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The Effect of Lactic Acidosis on Neonatal Outcomes in Premature Infants

Svetlana A. Perepelitsa[1,2]*, Igor V. Molchanov[2]

[1] Imannuel Kant Baltic Federal University
14 Aleksandr Nevsky Str., 236041 Kaliningrad, Russia
[2] Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology,
25 Petrovka Str., Bldg. 2, 107031 Moscow, Russia

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***Correspondence to:** Svetlana A. Perepelitsa, sveta_perepeliza@mail.ru, SPerepelitsa@kantiana.ru

Summary

The aim of the study was to evaluate neonatal outcomes in preterm infants.

Materials and methods. The study included 58 premature neonates divided into 2 groups: «A» (*N*=34) with an adverse neonatal period ending in death and «B» (*N*=24) who survived. Clinical assessment of the infant, measurement of blood gases, acid-base balance (ABB) and lactate, recording of lung ventilation parameters, calculation of mean airway pressure, oxygenation index (OI) and ventilation efficiency index (VEI), neurosonography and, in case of death, pathological and histological examination of the brain were performed.

Results. Elevated lactate was found in 24 patients (70.5%) in group A and in 12 patients (50%) in group B. The mean lactate levels in groups A and B were 8.1±3.3 and 6.3±2.8 mmol/L, respectively. In group A, 19 (55.9%) infants had severe acidosis, corresponding to a pH of 7.19 to 6.80. In group B, only 8 (33.3%) infants had a pH between 7.0 and 7.19. At birth, neonates in both groups were found to have a base deficit (BD), which was significantly lower in group A than in group B (*P*=0.004). There were no trends toward reduction of acidosis or normalization of ABB in infants in group A. Plasma BE levels in group B had returned to normal by 96 hours postpartum. The frequency of grade II, III peri/intraventricular hemorrhage (PIVH) and hemorrhage of other localization in group A were 8 (23.5%), 9 (26.5%), and 3 (8.8%), respectively. In group B, grade I PIVH and hemorrhage of other localization occurred in 5 (20.8%) and 1 (4.2%) cases, respectively. In neonates with grade II PIVH, severe lactic acidosis was diagnosed at birth: venous blood pH was 6.97 [6.8; 7.22], BE was (–21.6) [–30; –7.2] mmol/L, lactate level was 8.5 [6.3; 12.9] mmol/L, and pO_2 was 50.5 [20.5; 64] mm Hg. In infants with grade III PIVH, pH was 7.26 [7.12; 7.28], BE was (–8.1) [–8.9; –7] mmol/L, lactate was 7.6 [4.8; 8.9] mmol/L, and pO_2 was 33 [30; 50] mm Hg. Cell damage of varying severity affected all brain structures, as evidenced by absence or deformation of nuclei and nucleoli, and peripheral chromatin condensation. Morphological immaturity of brain structures was another negative factor.

Conclusion. Lactic acidosis diagnosed at birth in premature infants is one of the indicators of perinatal hypoxia severity. Critical pH, BE, and lactate levels, as well as lack of response to treatment, contribute to structural brain damage and worsen prognosis. Severe changes in oxygen and lactate levels that persist for two days after birth lead to severe PIVH and irreversible brain changes.

Keywords: preterm infants, hypoxia, neonatal lactate acidosis, oxygenation index, germinative matrix, hemorrhage, neurons, cerebral cortex

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

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Introduction

Neonatal brain injury remains a pressing issue in perinatal medicine. Main factors include antenatal hypoxia, intrapartum hypoxia and early postnatal hypoxia, which result in alteration of cerebral hemodynamics and microcirculation in various brain structures. The spectrum of possible changes is quite wide, depending on the duration of hypoxia and the severity of the hemodynamic disturbances. Short-term exposure to hypoxia in children causes transient ischemic changes, while prolonged severe hypoxia results in extensive damage localized in various brain structures, leading to death or permanent disability of the child [1–5].

Vutskits L., Camfferman F. A., et al. showed that premature infants have a higher incidence of brain damage compared to term infants, which is due to unfavorable factors such as morphological immaturity, the presence of the germinal matrix — especially in newborns with a gestational age of 22–28 weeks — insufficient vascularization of the white matter, and immaturity of autoregulation of cerebral blood flow. The presence of these factors leads to isolated and systemic fluctuations in cerebral blood flow, especially in combination with changes in central hemodynamics [6, 7].

Under hypoxic conditions, neurons switch to anaerobic metabolism, resulting in lower glucose and adenosine triphosphate (ATP) production and higher intracellular lactate. Low levels of ATP contribute to impaired function of energy-dependent ion channels in the cell membrane, intracellular Ca^{2+} and Na^{+} influx, abnormal membrane depolarization, and extracellular glutamate accumulation, while

high levels of intracellular lactate increase reactive oxygen species levels and cell damage [8–10].

The severity of hypoxia can be determined using blood lactate levels and the oxygenation index. Lactate levels gradually increase as ischemia and hypoxia worsen, while the oxygenation index decreases. In addition, the severity of lactic acidosis, pH, and time to normalization are associated with the severity of hypoxic and ischemic encephalopathy [5, 11] and neonatal mortality [3, 12].

Damage-associated molecular patterns (DAMPs) such as IL-33, high-mobility group protein B1 (HMGB1), and ATP activate microglia, astrocytes, cerebral vascular endothelial cells, and perivascular macrophages, resulting in a cascade of abnormal responses [13]. TNF (tumor necrosis factor)-R1, expressed on neurons and glial cells, activates apoptosis and necrosis, and upregulates MHC II and cell adhesion molecules in astrocytes. TNF-α production increases within hours of cerebral hypoxia, causing damage to the blood-brain barrier [2, 10, 14, 15].

A further cascade of reactions leads to an increase in interleukin-6 (IL-6) and IL-16, which are early biomarkers of the severity of brain ischemia in neonates and can be used to predict long-term outcome [16]. The level of IL-1β in residual cord blood and neonatal cerebrospinal fluid correlates with the severity of brain ischemia. IL-1β induces neuronal apoptosis and chemokine expression in microglia, astrocytes, and immature brain cells, and inhibits neuronal and oligodendrocyte proliferation [17,18].

The priority diagnostic task in the early neonatal period is to detect hypoxia and lactic acidosis, which trigger a cascade of abnormal responses leading to damage to organs and systems, including the brain. Changes in these biological markers can be used to predict how the child will respond to treatment.

The aim of the study was to evaluate the neonatal outcomes in premature infants.

Materials and methods

This retrospective study was approved by the Independent Ethics Committee of the Clinical Research Center of I. Kant Baltic Federal University (Protocol No. 14, dated October 27, 2020). All newborns included in the study were treated at the Maternity Hospital of Kaliningrad Region No. 1 and the Perinatal Center of Kaliningrad Region from October 2010 to October 2020. Scientific analysis of the results was conducted from January 2022 to May 2023.

Initially, a retrospective analysis of the medical records of 250 newborns was performed; as a result, 192 children were excluded from the study due to non-compliance with the inclusion criteria. Fifty-eight premature infants diagnosed at birth with varying degrees of hypoxia were included in the study (Fig. 1).

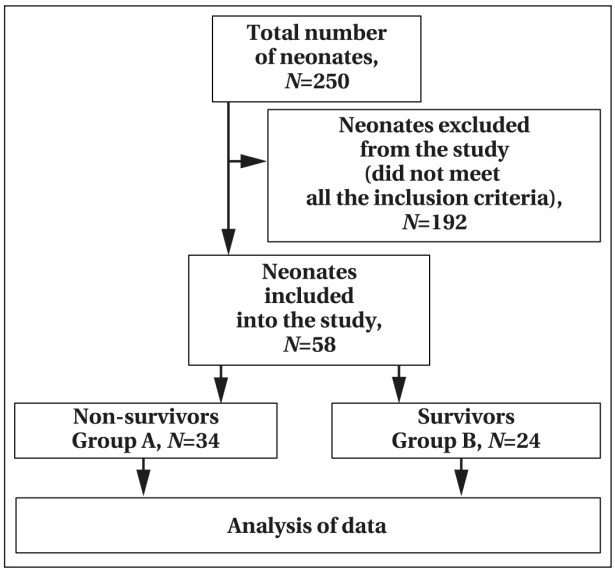

Fig. 1. Study flowchart.

Study inclusion criteria:

1. Moderate to severe birth asphyxia: Apgar score at 1 minute after birth less than 7 points;
2. Hyperlactatemia (blood lactate > 2 mmol/L);
3. Blood acidosis (pH < 7.35);
4. Blood base deficiency (BE < –2.5 mmol/L);
5. Ultrasonographic evidence of brain immaturity not consistent with gestational age [19];
6. Ultrasound evidence of peri-/intraventricular hemorrhage of varying degrees [20];
7. Mechanical or noninvasive ventilation.

Exclusion criteria were congenital malformations associated with severe hypoxia.

No preliminary sample size calculation was performed.

Patients were divided into two groups according to the disease outcome in the early neonatal period:

- Group A included 34 infants with a mean gestational age of 27.4±4 weeks, a birth weight of 992.9±560 g, and a mean Apgar score of 3 [2.0; 5.0] at 1 minute after birth and 5 [4.0; 6.0] points at 5 minutes after birth. Despite treatment, the neonates continued to deteriorate until death.
- Group B included 24 neonates with a gestational age of 28.9±2.3 weeks, a birth weight of 1138.1±320.9 g, and mean Apgar scores of 5 [3.5; 6.0] at 1 minute after birth and 6 [5.5; 7.0] at 5 minutes after birth. Neonates stabilized and improved as a result of treatment, with no deaths in the group.

There were no significant differences in birth weight or gestational age between the groups (P=0.258 and P=0.113, respectively). Median Apgar scores at 1 minute after birth were significantly lower in group A than in group B (P=0.009).

At birth, all neonates received primary or intensive care according to neonatal protocols [21].

Maternal factors such as age, course of pregnancy, causes of preterm labor, and labor activity were assessed.

Clinical evaluation of the newborn at birth included the following criteria: Apgar score (AS) at 1 and 5 minutes after birth, presence of regular spontaneous breathing, signs of acute respiratory failure of varying severity, and need for respiratory therapy.

Laboratory evaluation of blood gas and acid-base balance (ABB). Gas exchange, acid-base balance, and lactate concentration in the residual umbilical cord and arterialized blood were assessed using a Gem Premier 3000 analyzer (USA). The study was conducted at birth and at 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours postnatally.

Lung ventilation changes were recorded, including mode, ventilator respiratory rate (RR), fraction of oxygen in the gas mixture (FiO_2), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), and inspiratory time (T_{in}).

The calculation of the oxygenation index, mean airway pressure, and ventilation efficiency index. Calculation of the oxygenation index (OI): $OI = MAP \times ((FiO_2 \times 100) / pO_2)$, where MAP is the mean airway pressure, FiO_2 is the fraction of oxygen in the inspired gas mixture, and pO_2 is the partial pressure of oxygen in the blood.

The calculation of the mean airway pressure (MAP):

$$\mathbf{MAP=K\times(PIP–PEEP)\times(T_{in}/(T_{in}+T_{ex}))+PEEP,}$$

where **K** is a constant; **PIP** is the peak inspiratory pressure; **PEEP** is the positive end-expiratory pressure; $\mathbf{T_{in}}$ is the inspiration time; and $\mathbf{T_{ex}}$ is the expiration time.

The calculation of the ventilation efficiency index (VEI), which is an empirical analog of dynamic lung compliance:

$$\mathbf{VEI=3800/(\triangle P\times F\times PaCO_2)\ (mL/mmHg/kg),}$$

where $\triangle$**P** is the difference between inspiratory and expiratory pressures (PIP–PEEP) and **F** is the respiratory rate.

These parameters were recorded and evaluated at birth, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours postnatally.

Multiplanar neurosonography (NS). The study was performed on days 1–2 after birth through natural acoustic windows (large and small fontanels).

Histological examination of the brain. The following structures were examined: cortex, subcortical substance of the parietal region, hippocampus, striatum, cerebellum, and areas of hemorrhage. After labeling the material in plastic cassettes, standard histologic processing was performed, followed by embedding in Histomix and making paraffin blocks. Histological sections were stained with Nissl hematoxylin and eosin and examined using a Nikon Eclipse 55i microscope. In documenting the changes in the specimens, the correspondence of the morphological structure of the brain with gestational age, the degree of severity of cerebral edema, the condition of the vessels, the germinal matrix, and the presence and localization of hemorrhages were considered. The results of morphological examination were compared with gestational age, status of the child at birth and duration of the disease.

Statistical analysis of the data. Statistical analysis was performed using the Statistica 10.0 software package (StatSoft Inc., USA). The aim of the statistical analysis of the data was to identify the link between studied parameters and early neonatal period and disease outcomes in preterm infants. The Shapiro-Wilk test was used to evaluate the distribution of quantitative parameters. For variables with normal distribution, the arithmetic mean *(M)* and standard deviation *(SD)* were calculated. For quantitative parameters with non-normal distribution, the median *(Me)* and interquartile range *(Q1; Q3)* were determined, where *Q1* is the 1st quartile (25th percentile) and *Q3* is the 3rd quartile (75th percentile). Comparison of the results for dependent and independent samples with normal distribution was performed using the ANOVA test. Differences between two non-normally distributed samples were determined using the Mann–Whitney *U*-test. Pearson's parametric correlation method was used to analyze quantitative parameters with a normal distribution. In the study sample, qualitative data were analyzed by calculating the proportion of cases (percentage). The Wilcoxon test was used to compare two related groups, the Mann–Whitney test was used to compare unrelated groups by quantitative variables, and the Kruskal–Wallis test and post-hoc pairwise comparisons were used to compare three groups. Comparison of unrelated groups by qualitative variables was performed using Pearson's χ^2 test or Fisher's exact test. The two-tailed *P*-value was used. The non-parametric Spearman correlation method was used to analyze quantitative parameters with non-normal distribution. Differences were considered significant at $P \leqslant 0.05$.

Results

Maternal factors affecting the fetus and neonate. Table 1 shows the demographic characteristics and the most common conditions leading to perinatal hypoxia and lactic acidosis in the newborn. No significant differences were found between the groups in terms of age, parity, and mode of delivery.

Premature release of amniotic fluid was the cause of preterm labor in 9 (28.1%) pregnant women in group A and 3 (13%) in group B. Natural delivery was more common in group A and operative delivery was more common in group B (P=0.0087). The causes of operative preterm delivery in both groups were pre-eclampsia and eclampsia, critical disorders of uteroplacental blood flow, and placental abruption.

Table 1. Demographic characteristics of mothers and risk factors for neonatal hypoxia, *M*±σ; *Me [Q1; Q3]*; *N* (%).

Parameter	Values in groups		*P*-value
	Group A, *N*=32	Group B, *N*=23	
Age of mothers, years	31.2±6.5	30.5±6.7	0.715
Number of pregnancies	3 [1; 4]	3 [1; 4]	0.958
Parity	2 [1; 3]	2 [1; 3]	0.747
Premature rupture of membranes	9(28.1)	3 (13.0)	0.183
Natural delivery	11 (34.4) *	1 (4.3)	0.0087
Operative delivery	21 (65.6) *	22 (95.7)	0.0087
Causes of operative delivery			
Placental abruption	9(28.1)	4 (17.4)	0.349
Disorders of uteroplacental circulation	5 (15.6)	8 (37.8)	0.067
Preeclampsia, eclampsia	3(9.4)	6 (26.1)	0.094
Uterine scar	2 (6.3)	4 (17.4)	0.195
Abnormal fetal positioning	2 (6.3)	0 (0)	0.242

Note. Here and in the Table 2: * — significant differences between groups, $P \leqslant 0.05$.

Another cause of operative preterm delivery was the onset of spontaneous labor in patients with uterine scarring or abnormal fetal position.

Blood lactate measurement. The results of plasma lactate measurements are shown in Fig. 2, *a*. At birth, mean lactate levels were significantly higher (*P*=0.04) in children of group A vs. group B. Hyperlactatemia was found in 24 (70.5%) children in group A, mean blood lactate was 8.1±3.3 mmol/L. In group B hyperlactatemia was found in 12 (50%) children, the mean value was 6.3±2.8 mmol/L.

At 6 hours, the lactate level decreased significantly (*P*=0.015) in neonates in group A. The rate of decrease was 0.48 mmol/hour. A further significant decrease occurred at 48 hours (*P*=0.039); this trend continued for 120 hours of treatment (*P*=0.023). In the following hours, the lactate level began to increase.

In group B, the decrease in blood lactate occurred gradually. By 6 hours of postnatal life, its value significantly decreased (*P*=0.02), but by 12 hours, it had increased again. Normalization of lactate oc-

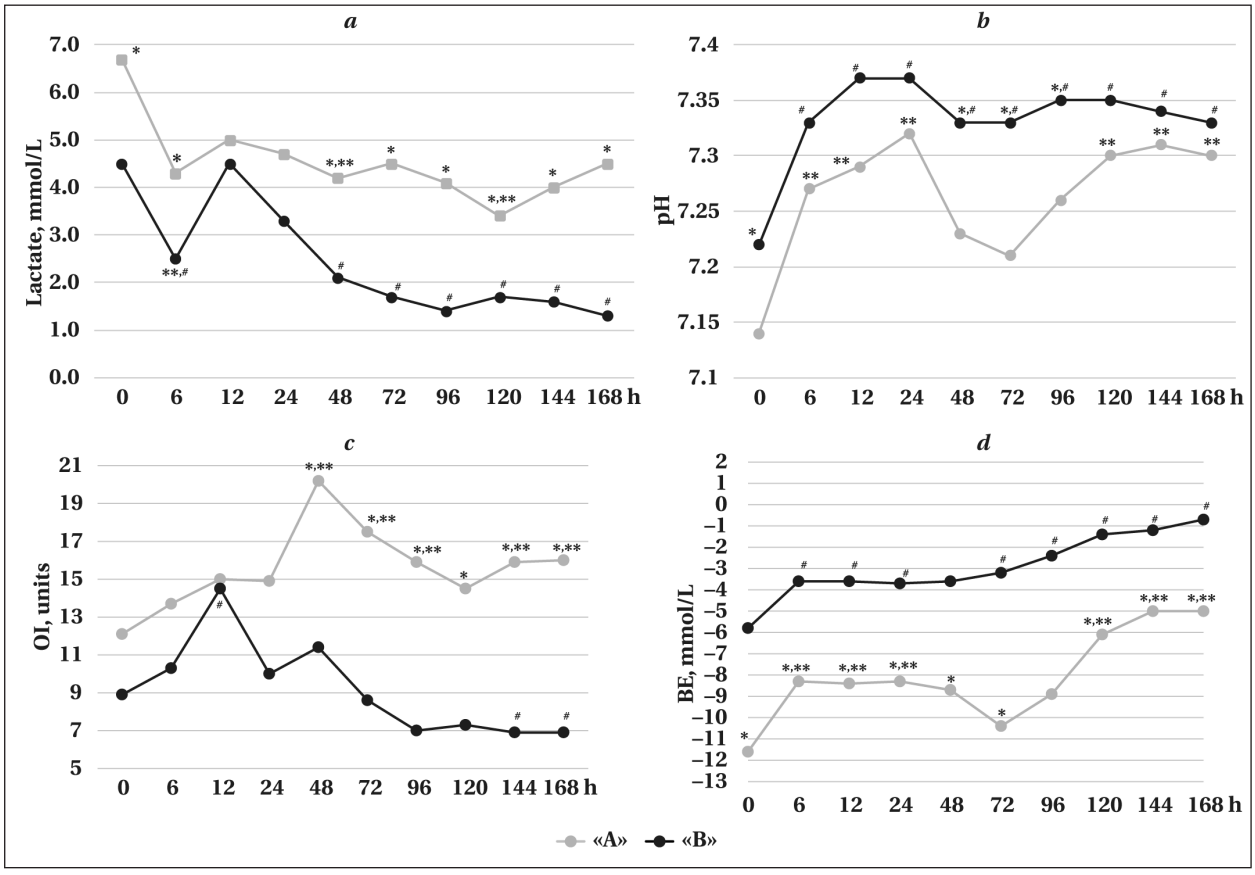

Fig 2. Change of the studied parameters during the treatment.
Note. Significant differences during the treatment, $P \leqslant 0.05$: * — between groups; ** — group A and # — group B,compared to the value at birth in both groups A and B.

curred by 48 hours of postnatal life, and the rate of reduction was also 0.48 mmol/hour (P=0.003). The lactate concentration was higher in group A than in group B throughout the observation period.

Study of blood ABB parameters. The integral parameter determining blood ABB disorders is pH (Fig. 2, *b*).

At birth, the pH of neonates in both groups indicated acidosis, but in group A the value was significantly lower than in group B (P=0.05). In group A, 19 (55.9%) neonates had severe acidosis, corresponding to a pH between 7.19 and 6.8, whereas in group B, only 8 (33.3%) neonates had a pH between 7.0 and 7.19.

In the first 6 hours after birth, the mean pH of the newborns in group A increased from 7.14±0.2 to 7.27±0.16; after 24 hours, it increased to 7.31±0.18, indicating a significant increase in this parameter (P=0.004, P=0.0006, respectively), reflecting a decrease in acidosis and representing the child's response to treatment. However, over the next 48 hours, the mean pH decreased to 7.2±0.2. Only after 96 hours of treatment was there a trend toward improvement in this parameter, but complete normalization did not occur.

In group B, normalization of ABB occurred after 12 hours of treatment, pH increased from 7.22±0.1 to 7.37±0.12 (P=0.00007), but after 48 hours the average pH value slightly decreased and was 7.33±0.07, the final normalization of pH occurred after 96 hours of treatment.

At birth, the neonates of both groups were found to have a base deficit (BD), which was significantly lower in group A compared to group B (P=0.004) (Fig. 2, *c*). Throughout the early neonatal period, a significant BD was detected in neonates of group A. Within 6 hours, plasma BE increased 1.5-fold, but remained unchanged in the following hours of treatment, i. e., signs of base deficit persisted. No tendency to decrease acidosis and normalization of ABB was observed in children of this group.

In group B, blood plasma BE increased 1.6 times within 6 hours (P=0.02) and gradually normalized by 96 hours after birth, i. e. the children responded to the treatment.

Oxygenation index (OI). The analysis showed that the OI was elevated at birth in both groups (Fig. 2, *d*). Its further change was multidirectional. In group A, OI increased significantly within 48 hours compared to the period at birth (P=0.00001), i. e., hypoxia resistant to therapy persisted during this period.

In the following hours of treatment, a slight decrease in OI persisted until 120 hours, after which its value began to increase, indicating that hypoxia persisted. In group B, the studied parameter increased up to 12 hours after birth (P=0.001), further confirming the presence of hypoxia and the lack of response to treatment during this period. In the following hours, OI gradually decreased and reached its minimum values at 144 hours after birth (P=0.009), indicating that the period of documented hypoxia was short and transient. In group A, OI values were significantly higher than in group B between 48 and 168 hours (Fig. 2, *c*).

Neurosonographic results. In the first hours after birth, the majority of neonates in group B showed only signs of morphological immaturity compared to group A (P=0.01). The incidence of grade II and III peri-intraventricular hemorrhage (PIVH) was significantly higher in group A than in group B (P=0.009 and P=0.006, respectively) (Table 2).

Subgroups of neonates were identified in each group based on NS changes. In group A, the following subgroups were identified: subgroup 1 with brain immaturity, subgroup 2 with PIVH grade II, and subgroup 3 with PIVH grade III and bleeding in other locations. In group B, subgroup 1 had brain immaturity, while subgroup 2 had PIVH grade I and bleeding in other locations. We examined the main parameters of hypoxia severity and oxygen status in each subgroup at birth, as well as blood ABB, ventilation parameters, and OI.

Table 3 summarizes the analysis of laboratory parameters and NS data for group A. Lactic acidosis was found in children from subgroup 1 who showed only signs of brain immaturity. Children in subgroup 2 also had lactic acidosis, but their pH and BE were in the critical range and significantly different from those in subgroups 1 and 3 (P=0.059 and P=0.023, respectively). OI was also higher in subgroup 2 than in subgroup 1 (P=0.007). The pH, BE, and OI values in subgroup 3 were different from those in subgroup 1 (P=0.047, P=0.04, P=0.036, respectively). Only in subgroup 3 was ventilation performed with a higher FiO_2 than in subgroups 1 and 2; no differences were found in this parameter, whereas MAP and VEI varied between subgroups.

Correlation analysis of the parameters in group B revealed several relationships of different strength and direction:

Table 2. Brain ultrasound findings, *N* (%).

Parameter	Frequency in groups		*P*-value
	Group A, *N*=34	Group B, *N*=24	
Brain immaturity	14 (41.2)*	18 (75)	0.01
PIVH, I grade	0 (0)*	5 (20.8)	0.005
PIVH, II grade	8 (23.5)*	0 (0)	0.009
PIVH, III grade	9 (26.5)*	0 (0)	0.006
Other hemorrhage	3 (8.8)	1 (4.2)	0.24

Table 3. Parameters in the subgroups of group A *(Me; Q1; Q3)*.

Parameters	Values in the subgroups of group A			P_{1-2}	P_{1-3}	P_{2-3}
	Subgroup 1, *N*=14	Subgroup 2, *N*=8	Subgroup 3, *N*=12			
pH	7.19 [7.09; 7.24]	6.97 [6.8; 7.22]*	7.26 [7.12; 7.28]**	0.059	0.474	0.047
BE, mmol/L	–8.7 [–10; –7]	–21.6 [–30; –7.2]*	–8.1 [–8.9; –7]**	0.023	0.923	0.04
Lactate, mmol/L	5.3 [1.6; 8.2]	8.5 [6.3; 12.9]	7.6 [4.8; 8.9]	0.138	0.43	0.29
pO_2, mm Hg	65 [47; 88]	50.5 [20.5; 64]	33 [30; 50]**,#	0.07	0.03	0.02
FiO_2, %	40 [35; 50]	40 [37.5; 71]	50 [40; 80]	0.0532	0.488	0.693
OI, units	8.2 [3.5; 12.9]	11.6 [8.3; 18.4]*	18.2 [8.2; 19.8]#	0.007	0.036	0.817
MAP, cm H_2O	9.6 [9.1; 10.4]	8.6 [8.4; 9.1]	9.3 [8.8; 10.6]	0.317	0.876	0.067
VEI, mL/mm Hg	0.09 [0.06; 0.09]	0.09 [0.05; 0.11]	0.11 [0.07; 0.13]	0.863	0.198	0.269

Note. Significant differences, $P \leqslant 0.05$: * — between subgroups 1–2; ** — between subgroups 2–3; # — between subgroups 1–3.

Table 4. Parameters in the subgroups of group B *(Me; Q1; Q3)*.

Value	Values in the subgroups of group B		*P*-value
	Subgroup 1, *N*=18	Subgroup 2, *N*=6	
pH	7.21 [7.16; 7.23]	7.18 [7.08; 7.32]	0.574
BE, mmol/L	–5.5 [–7.5; –3.9]	–7.1 [–10.2; –5.3]	0.413
Lactate, mmol/L	3.6 [2.2; 5.2]	4.8 [3.2; 7.6]	0.168
pO_2, mm Hg	47 [42; 52]	44.5 [40.5; 46]	0.345
FiO_2, %	40 [30; 45]	45 [40; 85]	0.183
OI, units	8.4 [5.9; 11.8]	9.5 [8.4; 18.3]	0.364
MAP, cm H_2O	8.8 [8.5; 9.6]	8.8 [8.85; 9.5]	0.748
VEI, mL/mm Hg	0.11 [0.09; 0.12]	0.09 [0.06; 0.2]	0.241

- Strong negative correlation between BE and plasma lactate at birth: R=–0.8053; P=0.0009;
- Strong positive correlation between plasma lactate and FiO_2 at birth: R=0.7897; P=0.0013;
- Strong negative correlation between plasma lactate and VEI at birth: R=–0.855; P=0.014;
- Moderate negative correlation between plasma BE and FiO_2 at birth: R=–0.573; P=0.04;
- Strong negative correlation between plasma pO_2 and OI at birth: R=–0.7585; P=0.0042.

Table 4 shows the results of the analysis of the laboratory parameters along with the NS data of the neonates in group B. In the second subgroup, the values of pH, BE, lactate, and OI were worse than those in the first subgroup, but no statistically significant differences were found. The values of FiO_2, MAP, and VEI were not significantly different in both subgroups.

Correlation analysis in group B revealed correlations of different strength and direction:

- Moderate negative correlation between BE and plasma lactate at birth: R=–0.708; P=0.0005;
- Strong negative correlation between HCO3 and plasma lactate at birth: R=–0.79; P=0.0003;
- Moderate positive correlation between OI and MAP at birth: R=0.6359; P=0.0355;
- Moderate negative correlation between lactate level and Apgar score at 1 minute after birth: R=–0.481; P=0.032.

Histologic examination of neonatal brains in group A. All neonates had immature brain structures for their gestational age, but only 10 (29%) did not have PIVH. The remaining cases were characterized by morphological immaturity and grade III–IV PIVH with hemorrhagic tamponade and blood leakage into the cerebello-medullary cistern, which was the primary cause of death.

Morphological analysis of brain structures revealed the presence of small hyperchromic (intensely stained) neurons in the molecular, outer, and inner granular layers of the cerebral cortex of the large hemispheres, with chromatin localized to the periphery and no nucleoli detected in a number of nuclei. The pyramidal cell layer consisted mainly of hyperchromatic pyramidal and rounded neurons. The inner pyramidal layer also contained pyramidal, predominantly intensely stained neurons, some of which were deformed, and rounded neurons with hyperchromic nuclei, whereas rounded and pyramidal neurons with hyperchromic nuclei were more common in the polymorphic cell layer. All cortical layers showed tortuosity and irregular blood filling of capillaries or their congestion and pericellular edema.

Neuronal polymorphism was seen in the white matter, including groups of dark neurons with shrunken or displaced nuclei and nucleoli, and cells with hypochromatic or unstained nuclei. Satellitosis and neuronophagia were prominent. Extensive hemorrhages were found in the white matter of the brain, including under the ventricular ependymas. Thrombi were observed in the ventricular cavity. Siderophages were seen at the margins of the hemorrhages. Capillary and venous congestion and focal gliosis were also observed.

Some vascular plexus epithelial cells had vacuolated cytoplasm, while others had unstained nuclei. There were areas without epithelial lining, with congested vessels and swollen stroma.

Some Purkinje cells in the cerebellum were absent, while other cells had shrunken or absent nuclei. Tigrolysis was common, and neither nuclei nor nucleoli were stained with Nissl stain. Pericellular edema was noted.

The cytoplasm of neurons in the striatum was homogeneous; cells with chromatin at the nuclear periphery were detected, but nucleoli were not detectable in some nuclei. Scattered glial cells were observed near some neurons. Nissl staining of the cells showed uniform cytoplasmic staining but no tigroid substance. There was also perivascular edema.

Discussion

Lactate, pH, and BE levels at birth indicate the severity of neonatal asphyxia. Lactate has been shown to be more diagnostically significant than pH [22–24]. Our study found multiple correlations between blood lactate at birth and pH, BE, and FiO_2, demonstrating lactate's diagnostic value in the context of hypoxia. Gjerris A. C. et al. investigated this issue and discovered correlations between lactate and pH (R=–0.73), standard base excess (R=–0.76), and actual base excess (R=–0.83). ROC analysis revealed that the lactate concentration threshold for detecting intrauterine asphyxia is 8 mmol/L [25].

The Apgar score is relatively important in the diagnosis of asphyxia in preterm infants because low scores at birth can be caused by immaturity of the surfactant system and respiratory center, as well as inadequate development of the respiratory muscles [19]. For a more accurate diagnosis of asphyxia, the study discovered that neonates in group A had a lower median Apgar score at 1 minute of life than neonates in group B, while lactate levels were higher. Correlation analysis revealed a negative correlation between Apgar score and lactate level at birth.

Lactate acidosis diagnosed at birth is associated with the development of acute respiratory failure. All infants with such signs were placed on a ventilator. Critical parameters of pH, BE and lactate measured in the early neonatal period were associated with grade II PIVH in group A (non-survivors).

The study by Tuuli et al. also showed that an elevated blood lactate concentration at birth (>3.9 mmol/L) increased the risk of adverse outcomes with a sensitivity of 83.9% (95% CI, 71.9–92.4%) and specificity of 74.1% (95% CI, 72.9–75.4%) [26].

In addition, Allanson E. R. et al. found an association between blood lactate at birth and short-term neurological outcomes [23] due to hypoxic brain injury. The effectiveness of lactate measurement in predicting neurological outcome in hypoxic and ischemic encephalopathy has been demonstrated. To improve diagnostic accuracy, measurement of pH and severity of base deficit is recommended [23].

In premature infants, PIVH is a leading cause of death [27, 28]. Most hemorrhages occur in the germinal matrix of the lateral ventricles [19, 20, 29]. However, prolonged and treatment-resistant perinatal hypoxia causes the hemorrhage to expand. With prolonged lactic acidosis, cerebral ventricular dilatation occurs, and the initial ventricular hemorrhages increase in volume or new hemorrhages form and spread to the brain parenchyma surrounding the ventricles.The etiology of PIVH is multifactorial. First, prolonged blood desaturation has been associated with the development of hemorrhages of any severity in brain structures [30]. Second, hemorrhages that occur during pregnancy or within the first 12 hours after birth are most likely caused by the production of free radicals and activation of pro-inflammatory cytokines, as well as persistent disturbances in oxygen status and metabolism [31, 32].

Hemorrhage in the first 72 hours after birth is caused not only by the immaturity of the vessels in the germinal matrix [33], but also by increased cerebral perfusion and fluctuations in systemic and cerebral blood flow [34–37]. Persistent disturbances in gas exchange and blood acid-base balance contribute to the development of grade III and IV PIVH [9, 31, 38]. It has been demonstrated that the severity of the lactic acidosis at birth correlates with the severity of PIVH, which can occur as early as 1–2 days after birth. The early neonatal period was extremely unfavorable in children with severe lactic acidosis that was not reversed in the first hours and days after birth, because the hypoxia that occurred intrapartum caused irreversible damage to the immature brain structures [33, 38].

The profound disturbance of oxygen balance and the depletion of compensatory responses cause a metabolic shift to anaerobic glycolysis, which is accompanied by lactate production. The high initial level of lactate in the infant's body at birth and its subsequent production lead to the accumulation of lactate in extracellular structures, exacerbating the existing acidosis [39, 40]. Zheng Y. and Wang X. demonstrated in an experiment that after an episode of cerebral hypoxia, the blood lactate level reaches its peak in 2–6 hours, but damage to astrocytes and neurons does not occur concurrently [41, 42]. The entire cascade of abnormal responses causes brain structure damage within 48–96 hours of birth [43].

The period of 24–48 hours after birth was used to determine the reversibility of the identified oxygen status and acid-base disturbances. If hypoxia and metabolic lactic acidosis were diagnosed in the newborn during this period, the likelihood of damage to immature brain structures increased in proportion to their severity. Failure of the body to respond to treatment aimed at eliminating hypoxia and normalizing ABB is most likely a negative prognostic factor, because persistent hypoxia and

lactic acidosis contribute to disease progression and the emergence of new foci of damage to brain structures, up to massive ischemic and hemorrhagic lesions.

Prematurity and brain morphological immaturity are unfavorable factors that contribute to the development of lactic acidosis in the presence of severe perinatal hypoxia.

Conclusion

Lactic acidosis is one of the criteria for determining the severity of birth asphyxia. Decompensated lactic acidosis diagnosed at birth in preterm infants and resistant to therapy, with laboratory values such as pH < 7.15, lactate > 7.5 mmol/L, and BE < (–12) mmol/L, is associated with the development of peri-intraventricular hemorrhage of varying severity. Death is caused by blood tamponade and blood leakage into the cerebello-medullary cistern. Failure to respond to treatment aimed at reversing hypoxia and restoring acid-base balance is a poor prognostic factor.

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