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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN CHILDREN WHO SUFFERED PERINATAL ASPHYXIA

Specialty: 3223.01 – Nervous Diseases

Field of science: Medicine

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GENERAL DESCRIPTION OF THE WORK

Relevance and degree of development of the topic. Hypoxic-ischemic encephalopathy (HIE) is an important cause of mortality as well as short-term and long-term morbidity. 25% of neonates with hypoxic-ischemic encephalopathy develop severe and irreversible neuropsychological secular, including mental retardation, cerebral palsy, epilepsy and neurosensory deficits. Neonatal hypoxic-ischemic encephalopathy most often occurs as a result of perinatal asphyxia. In the perinatal period, umbilical cord entanglement or abnormal amniotic fluid can cause fetal distress, asphyxia and hypoxia[1, 2, 3].

The incidence of hypoxic-ischemic encephalopathy is 3-12 per 1000 live births[4].

Other estimates put the morbidity hypoxic-ischemic encephalopathy of worldwide ranges from 1 to 3 per 1000 live births in developed countries and higher in developing countries. However, there are significant differences in the reporting of morbidity between population and hospital studies. The range of hypoxic-ischemic encephalopathy is assumed to be about 1-8/1000 live births [5].

Hypoxic-ischemic encephalopathy is a multi-system pathological process requiring intensive medical support for brain

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monitoring and monitoring of non-central nervous system organ dysfunction[6,7,8].

The high frequency of brain development disorders in children who have undergone perinatal asphyxia determines the need to find objective methods for timely diagnosis of changes in oxygenation of brain tissue and targeted application of adequate therapy.

In recent years, researchers and clinicians have been particularly interested in using non-invasive, safe and sufficiently informative infrared spectroscopy for this purpose.

Important diagnostic and prognostic information for children with HIE is provided by neuromonitoring. The continuous monitoring method includes near-infrared spectroscopy (NIRS) to provide clear and complete information about brain function and oxygen use. Cerebral near-infrared spectroscopy is a non-invasive technology used to evaluate the perfusion of the brain in the patient's bed.

Trends in cerebral perfusion using near-infrared spectroscopy may provide information on cerebral metabolism as hypoxic-ischemic encephalopathy progresses, which may provide insight into the extent of brain damage [9,10].

All this makes it advisable to carry out the work.

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[8] Safarova, A.Q. Electroencephalographic and magnetic resonance tomographic predictors of the effectiveness of treatment of neonatal seizures // - Baku: Azerbaijan Medical Journal, - 2020. No. 3 - p. 63-69.

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Object and subject of study. The study included 120 full term children from birth to 1 year of age, including 90 patients (main group) with hypoxic-ischemic encephalopathy of varying severity who underwent perinatal asphyxia and 30 healthy children (control group) without asphyxia and central nervous system pathologies. The subject of the study is the study of diagnostic and prognostic criteria of hypoxic-ischemic encephalopathy in full term newborns who have undergone perinatal asphyxia.

Purpose of the study. To study the degree of neurological lesions in full term children with hypoxic-ischemic encephalopathy who underwent perinatal asphyxia, to predict the course and outcomes of this pathology.

Objectives of the study:

1. To study anamnestic and clinical features of hypoxic-ischemic encephalopathy in full term newborns who underwent perinatal asphyxia;
2. To study the neurological symptoms of full term newborns who underwent perinatal asphyxia, depending on the severity of hie.
3. To assess the parameters of clinical, gas and electrolyte composition of blood of newborns with hie who underwent perinatal asphyxia
4. To study the peculiarities of cerebral oxygenation in full term newborns who underwent perinatal asphyxia and to evaluate the diagnostic capabilities of cerebral infrared spectroscopy (NİRS) in determining the degree of post-hypoxic brain damage;
5. To assess neuro-motor development in the first year of life in children with hypoxic-ischemic encephalopathy using the INFANIB scale and to identify possible long-term outcomes of hypoxic-ischemic encephalopathy developed after perinatal asphyxia.

Methods of research. Clinical and anamnestic, functional, laboratory, statistical.

Key points for defence:

- Determination of cerebral oxygenation indices by cerebral spectroscopy in newborns who underwent perinatal asphyxia revealed that statistically significant decrease in FTOE with

increasing severity of hypoxic-ischemic encephalopathy is a diagnostic predictor of neurological disorders.

- The low value of FTOE during hypoxic-ischemic encephalopathy in patients with lethal outcome compared to surviving patients indicates a lower degree of oxygen metabolism in tissues and is an informative prognostic indicator of unfavourable outcomes of hypoxic-ischemic encephalopathy.
- The use of the INFANIB scale for assessing neuromotor development and the application of a formula for a prognostic model for the development of fatal outcomes will allow the development of preventive measures for reducing long-term outcomes in children with hypoxic-ischemic encephalopathy who have suffered perinatal asphyxia.

Scientific innovation of the study:

- The comparative clinical and neurological and laboratory-functional characteristics of the course in the neonatal period of various degrees of hypoxic-ischemic encephalopathy in full term newborn infants who underwent perinatal asphyxia are presented;
- Spectrometric evaluation of regional oxygenation and oxygen status of the brain at hypoxic-ischemic encephalopathy of different degrees of severity in full term infants who underwent perinatal asphyxia was carried out; diagnostic and prognostic criteria of NIRS monitoring in children with different degrees of severity of hypoxic-ischemic encephalopathy who underwent perinatal asphyxia were revealed.
- The prognostic factors of neurological outcomes of hypoxic-ischemic encephalopathy in full term infants with perinatal asphyxia were analysed and neuro-motor development was evaluated using the INFANIB scale in the first year of life in these children depending on the severity degree.
- The use of quantitative assessment of the diagnostic significance of signs and risk factors of hypoxic-ischemic encephalopathy using conjugation tables made it possible to identify key predictors of lethal outcomes in hypoxic-ischemic encephalopathy. A model of the probability of unfavourable

outcomes based on the logistic regression method and having high diagnostic accuracy was developed.

Practical significance of the study;

- The features of clinical course, diagnosis in the neonatal period, and prognosis of hypoxic-ischemic encephalopathy in the first year of life in full term children who have undergone perinatal asphyxia have been determined.
- The optimal NIRS criteria for monitoring hypoxic-ischemic encephalopathy developing against the background of perinatal asphyxia in full term newborns were developed.
- A mathematical model was developed to assess the outcomes of patients with hypoxic-ischemic encephalopathy; the informativity of the INFANIB scale in the clinical assessment of neuromotor development parameters in the first year of life of children born full term with hypoxic-ischemic encephalopathy was evaluated to predict neurological disorders in the first year of life.

Name of the organization where the dissertation work was carried out: The dissertation work was carried out at the Department of Neurology of Azerbaijan Medical University, on the basis of Scientific Research Institute of Pediatrics, named after K.Y.Farajeva, maternity hospital No. 5 named after Sh. Aleskerova.

Approbation of the research results:

Materials and main results of the thesis were discussed at the interdepartmental meeting of the Departments of Neurology and Pediatrics of Azerbaijan Medical University (20 June 2024, protocol #09). The results of the thesis were reported and discussed at the 4th International Neurological Congress of Turkic-speaking countries (Baku, 19-20 December 2019); International Scientific and Practical Congress 'Actual problems of pediatrics' (Baku, 11-13 October 2022). 9th Congress of Pediatricians of Uzbekistan with International Participation "Current Issues of Pediatrics at the Current Stage of Reforming the Healthcare System of the Republic of Uzbekistan (Tashkent, October 4-6, 2024(online)). The initial testing of the work was carried out at the general interdepartmental meeting of the Department of Neurology and the Department of Pediatric Diseases II

of the Azerbaijan Medical University (Protocol No. 09 dated June 20, 2024). Discussion of the dissertation work was held at a meeting of the scientific seminar of the Dissertation Council ED 2.05 at the Azerbaijan Medical University (Protocol No. 04 dated December 4, 2024).

Publication of the main results of the dissertation work: The main results of the work were published in 12 journal articles, including 4 articles abroad and 8 articles in Azerbaijan. On the topic of the dissertation, 5 theses were published, including 2 abroad.

Application of the research results in practice: In the course of the work, the results of the research were applied in the practical activity of Scientific Research Institute of Pediatrics, named after K.Y.Farajeva. The results of the dissertation work are used in the educational process and in the resident training programme at the Neurology Department of Azerbaijan Medical University.

Structure and total volume of the dissertation:

The dissertation is written on 179 pages consisting of computer text in Russian. The total volume of the dissertation: 202487 characters. The dissertation consists of the following chapters: Introduction (8992 symbols); Literature Review (54504 symbols); Materials and Methods (15751 symbols); Results of Own Research (89375 symbols: Chapter III -32842, Chapter IV -16523, Chapter V - 40010 symbols); Conclusion (30628 symbols); Results (2298 symbols); Practical Recommendations (939 symbols). 158 literary sources were used in the writing of the dissertation, of which 8 were cited from the works of Azerbaijani and 150 from foreign scientists.

There are 30 tables and 8 pictures used in the dissertation.

RESEARCH MATERIALS AND METHODS

The dissertation research was carried out at the Department of Neurology of Azerbaijan Medical University in the period from 2019 to 2023, on the basis of the Research Institute of Pediatrics named after K.Y.Farajeva, maternity hospital No.5 named after Sh.Aleskerova.

120 children from birth to 1 year of age were examined, including 90 patients (main group) with hypoxic-ischemic

encephalopathy of varying severity who underwent perinatal asphyxia, and 30 healthy children (control group) without asphyxia and CNS pathologies. The study was approved by the Ethical Committee of Azerbaijan Medical University. Informed consent from parents was signed for participation in the study.

Inclusion criteria for the study

- Gestational age more than 37 weeks;
- Birth weight more than 2500 grams;
- Birth asphyxia;

Depending on the severity of HIE, the examined newborns of the main group were divided into 3 groups:

- Group 1 - 10 (11.1%) neonates with 1st degree of severity;
- Group 2 - 46 (51.1%) neonates with -2nd degree of severity;
- Group 3 - 34 (37.8%) newborns with the 3rd degree of severity of hypoxic-ischemic encephalopathy.

Inclusion criteria for the control group:

- Full term healthy neonates born without asphyxia and pathologies of the central nervous system.

Anamnestic method included a collection of perinatal, obstetric and gynecological anamnesis of the mother, social and biological anamnesis of the family, nature and type of nutrition of the newborn, blood group, length and body weight of the child at birth, etc.

The clinical method included examination of the child, somatic and neurological status, physiological reflexes.

The severity of hypoxic-ischemic encephalopathy was determined according to the modified scale of Sarnat N., Sarnat M. (1976) as modified by Stoll B., Kliegman R. (2004).

The study of the child's development in the next 12 months of life included examination by a neurologist and a pediatrician and identification of comorbidities.

During the first year of life, clinical examinations were conducted to assess neuromotor development using the standardized INFANIB (Infant Neurological International Battery) scale. This is a developmental screening tool used to assess neuromotor development in newborns and infants between 1 and 18 months of age. The original

INFANIB was a 20-item test with five factors; spasticity, vestibular function, head and trunk, knee angles and legs.

The score of each item is indicated on the assessment sheet itself according to age, and the calculation of the total score determines the neuromotor status of infants. This scale involves testing the child on 14 to 20 items with scores ranging from 0 to 5. According to the INFANIB score, the examined children fall into one of the ranges: 'normal', 'transient impairment' or 'pathology'.

NIRS technology (Somanatics İNVOS 5100C Covidien, Medtronic, USA, 2006) was used to determine cerebral perfusion on admission of the newborn to the hospital. A spectrophotometer was used for this purpose. The cerebral oximetry device includes a light source, an optode (photosensor), a radiation recording unit, a transducer and a computer module. The pediatric sensor (somasensor) of the oximeter was placed on the forehead skin of the newborn. Radiation from the light source was transmitted to the area under study, from where the signal from the optode is delivered to the radiation recording unit, then analogue processing, digitalisation and transmission to the computer module takes place in the transducer, which displays the results of these calculations on the screen. The oxygenation indices were updated every 5 seconds.

The technique of determination of cerebral oxygenation indices includes the following designations of regional oxygenation monitoring data: values of regional hemoglobin oxygen saturation (rSO_2 regional oxygen saturation) in the cerebral cortex vascular basin, which were recorded for 2 hours; fractional tissue oxygen extraction (FTOE-fractional tissue oxygen extraction), calculated by the formula [$FTOE= (SaO_2- rSO_2)/SaO_2$].

Structural features of the brain were studied according to the results of neurosonography. Neurosonography was performed in all patients, using transcranial-pertrhodontic technique. Using microconvex and linear transducers with a frequency from 4 to 8 MHz, B-mode, Doppler study in colour and energy modes, polyposis-ion scanning with access through the large small fontanelle were performed. Scanning was performed in sagittal, ansial, frontal and oblique planes. The main parameters of cerebral blood flow in the

anterior and middle cerebral arteries with calculation of the resistance index (RI) of vessels were determined using Dopplerometry of cerebral vessels. Magnetic resonance imaging of the brain to confirm ischemic damage was performed in those children whose condition allowed this examination and transportation. All newborns who had seizures underwent an electroencephalographic examination.

Hematological study of peripheral blood determined the level of hemoglobin, hematocrit, and the number of peripheral blood formed elements.

The acid-base state (ABS) of the blood was assessed at the time of the child's admission to the hospital in the neonatal period. The blood gas composition and electrolyte balance in the blood of newborns were analysed. Blood gas partial tension and acid-base state (ABS) parameters were determined, with estimation of hydrogen ion concentration (pH), partial tension of carbon dioxide (pCO_2) and oxygen (pO_2), bicarbonate concentration (HCO_3), and the degree of oxygen saturation (sO_2). These parameters are related to acid-base balance and pH regulation in the body.

These laboratory tests were performed in the neonatal period to assess the general condition of newborns on admission to hospital and to identify possible disorders in the systems of hematopoiesis and gas exchange.

Statistical processing of the data: The obtained data were subjected to statistical processing by methods of variation, dispersion, discriminant, correlation, regression and ROC analyses in the statistical package SPSS-26.

For comparison of intergroup numerical.

Data, methods of variation statistics were applied: comparative Student-Bonferroni t-test, nonparametric Wilcoxon rank U-test (Mann-Whitney) in case of 2 groups and median H-Kruskal-Wallis test in case of 3 or more groups. Wilcoxon-a ranked W-criterion was applied in longitudinal studies.

Pearson's $\chi 2$ test (Pearson Chi-Square) was used to compare intergroup qualitative traits. To assess the influence of factors on the result, methods of analysis of variance (test ANOVA) were used, with calculation of statistical significance of the results by Fisher's criterion

(F-Fisher). To study the relationships between the studied qualitative and quantitative characteristics, nonparametric Spearman rank correlation analysis (ρ-Spearman) was used, with the determination of statistical significance of the correlation coefficient by the 2nd way method.

On the basis of diagnostic values (sensitivity and specificity), ROC analysis was performed with calculation of the area of the ROC curve with 95% confidence interval and statistical significance of the diagnostic test. Regression analysis was performed by logistic regression methods of stepwise inclusion by Wald (Forward), exclusion by Wald (Backward) and forced inclusion (Enter). Further, the 'examination' of the obtained regression equations over the map was carried out and the specificity and sensitivity of each equation were calculated by determining the boundary values.

RESEARCH RESULTS

Anamnestic characterisation of preterm newborns with hypoxic-ischemic encephalopathy

A multiparametric analysis of the impact of environmental factors, pathologies and procedures on the health of newborns with HIE was carried out. The study of anamnestic characteristics showed that in the control group 90.0% of families lived in the city, in the main group this percentage was 34.4%, and 65.6% of families in the main group lived in the regions ($p<0.001$). In the main group, first births accounted for 57.8% and in the control group most of the births were repeated 63.3%. 27.8% of children with hypoxic-ischemic encephalopathy were born operatively, in the control group this number was 80% ($p<0.001$).

Analysis of the types of feeding showed that only 30% of the children in both groups were completely breastfed. The Apgar scale assesses the physical condition of the newborn during the first minutes of life, namely at the 1st and 5th minutes of life. The Apgar score in the main group was on average 3/3 at the 1st and 4/5 at the 5th minute of life, indicating asphyxia ($p<0.001$). The analysis of environmental factors in hypoxic-ischemic encephalopathy revealed significant

differences between the control and main groups. It was also noted that the frequency of operative delivery was significantly lower in children with hypoxic-ischemic encephalopathy compared to the control group, indicating that operative intervention in childbirth may be associated with a reduced risk of hypoxic-ischemic encephalopathy.

Clinical characteristics of neonates with hypoxic-ischemic encephalopathy

Concomitant traumatic and non-traumatic pathologies in the neonatal period in children with hypoxic-ischemic encephalopathy were studied, which included analysing various aspects of the central nervous system in newborns who had undergone hypoxic-ischemic encephalopathy.

34.4% of children with hypoxic-ischemic encephalopathy had cerebral edema ($p<0.001$) and in 40.0% of cases cerebral edema was noted in neonates of 2nd and 3rd degree of severity. Based on the analysis, it was found that traumatic injuries of cranial bones and soft tissues were registered in 13.3% of children with hypoxic-ischemic encephalopathy ($p<0.05$).

Combined non-traumatic central nervous system injuries in the group of children with hypoxic-ischemic encephalopathy were 12.2% ($p<0.05$).

Intraventricular hemorrhages of the first degree were found in 12.2% of cases, intravetricular hemorrhages of the II degree and III degree - in 4.4% of cases (PF=0.057; PH=0.017).

The study of the structure of central nervous system pathologies depending on the severity of hypoxic-ischemic encephalopathy revealed that the 1st degree of hypoxic-ischemic encephalopathy was characterized by a high level of combined non-traumatic central nervous system injuries 16.7% and intraventricular hemorrhages of the 1st degree 13.3%; Hypoxic-ischemic encephalopathy grade II - brain edema 40.0%, traumatic intracranial hemorrhages 13.3%; Hypoxic-ischemic encephalopathy grade 3 - traumatic damage to cranial bones, soft tissues 20.0%, brain edema 40.0% and 10% traumatic damage to the peripheral nervous system.

We studied the neurological symptoms of the examined newborns with hypoxic-ischemic encephalopathy, depending on the

severity of hypoxic-ischemic encephalopathy. Thus, seizures were more frequently observed in the 2nd degree of hypoxic-ischemic encephalopathy - 97.1% ($p<0.001$). The majority of patients with 2nd degree hypoxic-ischemic encephalopathy severity (97.1%) were in severe condition and a significant number of children with 3rd degree hypoxic-ischemic encephalopathy in very severe condition state 69.6% ($p<0.001$). Consciousness of newborns with hypoxic-ischemic encephalopathy was manifested by various degrees of severity, which depended on the extent of brain damage. Kephalohematoma in 1st degree hypoxic-ischemic encephalopathy occurred in 20.0% of cases, in 2nd degree hypoxic-ischemic encephalopathy 23.5%, and in 3rd degree hypoxic-ischemic encephalopathy 10.9% of cases ($p>0.05$). In neonates with 1st degree hypoxic-ischemic encephalopathy, the depth of the right lateral ventricles averaged 3.70 mm; 2nd degree, 4.69 mm; 3rd degree, 3.42 mm ($p<0.05$). The mean anterior horn dimensions of the right lateral ventricles were statistically significantly higher than the median values and were 3.70mm, 4.79mm, 3.29mm respectively in 1st, 2nd and 3rd degrees of hypoxic-ischemic encephalopathy ($p<0.05$). Echogenicity of periventricular area was statistically significantly increased at 1st degree 40.0%, 2nd degree - 8.8%, 3rd degree - 30.4% ($p<0.05$). Ultrasound examination of internal organs revealed increased echogenicity of kidneys and liver, as well as increased liver size ($p<0.001$).

Features of laboratory blood parameters in hypoxic-ischemic encephalopathy

Hypoxic-ischemic encephalopathy is associated with asphyxia and brain damage, and its effect on blood parameters may be limited. In newborns with hypoxic-ischemic encephalopathy, leukocytes and erythrocytes of blood are not statistically different from the control group.

Hemoglobin level in the main group of neonates with HIE was 14.4 g/d (95% CI:13.8-14.9), hematocrit was 45.4% (95% CI:43.7-47), Erythrocyte sedimentation rate values in the main group compared to the control group (1.8 vs 8.6) is statistically significant ($p<0.001$) but within the reference values.

The level of neutrophils and segmented neutrophils significantly differed in the main group compared to the control group 12.65% ($p<0.001$), but did not exceed the reference values. We studied the parameters of gas composition and acid-base state of venous blood in newborns with hypoxic-ischemic encephalopathy who underwent perinatal asphyxia. Thus, the level of PCO_2 in the main group was statistically lower than in the control group 33.8±1.0 mmHg and 41.8±0.4 mmHg, respectively ($p<0.001$). The pO_2 level in the main group was significantly lower than in the control group and was outside the normal range, so in the control group the pO_2 level was 100.7±0.9 mmHg, in the main group the pO_2 level was 56.6±2.7 mmHg.

Blood oxygen saturation SpO_2 in the main group was 86.7±1.2%, in the control group 97.9±0.2%. The values of Na^+, K^+, and Cl-, which play an important role in the balance of electrolytes in the body, were within the reference ranges. Calcium levels in the main group were significantly lower than in the control group 1.22±0.01 mg/dl and 0.77±0.02 mg/dl respectively ($p<0.001$). The mean glucose level in the group of neonates with hypoxic-ischemic encephalopathy was 2.44±0.24 mmol/L, which was statistically lower than the control group 5.76±0.13 mmol/L ($p<0.001$). The values of the metabolic component of blood pH HCO_3, reflecting disturbances in the functions of buffer systems and metabolism, in the main group were 19.8±0.2 mmol/l ($p<0.001$).

Correlation analysis (r) between ABS parameters and blood electrolytes showed that there was a positive significant relationship between pH and hematocrit $\rho=0.194$, HCO_3 $\rho=0.395$, Ca^{++} $\rho=0.295$, Cl $\rho=0.311$, Glc $\rho=0.464$ ($p<0.05$). A direct (positive) significant correlation was also found between pCO_2 and hematocrit $\rho=0.268$, sO_2 $\rho=0.319$, Ca^{++} $\rho=0.489$, HCO_3 $\rho=0.594$, Glc $\rho=0.191$ ($p<0.05$). A highly significant correlation was noted between sO_2 and the HCT $\rho=0.357$, Glc $\rho=0.277$, HCO_3 $\rho=0.220$, Ca^{++} $\rho=0.303$ ($p<0.05$). Along with this positively highly significant correlation was recorded between pO_2 and Ca^{++} $\rho=0.454$, HCT $\rho=0.289$, Glc $\rho=0.508$, HCO_3 $\rho=0.292$, sO_2 $\rho=0.318$ ($p<0.05$).

The sensitivity (Sn) of blood acidity level (pH) was 82.2±4.0% and specificity (Sp) was 93.3±4.6%. The ODV (overall diagnostic value) is above 100. The partial pressure of oxygen (pO_2) has a specificity of 100%, and a sensitivity of 91.1±3.0%. The overall diagnostic value of 93.3±2.3% highlights the effectiveness of the test in overall evaluation. The sensitivity (Sn) of blood Ca^{++} value was 97.8% indicating high ability of the diagnostic test and specificity (Sp) of the test at 100% indicates its reliability. The calcium overall diagnostic value of 98.3%, which takes into account both sensitivity and specificity of the test, indicates good diagnostic accuracy of the test. Arterial blood saturation sO_2 has an overall diagnostic value of 79.2%, sensitivity (Sn) of 72.2%, while specificity (Sp) of 100% is high.

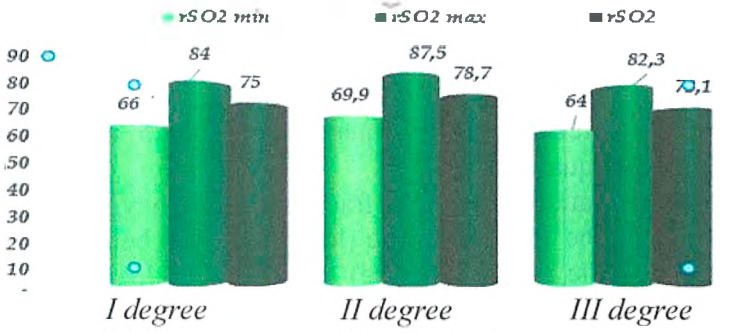
So, the results suggest that tests such as pH, pO_2, and Ca^{++} can be effective tools in the diagnosis of hypoxic-ischemic encephalopathy.

Results of cerebral oximetry in hypoxic-ischemic encephalopathy

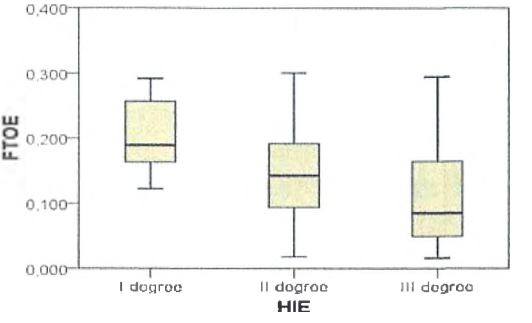
Regional cerebral oxygen saturation (rSO_2) indices were studied in preterm neonates with hypoxic-ischemic encephalopathy.

Hypoxic-ischemic encephalopathy who underwent perinatal asphyxia. No significant changes were observed in the indicators of regional cerebral oxygenation in comparison with the control group. Thus, oxygen saturation in the tissue of the frontal-parietal zone of the brain (rSO_2 average) was 75.4±1.2% [95% CI [72.9;77.9]] in the main group, and 77.9±1.0% [95% CI [75.9;79.8]] in the control group. Regional saturation indices were analyzed depending on the severity of with hypoxic-ischemic encephalopathy according to Sarnat. Thus, the mean rSO_2 value was 75.0±11.0% [95%CI [67.1;82.9]] in grade 1 hypoxic-ischemic encephalopathy, 78.7±10.4% [95%CI [75.1;82.3]] in grade 2, and 73.1±12.7% [95%CI [69.3;76.9]] in grade 3. Fractional tissue oxygen extraction (FTOE), which is used to determine the degree of activation of neuronal structures, was 0.204±0.061% [95%CI [0.160;0.248]] in grade 1, 0.145±0.067% [95%CI [0.122;0.168]] and 0.103±0.066% [95%CI[0.083;0.122]] in grades 2 and 3. Analysis of variance showed no statistical difference between

cerebral saturation values, whereas fractional tissue oxygen saturation decreased significantly as hypoxic-ischemic encephalopathy severity increased (P<0.001). Regional saturation thresholds were established using descriptive statistics and presented as percentile values. Fractional tissue oxygen saturation values were statistically significantly higher in the 1st degree hypoxic-ischemic encephalopathy group (PI- PII=0.046; PI- PIII=0.000), in turn Fractional tissue oxygen saturation values in 2nd degree hypoxic-ischemic encephalopathy were significantly higher than in 3rd degree as hypoxic-ischemic encephalopathy (PII- PIII=0.017).



Picture 1. Regional cerebral oximetry depending on the severity of HIE.



Picture 2. FTOE value in neonates with HIE depending on severity.

The percentile thresholds of oximetry parameters were determined, thus, in the main group the value of the 25th percentile of

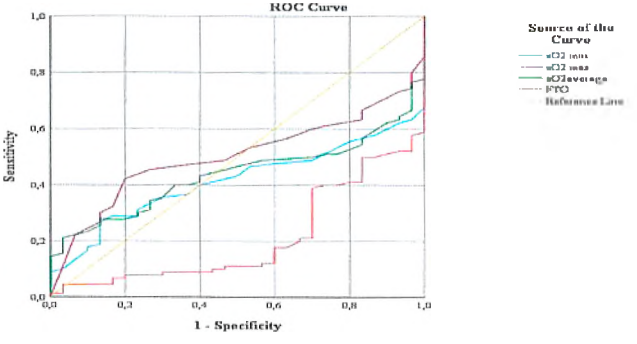
regional saturation was 68.5%, the value of the 75th percentile was 86%. The threshold value of FTOE in children with hypoxic-ischemic encephalopathy corresponding to the 75th percentile is 0.178, the 25th percentile (low threshold) - 0.063.

Among the neonates with hypoxic-ischemic encephalopathy included in the study, 13 had a fatal outcome. It was found that the mean minimum oxygen saturation sO_2 min in children with favourable outcome (alive) was 66.6+1.8, for children with lethal outcome was 65.5+4.3. The mean fractional tissue oxygen saturation was 0.143 for favourable outcome and 0.054+0.008 ($p<0.001$) for fatal outcome. Such a difference may indicate that fractional tissue oxygen saturation value may be a predictor or indicator of hypoxic-ischemic encephalopathy outcome in children. In hypoxic-ischemic encephalopathy, the regional saturation score (rSO_2) averaged 75.8 and the 25th percentile (lower quartile) was 68.5 and the 75th percentile (upper quartile) was 86.

For living patients, the mean fractional tissue oxygen saturation was 0.143, with the 25th percentile (lower quartile) being 0.090 and the 75th percentile (upper quartile) being 0.189. In the group of patients who had a fatal outcome, the mean fractional tissue oxygen saturation was 0.054, with the 25th percentile being 0.025 and the 75th percentile being 0.075 ($p<0.001$).

Informative significance of cerebral oximetry

ROC-analysis was used to assess the diagnostic significance of cerebral oximetry method.



Area Under the Curve						
	Area	SE	P	95% CI		
				Lower Bound		Upper Bound
sO_2 min	0.415	0.050	0.164	0.316		0.514
sO_2 max	0.503	0.052	0.964	0.400		0.605
sO_2average	0.437	0.050	0.304	0.338		0.536
FTOE	0.207	0.043	0.000	0.122		0.292

Sn	Sp	ODV	pPV	nPV	LR+	LR-
87.8±3.5	56.7±9.0	80.0± 3.7%	85.9±3.6	60.7±9.2	2.03 posr	0.22 otl

Note: ODV - Overall diagnostic value, CI -confidense interval, SE-statistical error, P-significance, LR-likelihood ratio, pPV/nPV -positive / negative predictive value.

Picture 3. ROC curve of cerebral oximetry indices in HIE.

Among the studied parameters, fractional tissue oxygen saturation was the most informative (AUC 0.207; 95%CI 0.122-0.292; P<0.001). The specificity of fractional tissue oxygen saturation was 56.7±9.0% and the sensitivity was 87.8±3.5%. Overall, the results suggest that the fractional tissue oxygen saturation value has good diagnostic accuracy and may be a useful tool in detecting as hypoxic-ischemic encephalopathy. The sensitivity (Sn) was 100.0%, specificity (Sp) was 68.8±5.3%, positive predictive value (pPV) was 35.1±7.8% and negative predictive value (nPV) was 100%. The overall diagnostic value (ODV) is equal to 73.3±4.7%. The fractional tissue oxygen saturation test has high sensitivity and specificity for both favourable and unfavourable outcomes.

Correlation analysis of cerebral oximetry values

The correlation between the severity of hypoxic-ischemic encephalopathy according to the Sarnat scale and fractional tissue oxygen saturation is -0.427. This correlation coefficient indicates an inverse relationship between the two variables, (p<0.001). An inverse correlation relationship was noted between the variables sO_2 average (mean oxygen saturation level) and fractional tissue oxygen saturation, the correlation coefficient is -0.561 (p<0.001). Statistically significant correlations were noted between fractional tissue oxygen saturation values with pH 0.203 (p<0.05), pCO_2 0.299 (p<0.001), PO_2 0.354 (p<0.001), HCT 0.181 (p<0.05), Ca^{++} (p<0.001), Glc 0.225 (p<0.05),

HCO_3 0.325 ($p<0.001$). Mean regional sO_2 values were significantly correlated with blood saturation SpO_2 0.720 ($p<0.001$) and hematocrit 0.217 ($p<0.05$). Strong correlations with pO_2, pCO_2, Ca^{++}, and HCO_3 may indicate the important role of oxygenation and gas exchange in the body.

Neuromotor characteristics of HIE in children in the first year of life.

Children with hypoxic-ischemic encephalopathy are at risk of long-term neurological disorders and disability, which is a serious problem in medical and social terms. In light of the complexity and uncertainty of the prognosis in children with hypoxic-ischemic encephalopathy, the assessment of neurophysiological functions and early diagnosis of their clinical disorders require reliable and easy-to –use non invasive screening methods. One of such methods is the use of the unified INFANIB (Infant Neurological International Battery) scale, which assesses muscle-postural tone. The purpose of our study was to clinically assess the indicators of neuropsychic development in the first year of life of full-term children with hypoxic-ischemic-encephalopathy using the INFANIB scale to predict neurological abnormalities. The prospective follow-up consisted of comprehensive clinical-instrumental, physical and psychomotor monitoring with health assessment, and analyses using the INFANIB scale at 3, 6, 9 and 12 months.

INFANIB test results in children with hypoxic-ischemic encephalopathy, regardless of severity at 3 months of age, revealed transient disorders-100%. In children with hypoxic-ischemic encephalopathy at the age of 6 months, INFANIB test results were distributed as follows: normal-0.0%; transient abnormalities: 1st degree-100.0%, 2nd degree-97.1%, 3rd degree-97.0%. No abnormalities were found in 1st degree, whereas pathological conditions were observed in 2nd degree and 3rd degree in 2.9% and 3.0%, respectively. At 9 months of age, all children (100%) with grade 1 hypoxic-ischemic encephalopathy, 91.2% of children with grade 2 and 87.9% of children with grade 3 hypoxic-ischemic encephalopathy had transient abnormalities. Pathologies were found in 8.8% of children with grade 2 and 12.1% of children with grade 3 hypoxic-

ischemic encephalopathy. No pathological conditions were found in children with 1st degree hypoxic-ischemic encephalopathy. INFANIB test results in children aged 12 months showed normal developmental parameters in 90.0% with 1st degree, 11.8% with 2nd degree and 12.1% with 3rd degree hypoxic-ischemic encephalopathy. And the INFANIB test results showed abnormalities in 10.0% of children with 1st degree, 88.2% of children with 2nd degree and 87.9% of children with 3rd degree hypoxic-ischemic encephalopathy.

We have studied the correlations between the results of the assessment of muscle tone and motor functions of children with HIE using the INFANIB scale at different stages of the first year of life and all the studied risk factors for asphyxia and hypoxic-ischemic encephalopathy. Statistically significant inverse correlations were found between the results of the INFANIB scale in the 3rd month of life and the level of muscle tone of the upper and lower limbs with correlation coefficients of -0.321 and -0.309, respectively ($p<0.001$), right anterior horn size of -0.256 ($p<0.05$) and left anterior horn size of the lateral ventricles of -0.249 ($p<0.05$). Similar statistically significant correlations were found at six months of life in patients of the main group: with limb muscle tone -0.310 ($p<0.001$), right anterior horn size -0.225 ($p<0.05$) and left anterior horn of lateral ventricles -0.211 ($p<0.05$).

At 9 and 12 months of life, statistically significant inverse correlations were found between INFANIB scores and limb muscle tone (correlation coefficients -0.259 and -0.328 respectively, $p<0.001$).

Hypoxic-ischemic encephalopathy prognostic model.

Mortality is an important statistical indicator necessary for analyzing the activities of each healthcare institution, but forecasting this indicator is a complex technical task. Accurate forecasting of patient mortality in the department intensive care, can significantly improve the efficiency of planning administrative-organizational, sanitary-epidemiological and treatment-diagnostic measures. We developed a prognostic model for patients with hypoxic-ischemic encephalopathy. Based on the results of data analysis, it was found that the number of patients with a favorable outcome of the disease was

77, while there were 13 deaths. The method used to build the prognostic model was - logistic regression. The quality of the model was assessed using a four-field conjugation table, ROC-analysis and AUC index.

The Enter (inclusion), Backward (backward exclusion of variables) and Forward methods were used to select variables for model building that are applied to the logistic regression. Only the following parameters were included in the final logistic regression equation:

- nutrition (F): breast-0, mixed-1, artificial-2, parenteral-3;
- liver size (right lobe RL),
- blood saturation (SpO2),
  resistance index (IR)
- fractional tissue oxygen extraction (FTOE).

$$Pp=40,836+1,008\times F-0,207\times RL-0,272\times sO2-6,074\times IR-80,334\times FTOE$$

This formula determines the probability of an unfavourable outcome of newborns with HIE who underwent perinatal asphyxia.

Thus, multivariate logistic regression analysis was performed to identify key predictors of unfavourable prognosis. Enter, Backward and Forward methods in logistic regression helped in selecting the optimal set of variables for modelling depending on various criteria such as accuracy, interpretability simplicity of the model.

CONCLUSIONS

1. Analysis of clinical and anamnestic characteristics of full term neonates with HIE revealed that regional residence (65.6%) and physiological delivery (72.2%) have a statistically significant impact on the occurrence of asphyxia and development of HIE ($p<0.001$). It was revealed that traumatic injury of cranial bones and soft tissues 13.3%, cerebral edema 34.4%, combined nontraumatic CNS injuries 12.2% ($p<0.05$) can influence the severity of the condition and prognosis of the disease [11,14].

2. Neurological status in HIE was characterized by high levels of tonic, clonic and myoclonic seizures, soporotic consciousness, hypo-reflexia, and decreased muscle tone depending on the severity of encephalopathy ($p<0.001$) [11,14].
3. Analysis of blood parameters in newborns with HIE revealed lymphocytosis of 52.1% and monocytopenia of 2.3%, which is a consequence of inflammatory factors and activation of the immune system ($p<0.001$). The blood gas composition was characterized by low levels of partial pressure pCO_2 and pO_2, decreased blood oxygen saturation (SpO_2). The study of electrolyte balance revealed hypocalcaemia 0.77±0.02 mg/dl and hypoglycaemia 2.44±0.24 mmol/l, as well as decreased bicarbonate HCO_3 19.8±0.2 mmol/l ($p<0.001$) [12,13,15].
4. Determination of cerebral oxygenation indices by cerebral spectroscopy in neonates with HIE of different severity revealed no statistically significant differences between cerebral saturation indices, only FTOE 0.130±0.008 (95% CI:0.115-0.145) showed a statistically significant decrease with increasing HIE severity ($p<0.001$) [4,5,6,9,10].
5. Assessment of postural muscle tone using the INFANIB scale in children with HIE in the first year of life showed that transient abnormalities prevail in the first 9 months of life in children with various degrees of HIE. Abnormalities begin to be detected from 6 months of age only in children with the 2nd and 3rd degrees of HIE, increasing with age, and recovery at 12 months was registered in 90% of children with the 1st degree of HIE [16].
6. As a result of multivariate logistic regress- ion analysis, a mathematical model was developed to predict the outcome of the disease in patients with HIE. The final logistic regression equation included the following parameters: nutritional status, liver size, blood saturation, resistance index and fractional tissue oxygen extraction [14,17].

PRACTICAL RECOMMENDATIONS

1. In full term infants born in asphyxia, place of habitation, physiological delivery, low level of gas and electrolyte composition (pCO_2, pO_2, SO_2, Ca^{++}, Glu, HCO_3) determine the risk group of children for the formation (development) of HIE.
2. In full term newborns with HIE who have undergone perinatal asphyxia, regional oxygenation should be monitored by means of cerebral oximetry. A high value of fractional tissue oxygen extraction (FTOE) is associated with a better prognosis for survival and long-term outcomes in neonates with HIE. A low FTOE value predicts more unfavourable outcomes including mortality or impaired neurological development.
3. In the clinical assessment of neuro-motor development parameters in the first year of life of children with HIE, the INFANIB scale is recommended. It is recommended to use the developed mathematical model to assess the prognosis of HIE outcomes.

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LIST OF ABBREVIATIONS

HIE	-	Hypoxic-Ischemic Encephalopathy
NIRS	-	Near Infrared Spectroscopy
FTOE	-	Fractional Tissue Oxygen Saturation
INFANIB	-	Infant Neurological International Battery
CNS	-	Central Nervous System

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