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Pharmacotherapy of psychomotor developmental delay in children aged 6-12 months, born prematurely and having suffered hypoxic-ischemic brain injury (double-blind comparative multicenter study) placebo-controlled study)

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Resume

Purpose of the study. Study of the efficacy and safety of the medicinal product (MP) hopantenic acid Pan- togam in the complex treatment of premature infants aged 6-12 months with delayed psychomotor development due to hypoxic-ischemic damage to the central nervous system.

Material and methods. We examined87 patients were randomized into two groups. Patients in group 1 (44 children) were prescribed standard therapy and additionally the drug Pantogam for 2 months, patients in group 2 (43 children) — standard therapy plus placebo. Pantogam (syrup 100 mg/ml) or placebo was administered orally 15-30 minutes after feeding 2 times a day at a daily dose of 30-50 mg per 1 kg of body weight. The duration of therapy was 67 days. All patients were examined twice (before and after the end of the treatment course) using the Griffiths scales for assessing the psychomotor development of children from birth to 2 years of age (the supplemented and revised version — GMDS-ER — was used). **Results.**ININ the 1st group, after treatment, an improvement in psychomotor development was noted by more than 6% (from the initial value of the total indicator according to the Griffiths scale) in 63.6% of patients, which significantly exceeded the similar indicator in the 2nd group - 39.5% (p=0.021). In the 1st group, a significant reduction in developmental delays was observed in the areas of "Personal and social" and "Manipulation with objects", as well as a tendency to reduce the delay in the other three areas: "Motor activity", "Hearing and speech", "Visual-motor coordination". More pronounced positive dynamics after treatment with Pantogam was determined in the subgroup of patients with late prematurity (34-36 weeks) compared to children with moderate prematurity (32-33 weeks). The favorable safety profile of Pantogam, comparable to placebo, was confirmed.

Conclusion. Pantogam is an effective and safe remedy in the complex treatment of psychomotor retardation. development in children of the first year of life.

Keywords:*premature babies, hypoxic-ischemic encephalopathy, delayed psychomotor development, Griffiths scales, treatment, LP Pantogam, double-blind multicenter placebo-controlled study.*

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Pharmacotherapy of psychomotor developmental delay in 6—12 months preterm infants with hypoxic-ischemic encephalopathy (the double-blind comparative multicenter placebo-controlled study)

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Abstract

Objective. To evaluate the efficacy and safety of hopantenic acid (Pantogam) in the complex treatment of prematurely born infants, aged 6—12 months, with psychomotor developmental delay due to hypoxic-ischemic encephalopathy.

Materials and methods. Eighty-seven patients were randomized into two groups: 44 received standardized treatment and pantogam for two months, 43 standardized treatment and placebo. Pantogam (syrup 100 mg/ml) or placebo were prescribed orally 15–30 minutes after feeding, twice a day, in a daily dosage of 30–50 mg/kg body weight. The assessment of psychomotor development from birth to two years was performed with the Griffiths Mental Development Scales (GMDS-ER) twice (before and after completion of therapy).

Results. The response to two month therapy was determined as the reduction of developmental delay for more than 6% of the initial GMDS-ER general quotient (GQ) score was significantly better in the group I after pantogam treatment (63.6% of patients) compared to group II (36.4%,*p*=0.021). Group I demonstrated the significant decrease of the developmental delay in two domains ("Personal-Social" and "Performance") and a trend to overcome the delay in three other domains: "Locomotor", "Hearing and Speech", "Eye and Hand Coordination". The improvement after pantogam treatment was more obvious in the subgroup of infants born late preterm (gestational age 34—36 weeks) compared to infants born moderate preterm (gestational age 32—33 weeks). The favorable safety profile of pantogam was confirmed, comparable to that of placebo.

Conclusion. Pantogam is efficient and safe medication in the complex treatment of psychomotor developmental delay in preterm infants, aged 6—12 months.

Keywords:*preterm infants, hypoxic-ischemic encephalopathy, psychomotor developmental delay, Griffiths Scales, treatment, Pantogam, double-blind multicenter placebo-controlled study.*

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Hypoxic-ischemic lesions of the central nervous system (CNS) in newborns and their consequences are the most important problems of pediatric neurology. Infants born prematurely are especially susceptible to CNS lesions. According to WHO, approximately 15 million children are born prematurely (before the completion of 37 full weeks of gestation) worldwide every year, which is more than 10% of all newborns [1]. Most premature babies (>80%) are born between 32 and 36 weeks of gestation (moderate and borderline prematurity), approximately 10% are born between 28 and 32 weeks of gestation (deep prematurity), and 5% are born before the 28th week of gestation (extreme prematurity) [1].

In children with moderate and borderline prematurity, neurological symptoms in the first year of life may be slightly pronounced. However, they are considered as a predictor of more severe disorders of psychomotor and, later, neuropsychic development. In subsequent age periods, especially when the child is exposed to physical and mental stress, including emotional and intellectual, a delayed manifestation of cerebral disorders is detected. C. Squarza et al. [2] confirmed the relationship between early development indicators and long-term cognitive outcomes in premature children with mild disorders. Therefore,

It is extremely important to identify early delays in psychomotor development using modern diagnostic methods and timely correction of deviations, and to carry out treatment taking into account the characteristics of the maturation of the central nervous system of premature babies.

Hypoxia and ischemia lead to changes at various levels of organization of cerebral systems (ion channels, receptors, neurotransmitters, gene expression, morphological structures) due to energy deficiency, lactate accumulation, edema and swelling of neurons and glial cells, oxidative stress, excitotoxicity, activation of apoptosis processes [3, 4]. Neuroprotectors are used in the treatment of hypoxic-ischemic lesions of the central nervous system and their consequences. Significant mechanisms of action of these drugs include stimulation of neuroplasticity processes, as well as nootropic effects.

A representative of drugs with neuroprotective action is the drug (LP) Pantogam - a calcium salt of D (+) - pantoyl-gamma-aminobutyric acid (GABA) or calcium salt of D-homopantothenic acid - the highest homologue of D (+) - pantothenic acid, in which β-alanine is replaced by GABA, which has a neurotropic activity similar to GABA, but unlike GABA, it is able to penetrate the blood-brain barrier. A number of studies have confirmed the efficacy and safety of this drug in various diseases of the central nervous system in children [5]. However, the number of studies on the efficacy and safety of neuroprotectors in CNS lesions in children in the first year of life is extremely limited, which determines the need to conduct them from the standpoint of modern evidence-based medicine.

The aim of the work is to study the efficacy and safety of the drug Pantogam (syrup 100 mg/ml, PIK-PHARMA LLC, Russia) in a double-blind, comparative, multicenter, randomized, placebo-controlled study in the complex treatment of premature infants aged 6-12 months with delayed psychomotor development due to hypoxic-ischemic damage to the central nervous system.

Material and methods

The study was conducted in 7 clinical centers in 6 cities of the Russian Federation. The patient cohort consisted of 90 children born prematurely at 32–36 weeks of gestation, whose chronological age was 6–12 months.

Patients were randomized into two groups: 45 patients were included in the 1st group, who were prescribed standard therapy supplemented with the drug Pantogam, 45 patients in the 2nd group took placebo instead. Standard treatment included physiotherapy methods, massage and drug therapy, with the exception of drugs specified in the exclusion criteria (see below).

A total of 87 patients completed the study, including 44 from Group 1 and 43 from Group 2. The characteristics of the studied groups of patients who completed participation in the study are presented in**table.1**As follows from her data, the groups were comparable in all respects.

Depending on the gestational age (GA) at birth [1, 6], children were divided into subgroups: those born at 32–33 weeks (moderate prematurity), and those born at 34–36 weeks (late, or borderline, prematurity).

*Inclusion Criteria*children in the study:1. Premature infants of both sexes aged 6 to 12 months, born at gestation periods of 32 to 36 completed weeks with weight and height indicators corresponding to the gestational age, with delayed psychomotor development due to perinatal hypoxic CNS damage for at least 2 months in at least two areas of development assessed using the Griffiths scale. 2. Confirmed diagnosis of perinatal hypoxic CNS damage in the anamnesis (grade II cerebral ischemia or grade II intraventricular hemorrhage) with the presence of perinatal transient hypoxic-ischemic encephalopathy or perinatal transient posthemorrhagic encephalopathy according to the classifications of the Russian Association of Perinatal Medicine Specialists [7]. 3. Signed information

***Table 1.*Characteristics of the groups of examined patients *Table 1.*The characteristics of two groups of patients in the study**

Indicator	1st group (*n*=44)	2nd group (*n*=43)
Gender, m/f		
abs.	22/22	16/20
%	50/50	44/56
Age at inclusion in the study, months		
M±*m*	8.1±0.3	8.2±0.2
range	6.0—11.75	6.0—11.75
Breastfeeding at birth, weeks		
32-33	24	19
34-36	20	24
Birth weight of children with 32-33 weeks of gestation, g		
M±*m*	1940.9±69.7	1764.1±91.6
range	946—2600	930—2350
Birth weight of children with 34-36 weeks of gestation, g		
M±*m*	2137.7±89.2	2416.8±89.3
range	1540—2890	1530—3150

*Note.*GW – gestational age. *Note:*GV - Gestational Age.

informed consent to participate in the study obtained from the patient's parent or adoptive parent.

Non-inclusion criteria: 1. Any hereditary diseases predisposing to delayed psychomotor and pre-speech development. 2. Progressive forms of hydrocephalus requiring conservative or surgical treatment. 3. History of severe drug intolerance or hypersensitivity to any components of the study drug or comparator drug. 4. Indications for use during treatment with the study drug or comparator drug of the following groups of drugs: nootropics, angioprotectors, barbiturates, antiepileptic drugs, local anesthetics based on procaine, etidronic acid. 5. Severe renal failure (creatinine clearance less than 30 ml/min). 6. Liver failure. 7. Any other diseases or conditions, serious deviations of laboratory parameters from the norm, which, in the opinion of the physician-study investigator, may distort the results of the study and limit the patient's participation in the study. 8. Preventive vaccinations in the previous 2 weeks before the screening visit. 9. Participation of the patient in another clinical study or taking any study drug within 1 month before the screening visit.

Pantogam (syrup 100 mg/ml) or placebo was administered orally 15-30 minutes after feeding. The dose was calculated based on the child's body weight and was 30-50 mg/kg depending on the severity of the disorder and drug tolerance. The frequency of administration was 2 times a day, except for the first and last weeks of therapy (during the period of gradual increase and decrease in dose), when the drug was recommended to be used once a day. The total duration of therapy was 67 days.

The study protocol included an assessment of general and biochemical blood tests, urine analysis before the start of the study (day 0) and again on the day of completion of therapy (day 67).

All patients were examined on days 0 and 67 using individual sections (domains) of the Griffiths Mental Development Scales from Birth to 2 Years, a revised and supplemented version (GMDS-ER) [8], in which the corresponding sections are designated as scales (Griffiths scales). This version of the Griffiths scales took into account the chronological age of the children. As is known, to assess the rate of psychomotor development in premature infants, specialists often use a correction for the degree of prematurity or “corrected age”. Such an adjustment, especially before the age of 2, is useful for reducing excessive anxiety about the development of premature infants and leveling out overdiagnosis of its disorders. However, it should be taken into account that in some cases, age adjustments can mask certain developmental problems, delay the start of necessary early intervention, provide inaccurate guidelines and contribute to false reassurance among both relatives and specialists working with the child.

Griffiths scales for children from birth to 2 years allow to determine the level of development of the child in five areas [8]: A. Motor activity; B. Personal and social; C. Hearing and speech; D. Visual-motor coordination; E. Manipulation with objects**(table.2)**.

The test results were recorded on individual cards, after which the scores were calculated for individual scales. Then, using centile tables for each of the five scales, the age equivalent of development in a given area in months was determined, as well as the standardized Z indicator. Thus, at the final stage of the individual assessment of the results, the general indicator of the level of neuropsychic development (general quotient - GQ) was analyzed, which was calculated as the average score for the five scales; the lag in months (the difference between the chronological age and the post-

Table 2.*Development areas assessed by Griffiths scales [8] in children *Table 2.

Developmental domains assessed by means of the Griffiths Scales [8]

Scale	Name of the scale	Skills and Abilities, Assessment Examples
A	Motor activity	Gross locomotion - the ability to maintain balance, coordinate and control movements. Movements from prone positions, supine positions, the ability to sit, crawl, stand up, holding on to support, take steps, walk are assessed
B	Personal-social	Social adaptation and everyday life skills, the ability to interact with other people. The child's reaction to his/her reflection in the mirror, to putting away a toy, turning the head towards the speaker, distinguishing between familiar and unfamiliar people, interest in the actions of other people, in unfamiliar children, the ability to play simple interactive games, the ability to clap hands in imitation are assessed. The ability to independently pick up food with fingers, use a spoon, hold a cup, help with dressing
C	Hearing and speech	Impressive and expressive speech. Examples: listens to tuning fork, rings bell. Responds when called, listens to conversation. Appreciates babble, uses voice to attract attention, produces words. May look at picture for short periods; shake head to mean “no”; looks at picture book with interest, listens to poetry, responds to music, singing; tries to sing
D	Visual-motor coordination	Coordination of visual control and hand movements, dexterity in manipulation of objects. The ability to hold objects, throw them, interest in toy cars with the ability to move them forward are assessed. Can hold a pencil and "poke" them on paper, point at the object with the index finger
E	Manipulations with objects	Manipulative activity with objects and the ability to play, based on visual-spatial perception, speed and accuracy of movements. Manipulations with objects (lid, box, cubes), a sheet of paper, searching for a hidden toy, the ability to insert figures of different shapes into holes on boards are assessed.

***Table 3.*The proportions of patients in the two groups with and without a decrease in the degree of psychomotor developmental delay67 days of observation**

***Table 3.*Patients' ratios in two groups with the decrease of developmental delay on the study Day 67**

The proportion of children with a decrease of at least 6% in the degree of delay in psychomotor development (according to the general indicator of the level of psychomotor development GQ on scales Griffiths) after a course of therapy	1st group		2nd group	
	abs.	%	abs.	%
There is a decrease	28	63.6	17	39.5
No reduction	16	36.4	26	60.5
Total	44	100	43	100
Null Hypothesis Testing (Fisher's Exact Test, One-Sided Hypothesis)		p=0.021		

***Table 4.*Delay from chronological age in months (*M±m*) in five areas of development when studied using Griffiths scales in patient groups**

***Table 4.*The delay from chronological age in months (*M±m*) in five developmental domains assessed by means of the Griffiths Scales in patients' grpups**

Scale	GV	1st group		2nd group	
		Day 0	Day 67	Day 0	Day 67
A: Physical activity	All children	2.8±0.3	2.5±0.3	3.1±0.3	2.9±0.4
	32-33 weeks	3.4±0.4	3.2±0.5	3.2±0.4	3.3±0.6
	34-36 weeks	2.1±0.3	1.6±0.4**	3.0±0.5	2.6±0.6
B: Personal and social	All children	2.6±0.2	2.2±0.2*	2.9±0.2	2.8±0.3
	32-33 weeks	2.9±0.2	2.7±0.3	3.2±0.2	3.3±0.4
	34-36 weeks	2.1±0.2	1.7±0.3*	2.7±0.2	2.4±0.3
C: Hearing and speech	All children	1.9±0.2	1.8±0.2	2.3±0.3	2.3±0.3
	32-33 weeks	2.2±0.3	2.3±0.3	2.6±0.5	2.8±0.6
	34-36 weeks	1.4±0.3	1.1±0.3	2.0±0.3	2.0±0.4
D: Visual-motor coordination	All children	2.4±0.2	2.2±0.3	2.6±0.2	2.6±0.3
	32-33 weeks	2.8±0.3	2.8±0.4	2.9±0.4	2.8±0.6
	34-36 weeks	1.9±0.2	1.5±0.3	2.4±0.3	2.4±0.4
E: Manipulation of objects	All children	2.8±0.2	2.3±0.3**	3.1±0.2	2.7±0.3
	32-33 weeks	3.2±0.3	3.0±0.4	3.3±0.3	3.2±0.5
	34-36 weeks	2.3±0.3	1.3±0.3***	2.9±0.3	2.4±0.5
General indicator of age development	All children	2.6±0.2	2.4±0.3	2.8±0.2	2.7±0.3
	32-33 weeks	3.1±0.3	3.0±0.4	3.1±0.3	3.1±0.5
	34-36 weeks	2.1±0.2	1.6±0.3**	2.6±0.2	2.4±0.4

*Note.*Reliability of improvement onDay 67 vs. Day 0 baseline: * —p<0.05, ** —p<0.01, *** —p<0.001. *Note.*Significant improvement on Day 67 compared with the initial results on Day 0: * —p<0.05, ** —p<0.01, *** —p<0.001.

age equivalent shown during the examination) for each of the five scales and the overall indicator of age development; the standardized Z score (for the overall indicator and assessments on the five scales) is a measure of the relative dispersion of the measured value, which shows how many standard deviations constitute its dispersion relative to the normal mean value. Z values from –2 and below correspond to a significant developmental delay, from –1 to –2 — to a moderate delay, from –1 to +1 — to the normal range [8].

In statistical processing of the results, descriptive and comparative analysis were performed. Quantitative variables are presented as mean values and standard error, qualitative and ordinal variables - as frequency and percentage. Comparative analysis was based on determining the reliability of the difference in indicators using Fisher's exact test and *U*- Mann-Whitney test for independent samples, *t*-test and the Wilcoxon test for dependent samples. Differences were considered significant at values p<0.05.

The study was approved by the National Ethics Council of the Ministry of Health of Russia and was conducted in accordance with the Declaration of Helsinki, the principles of good clinical practice approved at the International Conference on Harmonization (ICH GCP), and the National Standard of the Russian Federation GOST R 52379-2005 "Good Clinical Practice".

Results

The primary efficacy indicator was the proportion of children who showed a reduction in the degree of psychomotor developmental delay based on the results of the assessment of the overall GQ indicator after the course of therapy by more than 6%. **table.3**The proportions of patients in two groups with a decrease are presented. an increase in this development indicator after 67 days of observation compared to the initial level. A decrease in the degree of psychomotor developmental delay by more than 6% was achieved in the 1st group in 63.6% of patients, and this value significantly exceeded the corresponding indicator in the 2nd group - 36.4% (p=0.021).

***Table 5.*Gradation of individual assessments according to Griffiths scales in groups of examined patients before and after treatment, % *Table 5.* Ranking of individual scores on the Griffiths Scales in the groups of patients before and after the treatment, %**

Scale/Day of examination	1st group (*n*=44)				2nd group (*n*=43)			
	standardized values Z-indicator				standardized values Z-indicator			
	– 2 and below (significant-no lag)	from -1 to -2 (moderate lag)	from -1 to +1 (range norms)	*p*	– 2 and below (significant-no lag)	from -1 to -2 (moderate lag-(no)	from -1 to +1 (range norms)	*p*
A: Physical activity								
0th	40.9	52.3	6.8	* *	51.2	30.2	18.6	*
67th	36.4	27.2	36.4		44.2	16.3	39.5	
B: Personal and social								
0th	72.7	20.5	6.8	* *	83.7	16.3	—	*
67th	43.2	38.6	18.2		58.1	23.3	18.6	
C: Hearing and speech								
0th	25.0	29.5	45.5	*	34.9	25.6	39.5	—
67th	13.6	20.5	65.9		30.2	20.9	48.9	
D: Visual-motor coordination								
0th	54.6	29.5	15.9	* * *	60.5	20.9	18.6	* * *
67th	34.1	29.5	36.4		48.9	13.9	37.2	
E: Manipulation of objects								
0th	65.9	22.7	11.4	* * *	69.8	27.9	2,3	* * *
67th	25.0	29.5	45.5		39.5	18.6	41.9	
General indicator of age development								
0th	50.0	45.5	4.5	* * *	55.8	37.2	7.0	* * *
67th	29.5	29.5	40.9		41.9	18.6	39.5	

*Note.*Reliability of improvement in the group onDay 67 vs. Day 0 baseline: * —*p*<0.05, ** —*p*<0.01, *** —*p*<0.001. *Note.*Significant improvement on Day 67 compared with the initial results on Day 0: * —*p*<0.05, ** —*p*<0.01, *** —*p*<0.001.

The results of the assessment of the lag in months from the chronological age in five areas of neuropsychic development, studied using the Griffiths scales, are presented in**table.4**. In the 1st group, after a course of therapy with LP Pantogam, a significant reduction in developmental delays was observed in two areas - "Personal and social" and "Manipulation with objects", as well as a clear tendency to reduce the delay in the other three areas: "Motor activity", "Hearing and speech", "Visual-motor coordination". At the same time, more pronounced positive dynamics were determined in the subgroup of patients with GV at birth 34-36 weeks, in whom the reduction in developmental delays was significant in three areas: "Motor activity", "Personal and social", "Manipulation with objects".

During the same observation period, in the 2nd group (placebo), no significant reduction in developmental delay was found in any of the areas, although there was a tendency towards it in two areas ("Motor activity" and "Manipulation with objects").

Of great importance is the analysis of individual indicators according to the Griffiths scales in patients examined groups**(table.5)**More than .1/ patients, the study using the Griffiths scales revealed a significant delay in psychomotor development (Z values for the overall indicator were –2 and below) compared with age norms. Before the start of the therapeutic course, there were 22 such children (50.0%) in the 1st group (Pantogam), in the 2nd group (placebo) - 24 (55.8%). There were 20 children (45.4%) with moderate developmental delay (Z from –1 to –2) in the 1st group and 16 (37.2%) in the 2nd group. Only in isolated cases did the overall indicator of age development correspond to the normal range (Z from –1 to +1): in 2 (4.5%) children in the 1st group and 3 (7.0%) children in the 2nd group.

During the repeated examination on the 67th day, a significant improvement in individual indicators of psychomotor development was observed in both groups, and their compliance with the normal range was confirmed in 18 (40.9%) children who received treatment with the drug Pantogam and in 17 (39.5%) with placebo.**(rice.1 and 2)**However, significant differences were evident in the fact that in the 1st group there were far fewer patients with significant developmental delays - 13 (29.5%) children compared to the 2nd group - 18 (41.9%) children. Ana-

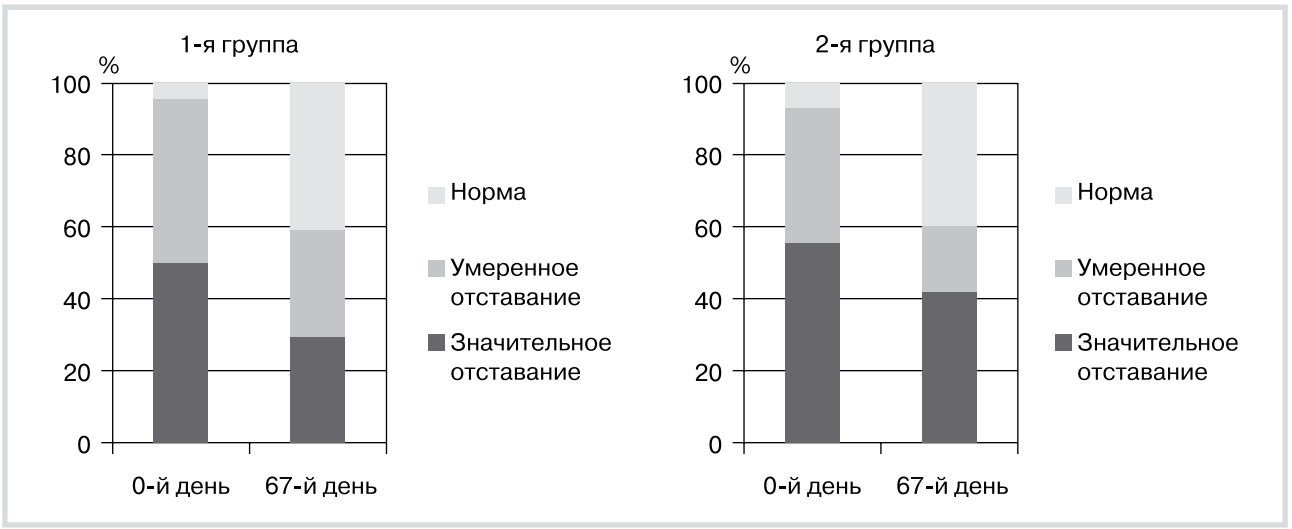

***Fig. 1.*Overall age-related development index according to Griffiths scales: gradation of individual assessments in two groups of patients before and after treatment.**

***Fig. 1.*General score of age development on the Griffiths Scales: ranking of individual scores in two groups of patients before and after the treatment.**

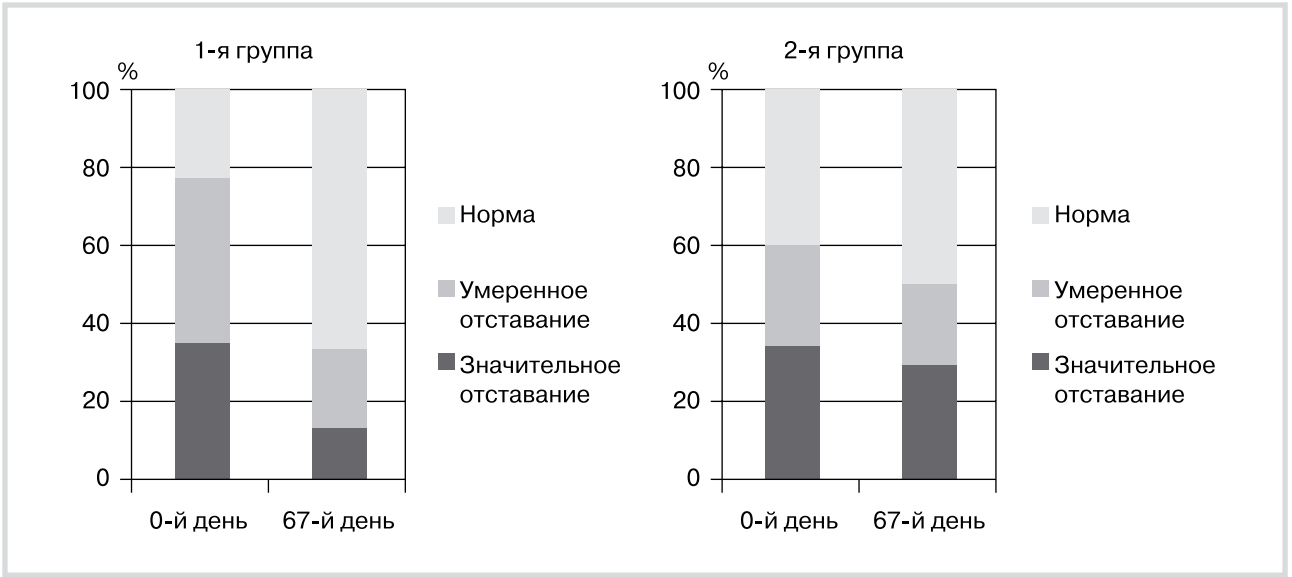

***Fig. 2.*Age-related development index according to the Hearing and Speech Scale: gradation of individual assessments in two groups of patients before and after after treatment.**

***Fig. 2.*General score of age development on the Hearing and Speech scale: ranking of individual scores in two groups of patients before and after the treatment.**

Logical trends and differences by the 67th day were traced in all areas of development, with the exception of "Hearing and speech". In the 2nd group (placebo), minimal changes in the gradation of the degrees of delay in the development of this area were noted. On the other hand, in the 1st group (Pantogam), the number of children with significant delay decreased from 25.0 to 13.6%, with moderate delay - from 29.5 to 20.5%, while the number of children with normal characteristics of pre-speech development increased from 45.5 to 65.9%.

Adverse events (AEs) were defined and classified according to MedDRA (Medical Dictionary for regulatory activities) — an international dictionary of adverse reactions that occur when using medicinal products for medical use [9]. Analysis of data on AE was performed for all randomized patients (45 in each group), taking into account the frequency of cases of development of AE, their severity, and relationship with the drug.

A total of 484 AEs were registered during the study, including 286 AEs in the 1st group “treatment with LP Pantogam” (59.1% of the total number of AEs) and 198 AEs in the 2nd group “placebo” (40.9%). At the same time, the number of patients who experienced at least one AE was 28 (62.2%) in the 1st group.

Table 6.*Distribution of AE cases by patient groups and their relationship with the drug *Table 6.
Distribution of undesirable events in patients' groups and their relation to medication

Classes by organ systems	Clinical manifestations	Number of cases of AE		Relationship of AE with the drug		
		1st group	2nd group	nature of connection	1st group	2nd group
Gastrointestinal disorders	Oral candidiasis	1	0	Absent	1	0
	Flatulence	1	1	»	1	1
	Teething	3	2	»	3	2
	Bowel disorder	0	1	»	0	1
Infections and infestations	Chicken pox	1	0	»	1	0
	Respiratory tract infection	5	3	»	5	3
Metabolic and nutritional disorders	Fast saturation	44	33	»	44	31
				Doubtful	0	1
				Possible	0	1
	Increased appetite	0	2	Absent	0	1
				Possible	0	1
Respiratory system disorders	Cough	0	1	Absent	0	1
	Rhinitis	0	1	»	0	1
	Rhinorrhea	0	1	»	0	1
Skin disorders Blood disorders	Rash	1	0	Possible	1	0
	Leukocytosis	1	0	Absent	1	0
Nervous system disorders	Anxiety	0	10	»	0	9
				Possible	0	1
	Excitation	78	52	Absent	76	38
				Possible	2	14
	Hypotension	1	0	Doubtful	1	0
	Neurological symptom	0	2	Absent	0	2
	Cry	29	18	»	28	9
				Possible	1	9
General violations	Hyperthermia	1	1	Absent	1	1
	Lack of energy	18	25	»	18	24
				Doubtful	0	1
	Temperature increase	4	3	Absent	4	3
Mental disorders	Hypersomnia	10	6	»	10	5
				Possible	0	1
	Behavioural childhood insomnia	88	36	Absent	85	30
				Conditional	0	1
				Doubtful	0	1
				Possible	3	4

and 31 (68.9%) in the 2nd group, these differences were not statistically significant (r=0.5057). According to the dynamic observation of patients, all AEs were completely resolved. No cases of serious AEs were registered.

The most frequent AEs in both groups were those related to the classes of “nervous system disorders”, “mental disorders” and “metabolism and nutrition disorders”. A comparative analysis of the incidence of AEs showed that there were no statistically significant differences between the groups in the number of AEs in all classes, with the exception of “nervous system disorders” (r =0.0015). Thus, compared with the “placebo” group, in the “Pantogam” group, such adverse events as agitation and crying were somewhat more common.**(table.6)**.

The analysis of the distribution of AEs by severity showed that 97.9% (474 of 484) of AEs were mild and only 2.1% (10 of 484) of AEs were of moderate severity. The most frequent AEs (agitation, crying, behavioral infantile insomnia) were of mild severity. As for AEs of moderate severity, in group 1 (Pantogam) they included chickenpox (1 case), agitation (1), crying (1), insomnia (1), and in the 2nd group (placebo) - rapid satiety (1), agitation (1), crying (2), insomnia (2).

For the majority of AEs, the degree of their relationship with the treatment was assessed by the investigators as absent. In the class of "nervous system disorders", the relationship with the study drug (Pantogam/placebo) of the AE "crying" was assessed as "absent" (28/9 cases), "possible" (1/9); the relationship with the AE "agitation" was "absent" (76/38) and "possible" (2/14). In the class of "mental disorders", the relationship with the study drug (Pantogam/placebo) of the AE "behavioral insomnia in children" was assessed as "absent" (85/30 cases), "conditional" (0/1), "doubtful" (0/1), "possible" (3/4). Thus, for the most frequently occurring AEs (agitation, crying, behavioral infantile insomnia), the relationship with the study drug (Pantogam/placebo) was often absent. For the AE “rash” (due to which the patient dropped out of the study), the relationship with the drug was assessed as “possible”.

Thus, based on the results of the comparative analysis of AE data, the two groups of patients had comparable favorable safety profiles.

Discussion

According to global statistics, over the past decade the proportion of children born prematurely has reached 11.1% of all live births per year [10]. The risk of developing neurological abnormalities in premature babies is 20–30 times higher than in the general population of newborns [11]. Premature babies are the most vulnerable group with respect to delays in psychomotor development, and subsequently motor disorders, intellectual and speech disorders, learning difficulties, and social adaptation. In recent years, there has been growing concern about neuropsychiatric developmental disorders that develop not only in children born with extreme or profound prematurity, but also in moderate and borderline prematurity.

We present the results of a double-blind, multicenter, randomized, placebo-controlled study in parallel groups in premature infants aged 6-12 months with delayed psychomotor development due to hypoxic-ischemic CNS damage. It included 90 children born prematurely at 32-36 weeks of gestation, randomized into two groups of 45 patients (Group 1 - treatment with the drug Pantogam, Group 2 - placebo). Forty-four patients in Group 1 and 43 patients in Group 2 completed all study procedures and completed their participation. One child withdrew from the 1st group due to an adverse event (skin rash), and two patients withdrew from the 2nd group (one due to worsening sleep, the other due to the parents' decision to leave the study early).

The characteristics of the psychomotor development of patients were assessed using the Griffiths scales, a modern diagnostic method that is increasingly used in different countries and allows for an objective assessment of both the general psychomotor development of the child and indicators in its main areas. In recent years, this method has been successfully used to assess the developmental characteristics of children born prematurely [2, 12–15].

In the present study, a decrease in the degree of psychomotor developmental delay by more than 6% (from the initial value of the general psychomotor development index GQ) was considered a response to the therapy administered within 2 months. Such an improvement was achieved in the 1st group after treatment with the drug Pantogam in 63.6% of patients, which significantly exceeded the similar indicator in the 2nd group (placebo) - 36.4% (p=0.021).

At the same time, in the 1st group, a significant reduction in developmental delays was observed in two areas ("Personal-social" and "Manipulation with objects"), as well as a clear tendency to decrease the delay in the other three areas: "Motor activity", "Hearing and speech", "Visual-motor coordination". At the same time, more pronounced positive dynamics were determined in the subgroup of patients born with late (borderline) prematurity (GA 34-36 weeks), compared with children with moderate prematurity (GA 32-33 weeks). Over the same period, neither in the entire 2nd group (placebo), Neither in its subgroups with different GA at birth was a significant reduction in developmental delay found in any of the areas examined using the Griffiths scales.

Since patients in both groups received treatment (Group 1 — standard treatment and a course of Pantogam, Group 2 — only standard treatment), the positive dynamics in both groups seems completely natural when analyzing individual assessments on the Griffiths scales. However, when grading the overall indicator of psychomotor development (significant, moderate delay, normal range), it was noteworthy that in Group 1, after 2 months of treatment, the number of patients with significant developmental delays significantly decreased (29.5%) compared to Group 2 (41.9%). A similar trend was observed in relation to assessments in most areas.

It is interesting that in the 2nd group (placebo) minor changes in the gradation of the degrees of delay in the development of the sphere of "Hearing and speech" were observed, whereas in the 1st group (Pantogam) the number of children with significant delays significantly decreased (from 25.0 to 13.6%), and with normal characteristics increased (from 45.5 to 65.9%). These results can be considered as confirmation of the positive effect of the drug Pantogam on the indicators of pre-speech development.

It should be noted that the value of the Griffiths scales is that, when individually assessing the characteristics of neuropsychic development, based on the results obtained, it is possible to draw conclusions not only about the global lag and its degree, but also about partial disorders in individual areas. This allows us to formulate differentiated recommendations for their correction, to form individual programs of observation and rehabilitation [15]. It is quite possible to do this already in the second half of the first year of life of infants born prematurely.

The results obtained allow us to draw the following conclusions:

1. When assessing children aged 6-12 months, born premature babies, response to therapy conducted over 2 months to reduce the degree of psychomotor developmental delay by more than 6% (from the initial value of the overall psychomotor development indicator GQ according to the Griffiths scales), improvement in the 1st group after treatment with the drug Pantogam (in 63.6% of patients) significantly exceeded the similar indicator in the 2nd group (placebo) (36.4%, p=0.021).

2. Inclusion of the drug Pantogam in the complex treatment of led to a significant reduction in developmental delays in two areas ("Personal-social" and "Manipulation of objects"), as well as to a tendency to reduce delays in three other areas: "Motor activity", "Hearing and speech", "Visual-motor coordination". More pronounced positive dynamics were determined in the subgroup of patients born with borderline prematurity (GA 34-36 weeks), compared with children with moderate prematurity (GA 32-33 weeks).

3. It has been shown that when grading the general psi-homocortic development (significant, moderate delay, normal range) before and after treatment in the 1st group (therapy with the drug Pantogam), the number of patients with significant developmental delays significantly decreased (29.5%) compared to the 2nd group (41.9%).

4. It has been confirmed that the drug Pantogam has favorable a positive safety profile comparable to placebo, as evidenced by good tolerability and a high level of perception of the prescribed therapy. Comparative analysis of the incidence of AEs showed that there were no statistically significant differences between the groups in the number of AEs in all classes, with the exception of "disorders of the from the nervous system" (r=0.0015). In the Pantogam group, adverse events such as agitation, crying and insomnia were somewhat more common, but they were mild and transient in nature.

The authors declare no conflicts of interest.

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