ®» С ЦЕЛЬЮ ИММУНОКОРРЕКЦИИ ПРИ ВТОРИЧНОМ ПИЕЛОНЕФРИТЕ У ДЕТЕЙ

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Актуальность. Некоторые аспекты диагностики и лечения вторичного пиелонефрита у детей продолжают оставаться актуальными задачами педиатрии, особенно это относится к иммунологическим изменениям при этом заболевании и поиске путей их оптимальной коррекции.

Цель исследования: изучение иммунологических нарушений у детей со вторичным пиелонефритом и определение эффективности использования для их коррекции таблетированного препарата «Полиоксидоний®».

Материалы и методы. Проведено открытое контролируемое проспективное сравнительное одноцентровое исследование, включающее две группы: наблюдения и контроля. Группу наблюдения составили 40 детей в возрасте 5–15 лет (*Me* = 10; Q_1 = 6; Q_3 = 14) со вторичным пиелонефритом, реализованным на фоне врожденной урологической патологии. Контрольную группу составили 100 практически здоровых детей (1-я и 2-я группы здоровья) в возрасте от 5 до 17 лет (*Me* = 10; Q_1 = 7; Q_3 = 14). Пациентам проводили стандартное обследование, в том числе углубленное иммунологическое. Выявленные нарушения иммунологической резистентности обосновали включение отечественного препарата «Полиоксидоний®» в комплексную терапию пациентов.

Результаты. Через 3 мес. после проведенного лечения иммуномодулятором «Полиоксидоний®» отмечено повышение уровня иммуноглобулина А, общего количества лимфоцитов, В-клеток, нормализация количества CD19-лимфоцитов, снижение количества Т-лимфоцитов и CD4-клеток, повышение показателей фагоцитоза и естественных киллеров.

Выводы. Доказана достаточно высокая эффективность Полиоксидония в комплексном лечении детей со вторичным пиелонефритом при выявлении у них исходно сниженного количества CD19-лимфоцитов и уровня иммуноглобули-

нов (особенно иммуноглобулина А) и высокого содержания хелперных клеток, для повышения показателей фагоцитоза и количества NK-лимфоцитов. Лечебная тактика в отношении детей со вторичным пиелонефритом должна быть определена с учетом индивидуальных иммунологических сдвигов.

Ключевые слова: вторичный пиелонефрит; иммунокоррекция; Полиоксидоний; дети.

BACKGROUND

Secondary pyelonephritis (SP) remains relevant in children because of its high prevalence and difficulties that arise during diagnostics, treatment, and prevention [3, 4, 6, 22]. Aggravation of congenital obstructive uropathy (such as vesicoureteral reflux, megaloureter, and hydronephrosis) is not only due to changes in the renal collecting system and medulla [8, 11, 12, 18, 19] but also due immunopathological processes [1, 5, 7, 9, 14, 15] that occur in the presence of high virulence of uropathogens that have overwhelmed the threshold of immunity [3, 4, 17]. Current scientific literature has abundant data on the course of immunopathological conditions associated with SP in pediatric patients and methods to minimize them [2, 10, 13, 20, 21, 23, 24]. However, the methods of possible immunocorrection are still insufficiently examined, and the long-term results of the complex therapy of SP in pediatric patients remain nearly uninvestigated.

This study aimed to analyze immunological disorders in pediatric patients with SP and to determine the efficiency of Polyoxidonium® (tablet drug) for their correction.

MATERIALS AND METHODS

An open, controlled, prospective, comparative, single-center study was conducted at the Kirov Regional Children's Clinical Hospital and the Department of Pediatric Surgery, Kirov State Medical University. The sample size was not calculated previously. The study group consisted of 40 pediatric patients aged 5–15 years ($Me = 10$; $Q_1 = 6$; $Q_3 = 14$) with SP associated with congenital urological pathology, including 18 boys (45%) and 22 girls (55%). All patients underwent general clinical, biochemical, bacteriological, radiological instrumental, ultrasound, and immunological studies. Subsequent changes in the studied parameters were assessed in stages, namely, upon hospital admission and three months after the inpatient treatment. All patients previously (3–7 years ago) were successfully operated on for unilateral congenital obstructive uropathy (congenital hydronephrosis, $n = 28$; vesicoureteral reflux, $n = 9$; megaloureter, $n = 3$). They were admitted to the hospital with incomplete clinical and laboratory remission and received standard examination and treatment according to the 2018 clinical guidelines [8]. Oral therapy with Polyoxidonium was initiated, with a dose of one tablet (12 mg) once a day for children aged >10 years and 1/2 tablet (6 mg) once a day for those aged 5–10 years for seven days. The tablet form of the drug, approved for use according to the instructions for three years, was used.

Polyoxidonium was used according to a special permit protocol of the local ethics committee. Parental consent was obtained in each case. Polyoxidonium was acquired by a medical institution by decision of a medical conference. The control group consisted of 100 apparently healthy children (health groups 1 and 2) aged 5–17 years ($Me = 10$; $Q_1 = 7$; $Q_3 = 14$), living in the Kirov region and city of Kirov, including 42 boys (42%) and 58 girls (58%).

Venous blood was collected to assess immune activities under the same conditions, strictly on an empty stomach, in the morning. This was due to the formation of certain biorhythms in the immune system. The venous blood of each patient was processed according to the standard procedure, i.e., "binding" with monoclonal antibodies + lysing without fixation and washing.

The CD3 cell count in the peripheral blood was determined by direct immunofluorescence (Preparat, Russia), using monoclonal antibodies. The CD16 lymphocyte (natural killer [NK] cells) count was determined using flow cytometry on FACS Canto™ II flow cytometers (Becton & Dickinson, USA) for cell immunophenotyping by multicolor flow cytofluorometry. The results were presented in absolute numbers and percentage. The counts of CD3 cell subpopulations (types CD8 and CD4 lymphocytes) and CD19 lymphocytes were determined by indirect immunofluorescence using monoclonal antibodies (Preparat, Russia). The levels of immunoglobulins (Ig) A, M, and G were determined by radial immunodiffusion according to Mancini using monospecific antisera. The immunoregulatory index (CD4/CD8) was the percentage of these cells. Changes in phagocytic parameters were assessed by studying the phagocytic index and phagocytic activity of neutrophils, which was determined using latex particles as a phagocytosed object. The result was presented as a percentage. The phagocytic index is an index of the average number of latex particles ingested by one phagocyte. The concentration of circulating immune

complexes in the sera of patients was determined using the precipitation method with PEG-600 using reagent kits (Vector-Best, Russia), and the result was expressed in units of optical density.

Data obtained were compared with the results of the specified indicators in 100 apparently healthy children (health groups 1 and 2) of the same age, living in the Kirov region and city of Kirov.

Immunogram parameters were represented by quantitative and qualitative features. Immunogram parameters presented as absolute values, namely, the count of cells per 1 μL (cells/μL) or count of cells $\times 10^{-9}$ per 1 L, were used as quantitative features in the study. The Shapiro–Wilk test was used to assess the normality of distributions of sample quantitative features. This test showed that part of the quantitative data has deviated from the normal distribution; thus, median Me and quartiles $[Q_1; Q_3]$ were used to describe quantitative features, and non-parametric methods were used for data analysis. Qualitative data were presented as relative values (p,%) and 95% confidence intervals (95% CI) for relative values; 95% CI values were calculated using the Wilson method. The significance of differences in related (dependent) quantitative data was assessed using the Wilcoxon test and that in independent sample quantitative data was performed using the Mann–Whitney test. The characteristic of the significance of differences in quantitative data was presented depending on the criterion selected, namely, the values of the Wilcoxon test (T), Mann–Whitney test (U), and level of significance (p). McNemar's test was used to assess the significance of the differences in the associated qualitative data (indicators of the immunogram, represented by relative values at admission to the hospital and 3 months after the treatment). Yates' continuity-corrected chi-square test (χ^2) was used to assess the significance of differences in independent qualitative data (indicators of the immunogram, represented by relative values 3 months after the treatment in the study group and control group). The frequencies in the cells of four-field tables when calculating these criteria were represented by the count of cells per 1 mL. The characteristic of the significance of differences in qualitative data was presented depending on the selected criterion, namely, the value of McNemar's test (χ^2 McNemar), value of the chi-square test (χ^2), degree of freedom (df), and level of significance (p). The p lower than 0.05 was selected as the critical level of the significance of differences (p). The analysis of the power of the selected criteria for assessing the significance of differences showed that given the number of cases in the study group ($n = 40$) and control group ($n = 100$) and the selected critical level of the significance of differences ($p < 0.05$), the power value of these criteria exceeded 0.9. Statistical processing was performed using Microsoft Excel and Statistica 10.0 software packages.

RESULTS AND DISCUSSION

An assessment of the significance of the difference between the study group and control group by age did not reveal any differences ($U = 1955.0$; $p = 0.84$). When comparing the study group and control group by gender, no significant differences were also found ($\chi^2 = 0.11$; $df = 1$; $p = 0.75$).

Various shifts in immune reactivity were revealed (Table 1), namely, a decreased level of IgA, a significant increase in the level of IgG, and the level of circulating immune complexes in children upon admission did not reach high concentrations. As regards the characteristics of cellular immunity in pediatric patients with secondary obstructive pyelonephritis, a significant increase in the relative counts of $CD3^+/CD19^-$ lymphocytes was noted with a decrease in their absolute counts and a downward trend in $CD3^-/CD19^+$ in their absolute and relative values. The existing immune shifts in children before the start of the complex therapy for obstructive pyelonephritis were also characterized by a significant increase in the count of NK cells. Signs of immune system stimulation in response to the antigen and possible occurrence of hyperreactive syndromes include a significant increase in the count of T-helper lymphocytes of the $CD3^+/CD4^+$ phenotype in these patients. The relative count of $CD3^+/CD18^+$ T cell tended to increase and their absolute count decreased. On admission of pediatric patients with SP, reduced rates of phagocytosis were noted.

Polyoxidonium was chosen for immunocorrective therapy because of the immunomodulatory, detoxifying, antioxidant, and moderate anti-inflammatory effects of its active substance, i.e., azoximer bromide. The main mechanism of action of this drug is attributed to its direct effect on phagocytic cells and NK cells and stimulation of antibody formation and synthesis of interferon-alpha and interferon-gamma [14].

Regarding the effects of Polyoxidonium on changes in humoral immunity, in comparison with the healthy group (Table 2), significant differences in dynamics were noted, which demonstrated an increase in the blood level of IgG ($p < 0.001$). However, the IgG level after the Polyoxidonium

Table 1 / Таблица 1

Immunogram parameters in children with secondary pyelonephritis upon admission to the hospital (n = 40)
Показатели иммунограммы у детей со вторичным пиелонефритом при поступлении в стационар (n = 40)

Parameter / Показатель	Median / Среднее значение Me [Q_1; Q_3]
$CD3^+/CD19^-$, cells in μkl / $CD3^+/CD19^-$, кл./мкл	1.7 [1.41; 2.53]
$CD3^-/CD19^+$, cells in μkl / $CD3^-/CD19^+$, кл./мкл	0.28 [0.21; 0.41]
$CD3^-/CD(16^+56^+)^+$, cells in μkl / $CD3^-/CD(16^+56^+)^+$, кл./мкл	4.99 [4.76; 5.69]
$CD3^+/CD4^+$, cells in μkl / $CD3^+/CD4^+$, кл./мкл	1.43 [1.28; 1.64]
$CD3^+/CD18^+$, cells in μkl / $CD3^+/CD18^+$, кл./мкл	0.29 [0.27; 0.32]
Immunoregulatory index / Иммунорегуляторный индекс	2.92 [2.44; 3.01]
IgA, g/l / IgA, г/л	1.3 [0.77; 1.7]
IgG, g/l / IgG, г/л	11.6 [9.6; 13.6]
IgM, г/л / IgM g/l	1.2 [0.85; 2.0]
Circulating immune complexes, units of optical density / Циркулирующие иммунные комплексы, ед. опт. плотн.	0.06 [0.04; 6.06]
Phagocyticindex / Фагоцитарный индекс	9.3 [7.7; 11.90]
$CD3^+/CD19^-$, % [CI 95% / ДИ 95 %]	76.12 [74.45–77.89]
$CD3^-/CD19^+$, % [CI 95% / ДИ 95 %]	12.80 [11.49–14.0]
$CD3^-/CD(16^+56^+)^+$, % [CI 95% / ДИ 95 %]	48.09 [47.16–49.02]
$CD3^+/CD4^+$, % [CI 95% / ДИ 95 %]	68.28 [66.3–70.76]
$CD3^+/CD18^+$, % [CI 95% / ДИ 95 %]	28.2 [25.46–30.95]
Phagocytic activity of neutrophils, % [CI 95%] / Фагоцитарная активность нейтрофилов, % [ДИ 95 %]	54.87 [45.31–64.45]

therapy was higher than its level before the start of the therapy, but the difference was not significant. The IgA level increased significantly after treatment with Polyoxidonium (Table 3). The amounts of circulating immune complexes were significantly lower in the Polyoxidonium group than in the healthy group ($p < 0.001$), and no significance was found when compared with the indicators measured on hospital admission.

The total leukocyte count in pediatric patients who received conventional treatment with a course of immunocorrective therapy with Polyoxidonium decreased in comparison with the indicators on admission and in healthy children ($p < 0.001$). The absolute count of lymphocytes after immunocorrective therapy was significantly higher than that before therapy ($p < 0.001$) and reached the normal values.

The absolute count of $CD3^+/CD19^-$ T-lymphocytes significantly decreased after treatment with Polyoxidonium relative to the parameters at admission ($p < 0.001$) and indices of healthy children ($p < 0.001$). The relative count of $CD3^+/CD19^-$ cells also decreased significantly after treatment with Polyoxidonium compared with the values at admission ($p < 0.001$). A significant effect was noted, which demonstrated an increase in the count of B-lymphocytes ($CD3^-/CD19^+$) after treatment with Polyoxidonium when compared with the indicators at admission ($p < 0.001$). However, this indicator was significantly lower in the healthy group after treatment ($p = 0.02$).

Changes in phagocytosis parameters were characterized by the following patterns. The phagocytic activity of neutrophils in pediatric patients who received Polyoxidonium increased relative to the parameters at admission, showing significance ($p < 0.001$); despite the positive effect of the therapy, the indicators did not reach normal values ($p = 0.09$). The phagocytic index after treatment was higher than at admission ($p < 0.001$) and reached the level of healthy children, and the difference was insignificant when compared with the control group ($p = 0.03$). A significant decrease was noted in the relative NK cell count in the Polyoxidonium group after treatment compared with the values at admission ($p < 0.001$), but they still remained high relative to the healthy group ($p < 0.001$).

Table 2 / Таблица 2

Comparative table of immunogram parameters after a course of treatment in patients receiving Polyoxidonium and control group
Сравнение показателей иммунограммы после курса лечения у пациентов, получавших Полиоксидоний, и показателей контрольной группы

Parameter / Показатель	After Polyoxidonium / После Полиоксидония (n = 40)	Control / Контроль (здоровые) (n = 100)	Criteria / Критерии	p
$CD3^+/CD19^-$, cells in μkl / $CD3^+/CD19^-$, кл./мкл, *Me* [Q_1; Q_3]	1.59 [1.33; 1.94]	2.0 [1.53; 3.3]	U = 1168	<0.001
$CD3^-/CD19^+$, cells in μkl / $CD3^-/CD19^+$, кл./мкл, *Me* [Q_1; Q_3]	0.39 [0.33; 0.45]	0.46 [0.3; 1.15]	U = 1684	0.02
$CD3^-/CD(16^+56^+)^+$, % [CI 95%] / $CD3^-/CD(16^+56^+)^+$, % [ДИ 95 %]	40.2 [39.67–40.91]	12.46 [12.01–12.91]	χ^2 = 4333.79 (df = 1)	<0.001
$CD3^-/(16^+56^+)^+$, cells in μkl / $CD3^-/(16^+56^+)^+$, кл./мкл, *Me* [Q_1; Q_3]	10.3 [6.6; 17.9]	2.57 [1.29; 5.57]	U = 960	<0.001
$CD3^+/CD18^+$, % [CI 95%] / $CD3^+/CD18^+$, % [ДИ 95 %]	23.37 [21.63–25.11]	27.63 [25.77–29.49]	χ^2 = 10.71 (df = 1)	0.001
$CD3^+/CD18^+$, cells in μkl / $CD3^+/CD18^+$, кл./мкл, *Me* [Q_1; Q_3]	0.51 [0.43; 0.61]	0.62 [0.6; 0.65]	U = 792	<0.001
IgG, g/l / IgG, г/л, *Me* [Q_1; Q_3]	11.76 [9.6; 14.2]	9.73 [9.12; 9.95]	U = 1804	<0.001
IgM, g/l / IgM, г/л, *Me* [Q_1; Q_3]	1.9 [0.93; 2.14]	1.26 [0.89; 1.49]	U = 1622	<0.001
Circulating immune complexes, units of optical density / Циркулирующие иммунные комплексы, ед. опт. плотн., *Me* [Q_1; Q_3]	0.06 [0.04; 0.07]	0.08 [0.07; 0.09]	U = 784	<0.001
Phagocytic index / Фагоцитарный индекс, *Me* [Q_1; Q_3]	11,00 [8,5; 11,4]	10,75 [10,5; 11,95]	U = 1912	0,19

Table 3 / Таблица 3

The most significant parameters of the dynamics of the immunogram in the group of children who received the course of Polyoxidonium (absolute values), *Me* [Q_1; Q_3]
Наиболее значимые показатели динамики иммунограммы в группе детей, получивших курс препарата «Полиоксидоний» (абсолютные величины), *Me* [Q_1; Q_3]

Parameter / Показатель	On admission / При поступлении (n = 40)	After Polyoxidonium / После курса Полиоксидония (n = 40)	T Wilcoxon / T-критерий Вилкоксона	p
IgA, g/l IgA, г/л	1.3 [0.77; 1.7]	2.56 [2.25; 3.01]	179.0	<0.001
$CD3^+/CD19^-$, cells in μkl / $CD3^+/CD19^-$, кл./мкл	1.7 [1.41; 2.53]	1.59 [1.33; 1.94]	0.0	<0.001
$CD3^-/CD19^+$, cells in μkl / $CD3^-/CD19^+$, кл./мкл	0.28 [0.21; 0.41]	0.39 [0.33; 0.45]	0.0	<0.001
$CD3^-/CD(16^+56^+)^+$, cells in μkl / $CD3^-/CD(16^+56^+)^+$, кл./мкл	4.99 [4.76; 5.69]	10.3 [6.6; 17.9]	0.0	<0.001
$CD3^+/CD4^+$, cells in μkl / $CD3^+/CD4^+$, кл./мкл	1.43 [1.28; 1.64]	0.92 [0.73; 1.14]	0.0	<0.001
$CD3^+/CD18^+$, cells in μkl / $CD3^+/CD18^+$, кл./мкл	0.29 [0.27; 0.32]	0.51 [0.43; 0.61]	0.0	<0.001
Lymphocytes, cells $\times 10^9$/l / Лимфоциты, кл. $\times 10^9$/л	34.0 [28.0; 45.0]	45.0 [38.0; 48.0]	0.0	<0.001
White blood cells, cells $\times 10^9$/l / Лейкоциты, кл. $\times 10^9$/л	6.2 [5.2;7.4]	5.09 [4.77; 6.73]	0.0	<0.001
Phagocytic index / Фагоцитарный индекс	9.3 [7.7; 11.90]	11.0 [8.5; 11.4]	0.0	<0.001

Table 4 / Таблица 4

The most significant parameters indicators of the dynamics of the immunogram in the group of children who received the course of Polyoxidonium (relative values)

Наиболее значимые показатели динамики иммунограммы в группе детей, получивших курс препарата «Полиоксидоний» (относительные величины)

Parameter / Показатель	On admission / При поступлении, %	After Polyoxidonium / После курса Полиоксидония, %	McNemar's test / Критерий Мак-Нимара(χ^2)	*p*
Phagocytic activity of neutrophils / Фагоцитарная активность нейтрофилов	54.87	68.21	12.02	<0.001
$CD3^+/CD19^-$	76.12	69.96	83.11	<0.001
$CD3^-/CD19^+$	12.80	16.55	62.01	<0.001
$CD3^-/CD(16^+56^+)^+$	48.09	40.29	46.11	<0.001
$CD3^+/CD4^+$	68.28	41.16	519.0	<0.001
$CD3^+/CD18^+$	28.2	23.37	239.1	<0.001

The absolute NK cell count increased significantly after treatment with Polyoxidonium ($p < 0.001$).

The treatment of pediatric patients with SP was reflected in the correction of not only immune parameters but also other laboratory and clinical parameters. After treatment, SP in all treated patients was in the stage of complete clinical and laboratory remission. This fact has already been recorded in some scientific publications [15, 25].

Thus, the inclusion of Polyoxidonium in the complex therapy of SP in children led to the most significant results, as when it was used, the level of IgA increased; the total lymphocyte count, B-cell count (but did not reach the norm), and CD18-lymphocyte count tends to normalize; the T-lymphocyte and CD4 cell counts decreased; and the parameters of phagocytosis and (most significantly) NK count increased, which was partially confirmed by other authors (Table 4) [10, 25]. The limitations of this study are possibly due to the relatively small size of the study group and the lack of randomization and preliminary calculation of samples.

CONCLUSION

This study found a rather high efficiency of Polyoxidonium in the complex treatment of pediatric patients with SP with an initially reduced CD19 lymphocyte count and immunoglobulin A level and excessively high levels of helper cells to increase phagocytosis parameters and NK cell count.

Nevertheless, the currently actively promoted Russian immunocorrector Polyoxidonium is certainly not a panacea, and it should not be included in the over-the-counter list, as it has traced effects on the body.

ADDITIONAL INFORMATION

Author contributions. All authors confirm that their authorship complies with the ICMJE criteria. All authors have made a significant contribution to the development of the concept, research, and preparation of the article, and they have read and approved the final version before its publication.

Conflict of interest. The authors declare no conflict of interest.

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