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NEAR-INFRARED SPECTROSCOPY: BILATERAL BRAIN MONITORING IN TERMED NEWBORNS WITH HYPOXIC-ISCHEMIC LESIONS

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Ключевые слова: *асфиксия, гипоксически-ишемическая энцефалопатия, гипотермия, нейросонография, около-инфракрасная спектроскопия, новорожденные*

Abstract. Near-infrared spectroscopy: bilateral brain monitoring in termed newborns with hypoxic-ischemic lesions. Mavropulo T.K., Sokolova K.Y. *Assessment of cerebral oxygenation using near-infrared spectroscopy (near-infrared spectroscopy, NIRS) has significant strong correlation with the assessment of brain perfusion using MRI in full-term infants with severe hypoxic-ischemic encephalopathy. However, there are still no recommendations on the use of NIRS monitoring data for making important clinical decisions in newborns with asphyxia and hypoxic-ischemic encephalopathy in routine clinical practice. The role of interhemispheric variations in the values of regional tissue oxygen saturation (rSO_2) in severe hypoxic-ischemic encephalopathy against the background of therapeutic hypothermia remains unexplored. The aim of the study was to evaluate the results of bilateral brain monitoring using NIRS in full-term newborns with severe hypoxic-ischemic lesions (with and without destructive changes in brain tissue). All examined children were full-term newborns with severe asphyxia at birth, who underwent therapeutic hypothermia. We analyzed the results of NIRS recordings of 33 newborns who did not have signs of destructive hypoxic-ischemic brain damage, and NIRS data of 15 newborns who were diagnosed with signs of destructive hypoxic-ischemic brain damage. The hemisphere difference in cerebral oximetry indices was presented in the form of statistical processing results - average, median, mode, 25th percentile, 75th percentile of pairwise comparisons, namely the difference of values (ΔrSO_2) of the measurement "$\Delta rSO_2 = rSO_{2on\ the\ right} - rSO_{2on\ the\ left}$" in each moment of recording (12000-22000 measurement moments during the monitoring session), as well as the percentage of recording time when the ΔrSO_2 value was recorded below the 25th percentile and above the 75th percentile. Reliable correlations between the fact of the formation of destructive hypoxic-ischemic brain lesions in full-term newborns and the average ΔrSO_2 values of the NIRS record (R=-0.410), median values (R=-0.400), modes (R=-0.357), and values of the 25th percentile ΔrSO_2 (R=-0.326) and the 75th percentile ΔrSO2 (R=-0.429) were registered. In 73.3% of children with destructive hypoxic-ischemic lesions, the average ΔrSO_2 values were higher for the right hemisphere (the average ΔrSO_2 value of the group was 0.11±2.39%). In 93.9% of children without destructive brain lesion the average rSO_2 values were higher for the right hemisphere (the average ΔrSO_2 value of the group was 6.92±0.80%). Significant differences in mean ΔrSO_2 (p=0.005) were determined. Secondary median of ΔrSO_2 for the group with destructive brain lesions was 0.33±2.38%, for the group without destructive lesions - 6.88±0.82% (p=0.004), the average ΔrSO_2 mode for the group with destructive brain lesions was 1,46±1.73%, for the group without destructive lesions - 6.51±0.92% (p=0.014). The average of the 25th percentile of ΔrSO_2 values for the group with destructive brain lesions was (-1.93)±2.72%, and for the group without destructive lesions it was 4.42±0.84% (p=0.026). The average of the 75th percentile of ΔrSO_2 values for the group with destructive brain lesions was 2.87±2.11%, and for the group without destructive lesions it was 9.33±0.80% (p=0.003). The results of bilateral brain monitoring using NIRS in full-term newborns with severe hypoxic-*

ischemic lesions on the background of therapeutic hypothermia have significant differences between groups of children with and without destructive changes in brain tissue. In newborns with destructive brain lesions, a decrease in manifestations of dominance of rSO_2 indicators of the right hemisphere was recorded, namely, significantly lower average ΔrSO2, median, mode, average values of the 25th and 75th percentiles ΔrSO_2.

Реферат. Спектроскопия в около-инфракрасном диапазоне: билатеральный мониторинг мозга у доношенных новорожденных с гипоксически-ишемическими поражениями. Мавропуло Т.К., Соколова К.Ю. *Оценка церебральной оксигенации с помощью спектроскопии в около-инфракрасном диапазоне (около-инфракрасной спектроскопии, near-infrared spectroscopy, NIRS) имеет достоверные сильные корреляционные связи с оценкой перфузии головного мозга с помощью МРТ у доношенных новорожденных с тяжелой гипоксически-ишемической энцефалопатией. Однако до сих пор отсутствуют рекомендации по использованию данных мониторинга NIRS для принятия важных клинических решений у новорожденных с асфиксией и гипоксически-ишемической энцефалопатией в рутинной клинической практике. Не исследованной остается роль межполушарных вариаций значений регионарной насыщенности тканей кислородом (rSO_2) при тяжелой гипоксически-ишемической энцефалопатии на фоне терапевтической гипотермии. Целью исследования была оценка результатов билатерального мониторинга мозга с помощью NIRS у доношенных новорожденных детей с тяжелыми гипоксически-ишемическими поражениями (с деструктивными изменениями мозговой ткани и без них). Все обследованные дети были доношенными новорожденными с тяжелой асфиксией при рождении, которым проводилась терапевтическая гипотермия. Были проанализированы результаты записей NIRS 33 новорожденных, которые не имели признаков деструктивных гипоксически-ишемических поражений мозга, и данные NIRS 15 новорожденных детей, у которых были диагностированы признаки деструктивных гипоксически-ишемических поражений мозга. Межполушарная разница показателей церебральной оксиметрии была представлена в виде результатов статистической обработки - среднее, медиана, мода, 25-й процентиль, 75-й процентиль данных парных сравнений, а именно разниц значений (ΔrSO_2) измерения «$\Delta rSO_2 = rSO_{2справа} - rSO_{2слева}$» в каждый момент регистрации (12000-22000 моментов измерения в течение сеанса мониторинга), а также проценты времени записи, когда регистрировались значения ΔrSO_2 ниже 25-го процентиля и выше 75-го процентиля. Регистрировались достоверные корреляционные связи между фактом формирования деструктивных гипоксически-ишемических поражений мозга у доношенных новорожденных детей и значениями средних ΔrSO_2 записи NIRS (R=-0,410), значениями медианы (R=-0,400), моды (R=-0,357), значениями 25-го процентиля ΔrSO_2 (R=-0,326) и 75-го процентиля ΔrSO_2 (R=-0,429). У 73,3% детей с деструктивными гипоксически-ишемическими поражениями средние значения показателей ΔrSO_2 были выше для правого полушария (среднее значение ΔrSO_2 группы – 0,11±2,39%). У 93,9% детей без деструктивных поражений мозга средние значения показателей rSO_2 были выше для правого полушария (среднее значение ΔrSO_2 группы – 6,92±0,80%). Определялись достоверные различия средних ΔrSO_2 (p=0,005). Среднее медианы ΔrSO_2 для группы с деструктивными поражениями мозга составляло 0,33±2,38%, для группы без деструктивных поражений – 6,88±0,82% (p=0,004); среднее моды ΔrSO_2 для группы с деструктивными поражениями мозга было 1,46±1,73%, для группы без деструктивных поражений – 6,51±0,92% (p=0,014). Среднее 25-го процентиля значений ΔrSO_2 для группы с деструктивными поражениями мозга составило (-1,93)±2,72%, а для группы без деструктивных поражений - 4,42±0,84% (p=0,026). Среднее 75-го процентиля значений ΔrSO_2 для группы с деструктивными поражениями мозга составляло 2,87±2,11%, для группы без деструктивных поражений – 9,33±0,80% (p=0,003). Результаты билатерального мониторинга мозга с помощью NIRS у доношенных новорожденных детей с тяжелыми гипоксически-ишемическими поражениями на фоне терапевтической гипотермии имеют достоверные различия между группами детей с деструктивными изменениями мозговой ткани и без них. У новорожденных с деструктивными поражениями мозга регистрировалось уменьшение проявлений доминирования показателей rSO_2 правого полушария, а именно достоверно меньшие значения средних ΔrSO_2, медианы, моды, среднего значения 25-го и 75-го процентиля ΔrSO_2.*

Hypoxic-ischemic lesions remain the most common cause of pathology of the central nervous system in full-term newborns. Therapeutic hypothermia is currently the only treatment for post-stroke brain damage with proven efficacy in reducing mortality and disability. However, despite the treatment, a certain group of children develops destructive hypoxic-ischemic lesions of brain tissue. One of the causes of such adverse effects is considered to be reperfusion damage [3, 9].

Assessment of cerebral perfusion is thus an important diagnostic and prognostic measure, especially in hypoxic-ischemic lesions, when the blood supply to the brain and oxygen metabolism change during the course of the disease. Near-infrared spectroscopy (NIRS) allows continuous monitoring

of cerebral hemodynamics and oxygenation at the patient's bedside by measuring changes in the concentrations of oxygenated and deoxygenated hemoglobin (cerebal oxymetry) [4, 5, 7, 9, 10].

NIRS does not provide direct measurement of cerebral blood flow in different areas of the brain, but registers regional tissue oxygen saturation (rSO_2) or tissue saturation (StO_2). Given that in the cerebral circulation arteries make up 10-20% of the total volume of blood vessels, capillaries – 5%, and veins 75-85%, the rate of tissue saturation is the predominant reflection of venous oxygen saturation of the brain. rSO_2 reflects the balance between oxygen delivered to brain tissue (i.e. cerebral blood flow or oxygen supply) and oxygen extracted at the level of brain tissues (i.e. oxygen utilization). The level of rSO_2 is influenced by the ratio of arterial and venous blood volumes, the concentration of hemoglobin in the blood, the content of oxyhemoglobin in the arterial blood, the partial voltage of carbon dioxide, the rate of oxygen metabolism [4, 6, 7, 9].

Experimental and observational studies confirm that low cerebral blood flow, cerebral blood flow fluctuations, hyper-, hypoxemia cause irreversible/destructive damage to brain tissue [1, 2, 5, 7, 10, 11, 12]. Therefore, the use of NIRS monitoring can help correct interventions that affect the blood and oxygen supply to the brain. Measurements of brain tissue oxygenation by NIRS and assessment of brain perfusion by MRI have been shown to demonstrate significant strong correlations in full-term infants with severe hypoxic-ischemic encephalopathy (but not moderate) [2, 9, 12,]. However, recommendations for routine clinical practice on the use of NIRS monitoring data to make important clinical decisions in neonates with asphyxia and hypoxic-ischemic encephalopathy cannot be implemented so far, as there is a wide range of physiological fluctuations in cerebral oximetry. and the variability of cerebral oximetry data relative to primary values, etc. [4, 5, 9].

In addition, studies have shown the presence of interhemispheric variations in rSO_2 values [9, 11]. When conducting bipolar monitoring in healthy full-term infants, cerebral oximetry was 79.2±4.06% in the left hemisphere and 84.89±5.1% in the right [1]. "Dominance of the right hemisphere" was explained by the fact that the right hemisphere develops earlier and is less prone to external influences than the left hemisphere [2, 6, 8, 11, 13].

P.Y. Lin et al. (2013) indicate the registration of higher values of blood volume, cerebral blood flow index, rate of oxygen metabolism for the right temporal and parietal areas compared to the left. Although differences in cerebral oximetry, according to published data, did not reach the level of statistical significance, the authors emphasize the fact that higher values of $rScO_2$ in the right frontoparietal position were registered in recovery periods after unstable tissue oxygenation [11]. P.M. Lemmers et al. (2009), R.G. Wijbenga et al. (2011) also emphasize the importance of bilateral monitoring of $rScO_2$ in clinically unstable preterm infants [6, 13].

Most studies on bilateral variations in neuromonitoring (including variations in rSO2 values) have been performed in healthy children or preterm infants, and the clinical role of similar phenomena in sick children, especially in severe hypoxic-ischemic encephalopathy on the background of therapeutic hypothermia is under-explored.

Therefore, the aim of the study was to evaluate the results of bilateral brain monitoring using NIRS in full-term infants with severe hypoxic-ischemic lesions (with and without destructive brain tissue damages).

MATERIALS AND METHODS OF RESEARCH

The study was conducted on the basis of the neonatal intensive care unit of the MI "Dnipropetrovsk Specialized Clinical Medical Center for Mothers and Children named after prof. M.F. Rudnev DRC". The study was one-centered, cohort and prospective. Scientific work is authorized by the Commission on Biomedical Ethics of the State Establishment "Dnipropetrovsk Medical Academy of Health Ministry of Ukraine".

Criteria for inclusion were: verified diagnosis of severe asphyxia at birth in full-term infants, therapeutic hypothermia, the presence of an informed parental consent to the intervention.

Determination of signs of severe asphyxia at birth, indications for therapeutic hypothermia and hypothermia procedure were performed in accordance with the provisions of the unified clinical protocol "Initial, resuscitation and post-resuscitation care of newborns in Ukraine" (order of the Ministry of Health of Ukraine from 28.03.2014 No. 225). All infants had a combination of history on undoubted severe obstetric complications in the mother and significant postpartum abnormalities in the infant (Apgar score at 10 minutes ≤ 5 points or need for mechanical ventilation for at least the first 10 minutes of life), signs of hypoxic-ischemic encephalopathy.

Exclusion criteria were: congenital malformations, signs of neuroinfections, uncompensated metabolic disorders, birth weight less than 2500 g, probable factors of maternal neonatal infection (chorioamnionitis, febrile fever during childbirth,

time period without amniotic fluid in the case of full-term pregnancy longer than 17 hours without antibiotics, severe acute infectious diseases in the mother at the time of childbirth). Considering the fact that the presence of intracranial hemorrhage can affect the indicators of the interhemispheric difference of NIRS data, the diagnosis of intracranial hemorrhage during the first four days of life the also was the exclusion criterion [4, 11].

All examined children were full-term infants with severe asphyxia at birth who underwent therapeutic hypothermia. The results of NIRS recordings of 33 neonates without signs of destructive hypoxic-ischemic brain lesion and NIRS data of 15 newborns diagnosed with signs of destructive hypoxic-ischemic brain lesions were analyzed. Therapeutic hypothermia was initiated in all patients in the first 6 hours of life.

To diagnose destructive hypoxic-ischemic lesions, neurosonographic examination was used, which was performed by the standard method on 1, 3, 5 and 7 day of life. Patterns of destructive hypoxic-ischemic lesions were distinguished – diffuse ischemic lesions, ischemic lesions of the thalamus and basal ganglia.

Standard clinical and instrumental examinations were supplemented by measuring the regional oxygen saturation of brain tissues (rSO_2). rSO_2 was recorded using an optical spectroscopy system (INVOS, Covidien) continuously with two neonatal sensors, which were placed above the area of the frontal lobes, respectively, on the right and left sides. Registration of rSO_2 changes was performed automatically every 15 seconds (absolute value on the monitor as a percentage, graph of tissue oxygenation monitoring in real time on the INVOS monitor with recording of information on electronic media for further statistical processing). Monitoring was performed during the 72-hour cooling period (12000-22000 measurement moments during monitoring session). The choice of monitoring time was determined by the data of studies that indicated the best prognostic qualities of NIRS between 18 and 60 hours of cooling [10].

In order to exclude the possible influence on the result of artifacts of signal loss during continuous NIRS monitoring, zero values of rSO_2 were not included in the statistical data processing [4, 11].

Data of interhemispheric variation of cerebral oximetry indicators are presented as results of statistical processing – average, median, mode, the 25th percentile, the 75th percentile of data of pair comparisons (differences of values of measurement on the right and on the left, "ΔrSO_2=rSO_2right-rSO_2left") at each moment of registration, as well as the percentage of recording time when $SOrSO_2$ values were recorded below the 25th percentile and above the 75th percentile.

Statistical data processing was performed using standard packages of applied statistical analysis Statistica for Windows v. 6.1. Calculated statistical criteria that can be used for samples with a distribution that does not correspond to the normal: Spearman's rank correlation coefficient, Fisher's exact test, Kruskall-Wallis H-test. For all types of analysis, the critical value of the significance level (p) was assumed to be <0.05.

RESULTS AND DISCUSSION

Neurosonographic signs of ischemic brain lesion were registered on 1 and 3 day of life in all examined children. These signs included increased differentiation of gray and white matter, blurred cerebral sulci, narrowing of the interhemispheric fissure, basal cisterns and ventricles. Patterns of destructive hypoxic-ischemic lesions were formed by the 5th day of life. The pattern of diffuse ischemic lesions was characterized by widespread areas of increased echogenicity of gray and white matter. The pattern of ischemic lesions of the thalamus and basal ganglia is characterized by bilateral hyperechogenicity of these areas of the brain.

In the group of newborns with destructive hypoxic-ischemic lesions, diffuse ischemic changes of brain tissue were diagnosed in 6 children (record numbers 2-5, 7, 13), ischemic lesions of the thalamus and basal ganglia – in 9 (record numbers 1, 6, 8-12, 14, 15) (Table 1). In this group, in 11 newborns (73.3%) the average values of rSO_2 were higher for the right hemisphere ($\Delta rSO_2>0$), in 4 (26.7%) - higher for the left hemisphere (record numbers - 5, 9, 12, 13 in table 1).

In the group with destructive hypoxic-ischemic lesions, the average value of the differences in the measurement of ΔrSO_2 was 0.11±2.39%, the median value was 0.33±2.38%%, mode – 1.46±1.73%, the average of the 25th percentile of ΔrSO_2 values – (-1.93)±2.72%, the average of the 75th percentile – 2.87±2.11%, the percentage of recording time when ΔrSO_2 values were recorded below the 25th percentile – 17, 41±1.84, the percentage of recording time when ΔrSO_2 values were recorded above the 75th percentile is 19.12±1.58.

Table 1

Monitoring of NIRS in full-term infants with destructive brain lesions during the cooling phase of therapeutic hypothermia: data from statistical processing of the interhemispheric difference of ΔrSO_2 values

Record number	Average	Median	Mode	25th percentile of ΔrSO_2	75the percentile of ΔrSO_2	Percentage of recording time when ΔrSO_2 values were recorded below the 25th percentile	Percentage of recording time when ΔrSO_2 values were recorded above the 75th percentile
1	15.18	16	15	13	18	20.64	20.88
2	4.58	5	5	3	6	19.01	22.25
3	5.89	6	7	5	8	24.25	14.58
4	2.70	2	2	1	3	11.42	23.66
5	-0.64	0	0	0	0	19.12	2.90
6	1.94	1	0	0	5	19.13	20.71
7	7.25	7	8	6	9	16.832	8.49
8	3.28	3	0	0	5	4.51	24.91
9	-6.53	0	0	-4	0	24.57	21.04
10	3.99	2	0	0	8	1.18	24.69
11	0.58	0	0	0	2	16.25	21.40
12	-21.19	-21	-17	-27	-16	20.30	21.26
13	-18.03	-19	0	-25	-12	24.71	22.56
14	1.23	1	0	-1	3	14.48	20.21
15	1.46	2	2	0	4	24.89	17.19

In 31 children (93.9%) without destructive brain lesions, the mean values of rSO_2 were higher for the right hemisphere, only 2 (6.1%) – higher for the left hemisphere (record numbers – 28, 29 in table 2). The significance of differences between these data in the observation groups according to the calculation of Fisher's exact criterion – p=0.008. In this group, the average value of the differences in the measurement of ΔrSO_2 was 6.92±0.80%, the average value of the median – 6.88±0.82%, the average value of mode – 6.51±0.92%, the average of the 25th percentile values of ΔrSO_2 – 4.42±0.84%, the average of the 75th percentile – 9.33±0.80%%, the percentage of recording time when recording values of ΔrSO_2 below the 25th percentile were recorded – 18.80±1.02, the percentage of recording time when rSO_2 values above the 75th percentile were recorded is 19.76±0.67.

Table 2

Monitoring of NIRS in full-term infants without destructive brain lesions during the cooling phase of therapeutic hypothermia: data from statistical processing of the interhemispheric difference of ΔrSO_2 values

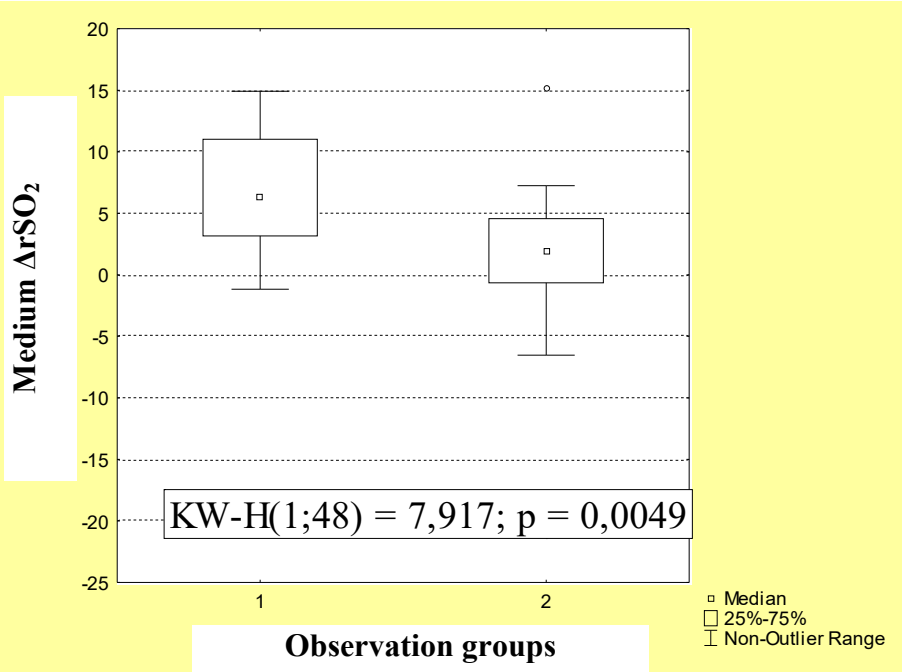
Record number	Average	Median	Mode	25th percentile of $SOrSO_2$	75th percentile of ΔrSO_2	Percentage of recording time when $SOrSO_2$ values were recorded below the 25th percentile	Percentage of recording time when $SOrSO_2$ values were recorded above the 75th percentile
1	4.89	5	5	4	6	19.79	12.59
2	11.03	11	13	9	13	16.36	18.61
3	7.88	8	8	4	12	22.10	19.63
4	1.99	2	0	0	4	13.72	16.31
5	4.07	6	7	-1	10	22.77	22.12
6	12.67	13	14	12	14	24.39	16.65
7	14.92	15	15	12	17	17.54	23.92
8	5.80	6	7	4	8	20.77	16.69
9	12.30	12	12	11	13	12.70	22.71
10	8.14	9	11	6	11	20.84	12.12
11	12.78	11	11	10	15	16.69	23.75
12	3.16	1	0	0	7	0.13	21.57
13	1.20	1	0	-1	3	14.52	19.61
14	6.86	7	7	5	9	16.61	20.14
15	3.75	4	5	2	5	26.62	24.93
16	14.08	14	13	12	16	16.33	17.88
17	13.36	13	13	11	16	16.77	18.49
18	2.42	2	2	1	4	22.78	20.56
19	5.84	6	5	4	8	23.54	23.34
20	9.92	11	11	8	13	20.61	13.91
21	6.40	6	6	5	8	22.30	21.91
22	1.10	1	0	-1	2	13.56	23.12
23	7.18	7	8	4	9	24.01	24.30
24	9.03	8	7	7	11	21.55	22. 11
25	4.36	4	7	0	8	22.906	23.985
26	2.90	2	0	0	4	1.45	24.82
27	3.04	3	0	0	7	21.10	20.46
28	-1.02	0	0	-3	2	24.50	16.73
29	-1.17	-1	0	-4	2	21.30	17.43
30	9.74	12	0	3	15	23.52	17.67
31	12.79	13	15	11	15	16.618	11.39
32	11.70	12	12	10	14	22.70	18.53
33	5.08	3	1	1	7	19.22	24.167

Significant correlations were recorded between the formation of destructive hypoxic-ischemic brain lesions in full-term infants and the values of mean ΔrSO_2 NIRS (R= -0.410), median values (R= -0.400), mode values (R= -0.357), values of the 25th percentile of ΔrSO_2 (R= -0.326) and 75th percentile of ΔrSO_2 (R= -0.429).

According to the calculation of the Kruskall-Wallis H-test, significant differences of average ΔrSO_2 (p=0.005) (Fig.), median (p=0.004), mode (p=0.014), mean values of the 25th percentile of ΔrSO_2 (p=0.026) and the 75th percentile (p=0.003) of the observation groups were determined.

There were no significant differences in the percentage of recording time when ΔrSO_2 values below the 25th and above the 75th percentile were recorded in different observation groups.

The proportion of zero values of ΔrSO_2 mode in full-term infants without destructive ischemic lesions of brain tissue was 27.3% (9 children out of 33). In full-term infants with destructive ischemic lesions of brain tissue, the proportion of zero values of ΔrSO_2 mode reached 53.3% (in 8 of 15 children). However, according to the calculation of Fisher's exact criterion, this difference was not significant (p>0.05), possibly insufficient statistical significance is due to the small sample size.



Significance of differences of median ΔrSO_2 of observation groups (group 1 - full-term infants without destructive brain lesions, group 2 - full-term infants with destructive brain lesions) according to the calculation of the Kruskall-Wallis (KW-H) H-test

CONCLUSIONS

1. The results of bilateral brain monitoring using NIRS in full-term infants with severe hypoxic-ischemic lesions on the background of therapeutic hypothermia had significant differences between groups of children with destructive changes in brain tissue and without them. In newborns with destructive brain lesions, a decrease in the dominance of rSO_2 in the right hemisphere was registered, namely: significantly lower values of mean ΔrSO_2, median, mode, the mean value of the 25th and 75th percentile ΔrSO_2.

2. Of course, conclusions on the specific values of the difference between interhemispheric measurements which have a negative diagnostic and prognostic value, and the target reference corridors of NIRS indicators in full-term infants during therapeutic hypothermia on the basis of the presented data can not be made.

3. However, current guidelines for the use of NIRS monitoring in clinical practice suggest to be guided not by specific values but by rSO_2 “trend lines”. Therefore, based on the results of this work we can assume that for this purpose we should use not only the variability of unilateral monitoring data of cerebral oximetry relative to primary values, but also bilateral monitoring data, namely the dynamics

of rSO_2 difference between measurements of right and left hemispheres. And further research will help improve our understanding of changes in perfusion and oxygenation in newborns during hypothermia and the possibility of using NIRS in these children to adapt therapeutic strategies.

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