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Clinical and Electroencephalographic Assessment of the State of Premature Children Treated with Cytoflavin during the First Year of Life

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The aim of the present work was to perform clinical and neurophysiological assessment of the rates of neuromental development during the first year of life in preterm neonates with cerebral ischemia grade II–III, allowing for the effects of treatment with Cytoflavin and resuscitation measures. A total of 120 children with gestational ages of 28–36 weeks and body weights of 1060–3150 g were studied. The study group included 61 children whose complex treatment included Cytoflavin at a dose of 2 ml/kg/day i.v. for five days. The control group consisted of 59 patients who received basal treatment without Cytoflavin. Follow-up to a corrected age (CA) of one year included assessment of overall condition and neurological status (using a quantitative assessment of postural muscle tone on the INFANIB scale, psychomotor development on the BSID-II scale, and the functional state of the CNS by computerized electroencephalography by monitoring of physiological sleep). The results demonstrated faster normalization of all study measures of development in children receiving Cytoflavin in their complex treatment as compared with the control group.

Keywords: preterm birth, intensive therapy, cerebral hypoxia-ischemia, cerebroprotective therapy, neuromental development, computerized electroencephalography, Cytoflavin.

Contemporary advances in the worldwide science and practice of neonatology have increased the potential for nursing premature children to health. The non-Russian literature [4, 10, 15] shows that among preterm children with very low body weight (VLBW) or extremely low body weight (ELBW), the proportion surviving is 50–80%, though the proportion reaching full health is no more than 10–25% and the proportion with severely disabling neurological manifestations is 12–32%. In Russian clinical practice, the introduction of highly effective contemporary techniques for the intensive care and nursing of preterm infants has allowed us to approach world standards for healthcare provision in this category of patients. Thus, in the specialist Moscow City Hospital No. 8, the proportion of children with VLBW and ELBW surviving was greater than 75% in 2009–2010.

The most severe neurological deficits are seen in preterm children requiring resuscitation and intensive care because of impairments to the process of early postnatal cardiorespiratory adaptation [3, 13, 14]. This makes the problems of the diagnosis, selection of pathogenetic treatment methods, and prognosis of perinatal hypoxic CNS injuries very relevant.

Pathogenetic treatment is based on knowledge of the biochemical and histopathological processes associated with intranatal hypoxia-ischemia and subsequent reperfu-

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sion and reoxygenation developing in the brain tissues of newborn infants over the period from a few hours to 5–7 days after the initial pathological process. The leading mechanisms of injury are oxidant stress and excitotoxicity, as well as the nonspecific inflammatory reactions of the microglia initiated by these factors. Repair and recovery processes are activated 72–96 h later. The death of neurons and glial cells starts in the first hours and continues over subsequent weeks and months [5, 11]. Necrotic changes dominating at the early stages are gradually replaced by the signs of apoptosis. The occurrence of a time sequence of stages in the development of injury to components of brain tissue due to hypoxia-ischemia underlies the concept of the so-called therapeutic window [19]. The duration of this period varies from 2 to 48 h after hypoxia, providing the potential for effective pharmacological intervention with the aims of protecting the brain [18, 20].

Currently, the neuroprotectors with the greatest potential are agents and their combinations maintaining anaerobic production of macroergic compounds in conditions of oxygen deficiency and having antioxidant activity [2, 7, 8]. These criteria are met by the Russian formulation Cytoflavin. This is a solution for intravenous administration (P No. 003135/01) developed by NTFF Polisan (St. Petersburg). The formulation contains sodium succinate (SS), inositol, riboflavin, and nicotinamide, and has a complex correcting action on intracellular energy metabolism both in conditions of tissue hypoxia-ischemia and during postischemic reperfusion [9].

Studies of the therapeutic efficacy of the formulation from an evidence-based medicine perspective requires assessment not only of changes in patients' clinical status and objective laboratory and instrumented study methods before and after courses of treatment, but also evaluation of long-term treatment results and studies of disease outcomes. For preterm infants with perinatal CNS hypoxia, this applies to the level of neuromental and motor development at age one year. In the case of preterm children, the concept of corrected age (CA) is used.

The aim of the present work was to undertake a clinical and neurophysiological (electroencephalographic) assessment of neuromental development in preterm infants with grade II–III cerebral ischemia during the first year of life and treated with Cytoflavin (solution for infusion) as part of the complex treatment used during resuscitation and intensive care.

MATERIALS AND METHODS

This study is a component of a multicenter, randomized, control-comparison study performed at the clinical bases of the Department of Neonatology, Faculty of Advanced Medical Studies, Russian State Medical University, in the Departments of Resuscitation and Intensive Care (DRICN No. 1 and DRICN No. 2), Moscow City Hospital No. 8 (Medical Director: Dr A. B. Dulenkov) and the Department of Follow-Up Investigations at the Clinical Diagnostic Center, N. F. Filatov Pediatric City Hospital No. 13 (Medical Director: Dr V. V. Popov).[1]

A total of 120 preterm children born at 28–36 weeks of gestation were studied; birth weight was 1060–3150 (mean 1781.7 ± 508.98) g and body length was 25–50 (mean 40.6 ± 3.93) cm. There were 73 boys (60.83%) and 47 girls (39.17%). There were 24 neonates from twins and four from triplets. In 12 cases, multifetal pregnancies resulted from in vitro fertilization. Among children from multifetal pregnancies, two involved antenatal death of the second fetus.

Chronic intrauterine fetal hypoxia was noted in 50 of the 120 cases. Acute intranatal hypoxia was diagnosed in six children. All children had complicated early postnatal adaptation periods requiring intensive care and further treatment at the second stage of nursing.

The main inclusion criteria were: presence of written informed consent from the patients' parents before enrolment, neonates, preterm, need for cardiorespiratory resuscitation and intensive care, presence of cerebral hypoxia-ischemia grade II–III, Apgar scores of 3–8 (or below), and low blood oxygen saturation ($SaO_2 < 93\%$) on mechanical ventilation during the first hour after birth. Exclusion criteria were parental refusal to take part in the study at any stage, individual intolerance of the study agent, congenital developmental anomalies of the brain and internal organs, Down's syndrome, and maternal HIV infection.

Randomization was performed by the converts method. Even numbers placed the patient in the study group treated with Cytoflavin, while odd numbers placed patients in the control group receiving basal therapy only.

The study consisted of 61 preterm neonates. These cases received, along with basal intensive therapy, slow i.v. infusions of Cytoflavin at a dose of 2 ml/kg/day for the first five days after birth. The calculated daily dose was diluted in 5% or 10% glucose at a ratio of 1:5. Cytoflavin was given simultaneously with the solutions used for correction of water-electrolyte balance and circulating blood volume (CBV), as well as solutions for parenteral nutrition. The rate of administration of prepared Cytoflavin solution was controlled using infusion pumps and was 1–4 ml/h depending on the calculated daily volume of liquid for basal therapy, the state of the patient's hemodynamics, and measures of acid-base status (ABS).

The control group consisted of 59 preterm neonates who received only the required basal intensive treatment.

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TABLE 1. Characteristics of Patient Study Groups

Parameter		Study group (n = 61)		Control group (n = 59)	
		n	%	n	%
Gestational age, weeks	28–30	17	27.87	17	28.82
	31–33	27	44.26	18	30.50
	34–36	17	27.87	24	40.68
	Mean	31.92±2.12		32.31±2.51	
Gender	Male	35	57.38	38	64.41
	Female	26	42.62	21	35.59
Body weight, g	Range	1060.0—3250.0		1090.0—3110.0	
	Mean	1717.54±456.86		1848.20±553.87	
Apgar score, points					
1 min	Range	3—7		2—7	
	Mean	6.28±1.1		6.1±1.35	
5 min	Range	4—8		3—8	
	Mean	7.03±0.75		6.88±0.98	

The characteristics of the study and control groups are presented in Table 1.

All the children were born in a severe state and were transferred immediately from the delivery room to DRICN No. 1, City Hospital No. 8. The in-patient stay at DRICN No. 1 was 4–38 days, after which the children were transferred to DRICN No. 2 or the pediatric departments for the second stage of nursing. The in-patient durations of the study and control groups in DRICN No. 1 and No. 2 were not significantly different, at 18.9 ± 9.9 and 18.7 ± 8.4 days respectively. There were no deaths in either the study group or the control group during the in-patient period at DRICN No. 1. After transfer of DRICN No. 2 and neonatal pathology departments for the second stage of nursing, all neonates continued their ongoing treatment.

Analysis of the course of the early neonatal period showed faster reductions in the need for high oxygen concentrations for respiratory support (mechanical ventilation of the lungs; constant positive airways pressure (CPAP)), elimination of signs of centralization of the blood flow, improvements in tissue perfusion, normalization of ABS pH, and elimination of lactic acidosis in children of the study group. In addition, children of the study group had no severe forms of peri- or intraventricular bleeding (PVB/IVB) or focal ischemic lesions to the periventricular white matter; there was also faster normalization of serum neurospecific protein concentrations.

By CA one month, all the children were discharged home in a satisfactory state. The total durations spent in hospital among children of the study and control groups were not significantly different, at 40.7 ± 15.2 and 41.3 ± 19.3 days ($p > 0.05$), respectively.

Follow-up observations of all children included complex clinical and instrumented investigations, with assessment of clinical status, neurological status, and psychomotor development using the corresponding quantitative methods. These included the postural muscle tone scale of the INFANIB [17] and the neuromuscular development scale of the Bayley Scales of Infant Development (2nd edition) (BSID-II) [16]. Electroencephalographic investigations were also performed. Correct comparative analysis of data from preterm children of different gestational ages (GA) was obtained by evaluating all results on the basis of CA in weeks calculated as CA = GA + chronological age – 40.

The INFANIB scale involves testing of 20 items on a scale of 0–5. The total assessment can correspond to one of three ranges – "pathology," "transient impairment," or "normal." The numerical value of the range depends on the child's age, taking account of gestational maturity.

The BSID-II scale provides both qualitative and quantitative objective assessment of the level of neuromental development. Test results represent a preliminary evaluation indicating the proportion of tasks performed, and centile tables are used to calculate the Mental Development Index (MDI) and Psychomotor Development Index (PDI), which indicate the correspondence of the levels of neuromental and psychomotor development to the child's age. Testing on the BSID-II identifies four groups of children: 1) those with accelerated development (greater than 116 points); 2) those with the optimum levels of motor and/or neuromental development (85–116 points); 3) those with moderate (borderline) delay in motor and/or neuromental development (70–84 points); and 4) children with marked delays in neuromental development (69 points or less). Studies are performed in standard conditions in the presence of one or both parents. The program consists of testing the children and questioning the parents. The duration of each test is about 1.5 h.

To evaluate the functional state of the CNS, children of the control group underwent computerized EEG at CA 44–46 weeks from conception and CA three months, with monitoring of non-medicated physiological sleep. Trace duration was from 25 min to 1 h, depending on when the

child woke spontaneously. An obligatory condition was that traces had to contain slow-wave sleep phases. Recordings were made using programmable Neiron-Spektr-4VP (Neirosoft, Ivanovo) and Neurotravel 24D (ATES Medica Device, Italy) instruments. A frequency bandpass of 0.5–35 Hz and a time constant of 0.3 sec were used for all instruments. The international scheme was used, with a reduced number of electrodes. Recordings were made from monopolar leads with combined ear reference electrodes.

The correspondence of the overall EEG pattern to age from conception and deviations from normal at CA 40 and 44 weeks from conception was assessed using the typological classification of sleeping EEG patterns in neonatal children [12] as well as ontogenetic markers of the maturation of brain bioelectrical activity [6], including assessment of: sleep structure (ability to identify sleep phases, their sequence in the cycle, durations, presence of undefined sleep phases); the characteristics of the EEG phases of restful sleep (amplitude, topographic distribution of baseline activity, presence of alternation); presence of pathological patterns (their semiotics, number, amplitude, locations); and the stability of the interhemisphere amplitude-frequency asymmetry. This classification gives five types of overall sleep EEG patterns in one-month children with perinatal CNS injuries. The classification is based on the severity of impairments to the functional state of the brain. A total of five types of pattern reflect the sequence of gradation of the severity of the functional state of the child's brain, from I to V.

Expert visual assessment of EEG patterns at CA 3 months included assessment of: sleep structure (sequence of phases in the cycle, ability to identify them, their durations, presence and duration of undefined sleep); overall patterns of resting sleep (amplitude, topographical distribution of baseline activity, characteristics of sleep spindles and vertex potentials, i.e., their amplitude, topography, and production, as well as number per minute); presence of pathological patterns (paroxysmal, epileptiform) and stable local changes; presence and stability of amplitude-frequency interhemisphere asymmetry; presence of dysfunction of the brain regulatory systems; overall correspondence of the characteristics of bioelectrical activity to the child's CA.

During visual expert assessments, neurophysiologists had no information as to whether the child was in the study or control group or any details of treatment.

RESULTS

The INFANIB Scale

At initial assessment, at age 14 days of life, the mean INFANIB scores in both groups were similar, at 47.77 ± 4.8 and 47.08 ± 5.1 in the study and control groups respectively. Assessment of 47.54% of children in the study group and 40.35% in the control group corresponded to the "transient impairment" range and 52.46% of children in the study group and 59.65% in the control group to the "pathology" range. Points scores did not correspond to normal in any case. Assessment at CA 44 weeks showed improvements, with increases in points scores in both the study group (59.5 ± 4.86 points) and control group (58.9 ± 4.23 points), $p = 0.000$ and $p = 0.000$, respectively, Wilcoxon test. The mean score in the study group was greater than that in the control group, though the difference was not statistically significant. On assessment at CA 44 weeks, assessment of 13.73% of children in the study group corresponded to the "normal" range, the remainder being in the "transient impairment" range. In the control group, only 4.35% of children corresponded to the "normal" range, 93.48% being in the "transient impairment" range and 2.17% in the "pathology" range. There were no statistically significant differences in the distributions of assessments at CA 44 weeks.

On the INFANIB scale, by CA two months of life, assessments in children on the study group (67.7 ± 3.47 points) were significantly greater than those in the control group (64.8 ± 3.93 points), $t(df = 73) = 3.43$; $p = 0.001$. At CA two months, points scores in 81.08% of children of the study group corresponded to the "normal" range, while 55.26% of those in the control group remained in the "transient impairment" range, i.e., there was a statistically significant difference in the distributions of assessments by range, $\chi^2(df = 1) = 10.58$, $p = 0.001$.

By CA three months, all children of the study group were in the "normal" range, while 11.76% of those of the control group were in the "transient impairment" range.

Subsequent follow-up observations in the study group showed further improvements in INFANIB scores, assessments in all children of the study group continuing to correspond to the "normal" range throughout the observation period. At the same time, changes in INFANIB assessments in children in the control group were uneven, with periods of deterioration over the period 6–9 months due to the age-related formation of motor impairments and delays in decreases in tonic reflexes and spinal automatisms. The number of children whose assessment corresponded to normal decreased (39.29%), while assessments in 3.57% of the children were in the "pathology" range (Fig. 1). Thus, the rates of normalization of postural muscle tone and motor functions assessed on the INFANIB scale were significantly greater in children of the study group after discharge from hospital than in children of the control group.

The BSID-II Scale

Comparative analysis of test results from children on the BSID-II scale showed that at CA one month, the mean indexes of both mental and motor development in the two groups were comparable. However, the score on the mental development scale corresponded to the "marked developmental delay" range in children of the control group more frequently than in children of the study group; $\chi^2(df = 1) = 4.7$; $p = 0.03$ (Fig. 2). At CA three months, the index of

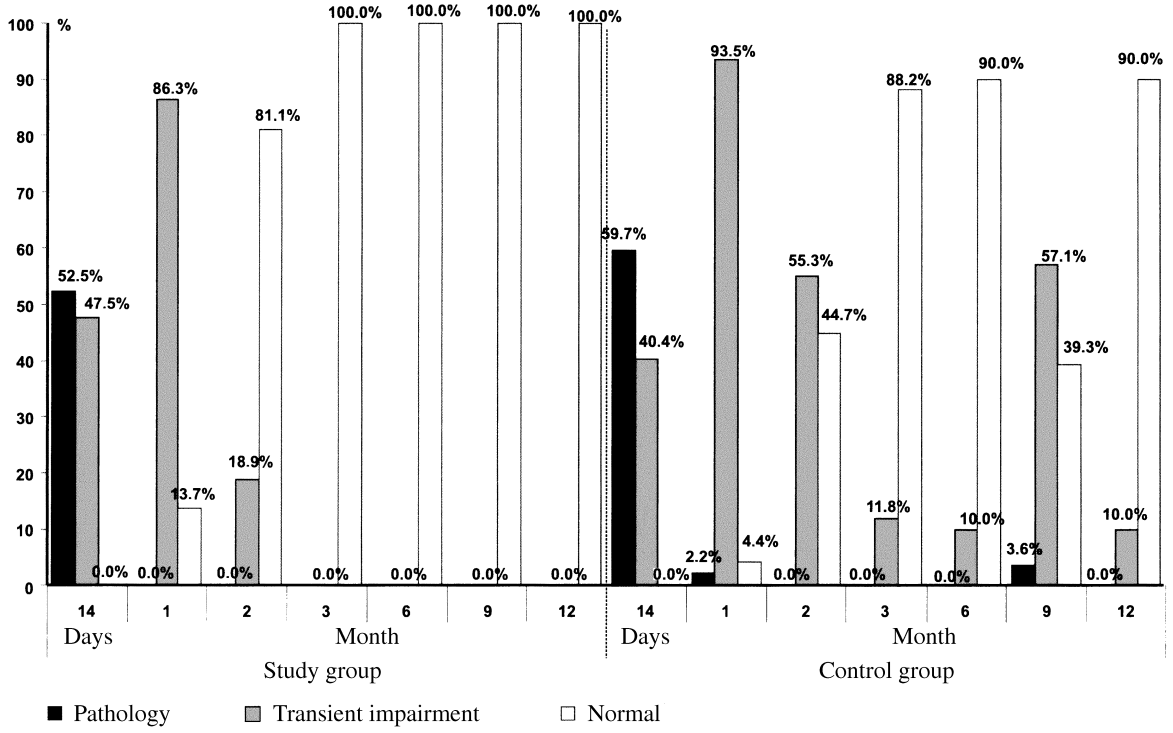

Fig. 1. Quantitative assessment of postural muscle tone on the INFANIB scale in children of the study and control groups at one year of life. Here and henceforth: abscissas show the corrected ages of children in the study and control groups; the ordinates show the proportions of children (%) with INFANIB scores corresponding to the "pathology," "transient impairment," and "normal" ranges.

motor development was significantly greater in children of the study group (98.3 ± 7.05) than in those of the control group (93.42 ± 7.74); $t(\text{df} = 67) = 2.74$; $p = 0.008$. Assessments of all children of the study group on the mental development scale corresponded to the "optimum development" range. At the same time, assessments of 15.15% of the children in the control group corresponded to the "moderate developmental delay" range; $\chi^2(\text{df} = 1) = 5.88$; $p = 0.015$. Comparison of the indexes of motor development at CA three months showed a tendency to higher values in children of the study group than in those of the control group (97.75 ± 6.66 and 94.64 ± 9.54, respectively), though the difference did not reach significance. At the same time, analysis of the distribution of assessments by range showed a significant difference: assessments of 21.21% of children in the control group corresponded to "moderate developmental delay," while assessment of all children in the study group corresponded to "optimum development;" $\chi^2(\text{df} = 1) = 8.5$; $p = 0.004$. Subsequently, the indexes of both mental and motor development in all children of the study group corresponded to the "optimum development" range throughout the observation period (to CA 12 months). During the periods from three to six months and from nine to 12 months, there were significant increases in the index of motor development – $t(\text{df} = 31) = -2.6$; $p = 0.014$ and $t(\text{df} = 22) = -3.85$; $p = 0.001$, respectively. The mean indexes of mental and motor development of children in the control group remained lower than those in the study group throughout the observation period (Fig. 3). The indexes in all children corresponded to "optimum development" only by CA 12 months.

Thus, children receiving Cytoflavin during the acute period of perinatal hypoxic-ischemic injury showed more successful and faster formation of normal values for neuromental development at one year of life.

Electroencephalography

In children of the study group, EEG patterns of types II ("delayed maturation") and III ("impaired maturation") at CA 40 weeks were seen in 21.43% and 78.57% of cases, respectively. In the control group, type II EEG patterns were seen in only 2.63% of children, while the functional state of the brain in the vast majority of children (97.37%) corresponded to EEG pattern type III ("impaired maturation;" Fig. 4). Thus, in children receiving Cytoflavin, type II EEG patterns were seen significantly more frequently – Pearson $\chi^2(\text{df} = 1) = 6.71$; $p = 0.01$.

Assessment at CA 44 weeks showed improvements due to significant increases in the proportion of children with type II EEG patterns, characterizing a relatively satisfactory functional state of the CNS, normalization of the ontogenetic formation of bioelectrical activity, and a significant decrease in the proportion of children with type III

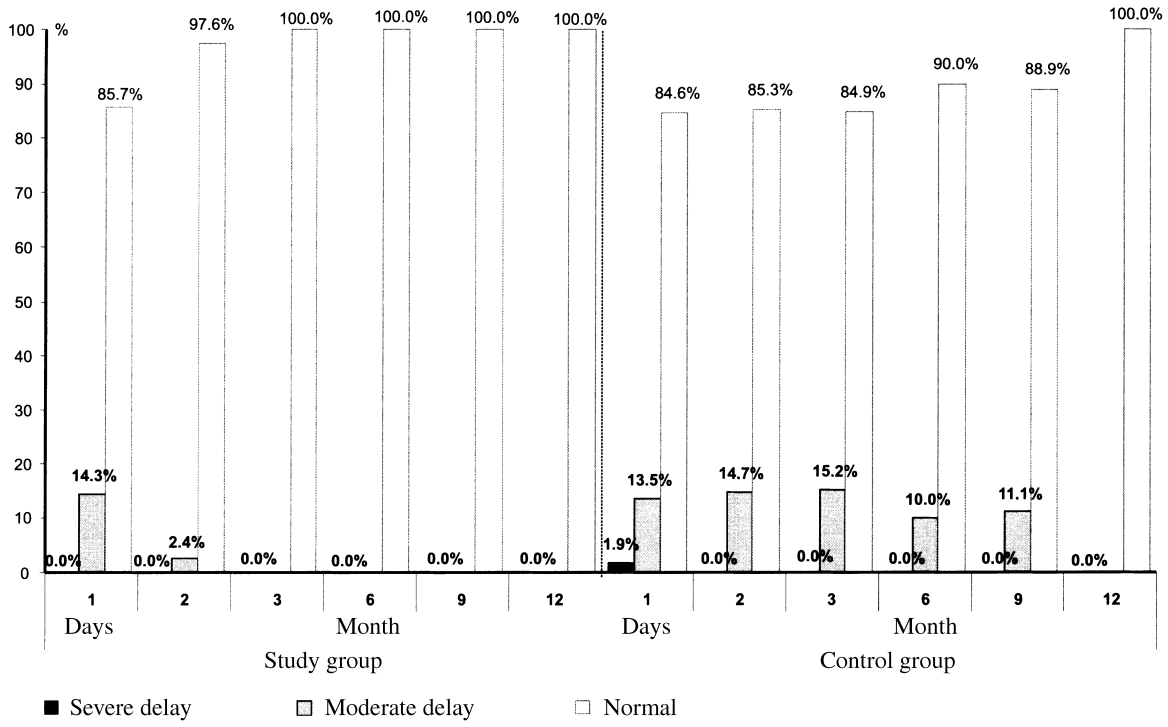

Fig. 2. Quantitative assessment of mental development on the BSID-II in children of the study and control groups at one year of life. The ordinate shows the proportions of children (%) with BSID-II mental development indexes corresponding to the "severe developmental delay," "moderate developmental delay," and "normal" ranges.

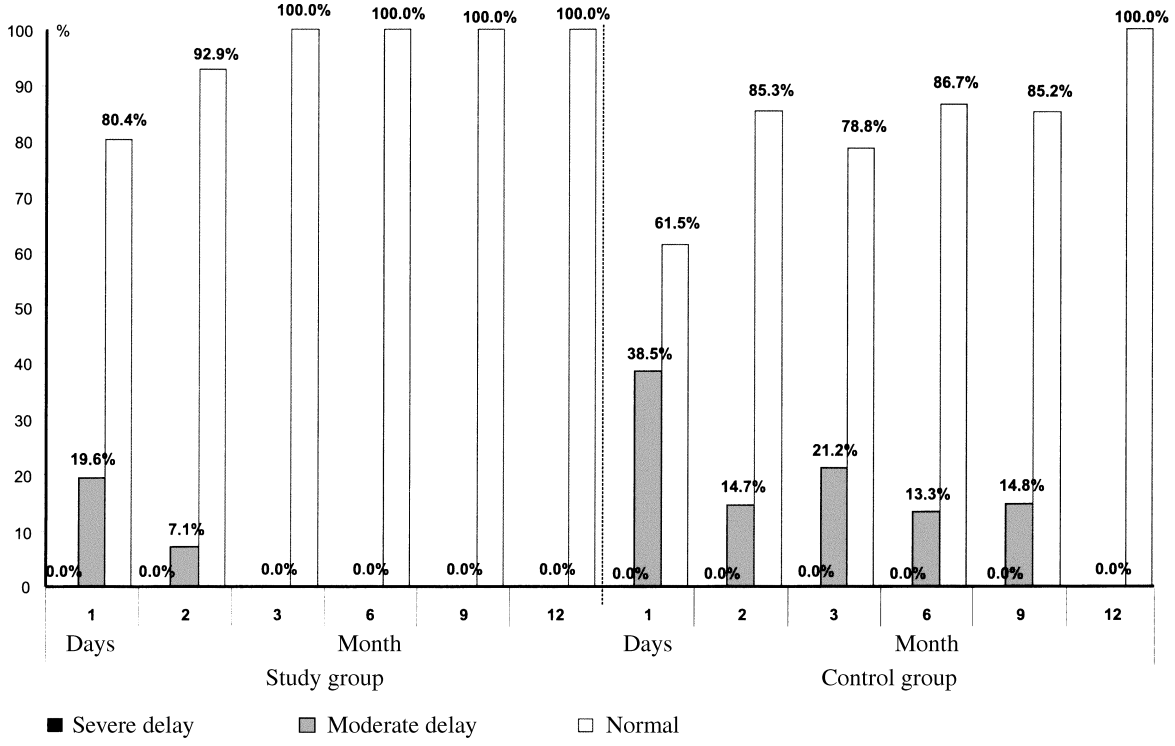

Fig. 3. Quantitative assessment of motor development on the BSID-II in children of the study and control groups at one year of life. The ordinate shows the proportions of children (%) with BSID-II motor development indexes corresponding to the "severe developmental delay," "moderate developmental delay," and "normal" ranges.

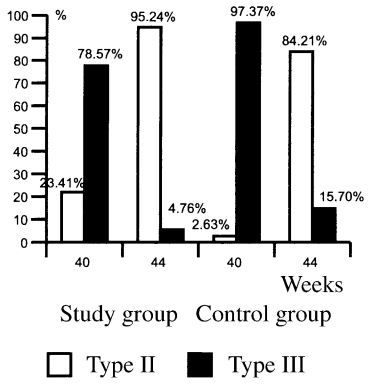

Fig. 4. Dynamics of EEG characteristics of slow-wave sleep at CA 36–40 weeks and 44–46 weeks in children in the groups studied. The ordinate shows the proportion of children (%) with EEG patterns of type II ("delayed maturation") and type III ("impaired maturation").

EEG patterns. This dynamic was seen in patients of both the study group (p = 0.002, Wilcoxon test) and the control group (p = 0.001; see Fig. 4).

None of our cases showed deterioration of the EEG (appearance of pathological patterns, increases in their total number, or increases in amplitude).

By CA three months, the EEG characteristics corresponded to age norms in all the children assessed. The exception was one child with severe perinatal hypoxic-ischemic CNS injury, with marked structural changes to the brain and severe somatic pathology (including intravascular hemolysis, prolonged and severe hyperbilirubinemia), in whom sequential deterioration of the functional state of the CNS was noted on EEG traces, with formation of a pattern of atypical hypsarrhythmia by CA three months and the onset of infantile spasms (the child is currently under the care of an epileptologist and has diagnoses of "symptomatic early childhood epilepsy" and "infantile spasms").

Thus, the results obtained from follow-up neurophysiological investigations showed that children in the study group showed significantly earlier (by CA 40 months from conception) improvements during the neonatal period, with normalization of the functional state of the CNS and recovery of the normal course of ontogenetic maturation of bioelectrical activity.

Overall, follow-up investigations of children with grade II–III perinatal cerebral ischemia whose intensive treatment included Cytoflavin showed faster improvements in postural muscle tone and reflexes and in measures of neuromental development throughout the first months of life, along with faster improvements in the characteristics of brain bioelectrical activity. Inclusion of a succinic acid agent in the complex treatment directed to early correction of systemic metabolic impairments in neonates during the early neonatal period is pathogenetically based. Clear antihypoxic and antioxidant properties of succinic acid salts have also been demonstrated in studies reported by Russian investigators both in adult patients and children with a whole series of states and diseases of accompanied by systemic tissue hypoxia [1, 2, 7].

The early correction of nervous tissue energy metabolism allows cell losses to be minimized, creating optimum conditions for subsequent realization of the ontogenetic program of nervous system maturation in preterm infants suffering from perinatal hypoxia.

This study leads to the following conclusions.

In preterm infants suffering from perinatal hypoxia and given a complex of treatment measures and intensive therapy including Cytoflavin during the neonatal period, the rate of normalization of postural muscle tone and motor functions after discharge from hospital was significantly faster than that in children treated without use of Cytoflavin. The use of Cytoflavin in the acute period of perinatal CNS injury gave higher indexes of mental and motor development at one year of life. In children given Cytoflavin during the neonatal period, there was also a significantly earlier (by CA 40 weeks from conception) improvement in the state of the CNS in terms of EEG results, with recovery of the normal course of ontogenetic maturation of brain bioelectrical activity.

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