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CLINICAL SIGNIFICANCE OF DYNAMICS BETWEEN OXIDATIVE STRESS LEVELS DURING MECHANICAL LUNG VENTILATION IN PREMATURE INFANTS WITH PERSISTENT PULMONARY HYPERTENSION

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The aim *of this study was to determine the clinical significance of the levels and dynamics of the urinary 8-hydroxy-2-deoxyguanosine, degree of pulmonary hypertension on choosing the duration and form of respiratory support in premature infants with respiratory distress syndrome in combination with perinatal asphyxia.*

Materials and methods. *The levels of the urinary 8-hydroxy-2-deoxyguanosine (8-OHdG), ng/ml were determined by enzyme immunoassay (ELISA) method and the degree of pulmonary hypertension (PH) – by echocardiography in 60 premature new-borns at 26–32 weeks of gestation on the* 1^{st} *and the* 3^{rd}*–*5^{th} *days of life. A comparative analysis of indicators was carried out in 2 groups: I – 32 children with respiratory distress syndrome (RDS); II – 28 children with RDS combined with perinatal asphyxia. All infants received a respiratory support, depending on the clinical condition, blood gas analyses, and the chest X-ray.*

Results. *The level and dynamics of the urinary 8-OHdG correlated to degree of PH, form, and duration of respiratory support. Children of the group II on the* 1^{st} *day of life had echocardiogram indicators of mild PH and indicators of the urinary 8-OHdG 2.27±0.39 ng/ml; by* 3^{rd}*–*5^{th} *days of life – level of the urinary 8-OHdG increased to 4.10±0.42 ng/ml and the level of PH – to moderate, required 76.2 % longer respiratory support compared to children of the group I.*

Conclusions. *Prematurely born infants with RDS in combination with perinatal asphyxia have a higher oxidative stress (OS) levels and more significant pulmonary hypertension, which requires a longer respiratory support by 76.2 % and more often use of high frequency oscillatory ventilation (HFOV) by 9.3 %*

Keywords: *pulmonary hypertension, mechanical lung ventilation, oxidative stress, RDS, asphyxia, new-born*

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1. Introduction

Persistent pulmonary hypertension (PPH) is a syndrome associated with significant morbidity and mortality in premature infants [1]. According to an expert consensus of the European Pediatric Pulmonary Vascular Disease Network updated in 2019, pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) greater than 20 mm Hg [2]. The lack of studies in the population of premature new-borns causes difficulties in the management of infants with PPH, since most therapeutic strategies are extrapolated from studies in adult patients [1, 3].

Oxidative stress (OS) is an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system. OS participates in the pathogenesis of PPH through the influence of ROS on the tone and density of pulmonary vessels, walls of pulmonary arterioles. OS is recognized as a trigger in the development of inflammation, hypoxia, ventilation-induced lung injury [4]. OS biomarkers are products of oxidative damage to proteins, lipids, and nucleotides that can be measured in blood, urine, cerebrospinal fluid, or amniotic fluid. 8-hydroxy-2-deoxyguanosine belongs to the biomarkers of nucleotide damage, which is determined in urine and is the most sensitive to oxidative stress in premature babies [5, 6].

Despite the implementation of new methods of lung ventilation in premature infants with respiratory distress syndrome, the questions of choosing the safest ventilation strategy, considering the levels of OS and pulmonary hypertension, remains relevant [4, 7].

The aim of the study was to determine the clinical significance of the levels and dynamics of the urinary 8-hydroxy-2-deoxyguanosine, severity of pulmonary hypertension on choosing the duration and form of respiratory support in premature infants with respiratory distress syndrome in combination with perinatal asphyxia.

2. Materials and methods

There was analyzed the observation of 60 prematurely born infants at gestational age of 26/1–32/6 weeks, which were carried out between 2020-2021 in the intensive care unit for premature new-borns at the Kharkiv City Perinatal Center in accordance with modern protocols. All infants received a respiratory support, depending on the clinical condition, blood gas analyses, and the chest X-ray.

The study was conducted following the requirements of the World Medical Association Declaration of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine, Good Clinical Practice and approved by the Bioethics Commission of Kharkiv Medical Academy of Postgraduate Education (Protocol No. 5 dated December 18, 2020). Participants were only included in the study after their parents were signing the voluntary informed consent.

The correlation relationship between the dynamics of the urinary 8-hydroxy-2-deoxyguanosine, severity of persistent pulmonary hypertension and the duration and method of respiratory support in premature infants with RDS and asphyxia was studied.

Considering the presence of combined pathology, new-borns were divided into two groups; group I consisted of 32 children with RDS, group II – 28 children with RDS in combination with birth asphyxia. The inclusion criteria for both groups were the presence of PPH, RDS and asphyxia, the need for mechanical ventilation/ CPAP. Measurement of PPH and its severity was carried out according to clinical and echocardiological signs according to European recommendations [2, 8, 9].

All children had quantitative determination of the urinary 8-OHdG level (ng/ml) on the first day of life, and again on the 3rd–5th day by the ELISA method using the DNA Damage ELISA reagent kit, Enzo Life Sciences (USA) according to the manufacturer's instructions.

Statistical analysis was performed using Microsoft Excel 2019 software. Under the conditions of normal distribution of quantities, parametric statistical methods were used to calculate the arithmetic mean (M) and the representativeness error of the mean (m). Using Fisher`s exact test we analyzed – the quantitative parameters.

Pearson's linear correlation coefficient (r) was applied to find the correspondence between the value of the urinary 8-OHdG and the quantity of mechanical ventilation (hours).

3. Results

According to the study design, all examined newborns were divided into two groups that could be compared with each other (Table 1).

Table 1

Clinical characteristics of the study groups, M ± m

Indicator	Group I (n =32)	Group II (n =28)
Gestational age, weeks	30.55±0.56	30.81±0.69*
Body weight at birth, g	1352±108	1650 ±149*

*Note: * – p<0.05 – difference between groups*

After analyzing the mean mPAP, mm Hg. in children by groups, the following results were obtained: in the group I on the 1st day of life, the mean mPAP was 24.04±0.41, p<0.05, which equates to mild PPH; in the II group on the 1st day of life, the indicator was 27.60±0.32, p<0.05, which also equates to mild PPH.

During treatment, on the 3rd – 5th day of life, the mean mPAP in the Ist group of children decreased by 17.01 %, and amounted to 19.95±0.30, p<0.05, which meets the criteria for the absence of PPH. In the IInd group of children, there was an increase in the mean mPAP to 40.91±0.67, p<0.05, which equates to the criteria of moderate PPH.

Levels of the urinary 8-OHdG, were analyzed: on the first day of life in children of group I quantity of 8-OHdG index was 1.83±0.29 ng/ml; in the group II the indicator was higher – 2.27±0.39 ng/ml, p<0.05. By the 3rd-5th day of life, in children of group II, we noted an increase in the level of 8-OHdG – 4.10±0.42 ng/ml while in group I the quantity of 8-OHdG index decreased – 1.06±0.28 ng/ml, p<0.05 (Table 2). Thus, in the group of children with perinatal asphyxia, the level of the OS indicator increases, which also correlates with the average pressure in the pulmonary artery and the severity of PPH [10].

We analyzed the duration (hours) of respiratory support, consisting of traditional, non-invasive ventilation (NIV), HFOV, and spontaneous breathing under continuous positive airway pressure (CPAP), in children by groups, and the following results were obtained: group II need more hours of respiratory support until complete restoration of spontaneous breathing than group I (171±19.0 vs 97±12.8 hours, p<0.05) (Table 3). It should be noted that all children received mechanical ventilation with a starting PEEP of at least 6 cm H_2O. Next, ventilator parameters were adjusted according to the clinical condition, blood gas analysis, data from the chest X-ray.

Use case analysis of the different methods of ventilation by groups showed that the use of traditional, NIV and HFOV was more often higher in the group II by 6.1 %, 3.3 % and 9.3 %, respectively. CPAP therapy was used 18.7 % more often in the group of children with RDS (Table 4).

The correlation analysis between the degree of persistent pulmonary hypertension, considering the severity of oxidative stress and features of respiratory support, showed a direct strong positive correlation between the level of 8- OHdG and the duration of respiratory support (r=0.80, p<0.001) (Fig. 1).

Table 2

Characteristics of the urinary 8- OHdG levels and average mPAP in premature infants with RDS and asphyxia in the early neonatal period

Index	Group I (n=32)	Group II (n=28)
8-OHdG level on the 1st day of life, ng/ml	1.83±0.29	2.27±0.39 *
8-OHdG level on the 3rd - 5th day of life, ng/ml	1.06±0.28	4.10±0.42*
Dynamics of changes over the lifetime, *n (%)*	–0.77 (–42.07 %)	+1.83 (+44.63 %)
Mean mPAP on the 1st day of life, mmHg	24.04±0.41	27.60±0.32*
Mean mPAP on the 3rd - 5th day of life, mmHg	19.95±0.30	40.91±0.67*
Dynamics of changes over the lifetime, *n (%)*	–4.09 (–17.01 %)	+1 3.31 (+4 8.22 %)

*Note: * – p<0.05 – difference between groups*

Table 3

Characteristics of ventilation strategies and their duration (in hours) in new-borns by groups

Ventilation strategy	Group I(n=32)	Group II (n=28)
Traditional mechanical ventilation, hours	28,0 ±7.3	54,0±4.4*
Non-invasive ventilation, hours	48,0 ±6.7	60,0±6.3*
High-frequency ventilation, hours	6,0 ±2.3	32,0 ±7.5*
nCPAP, hours	15,0 ±2.5	24,0±5.4*
Total duration of ventilation, hours	97,0 ±12.8	171,0±19.0*

*Note: * – p<0.05 – difference between groups*

Table 4

Use case analysis of the different methods of ventilation by groups (quantity of cases, n (%)

Method of ventilation	Group I	Group II
Traditional mechanical ventilation	9 (22.5 %)	14 (28.6 %) *
NIV	15 (37.5 %)	20 (40.8 %) *
HFOV	2 (5 %)	7 (14.3 %) *
CPAP	14 (35 %)	8 (16.3 %) *

*Note: the quantity of cases ≠ the number of children, because one child may need different types of ventilation depending on its condition; * – p<0.05 – difference between groups*

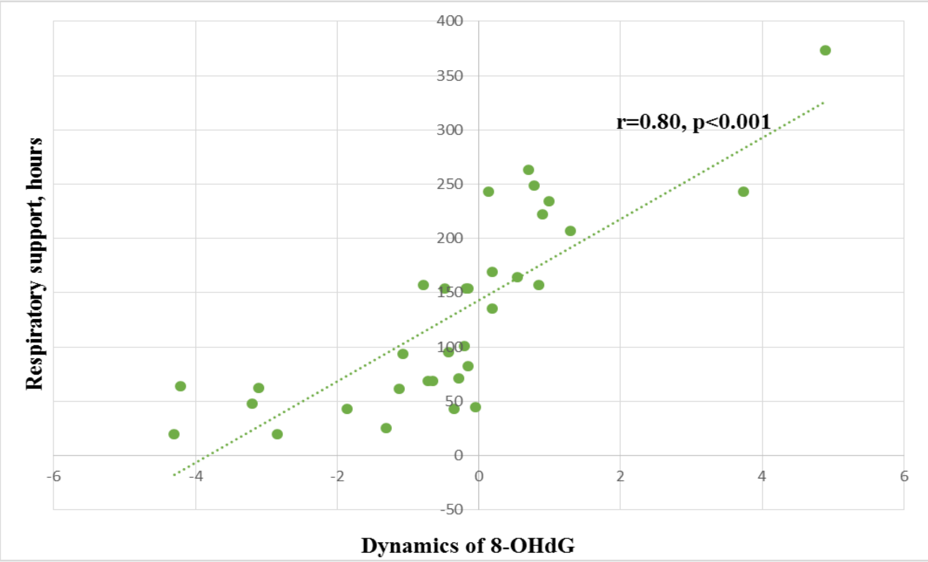

Fig. 1. Correlation between the dynamics of 8 -OHdG and the duration (hours) of respiratory support

4. Discussion

Persistent pulmonary hypertension is a complex pathology that occurs because of a violation of the postnatal decrease in pulmonary vascular resistance [11]. Premature babies are born with immature lungs, antioxidant defense systems, and often require mechanical ventilation with 100 % oxygen in the delivery room to stabilize the condition. The combination of hyperoxia, which enhances the generation of ROS, and an immature antioxidant defense system contributes to the development of OS, leading to an increased resistance of pulmonary vessels [12].

The main method of treatment of PPH in premature infants is mechanical lung ventilation. Mechanical ventilation with adequate PEEP reduces pulmonary vascular resistance and prevents end- expiratory alveolar collapse, keeping the lungs "open". Technological advances over the past 40 years have yielded a decrease in the morbidity and mortality associated with lung injury in new-borns. Lung protection strategy was developed - a set of postnatal measures, which are used in the delivery room (operating room) and intensive care units (wards) for premature babies with RDS and contain recommendations for the use of CPAP in the delivery room, the use of more modern ventilators, prenatal corticosteroids therapy, early surfactant administration and usage of caffeine citrate [3, 13]. But there is currently no consensus on a specific ventilation strategy for each individual case, considering the degree of severity of PPH and the levels of oxidative stress.

Perspective is studying the oxidative stress biomarkers in PPH and taking into account their dynamics when choosing a ventilation strategy in prematurely born infants. Our previous studies showed a moderate direct correlation between the biomarker of oxidative stress – the urinary 8- OHdG and mean pressure in the pulmonary artery on the 1st and 3rd - 5th days of life in prematurely born infants with asphyxia and with asphyxia in combination with RDS, which indicates the presence of a direct relationship between the severity of PPH and the severity of OS [10].

In the present study, analyzing the type of respiratory support and its duration in premature infants, we showed that the total duration of respiratory support was higher in the group of children with asphyxia and amounted to 171±19 hours, which is 76.2 % more than in the group of children with RDS. On a traditional mechanical ventilation, children from group II spent an average of 54±4.4 hours, which is 192 % higher than that children from group I. Also, children from group II spent more hours on non-invasive and high-frequency mechanical ventilation than children from group I by 125 % and 533 %, respectively. Children from the group with birth asphyxia by 60 % needed more days of respiratory support with CPAP.

Use case analysis of the different methods of ventilation showed that in the group of children with perinatal asphyxia, traditional, non-invasive, HFOV were used more often. CPAP therapy was more often used in the group of children with RDS without combined asphyxia, which is because for most children in this group it was the only necessary method of respiratory support with a short duration.

Our correlational analysis between the degree of persistent pulmonary hypertension, considering the severity of oxidative stress and features of respiratory support, showed a direct strong positive correlation between the level of the urinary 8- OHdG and the duration of respiratory support. That is, the more intensive dynamics of the decrease in the level of the urinary 8 -OHdG, which is a biomarker of oxidative stress and correlates with the mean pressure in the pulmonary artery, less duration of respiratory support infants are needed to restore spontaneous breathing. Conversely, when the level of oxidative stress increases by 3rd-5th days of life, the duration of respiratory support increases. This makes it possible to use the OS biomarker studied by us in the management of newborns with perinatal pathology, including the choice of respiratory support. Similar results were obtained in studies of Z. Elbakany, where a direct moderate positive correlation was established between the level of 8-OHdG and the number of days on mechanical ventilation (r=0.574, p=0.02) in children with RDS [14].

Study limitations. This study had a relatively small sample size for determination of the 8-OHdG.

Prospects for further research. Prospects for further research are the development of a differentiated approach to the management of persistent pulmonary hypertension in premature infants, considering the degree of pulmonary hypertension and the level of markers of oxidative stress.

5. Conclusions

1. Perinatal asphyxia complicates the course of RDS in premature infants at a gestational age of 26–32 weeks, which is reflected in a longer respiratory support of new-borns and a greater need for the use of traditional and high-frequency mechanical ventilation.

2. Level of the urinary 8- OHdG and its dynamics correlates with the severity of pulmonary hypertension and the duration of respiratory support, which could be considered in the management of premature infants with RDS and with RDS in association with birth asphyxia for the choosing of respiratory support method.

Conflict of interests

The authors declare there is no conflict of interest.

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