ORIGINAL ARTICLE

PREDICTORS OF BRONCHOPULMONARY DYSPLASIA DEVELOPMENT AND COMORBIDITIES OF PREMATURITY ASSOCIATED WITH RESPIRATORY SUPPORT TECHNIQUES IN PREMATURE NEONATES

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ABSTRACT

The aim of the study was to analyze and identify risk factors for the development of moderate and severe bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis in preterm neonates in intensive care unit and during any kind of respiratory support.

Materials and methods: A simple retrospective-prospective blind controlled non-randomised study included 28-32 weeks of gestational age 122 newborns with respiratory distress syndrom, who were treated in the neonatal intensive care units of two medical institutions of Dnipro from 2016 to 2020. Among 122 children neonates were divided into two groups according to particularities of respiratory support, prior type of noinvasive ventilation and infusion volume per day. The uni-variate Cox regressions using clinical variables identified specific clinical variables associated with development of moderate and severe BPD, retinopathy of prematurity, necrotizing enterocolitis, mortality rate (based on odds ratio and 95% confidence interval (95% CI). Then, significant clinical variables were used to build a multivariate Cox regression models. by backwards elimination of non-significant clinical variables. To estimate discriminative ability of comorbidities predictors we conducted ROC-analysis.

Results: The patients with moderate and severe BPD significantly longer were mechanically ventilated and received O_2 more than 30% in inhaled gas mixture, therefore every day of MV and/or additional oxygen >30% led to increase in probability of BPD development by 15% (p=0,01), AUC=0,78 (95% CI 0,66-0,89).

Significant predictors of moderate and severe retinopathy of prematurity were body weight (AUC 0,64 (95% CI 0,51-0,77) (p=0.03), duration of non-invasive ventilation by NIV PC (AUC 0,68 (95% CI 0,54-0,83) (p <0.01), CPAP (AUC 0.63) (95% CI 0.49-0.76) (p = 0,04) and caffeine administration (AUC 0,68 (95% CI 0,59-0,77) (p=0.01). Patients who developed NEC had a statistically significantly lower daily infusion volume AUC 0,68 (0,59-0,77) p <0.01, later onset of enteral nutrition AUC 0,68 (95% CI 0,59-0,77) p <0.01, lower hemoglobin levels on the first, third and seventh days of life AUC 0,67 (95% CI 0,57-0,77) p <0.01, as well as the level of leukocytes AUC 0,65 (95% CI 0,56-0,75) p = 0,01 and platelet count AUC 0,67 (0,58-0,77) (p <0.01) during the first 7 days of life.

Conclusions: The results of the study revealed risk factors for intensive care in general and respiratory support in particular, which significantly increase the risk of developing comorbidities of prematurity. Among them are relatively controlled, it is the duration of mechanical ventilation and NIV, which increase the risk of BPD and retinopathy of prematurity. Other risk factors which we can manage include nutrition state, anemia and supplemental oxygen.

KEY WORDS: premature neonate, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, respiratory support, ventilation

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INTRODUCTION

Respiratory distress syndrome (RDS) of premature neonates is acute pulmonary disease, associated with surfactant deficit, and as a result combined with alveoli rupture and lung compliance disturbances. Early known as hyaline membrane disease, this state is usual for premature neonates with gestational age less than 32 weeks. The frequency and severity of RDS is inversely proportional to the gestational age. Surfactant production starts from 22nd week of gestation, therefore as more immature lungs as more severe RDS. Among other risk factors of RDS – mother's diabetes, cesarean section without delivery process [1], the second fetus from twins, perinatal asphyxia, chorioamnionitis or/and early-onset sepsis, persistent ductus arteriosus [2,3].

The complications of RDS can be acute and chronic. Children with RDS are under risk of atelectasis, interstitial emphysema, infection, intraventricular hemorrhage, retinopathy of prematurity, neurological deficit and sudden infant death. [4]

We have to mention that arterial blood gases used to confirm RDS and make choice about respiratory support method. The verification parameter for RDS is hypoxemia paO_2 <50 mmHg. If there is hypercapnia > 60 mmHg with additional FiO_2>60%, or if CPAP with PEEP more than 8 cmH_2O or/and acidosis with pH <7,25, it is an indication for mechanical ventilation [5].

Surfactant usage increased premature neonates' survival, clinician's view shifts to the use of various respiratory support techniques that will reduce complications and improve the standard of living of patients with RDS.

The problem of prolonged and expensive treatment of prematurity often becomes an object of study. [6] Long-

term research of Kuint et al. (2019) had finished after 18 years and analyzed comorbidities of premature neonates with very low birth weight. 3956 children before 1 year old needed minimum one readmission to the hospital and in 11595 cases registered rehospitalizations due to intraventricular hemorrhages (IVH), necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD), confirmed with reliable higher odds ratio (OR) in comparison with control group for hospitalizations in pediatric unit (OR 1,28-1,55), surgical unit (OR 1,18 -1,55), pediatric intensive care unit (PICU) (OR 11,57-2,04).

Bronchopulmonary dysplasia and retinopathy of prematurity (RP) are common complications of prematurity with pathology of lung and retina development [7, 8].

Mechanical ventilation (MV) and additional oxygen are a couple of main risk factors of BPD. In number of studies, the usage of non-invasive ventilation (NIV) demonstrated the decrease in MV and risk of BPD development [9]. BPD increases the sensitivity to infection and bronchospastic syndrome in these patients; it is an independent predictor of problems with normal weight gain, delay in motor and intellectual development, risk for readmissions to other clinics and prolonged hospital stay after discharge from neonatal intensive care unit (NICU) [10].

According to Wu J. et al. (2020) meta-analysis of data about different ways of respiratory support, Nasal Intermittent Positive Pressure Ventilation (NIPPV) is safer method of ventilation in comparison with Synchronized Intermittent Mandatory Ventilation (SIMV), High-Frequency Oscillatory Ventilation (HFOV). As a respiratory support strategy it decreases frequency of intraventricular hemorrhages (IVH), persistent ductus arteriosus (PDA) and retinopathy of prematurity as well as mortality from these reasons (OR 3,33, 95% CI 1,08-16,67, P<0,05 for HFOV, OR 8,22, 95% CI: 1,25-29,44, P<0,05 for SIMV) [11].

The role of weight gain of premature neonate is underestimated. The research in premature neonates with VLBW established in 2014 included study group with weight non-reliable to the gestational age. Verified that in group of research the mortality rate was higher in 1,89 times [95% CI 1,39-2,58], severe retinopathy of prematurity in 1,56 times [95% CI 1,13-2,14], bronchopulmonary dysplasia in 2,08 times [95% CI 1,58-2,75] in comparison with premature neonates with weight appropriate for their gestational age. In addition, revealed that weight influences the frequency of BPD development in subgroups with gestational age 27-32 weeks. However, there was reliable correlation between severe retinopathy of prematurity and weight only in subgroup with 27-29 weeks gestation. [12]

Thereby, it is a question what factors are main for prophylaxis of severe bronchopulmonary dysplasia, because not only respiratory support influences the process of this pathology in premature neonates. It is important to understand that not enough to know such key points of investigation as BPD itself and reintubation rate, but also the hospital stay in NICU and other complications of prematurity, which change the quality of life.

THE AIM

The aim of research was to analyze the influence of respiratory support in complex of intensive care of premature neonates with respiratory distress, bronchopulmonary dysplasia development and comorbidities.

MATERIALS AND METHODS

The research conducted in two neonatal intensive care units (NICU) of CE "Dnipropetrovsk Regional Clinical Children's Hospital of Dnipropetrovsk Regional Council" and CE "Dnipropetrovsk Regional Center of Perinatology of Dnipropetrovsk Regional Council" between January 2016 and March 2020. All patients admitted to NICU had written informed consent from parents/caregivers in their medical data for treatment and research in according to national guidelines for RDS.

122 premature neonates of 28-32 weeks of gestation with respiratory distress, admitted to the hospital on the first day of life, were included to the study.

The inclusion criteria were gestational age 28-32 weeks, RDS identification after delivery, the informed consent signed by parents/caregivers, ophthalmologic examination.

Exclusion criteria was gestational age not less than 28 weeks and no more than 32 weeks, no need in respiratory support, the weight less than 750 g, verified IVH IV stage, inherited malformations, which can independently influence respiratory effort or retinopathy of prematurity development.

The stratification criteria was the prior method of respiratory support of non-invasive ventilation and volume intake per day during first 7 days.

In 1st group (52 neonates) were included premature neonates who received triggered noinvasive ventilation with pressure control (NIV PC) during early or/and late neonatal period and restrictive infusion therapy in first week of life.

In 2nd group (70 neonates) were recruited premature neonates who received continious positive airway pressure ventilation (CPAP) during early or/and late neonatal period and traditional liberal infusion therapy in first week of life.

The data was collected and analyzed on 1st day (on admission) to the NICU, when the respiratory support started, 3rd day – risk period for IVH, 7th day – weaning from respiratory support (MV or NIV), 14th day – primary ophthalmologic examination and risk of NEC manifestation, 21th – secondary ophthalmologic examination, 56th day of life or postnatal age of 36 weeks or on discharge from hospital (BPD verification, the severity of retinopathy verification).

For primary analyze we accounted gender, gestational age (weeks), birth weight (gram), length of the body (cm), circumference of head and thorax (cm), Apgar score on 1st, 5th and 20th minutes after delivery. Also we analyzed the result of pathohistology of placenta to confirm or exclude chorioamnionitis, maternal RDS prophylaxis with glucocorticoids, surfactant prescription after delivery, registered such complications of delivery as detachment of the

normally located placenta and the presence of meconium in amniotic fluid as risk factors for hypovolemia and systemic inflammatory response syndrome.

Index of oxygenation (OI) was used to verify RDS when patients were mechanically ventilated.

In accordance to protocol №1 16.01.2017 of committee of bioethics of SE "DMA of Ministry of Health of Ukraine" the scientific study recognized as meeting the generally accepted norms of morality, the requirements of observance of the rights, interests and personal dignity of research participants

In both NICU all children received full range of diagnostic and treatment procedures according to clinical guideline of help in neonates with respiratory disorders № 484 21/08/2008.

From the first day of intensive care (IC) newborns were in specialized incubators for newborns Giraffe Omnibed, Weyer, Drager, Atom Medical with the ability to maintain a constant temperature and target humidity depending on the needs of a particular newborn. The temperature was regulated by the child's temperature, measured in the groin area at the level of 36.6-37.5 °C, humidity averaged from 60% to 80% depending on the gestational age of the child and weight, as well as thermolability.

Respiratory support in patients of groups 1 and 2 was performed using devices of expert class Maquet Servo-i Neonatal and Maquet Servo-n (Maquet Critial Care, Gettinge, Sweden)

Respiratory support in patients of groups 1 and 2 was performed using devices of expert class Maquet Servo-i Neonatal and Maquet Servo-n (Maquet Critial Care, Gettinge, Sweden), as well as in the case of relative stability of respiratory function on the device Babylog (Dragaer, Germany) under the control of blood saturation and venous blood gases in order to ensure the target values of SpO_2 92-98% and pCO_2 31-41 mm Hg.

When performing IC hemodynamic disorders, the correction of relative hypovolemia with signs of low filling of the heart chambers and calculation of the cardiac index according to echocardiographic examination and reduced resistance index according to brain ultrasound examination included crystalloid solutions in dosage of 20 ml/kg for 20 minutes, and in case of bleeding or blood loss transfusion of RBC 10 ml/kg with the subsequent reassessment of venous blood count and gases.

If cardiac output was low, control and maintenance of stable hemodynamics was performed using inotropes and/or vasopressors, the starting drug was dobutamine 0.5% or dopamine 4% depending on the hospital in the starting dosage of 10 and 5 μg/kg/min respectively, not exceeding a dosage 20 μg/kg/min. The target of stable hemodynamics was the lower limit of mean pressure, which corresponds to the gestational age of the premature newborn.

Statistics was performed with LibreOffice program and R (version 3.6.3). The Shapiro-Wilk test was used to assess normality type. Considering 75% of the data had nonnormal distribution, they were performed as mediana and from 25th to 75th percentiles: Me [25%; 75%]. The Mann-Whitney test was used to evaluate quantitative parameters in independent groups. Qualitative parameters were described as n (%). The comparison of qualitative parameters in independent groups was done with Pearson's chi-squared test (χ^2) without yate's continuity correction. To estimate survival function in lifetime data we used Kaplan-Meier estimator [13]. While building Kaplan-Meier curves we evaluated the significance of difference with log-rank test. *P* values < 0.05 were considered statistically significant.

Moreover, the comparison by Craskell-Wallis criterion of quantitative values in independent samplings was used to evaluate potential confounders of BPD, retinopathy of prematurity and NEC and tried to find those for mortality rate. Qualitative parameters were described as n (%). Qualitative parameters were described as n (%). The comparison of qualitative parameters in independent groups was done with Pearson's chi-squared test (χ^2) without yate's continuity correction.

The uni-variate Cox regressions using clinical variables (independent variables) identified specific clinical variables associated with development forecast of moderate and severe BPD, retinopathy of prematurity, NEC (based on odds ratio and 95% confidence interval (95% CI) .[14]. Then, significant clinical variables were used to build a multivariate Cox regression models. by backwards elimination of non-significant clinical variables. To estimate discriminative ability of moderate and severe BPD predictors and for other comorbidities we conducted ROC-analysis (receiver operating charachteristics) with calculation of area under curve (AUC) with 95% CI. The comparison of ROC-curves was done with DeLong et al. method. [15]. *P* values < 0.05 were considered statistically significant.

RESULTS

To verify the severity of respiratory distress syndrome we analyze primary state of premature neonates in 1st and 2nd group.

We analyzed the severity of RDS in accordance to Downe's and Silverman-Andersen retraction scoring, the main symptoms which were accounted shallow breathing, upper and lower chest retractions and/or xyphoid process retractions. In 1st day of life there were registered 22,8% of 1st group patients with shallow breathing, in 45,6% of premature neonates were see-saw breathing and retractions. In 2nd group 25,7% neonates had shallow breathing and tachypnea and chest and/or xyphoid retractions had 62,2% of patients, and this number significantly different in 1,5 times (p=0,02).

On 1st day in NICU patient of 1st group had breathing rate (BR) 56 per minute [50,0; 60,0], which corresponds to the physiological norm for the newborn (N = 40-60 per minute). And at the same time venous blood pH was 7,3 [7,3; 7,4] which correlates with subcompensated acidosis while using additional oxygen with FiO_2 0,4 [0,3; 0,6] in first day of treatment. The patients of 2nd group had breathing rate 52,0 per minute [44,0; 64,0], and didn't differ from

Table 1. The predictors of BPD development during respiratory support in patients of research samples

Predictor	OR (95% CI)	P	AUC (95% CI)
The length of respiratory support, days	1,01 (0,99-1,03)	0,42	-
The length of MV, days	1,07 (1,03-1,12)	<0,01	0,74 (0,62-0,86)
The length of NIV, days	1,07 (1,02-1,12)	0,01	0,64 (0,5-0,78)
The length of CPAP, days	1,03 (0,97-1,09)	0,34	
Usage of supplemental O_2, days	1,10 (1,04-1,17)	<0,01	0,70 (0,58-0,82)
SpO_2/O_2 ratio (1 day)	1.00 (1.00-1.00)	0.75	-
Multiple regression model			
The length of MV, days	1,06 (1,03-1,11)	<0,01	0,78 (0,66-0,89)
Usage of supplemental O_2, days	1,09 (1,03-1,17)	<0,01	0,78 (0,66-0,89)

1st group significantly (p=0.16). Their venous blood gases also showed signs of metabolic acidosis, when pH was 7,3 [7,2-7,3].

As a result of correlation analysis performed according to Spearman's rank criterion, it was determined that the initial level of BR in premature infants with respiratory distress syndrome on admission to NICU correlated with the level of mean blood pressure (R = 0.186; p = 0.038), IO (R = 0.237; p = 0.007), FiO_2 (R = 0.249; p = 0.005) and the level of consciousness in the Glasgow Coma Scale (R = -0.197; p = 0.025). From the first day of observation, the venous blood pH level probably correlated with oxygen therapy in patients of the observation groups (R = -0.316; p = 0.001).

To assess the severity of RDS we used the ratio of SpO_2/FiO_2 in the first day of life, which was in 1st group – 245,0 [161,7; 330,0], and in 2nd group – 274,3 [211,8; 376,0], respectively, the data probably did not differ between groups (p = 0.30), but in 2nd group the figure was higher, which corresponded to the easier course of RDS [16].

The oxygenation index (IO) in the first day of life in patients of group 1 was statistically significantly higher 16,56 [9,95; 40,16], which indicates a more severe RDS than in patients of group 2 – 10,35 [6,99; 16,76]. The level of IO in premature infants with respiratory distress syndrome correlated with the level of inflammation at 3rd, 5th and 14th days of intensive care. In particular, on day 3 with leukocytosis (R = -0,174; p = 0,083), platelet count (R = -0,323; p = 0,001). On day 5, intensive care values probably correlated with the level of C-reactive protein (CRP) (R = 0,286; p = 0,010) and platelet count (R = -0,342; p = 0,001), on day 14 – the level of blood leukocytes (R = 0,187; p = 0,072), platelets (R = -0,237; p = 0,020) and CRP (R = 0,210; p = 0,057).

While analyzing the baseline status of newborns in both samples, it was found that patients in 1st and 2nd group had heart rate 152,0 beats per minute [137,0; 163,0] and 146,0 beats. per minute [139,8; 153,2], respectively. This corresponded to the age norm – 100-160 beats per minute and probably did not differ between groups (p = 0,12). As a result of correlation analysis, it was determined that heart rate in newborn observation groups correlated with the level of blood saturation (R = -0,174; p = 0,049).

The index of resistance in the first day of life in group 1 was 0,7 [0,6; 0,8] and probably did not differ in group 2 – 0,8 [0,7; 0,8], (p = 0,70). In both groups, the resistance index was within the physiological norm with a tendency to vasoplegia, which speaks in favor of stable hemodynamics and does not exclude the presence of a functioning ductus arteriosus in both samples of patients.

According to the data, it was determined that patients of group 1 received mechanical ventilation for a longer period 8,0 [4,5; 18] days than patients of group 2, who were on mechanical ventilation for 4,8 days [0,0; 4,8] (p <0,01). Patients of group 1 after weaning from the respirator were mainly on triggered non-invasive ventilation, the duration of which was 8 days [3,0; 15,0], which is probably different from group 2, because in this group, even if triggered NIV was used, its duration was 2 days [0,0; 6,0] ($p_{1,2}$ <0.01).

Patients in group 2 were mainly on respiratory support by the method of continuous positive airway pressure (CPAP), the duration of which was 5,5 days [2,0; 11,8], in group 1 this method of respiratory support was not used (p <0,01). These indicators significantly affect the development of complications of the neonatal period, so we meticulously studied the entire process of respiratory support.

Oxygen therapy from the first day of intensive care in patients of the observation groups correlated with BR (R = 0,215; p = 0,015), IO (R = 0,254; p = 0,004), FiO_2 (R = 0,518; p <0,001) and the level of consciousness (R = -0,317; p <0,001), venous blood pH (R = -0,316; p = 0,001).

The respiratory volume as an indicator of mechanical ventilation reliably correlated with inflammation throughout the observation period, in particular with the level of blood leukocytes at 1st, 5th, and 7th day of intensive care (R = -0,258; p = 0,006), CRP at 3rd, 5th, and 7th day = 0,347, p = 0,001, R = 0,395, p <0,001 and R = 0,436, p <0,001, respectively), platelet count at 5th, 7th and 14th day of intensive care (R = -0,368; p <0,001, R = 0,450; p <0,001 and R = -0,333; p <0,001, respectively).

To determine the ability of clinical characteristics of patients to predict moderate and severe BPD, a logistic regression analysis was performed to calculate the odds ratio. Significant predictors of BPD development, according to our results, were the duration of mechanical ventilation,

Table 2. The study of predictors for retinopathy of prematurity development in research groups

Predictor	OR (95% CI)	P	AUC (95% CI)
Body weight, 100 g	0,86 (0,75-0,98)	0,03	0,64 (0,51-0,77)
The length of NIV, days	1,09 (1,04-1,15)	<0,01	0,68 (0,54-0,83)
The length of CPAP, days	1,07 (1,00-1,13)	0,04	0,63 (0,49-0,76)
Caffeine (yes/no)	6,08 (1,92-27,06)	0,01	0,68 (0,59-0,77)
Multiple regression model			
Multiple regression model	1,09 (1,03-1,15)	<0,01	0,77 (0,68-0,87)
Caffeine (yes/no)	5,98 (1,78-28,02)	0,01	

triggered non-invasive ventilation and the number of days with additional oxygen or FiO_2 >30%. (Table 1).

The discriminate characteristics of predictors according to ROC-curves didn't differ significantly, although the largest area under curve was estimated for length of MV (0,74 [95%CI 0,62-0,86]). Using stepwise inclusion of statistically significant predictors we formed a model of multiple log-regression which consisted of length of MV and supplemental O_2 usage. When we included two predictors to the model, it increased its discriminative ability to AUC 0,78 (95% CI 0,66-0,89) but it wasn't significantly different from models with one predictor (p<0,05).

The patients with moderate and severe BPD significantly longer were mechanically ventilated and received O_2 more than 30% in inhaled gas mixture, therefore every day of MV and/or additional oxygen >30% led to increase in probability of BPD development by 15% (p=0,01), AUC=0,78 (95% CI 0,66-0,89).

Besides, the prolongation of MV or NIV 1 day more increased risk of moderate and severe BPD by 7%. Every day with supplemental oxygen increased that risk by 10%.

Moderate and severe retinopathy of prematurity was registered in patients of 1st and 2nd group of the study in 31,8% and 68,2% of cases, respectively. Intergroup differences were significant.

In patients without retinopathy or with mild retinopathy, the duration of respiratory support was 12,5 days [4,8; 24,0], and in this group children didn't need prolonged NIV – 3,0 days [0,0;9,0], and usually didn't need CPAP – 0,0 days [0,0:5,5]. It was determined that oxygen therapy with FiO_2> 30% was performed for 1,0 day [0,0; 3,0]. In patients with moderate and severe retinopathy, the duration of respiratory support was 14,5 days [5,2; 27,8]. At the same time, the duration of non-invasive mechanical ventilation increased to 12,0 days [4,2; 21,8], mechanical ventilation – up to 7,0 days [0,0; 10,5], CPAP – 4,5 days [0.0; 13.5].

It was determined that significant predictors of moderate and severe retinopathy of prematurity were body weight (AUC 0,64 (95% CI 0,51-0,77) (p=0.03), duration of non-invasive ventilation by NIV PC (AUC 0,68 (95% CI 0,54-0,83) (p <0.01), CPAP (AUC 0.63) (95% CI 0.49-0.76) (p = 0,04) and caffeine administration (AUC 0,68 (95% CI 0,59-0,77) (p=0.01) (Table 2).

Thus, an increase in body weight per 100 g reduced the chances of moderate/severe retinopathy development by 16%.

The chance of moderate/severe retinopathy of prematurity development increased with every day on NIV by 9%, CPAP by 7%. Caffeine use increased the chances of moderate/severe retinopathy of prematurity by 6.08 times. It is necessary to remind that caffeine is used to make prophylaxis of apnea of prematurity. Instead of caffeine in group 1 NIV was used.

As a result of correlation analysis, it was determined that mechanical ventilation in premature infants with respiratory distress syndrome correlated with the duration of NEC in patients of the study groups (R = -0,4845; p < 0,001). The duration of NEC correlated with the balance of weight of patients at 14th , 21st, 28th and 56th days of intensive care (R = -0,210; p = 0,025, R = -0,280; p = 0,004, R = -0,271; p = 0,009 and R = -0,519; p <0,001, respectively), indicators of inflammation, in particular leukocytes, platelets and CRP from 1st to 7th day of intensive care (p <0,001). It was proved that in patients of the study groups the development of NEC was accompanied by an increase in bed days (R = 0,350; p <0,001). Therefore, we analyzed the frequency of development of NEC depending on the method of non-invasive ventilation and analysis of predictors of its development.

The frequency of NEC correlated with duration of inotropes/vasopressor therapy in both study groups. (R=0,402; p<0,001), the day of the enteral feeding start (R=0,412; p<0,001), blood saturation along all period of research (p<0,05), volume of infusion therapy from 1st till 14th day(p<0,001), calorie rate from 3rd till 28th (p<0,001), type of nutrition (total pareneteral feeding/ enteral feeding/ their combination), nutrition therapy all period of research (p<0,001).

Among patients with NEC in prevalence were neonates from 1st group, this quantity was higher in 5,9 times in comparison to 2nd group (Table 3). According to ROC analysis, it was determined that the presence of moderate/ severe asphyxia itself increased the risk for developing NEC by 2,1 times (AUC 0,59 (0,50-0,67) (p = 0,04).

Patients who developed NEC had a statistically significantly lower daily infusion volume AUC 0,68 (0,59-0,77) p <0.01, later onset of enteral nutrition AUC 0,68 (95% CI 0,59-0,77) p <0.01, lower hemoglobin levels on the first,

Table 3. Research for NEC development predictors in both samples

Predictor	OR (95% CI)	P	AUC (95% CI)
Group 2	0,17 (0,08-0,36)	<0,01	0,70 (0,62-0,78)
Moderate / severe asphyxia (yes/no)	0,48 (0,23-0,97)	0,04	0,59 (0,50-0,67)
Pathogenic flora in faeces (yes/no)	0,72 (0,36-1,45)	0,36	-
The volume intake, ml/kg (1 day)	0,97 (0,95-0,99)	<0,01	0,68 (0,59-0,77)
Start of enteral feeding, days	1,08 (1,03-1,14)	<0,01	0,68 (0,59-0,77)
Hemoglobin, g/l (1 day)	0,98 (0,97-0,99)	<0,01	0,67 (0,57-0,77)
Hemoglobin, g/l (3 day)	0,98 (0,97-0,99)	<0,01	0,70 (0,59-0,80)
Hemoglobin, g/l (7 day)	0,98 (0,97-0,99)	<0,01	0,69 (0,58-0,79)
Average level of leucocytes, $1*10^9$ for 7 days	0,94 (0,89-0,98)	0,01	0,65 (0,56-0,75)
Average level of platelets for 7 days ($100*10^9$/ml)	0,48 (0,28-0,78)	<0,01	0,67 (0,58-0,77)
Multiple regression model			
Average level of platelets for 7 days ($100*10^9$/ml)	0,40 (0,21-0,71)	<0,01	0,77 (0,68-0,86)
Start of enteral feeding, days	1,10 (1,04-1,18)	<0,01	

third and seventh days of life AUC 0,67 (95% CI 0,57-0,77) p <0.01, as well as the level of leukocytes AUC 0,65 (95% CI 0,56-0,75) p = 0,01 and platelet count AUC 0,67 (0,58-0,77) (p <0.01) during the first 7 days of life.

Therefore, the risk of NEC development decreased by 3,0% if the volume intake increased by 1 ml/kg in 1 day, by 2,0% if the level of hemoglobin by 1 g/l on 1st, 3rd and 7th days of intensive care, and in 2,1 times – if the level of platelets increases on $100*10^9$ during 7 days.

Delaying the start of enteral nutrition for 1 day increased the risk for NEC development by 8%. An increase in the average level of leukocytes in 7 days by $1*10^9$ increased the risk of NEC by 6%.

DISCUSSION

Bronchopulmonary dysplasia (BPD) and a longer duration of invasive ventilation associated with growth retardation and impaired neurodevelopment [17]. In our study we analyzed the influence of different comorbidities on hospital stay, mortality and found changes in quality of infant life after discharge. 38 children of 2nd group (63,3%) in comparison to 17 children (42,5%) from 1st group had significant health problems on discharge from NICU (IVH, seizures, retinopathy, PDA, BPD) which could be the reason for future surgery and rehospitalizations. ($p_{1,2=}$0,04). Adverse neurodevelopment was frequently found in preterm infants with retinopathy of prematurity (ROP), especially with severe disease, with or without visual impairment [18]**.** This study was time-limited, we only received statistics about survival thanks to function analysis with Kaplan-Meier curves. They didn't find significant differences in time of survival between groups (p=0,98). It is known, sepsis and necrotizing enterocolitis (NEC) are associated with adverse neurodevelopmental outcomes, which might be mediated by the degree of white matter injuries [19]**.** Our results didn't find statistically significant evidence for association between sepsis and comorbidities development, even there was no evident AUC for sepsis and NEC. At the same time, we accounted into the research the registration of low-grade IVH in both groups. In 1st group the quantity of infants with IVH I-II grade was 17 (29,3%) and 20 (34,5), respectively. In 2nd group numbers didn't differ significantly. IVH I grade had 29 (39,2%) of neonates and IVH II grade – 23 (31,1%), ($p_{1,2}$ = 0,66). Because many last researches spoke about role of brain injury and other systemic damages in premature neonates. [20,21] One more important point of discussion is the transformation of apnea of prematurity to symptomatic epilepsy on discharge. For comparison, on 7th day of life 13 infants of both groups had apnea and most of them were not fully weaned from respiratory support. But at 56th day the majority of infants were self-breathing, but 4 infants still had any kind of seizures or apnea, whilst they had gained their 36 weeks postdelivery age and finished caffeine medications. Due to the little amount of group we couldn't analyse any link to intensive care interventions and persistent seizures. So, this issue needs additional data.

The mortality rate in this setting didn't significantly differ from the data in last researches of premature neonates of VLBW and of 28-32 weeks of gestation [22,23] In 1st group the mortality was 17,2% and in 2nd group – 12,0%. And important to say that in 81,8% cases NEC was the reason of the death and only in equal 9,1% – IVH III-IV grade or severe RDS. Therefore, we made an accent on combined pathology of prematurity to protect these infants from early death and severe impairment as a result of intensive care and prenatal relatively controlled factors.

CONCLUSIONS

The results of the study revealed risk factors for intensive care in general and respiratory support in particular, which significantly increase the risk of developing comorbidities

of prematurity. Among them are relatively controlled, it is the duration of mechanical ventilation and NIV, which increase the risk of BPD and retinopathy of prematurity.

Careful decisions about timely weaning from the respirator, avoidance of preventive ventilation can reduce the risk of severe forms of these pathologies. The use of supplemental oxygen should also be controlled with blood gases and the oxygen fraction in the inhaled air should be reduced as soon as possible <30%. Inhalation therapy should not be performed using a free flow of oxygen.

Choose one of the methods of prevention apnea of premature neonates, which does not sum up the risks of different treatments: respiratory support and drug therapy.

Conditionally controlled risk factors include phenomena such as asphyxia in the premature infant, which cannot be physically influenced by a neonatologist and pediatric anesthesiologist.

And controlled risk factors include volemic and nutritional status of the patient, in order to reduce the risk of NEC it is recommended to provide premature infants with early enteral feeding, if impossible, the appointment of complete parenteral nutrition and weight control.

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