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Diagnostic value of markers of oxidative stress and metabolic disorders in preterm infants in the early neonatal period

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The aim of the study was to evaluate the markers of oxidative stress and metabolic disorders in preterm infants and to examine their association with short-term outcomes in the early neonatal period to identify the predictors of unfavourable outcome. The study included 46 preterm infants, gestational age ≤32 weeks, in the early neonatal period, i.e. group 1 of 12 infants with lethal outcome and group 2 of 34 preterm infants with favourable outcome. Markers of metabolic disorders, oxidative stress and antioxidant system were analysed in cord blood and urine on the first/second day of life. Evaluation of oxidative (8-isoprostane) and antioxidant system (catalase and superoxide dismutase (SOD) activity) and metabolic (lactate, pyruvate, lactate to pyruvate ratio (LPR), NAD^+/NADH) stress parameters confirmed energy imbalance and presence of tissue hypoxia in preterm newborns with adverse outcomes. The following risk factors of unfavourable prognosis in preterm infants in the early neonatal period were identified: asphyxia (p=0.038), early-onset sepsis (p=0.003), intraventricular haemorrhage (p=0.029), hyperlactatemia (p=0.013), increased pyruvate level (p=0.002), increased LPR (p=0.008), decreased catalase (p=0.003) and SOD (p=0.001) activity. Logistic regression indicated that mortality rate was positively related to asphyxia, early-onset sepsis and lactate level, and negatively related to SOD activity. In conclusion, intensive oxidative and metabolic stress in preterm infants is associated with adverse outcomes in the early neonatal period. A combination of asphyxia and early-onset sepsis together with high lactate level and decreased SOD activity is a predictor of unfavourable outcome in the early neonatal period.

Key words: METABOLIC DISEASES; OXIDATIVE STRESS; INFANT, PREMATURE

INTRODUCTION

Preterm infants are a special cohort of neonates with functional immaturity and specific pathological conditions during adaptation to extrauterine life. Low-birth weight (LBW) and very-low-birth weight (VLBW) infants are special risk groups due to the presence of hypoxia, reoxygenation and tissue hypoperfusion in the early neonatal period in combination with multisystem disturbances and high morbidity with proinflammatory cascade (1). The imbalance between the overproduction of free radicals and immature antioxidant protective systems in preterm infants leads to an increased risk of oxidative stress. Immaturity of the respiratory, digestive, immune and antioxidant systems along with numerous medical interventions after preterm birth (resuscitation, ventilation, parenteral nutrition, and blood transfusions) exacerbate the level of oxidative stress (2, 3).

Oxidative stress is an integral pathogenic component of pathological conditions in premature infants. It takes an important role in the variety of 'free radical related diseases of prematurity', which contribute to and predetermine development of bronchopulmonary dysplasia, sepsis, necrotiz-

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ing enterocolitis, intraventricular haemorrhage, periventricular leukomalacia and retinopathy of prematurity, all of which affect the prognosis (3, 4).

Therefore, the aim of the study was to evaluate the markers of oxidative stress and metabolic disorders in preterm infants and their association with short-term outcomes in the early neonatal period, and to identify the predictors of unfavourable outcome.

PATIENTS AND METHODS

Study design and participants

A single-centre, cohort, prospective study was performed at the neonatal intensive care unit of a regional perinatal centre. The research included 46 preterm infants, gestational age (GA) less than 32 weeks, in the early neonatal period (group 1: 12 infants with lethal outcome and group 2: 34 preterm babies with favourable outcome). The research was conducted in accordance with the World Medical Association Helsinki Declaration and was approved by the local Ethics Committee of the I. Horbachevsky Ternopil National Medical University (protocol No 43 issued on October 23, 2017).

Prematurity (GA ≤32 weeks) and birth weight less than 1500 g were the criteria for inclusion in the study. Exclusion criteria were chromosomal disorders, congenital malformations and absence of parent consent.

METHODS

The investigation included clinical examination of infants and laboratory determination of markers in metabolic disorders (lactate, pyruvate, lactate to pyruvate ratio (LPR), NAD^+/NADH), oxidative stress (8-isoprostane, reactive oxygen species (ROS)) and antioxidant system (catalase and superoxide dismutase (SOD) activity). Lactate and pyruvate levels in umbilical cord serum were measured by enzymatic methods using standard Sigma-Aldrich kits (Sigma-Aldrich Co. LLC, USA) followed by spectrophotometry/colorimetry at the appropriate wavelength. The NAD^+/NADH ratio was assessed based on the lactate and pyruvate levels. The 8-isoprostane concentration in urine was determined by enzyme-linked immunoassay (ELISA KitBuffer, Cayman Chemical, Michigan, USA) according to the manufacturer's instructions. ROS in blood mononuclear cells were evaluated by a flow laser cytometer. Catalase and SOD activity in umbilical cord blood were determined by spectrophotometric method. All markers were tested in cord blood and 8-isoprostane concentration was analysed in urine on the first/second day of life.

Statistical analysis

Statistical analysis was performed using StatSoft STATISTICA Version 13 (Tulsa, OK). Quantitative indices with non-normal distribution were expressed as median (Me) and lower (Lq) and upper (Uq) quartiles. Mann-Whitney test was used to compare the two groups. Kruskal-Wallis test was used to compare the groups with Bonferroni correction ($p<0.017$) in the next pairwise comparison of the groups. Two-tailed Fisher exact test was used to compare qualitative parameters. Odds ratio (OR) and its 95% confidence interval (95% CI) were calculated.

Prognostic model for mortality rate prediction in the early neonatal period was made in logistic regression.

The probability of an event was calculated by the formula:

$$P = \frac{1}{1 + e^z},$$

where P is the probability of the predicted event;
$z = a + b_1 * X_1 + b_2 * X_2 + \cdots b_n * X_n$;
e is mathematical constant 2.72;
a is model constant;
X_1, X_2, X_n are values of independent variables;
b_1, b_2, b_n are regression coefficients; X_1, X_2, X_n
n is serial number of the predictor included in the equation.

Wald χ^2 statistics was used to find statistical significance (p) of individual regression coefficients (b_1, b_2, b_n).

RESULTS

Clinical and laboratory examination included 46 preterm infants with GA less than 32 weeks. There were 18 neonates were born at ≤28 weeks of gestation with birth weight less than 1000 g (extremely low birth weight (ELBW)) and 28 patients with GA 29-32 weeks and birth weight over 1000 g (VLBW). Analysis of clinical characteristics of preterm infants according to GA showed that birth weight was one of the important factors for neonatal morbidity and mortality ($p<0.001$). At the same time, there was no significant gender difference according to GA ($p>0.05$). There was no significant difference in the neonatal morbidity incidence (respiratory distress syndrome, early- and late-onset sepsis, intracranial haemorrhages (subarachnoid, intraventricular), periventricular leukomalacia and bronchopulmonary dysplasia) according to GA ($p>0.05$). Only the prevalence of retinopathy of prematurity was significantly higher among infants with GA ≤28 weeks ($p<0.05$) (Table 1).

All patients were divided into two groups depending on short-term outcomes in the early neonatal period. Group 1 included 12 infants who died during the early neonatal pe-

riod (7 ELBW and 5 VLBW newborns). Group 2 included 34 preterm babies with favourable outcome.

Study results showed no differences in GA, sex and birth weight between groups 1 and 2 (p>0.05) (Table 2).

TABLE 1. **Clinical characteristics of preterm infants according to gestational age**

Parameter		Gestational age (weeks) ≤28 (n=18) (%)	29-32 (n=28) (%)	p
Gender	Boys	8 (44.44)	19 (67.86)	0.137
	Girls	10 (55.56)	9 (32.14)	
Birth weight, g		800.00 (710.00; 900.00)	1475.00 (1300.00; 1760.00)	<0.001
Asphyxia		2 (11.11)	1 (3.57)	0.552
Early-onset sepsis		4 (22.22)	7 (25.00)	0.999
Late-onset sepsis		8 (44.44)	7 (25.00)	0.208
Respiratory distress syndrome		11 (61.11)	12 (42.86)	0.365
Intracranial haemorrhag		9 (50.00)	9 (32.14)	0.354
Retinopathy of prematurity		11 (61.11)	7 (25.00)	0.029*
Congenital pneumonia		3 (16.67)	9 (32.14)	0.315
Patent ductus arteriosus		3 (16.67)	1 (3.57)	0.284
Necrotizing enterocolitis		0 (0)	7 (25.00)	0.032*
Periventricular leukomalacia		2 (11.11)	2 (7.14)	0.639
Anaemia of prematurity		8 (44.44)	10 (35.71)	0.758
Bronchopulmonary dysplasia		3 (16.67)	0 (0)	0.054

*statistically significant

Early-onset sepsis with multiple organ failure, intraventricular haemorrhage grade III-IV and asphyxia were significantly more common in group 1 (p<0.05) and were dominantly the main reasons for early neonatal mortality (Table 2).

It was found that the presence of asphyxia could increase mortality rate in the early neonatal period 25 times (OR=25.42; 95% CI=1.21-536.25; p<0.05); early-onset sepsis could increase this risk 10 times (OR=10.50; 95% CI=2.23-49.52; p<0.05); and intraventricular haemorrhage 5 times (OR=4.80; 95% CI=1.17-19.64; p<0.05) (Table 2).

Evaluation of the oxidative and metabolic stress parameters yielded significant differences between the groups (Table 3). These findings confirmed energy imbalance and presence of tissue hypoxia in preterm babies, predominantly in group 1 as compared to group 2 (higher levels of lactate (p<0.001), pyruvate (p<0.02), LPR (p<0.001), 8-isoprostane (p<0.001), along with significantly lower antioxidant system activity (SOD, catalase) (p<0.001) (Table 3).

Analysis of the NAD^+/NADH ratio indices revealed significant difference between the study groups (p<0.001) (Table 3), that reflected inhibition of redox processes at the cellular level and impaired metabolic processes in infants with unfavourable outcome.

Hyperlactatemia increased mortality rate in the early neonatal period 40 times (OR=39.81; 95% CI=2.17-729.07; p=0.013); increased pyruvate level 14 times (OR=13.89; 95% CI=2.54-75.93; p=0.002); and increased LPR 51 times (OR=51.09; 95% CI=2.77-941.01; p=0.008). Simultaneously, de-

TABLE 2. **Clinical characteristics of study groups**

Parameter		Group 1 n=12 (%)	Group 2 n=34 (%)	p	OR (95% CI)	p for OR
Gestational age (weeks)		26.50 (25.50; 30.00)	30.00 (27.00; 31.00)	0.076		
Gender n (%)	Boys	9 (75.00)	18 (52.94)	0.307	2.67 (0.61-11.60)	0.191
	Girls	3 (25.00)	16 (47.06)		0.38 (0.09-1.63)	0.191
Birth weight, g		935.00 (710.00; 1560.00)	1300.00 (900.00; 1700.00)	0.211		
Asphyxia		3 (25.00)	0 (0)	0.015*	25.42 (1.21-536.25)	0.038*
Early-onset sepsis		7 (58.33)	4 (11.76)	0.003*	10.50 (2.23-49.52)	0.003*
Respiratory distress syndrome		4 (33.33)	14 (41.18)	0.739	0.71 (0.18-2.84)	0.633
Intraventricular haemorrhage		8 (66.67)	10 (29.41)	0.038*	4.80 (1.17-19.64)	0.029*
Congenital pneumonia		0 (0)	12 (35.29)	0.020*	0.07 (0.004-1.32)	0.076

*statistically significant

TABLE 3. Parameters of metabolic and oxidative stress in study groups (Me (Lq; Uq))

Parameters	Group 1 n=12 (range)	Group 2 n=34 (range)	Mann-Whitney test
Lactate, mmol/L	7.34 (7.06 - 7.64)	4.12 (3.88 - 4.58)	p<0.001*
Pyruvate, mmol/L	0.08 (0.08 - 0.09)	0.07 (0.06 - 0.08)	p<0.02*
Lactate/pyruvate ratio	90.31 (84.47 - 98.50)	62.63 (51.73 - 68.98)	p<0.001*
NAD^+/NADH	123.05 (113.00 - 131.55)	177.35 (161.10 - 214.80)	p<0.001*
8-isoprostane, mg/mL	625.45 (584.35 - 689.90)	577.10 (532.20 - 607.50)	p<0.001*
Reactive oxygen species, IU	0.50 (0.40 - 0.57)	0.47 (0.43 - 0.52)	p>0.05
Catalase, IU/mL	0.38 (0.36 - 0.40)	0.47 (0.42 - 0.50)	p<0.001*
Superoxide dismutase, mmol/hour*L	1.38 (1.30 - 1.89)	2.46 (2.12 - 2.95)	p<0.001*

*statistically significant

TABLE 4. Predictors of mortality in the early neonatal period (results of logistic regression)

Predictors	Regression coefficient, b	Standard error	p
Asphyxia	0.439	0.107	<0.001*
Early-onset sepsis	0.150	0.073	0.049*
Lactate	0.182	0.026	<0.001*
Superoxide dismutase	-0.118	0.057	0.045*

*statistically significant

creased activity of the antioxidant system increased the risk of early neonatal mortality (catalase: OR=91.67; 95% CI= 4.85-1733.61; p=0.003; and SOD: OR=14.00; 95% CI=2.89-67.72; p=0.001.

Multivariate analysis with logistic regression was carried out to determine predictors of early neonatal mortality. Death of the patient was the binary logistic parameter (mortality outcome – 1; survival – 0). Gestational age, intraventricular haemorrhage, asphyxia, early-onset sepsis, lactate level, pyruvate level, NAD^+/NADH, 8-isoprostane, ROS and SOD activity were the independent predictors. Categorical factors (intraventricular haemorrhage, asphyxia and early-onset sepsis) were coded as 0 – absence of the event and 1 – presence of the event. Continuous factors were presented as absolute parameter levels.

Based on the results of logistic regression, only few variables had a significant influence on the outcome (early neonatal mortality), i.e. asphyxia (p<0.001), early-onset sepsis (p< 0.05), lactate level (p<0.001), NAD^+/NADH (p<0.05) and SOD activity (p<0.05), and were predictors of early neonatal mortality (Table 4).

Therefore, mortality risk in preterm infants could be predicted by the following formula:

$$P_{(mortality\ rate)} = \frac{1}{1 + e^z},$$

where X is linear combination of predictors.

In our research,

$$z = (-0.710) + (0.439)X_1 + (0.150)X_2 + (0.182)X_3 + (-0.118)X_4,$$

where X_1 – asphyxia, X_2 – early-onset sepsis, X_3 – lactate level and X_4 – SOD activity.

According to the obtained model, mortality rate was positively related to asphyxia, early-onset sepsis, lactate level, and negatively related to the SOD activity.

DISCUSSION

The results of our study confirmed that the oxidative and metabolic stress indices in preterm infants could be used as indicators of the severity of perinatal pathology with signs of tissue hypoxia and for prediction of short-term outcomes in these patients.

Lactate is a product of cellular metabolism under anaerobic conditions, so its increased serum concentration indicates tissue hypoxia and may be caused by severe hypoxia of different origin and anaerobic metabolism (5). According to our study, significantly higher levels of lactate and pyruvate were found in the group of infants with unfavourable outcomes in the early neonatal period, thus confirming them as markers of complex metabolic disorders in patients in critical conditions (6, 7) and predictors of severe complications. Our data are consistent with other studies which showed the association of lactate/pyruvate levels with severe complications such as multiorgan failure, cardiogenic shock, septic endocarditis, and adverse disease outcome (8, 9).

The levels of lactate, pyruvate and lactate/pyruvate ratio are important predictors of neonatal morbidity, severity of perinatal tissue hypoxia, and short-term outcome prognosis. Thus, the high level of lactate in the first hours of life is an early prognostic marker of neurological disorder after intrauterine hypoxia, as well as asphyxia (10), and is associated with unfavourable outcomes in preterm VLBW infants (11, 12), which also coincides with our results.

In our study, the NAD^+/NADH ratio in preterm infants with severe perinatal pathology showed profound energy imbalance and tissue hypoxia in the background of significant microcirculatory systemic disorders, thus serving as an indicator of unfavourable early neonatal outcome. Reduced and oxidized forms of NAD^+ are the key components of the energy formation process. The balance of NAD^+/NADH determines the redox status of the cells along with their metabolic activity and confirms tissue damage in various pathological conditions (13). Nicotinamide adenine dinucleotide (NADH) levels are thought to be the most sensitive indicator of tissue oxygenation at the level of mitochondria and an early marker of death risk (14).

Perinatal pathology of premature infants, which is often accompanied by hypoxic episodes, recurrent apnoea, the need for resuscitation, ventilation support and additional oxygen supply contributes to the development of oxidative stress in these patients (15-17). Newborns, especially premature infants, have an immature protective antioxidant system and are especially vulnerable to oxidative stress, which is associated with neonatal morbidity, neurodevelopmental disorders, and increased mortality (4, 18-20).

F2-isoprostanes are important diagnostic indicators of oxidative stress and its levels are evaluated in various pathologies (2). According to literature review, higher levels of isoprostane were detected in premature infants with respiratory disorders and manifestations of bronchopulmonary dysplasia compared to preterm infants without respiratory pathology (21). Monitoring of 8-isoprostane in preterm infants with patent ductus arteriosus revealed its decreased level during ibuprofen therapy, confirming the effectiveness of the proposed treatment (22). Our study showed the 8-isoprostane level in preterm infants to differ significantly between the groups, thus confirming intensive oxidative stress in infants with unfavourable outcomes in the early neonatal period.

The antioxidant system with its components (SOD and catalase) is an important link in cellular protection against oxidative stress and peroxidation processes. SOD participates in oxygen metabolism inside the cells, catalysing dismutation of superoxide radicals (O_2^-) to molecular oxygen (O_2) and hydrogen peroxide (H_2O_2), thus reducing the overall toxic effect of ROS. The catalase function is to prevent accumulation of hydrogen peroxide by detoxifying it to oxygen and water (23).

The decreased activity of SOD, catalase in our study, coincides with the results reported by *Inayat et al*. (24) regarding early detection and prognosis of hemodynamically significant patent ductus arteriosus in premature infants with low birth weight. The study by *Perrone et al*. demonstrated strong correlation between the oxidative stress marker levels and the occurrence of so-called free radical diseases in newborns (intraventricular haemorrhage, periventricular leukomalacia, patent ductus arteriosus and retinopathy of prematurity, bronchopulmonary dysplasia) (25).

According to the results of our study, increased levels of lactate, lactate/pyruvate ratio and 8-isoprostane with significant inhibition of antioxidant protection (decreased catalase and SOD activity) in premature infants are associated with adverse prognosis in the early neonatal period and may be considered as risk factors for predicting early outcomes, which is consistent with other authors (26). The major limitation of this study was a small number of study subjects.

CONCLUSIONS

High levels of lactate, pyruvate, lactate/pyruvate ratio, 8-isoprostane, along with a combination of decreased NAD^+/NADH ratio, activity of SOD and catalase indicate that intensive oxidative and metabolic stress is associated with adverse outcomes in premature infants in the early neonatal period. A combination of asphyxia and early-onset sepsis together with high lactate level and decreased SOD activity is a predictor of unfavourable outcome in the early neonatal period.

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SAŽETAK

Dijagnostička vrijednost biljega oksidativnog stresa i metaboličkih poremećaja kod nedonoščadi u ranom neonatalnom razdoblju

Halyna Pavlyshyn, Iryna Sarapuk, Kateryna Kozak, Olga Klishch

Cilj istraživanja bio je procijeniti biljege oksidativnog stresa i metaboličkih poremećaja kod nedonoščadi te ispitati njihovu udruženost s kratkoročnim ishodima u ranom neonatalnom razdoblju kako bi se utvrdili prediktori nepovoljnih ishoda. Istraživanje je obuhvatilo 46 nedonoščadi gestacijske dobi ≤32 tjedna u ranom neonatalnom razdoblju: 1. skupina od 12 nedonoščadi sa smrtnim ishodom i 2. skupina od 34 nedonoščadi s povoljnim ishodom. Biljezi metaboličkih poremećaja, oksidativnog stresa i antioksidantnog sustava analizirani su u pupčanoj krvi i mokraći prvog i drugog dana života. Procjena parametara oksidativnog (8-izoprostan) i antioksidantnog sustava (aktivnost katalaze i superoksid dismutaze (SOD)) te metaboličkog stresa (laktat, piruvat, omjer laktata i piruvata (LPR), NAD^+/NADH) potvrdila je energetsku neravnotežu i prisutnost tkivne hipoksije kod novorođenčadi s lošim ishodom. Utvrđeni su sljedeći rizični čimbenici nepovoljne prognoze kod novorođenčadi u ranom neonatalnom razdoblju: asfiksija (p=0,038), rana sepsa (p=0,003), intraventrikulsko krvarenje (p=0,029), hiperlaktatemija (p=0,013), povišena razina piruvata (p=0,002), povišen LPR (p=0,008), snižena aktivnost katalaze (p=0,003) i SOD (p=0,001). Logistička regresija pokazala je da je stopa smrtnosti pozitivno povezana s asfijksijom, ranom sepsom i razinom laktata te negativno povezana s aktivnošću SOD. U zaključku, intenzivan oksidativni i metabolički stres kod nedonoščadi udružen je s nepovoljnim ishodima u ranom neonatalnom razdoblju. Kombinacija asfiksije i rane sepse zajedno s visokom razinom laktata i sniženom aktivnošću SOD predviđa nepovoljan ishod u ranom neonatalnom razdoblju.

Ključne riječi: METABOLIČKI POREMEĆAJI; OKSIDATIVNI STRES; NEDONOŠČAD