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RISK FACTORS OF PRETERM INFANTS WITH CPAP INTUBATED FOR MECHANICAL VENTILATION

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Early use of continuous positive airway pressure (CPAP) is equal to the prophylactic administration of a surfactant to prevent neonatal respiratory distress syndrome (nRDS) in high-risk infants. However, almost half of the smallest infants still require intubation and mechanical ventilation in the first 72 hours after birth. It is known that ineffective initial CPAP is associated with a poorer prognosis. Therefore, the search for reliable prognostic risk factors for ineffective CPAP in very preterm neonates whose respiratory support is started with CPAP is still relevant today. The results of a retrospective cohort study conducted at the Lviv Regional Clinical Hospital (Ukraine), which included 151 children with birth weight <1500 g and gestational age <32 weeks, showed that CPAP failure occurred at a median age of five hours in 31% of infants initially treated with CPAP and average (SD) FiO_2, while the failure point was 0.48 (0.15). The prevalence of the main risk factors for severe nRDS did not differ significantly between two groups (CPAP success and CPAP failure). The risk of CPAP failure was significantly associated with surfactant treatment (OR – 7.46; 95% CI: 2.3–24.2), severe RDS (OR – 12.17; 95% CI: 3.8–39.3), requirement in resuscitation after birth (OR – 3.10; 95% CI: 1.2–8.1), initial CPAP pressure (OR – 0.38; 95% CI: 0.15–0.99). Earlier administration of exogenous surfactant to children at high risk of developing severe RDS could prevent the need for mechanical ventilation.

K e y w o r d s: preterm infants, CPAP failure, neonatal respiratory distress syndrome mechanical ventilation, surfactant.

Respiratory distress syndrome (RDS) remains one of the main causes of neonatal morbidity and mortality [1]. There is no doubt that extremely preterm infants represent the most important risk group for RDS development, including severe forms of the disease, as their immature lungs are especially vulnerable to the influence of various harmful factors.

The greatest challenge in modern neonatology is the practical application of effective methods of prevention and treatment of RDS aimed at decreasing mortality, averting the development of bronchopulmonary dysplasia (BPD) and improvement of long-term outcomes. It is believed that avoidance of mechanical ventilation (MV) after birth and early use of continuous positive airway pressure (CPAP) are among the key interventions [2].

The main factor contributing to lung protection is the support of self-breathing by means of creating a continuous positive airway pressure. CPAP is based on the so-called "open lung" strategy. When used in premature infants, CPAP enables adequate functional residual capacity, improves pulmonary compliance, decreases overall airway resistance, significantly reduces respiratory function, lessens the risk of pulmonary edema and atelectasis, as well as

averts V/Q mismatch and improves gas exchange, especially oxygenation [3]. Apart from that, CPAP facilitates the synthesis and improves the metabolism of endogenous surfactant, as well as helps to reduce the frequency of apnea episodes and avoids MV [2].

The effectiveness of the early use of CPAP, applied immediately after birth and in most cases before the onset of clinical signs of RDS, has been studied intensively. It was shown that early CPAP could prevent mechanical ventilation in very premature infants, while also reducing chronic morbidity (primarily BPD) and mortality without causing significant side effects [4-7].

The need for intubation after the initial administration of CPAP to extremely preterm infants is a fairly common problem. According to the data obtained in large-scale randomized control trials (RCT) that assessed the routine use of CPAP compared to planned intubation, the frequency of CPAP failure ranged widely from 21% to 74%. Almost 50% of infants at age 25–27 weeks failed the initial CPAP, even though this proportion progressively decreased with each additional week of pregnancy [5-8].

Having analyzed many infants born at 25–32 weeks of gestational age, the risks and consequences of failed CPAP were estimated by Dargaville et al. [9]. Based on the data from the Australian and New Zealand Neonatal Network for the years from 2007 to 2013, 11,684 very preterm infants (<33 weeks) out of the total 19,103 (61%) were initially managed with CPAP.

Within the CPAP group, there was a clear difference in the risk profile for the development of adverse effects depending on whether intubation was avoided during the first 72 hours of life. The presence of at least one severe pathology (severe intraventricular hemorrhage (IVH), cystic changes in the brain, retinopathy ≥ stage 3 or BPD), death and combined indicators like death/BPD or death/any morbidity was significantly higher in infants who failed CPAP, regardless of gestational age.

Worse neonatal outcomes in the case of CPAP failure with the need for mechanical ventilation in the first 72 hours after birth have been underscored by other researchers. Thus, Fuchs et al. [10] found a higher incidence of air leak syndrome, severe IVH, necrotizing enterocolitis, BPD and death in infants <29 weeks, whereas the study by De Jaegere et al. [11] only showed significantly higher rates of BPD and death in neonates <30 weeks with CPAP failure.

Although the results presented by Rocha et al. [12] did not reveal a clear difference in any of the mentioned indicators depending on CPAP failure, the very preterm infants who needed intubation within the first 72 hours after birth did have a two times higher BPD incidence than the babies with successful CPAP.

According to a systematic review by G. Schmölzer (2013), encompassing four RCTs and a total of 2,782 extremely preterm infants, the early use of CPAP (as compared to MV) enabled one out of 25 infants to survive without BPD [3].

The Cochrane Review (Subramaniam et al., 2016) [13] aimed to determine if early preventive use of nasal CPAP in preterm infants (with the gestational age of less than 32 weeks and body weight less than 1500 g shortly after birth, aged 5–15 min, regardless of respiratory status) reduces the need for mechanical ventilation and decreases the incidence of BPD without causing side effects. The meta-analysis included three RCTs where the effectiveness of CPAP was compared with mechanical ventilation with or without surfactant. The obtained results demonstrated a moderate but clinically significant decrease in total death and/or BPD (RR 0.89, 95% CI 0.81–0.97), BPD at 36 weeks (RR 0.89, 95% CI 0.79–0.99) as well as the need for mechanical ventilation (RR 0.50, 95% CI 0.42–0.59) in infants with a background of early use of CPAP.

Considering the potential negative impact of CPAP failure on neonatal outcomes in very preterm infants, it remains relevant today to focus on the elaboration of simple and reliable indicators to predict CPAP failure and timely effective interventions to avoid it.

Materials and Methods

A retrospective cohort study was conducted in 2017 and 2018 at Lviv Regional Clinical Hospital and included 151 children with birth weight <1500 g and gestational age <32 weeks, who breathed spontaneously after birth and were treated with CPAP in the maternity hospital.

All of these infants had respiratory distress and were transported for further treatment by neonatal ambulance equipped with a transport incubator and a portable ventilator to the neonatal intensive care unit (NICU) of Lviv Regional Clinical Hospital, which is a tertiary-care hospital. This time period was chosen because this institution had provided

treatment for almost all preterm infants born in Lviv and that region.

The exclusion criteria for this study were as follows: Apgar score ≤ 3 at the fifth minute, congenital malformations incompatible with life, death within the first 24 hours after birth, intubation and mechanical ventilation after birth or later (if the duration of mechanical ventilation before intubation was less than one hour) and free oxygen flow instead of CPAP after birth.

Methylxanthines (eufiline or caffeine citrate) were prescribed for the prevention of apnea in preterm infants immediately after admission to the NICU. Blood oxygen saturation level was continuously monitored with pulse oximetry to maintain the target measures within 90–94%.

In the NICU, CPAP and mechanical ventilation devices used included Servo-i Mechanical Ventilator (Maquet Medical Systems, Wayne, NJ, USA) and/or Leoni 2 (Heinen Lowenstein, Germany). Long binaural cannulas of the appropriate size were used for CPAP. The non-invasive ventilation through nasal cannulas was performed in some patients to avoid intubation.

Ineffective CPAP (or CPAP failure) was defined as the need for intubation and mechanical ventilation in the first 120 hours of life. The indications for intubation were: the need to increase the oxygen concentration (FiO_2) >0.4–0.6 with the use of PEEP 7 cm H_2O in order to maintain an oxygen saturation of >89%; severe respiratory distress and/or radiological signs of severe neonatal respiratory distress syndrome (nRDS) (III–IV grades), emphysema, pneumothorax; frequent apnea (more than three episodes within one hour accompanied by bradycardia or one episode of apnea requiring bag and mask ventilation); hypercapnia based on arterial blood gas analysis $PaCO_2 \geq 60$ mmHg and pH < 7.25. Exogenous surfactant was administered to infants after intubation.

Indications for surfactant administration were as follows: a requirement for $FiO_2 > 0.40$ on CPAP with a PEEP ≥ 7 cm H_2O. If the baby had to be intubated for surfactant replacement therapy (INSURE method) and required mechanical ventilation after administration of the drug, the infant was assigned to the ineffective CPAP group. Some infants received surfactant in a minimally invasive way (LISA) with-

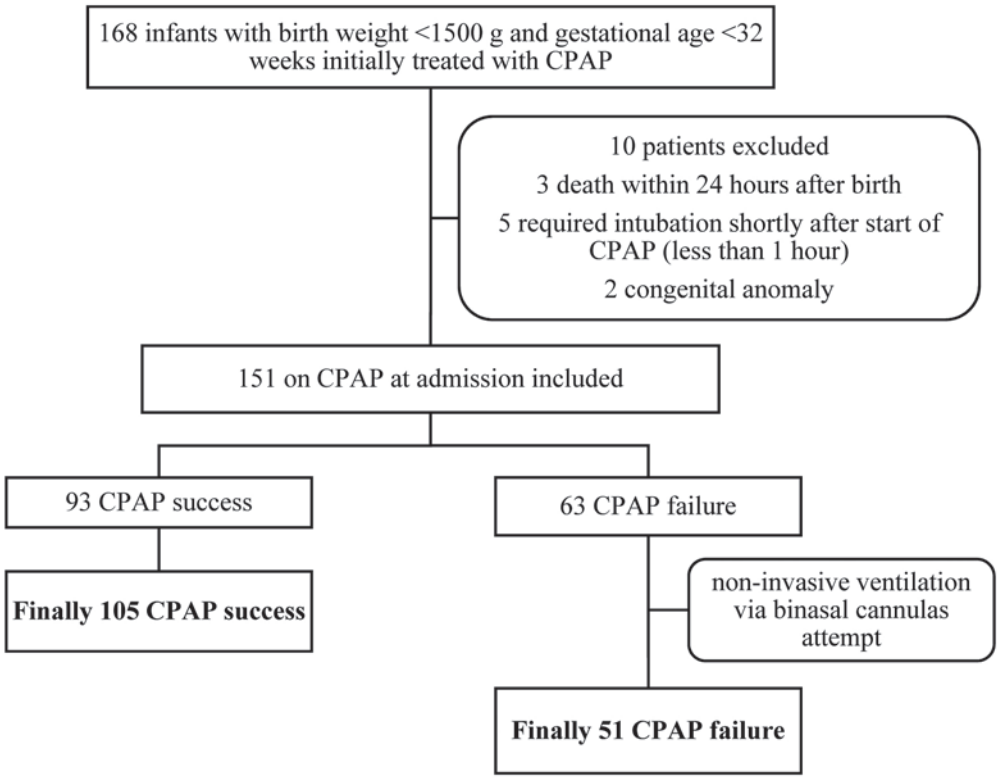

Fig. Patients who were eligible for the study

out interrupting CPAP or were intubated just to administer the surfactant and immediately extubated (INSURE method). CPAP was considered successful in these patients.

CPAP failure group (CPAP-F) involved 46 infants requiring intubation. One hundred five infants who avoided mechanical ventilation were included in the CPAP success group (CPAP-S).

Prevalence of the main risk factors associated with ineffective CPAP according to other authors [8, 10-12] – including pathology of pregnancy and childbirth, antenatal steroid administration, birth weight and gestational age, first and fifth minutes Apgar scores, severity of the newborn's condition, the need for resuscitation after birth, etc., – were compared in the formed groups.

RDS was diagnosed on the basis of clinical course and radiological findings taking into account the need for exogenous surfactant administration. The presence of intraventricular hemorrhages and periventricular leukomalacia was determined by cranial ultrasound. If clinical signs of a patent ductus arteriosus (PDA) appeared, echocardiography was performed to confirm the diagnosis.

The current recommendations for respiratory support, monitoring of vital functions and arterial blood gases control were used in the NICU.

The obtained data was analyzed with standard comparative statistics methods and multivariable logistic regression analysis. Risk estimates for early nasal continuous positive airway pressure failure were calculated. Means (SD) or medians (IQR) were given. All values were considered significant if $P < 0.05$.

Results

CPAP turned out to be ineffective in 31% of infants who received respiratory support with this method immediately after birth but required intubation and mechanical lung ventilation at an average age of five hours. The oxygen concentration at the time of intubation was 48 ± 0.15%.

Age at the time of admission to the NICU was almost the same. There were no statistically significant differences between the groups in the frequency of cases of maternal obstetric and infectious risk factors, pre-eclampsia, placental abruption, etc. However, in the CPAP-F group, the frequency of antenatal steroid administration was lower. The proportion of boys and infants born small for gestational age was almost the same in the groups (Table 1).

Although birth weight did not differ significantly between the groups and was 1103.75 ± 233.32 g in the CPAP-F group and 1154.86 ± 247.0 g in the CPAP-S group ($P = 0.089$), newborns who failed initial CPAP had a lower GA (28.60 ± 2.21 weeks vs. 29.58 ± 1.86 weeks; $P = 0.014$) and a lower Apgar score at five minutes (Table 1).

The initial PEEP on CPAP was significantly lower but the initial concentration of oxygen was higher in infants from the CPAP-F group and increased to 49.17 ± 11.27% at the time of intubation.

The non-invasive mechanical ventilation was used in 26 infants in whom CPAP turned out to be ineffective, thus preventing intubation of 12 (11%) newborns. Eighty-nine infants received exogenous surfactant. Forty-three (93%) of them were in the CPAP-F group ($P = 0.000001$).

The mean age of surfactant administration did not differ significantly and was five (IQR 3–6) hours in the CPAP-S group and four (IQR 3¬7) hours in the CPAP-F group ($P = 0.745$).

Severe RDS was diagnosed before intubation by chest X-ray findings in 50% of infants who failed CPAP. Nine percent of children had pneumothorax. All patients with pneumothorax underwent high-frequency ventilation after intubation.

Hemodynamically significant patent ductus arteriosus, which usually aggravates respiratory distress with subsequent need for mechanical ventilation, was found in newborns of both groups. Although the percentage of PDA was higher in infants who failed CPAP, 30% compared to 9%, this difference between the groups was statistically significant (Table 2).

Severe IVH was diagnosed exclusively in children from the ineffective CPAP group – 7 (15%), ($P = 0.0004$). The overall rate of IVH was also higher in this group, though the difference was only clinically significant.

The rate of BPD was two times higher in infants who required intubation and mechanical ventilation after initial CPAP compared to those who were exclusively on CPAP – 8 (19%) vs. 8 (8%), respectively (P = 0.050). Four (9%) infants from ineffective CPAP group died ($P = 0.002$).

The risk factors of CPAP failure were also assessed in two gestational age ranges (<29 weeks and 29–32 weeks). The results are shown in Table 3.

Lower frequency of antenatal steroid administration, development of severe RDS and higher requirement in surfactant treatment were statistically

Table 1. Demographic and clinical comparison of the groups

Characteristics	CPAP-S group (*n* = 105)	CPAP-F group (*n* = 46)	*P*
Birth weight, g[1]	1154.86 (247.0)	1103.75 (233.32)	0.089
Gestational age, weeks[1]	29.58 (1.86)	28.60 (2.21)	0.014
Admission age[3]	3.33 (2-4)	3.80 (2-4)	0.443
Antenatal steroids (24 mg)[2]	79 (75)	24 (53)	0.008
Male[2]	48 (46)	22 (48)	0.811
Small for gestational age[2]	37 (35)	15(33)	0.754
Caesarean section[2]	59 (56)	29 (63)	0.431
Maternal infectious risk factors[2]	32 (30)	9 (20)	0.165
Preeclampsia[2]	26 (25)	12 (26)	0.862
Apgar score 5 min[3]	6 (6-7)	6 (5-6)	0.0003
Birth asphyxia[2]	8 (8)	8 (17)	0.072
Surfactant therapy[2]	46 (44)	43 (93)	0.000
Two doses of surfactant[2]	2 (2)	12 (26)	0.000

Notes: 1 – Mean (SD); 2 – Number of cases (%); 3 – Median (IQR)

Table 2. Features of respiratory support and secondary neonatal outcomes

Characteristics	CPAP-S (*n* = 105)	CPAP-F (*n* = 46)	*P*
Additional non-invasive ventilation[1]	12 (11)	14 (30)	0.044
Start CPAP FiO_2, % [2]	34 (30-40)	39 (20-40)	0.005
Initial PEEP, cm H_2O[3]	5.39 (0,50)	5.19 (0.58)	0.04
Average age of surfactant administration, h	5 (3-6)	4 (3-7)	0.745
Severe respiratory distress syndrome[1]	6 (6) 1	23 (50)	0.0000
Pneumothorax[1]	1 (1)	4 (9)	0.014
Patent ductus arteriosus[1]	9 (9)	14 (30)	0.0006
Intraventricular hemorrhage[1]	16 (15)	13 (28)	0.061
Severe intraventricular hemorrhage[1]*	0 (0)	7 (15)	0.0004
Necrotizing enterocolitis[1]	2 (2)	1 (2)	0.913

Notes: 1 – number of cases (%); 2 – Median (IQR); 3 – Mean (SD), *Grade 3 and 4

significant for infants with GA less than 29 weeks who required intubation after initial CPAP.

For infants who were born in GA 29–32 weeks and failed CPAP, in addition to the higher incidence of severe RDS and more frequent administration of exogenous surfactant, there was also a difference in the incidence of cesarean section and hemodynamically significant PDA.

The impact of several antenatal (such as birth weight, gestation age, male sex, elective cesarean section, birth asphyxia, eclampsia, maternal infection, PROM, intrauterine growth retardation, prophylactic steroid administration, asphyxia and the need for resuscitation after birth) as well as postnatal factors (initial FiO_2 and PEEP, severe RDS, surfactant administration, early onset sepsis, PDA, etc.) affecting the risk of a successful CPAP were assessed. According to the results, the most important preventive factor was prophylactic steroid administration. The provoking factors were the following: resuscitation after birth, severe RDS, early onset sepsis and hemodynamically significant PDA.

The contribution of the same factors to the risk of CPAP-F was also estimated for two gestational age ranges, <29 weeks and 29–32 weeks, respectively (Table 4).

According to the logistic regression analysis (LRA), results by the Wald test method with step-

Table 3. Demographic and clinical comparison for gestational age ranges

Characteristics	25–28 weeks			29–32 weeks		
	CPAP-S (*n* = 34)	CPAP-F (*n* = 19)	*P*	CPAP-S (*n* = 71)	CPAP-F (*n* = 27)	*P*
Antenatal steroids (24 mg)[1]	26 (76)	9 (47)	0.031	53 (75)	15 (56)	0.066
Birth weight less than 1000 g[1]	16 (47)	12 (63)	0.260	15 (21)	5 (19)	0.774
Male[1]	12 (35)	9 (47)	0.388	36 (51)	13 (48)	0.821
Caesarean section[1]	12 (35)	5 (26)	0.501	47 (66)	24 (89)	0.02
Maternal infectious risk factors[1]	12 (35)	6 (32)	0.784	20 (28)	3 (11)	0.075
Preeclampsia[1]	5 (15)	2 (11)	0.666	21 (30)	10 (37)	0.478
Birth asphyxia[1]	4 (12)	6 (32)	0.077	4 (6)	2 (7)	0.743
Resuscitation after birth[1]	11 (32)	8 (42)	0.478	13 (18)	13 (48)	0.002
Surfactant therapy[1]	22 (65)	18 (95)	0.014	24 (34)	24 (89)	0.000
Start CPAP FiO_2, %[2]	32.5 (30-40)	40 (30-60)	0.165	30 (30-40)	40 (30-40)	0.02
Initial PEEP, cm H_2O [3]	5.32 (0.47)	5.05 (0.62)	0.08	5.42 (0.53)	5.30 (0.54)	0.294
Severe respiratory distress syndrome[1]	2 (6)	9 (47)	0.0004	4 (6)	14 (52)	0.000
Patent ductus arteriosus[1]	12 (35)	8 (42)	0.623	5 (7)	8 (30)	0.003
Early sepsis[1]	14 (41)	8 (42)	0.947	11 (15)	11 (41)	0.074

Notes: 1 – number of cases (%); 2 – Median (IQR); 3 – Median (IQR)

Table 4. Factors affecting the risk of CPAP failure (all infants, n = 151)

Factors	Relative risk (RR)	Odds ratio (OR)	*P*
Completed course of antenatal steroids	0.51	0.36	0.005
Resuscitation after birth	1.98	2.84	0.004
Severe respiratory distress syndrome	4.21	16.5	0.0001
Early onset sepsis	1.71	2.25	0.031
Hemodynamically significant patent ductus arteriosus	2.43	4.67	0.001
<29 weeks, *n* = 53			
Completed course of antenatal steroids	0.46	0.28	0.03
Severe respiratory distress syndrome	3.44	14.4	0.002
Surfactant therapy	5.85	9.82	0.035
29–32 weeks, *n* = 98			
Caesarean section	3.04	4.09	0.03
Resuscitation after birth	2.57	4.14	0.002
Surfactant therapy	8.33	15.67	0.0002
Severe respiratory distress syndrome	4.79	18.04	0.0001
Early onset sepsis	2.38	3.75	0.005
Hemodynamically significant patent ductus arteriosus	2.75	5.56	0.006

Table 5. Factors associated with CPAP failure based on LRA data (all infants, n = 151)

Factors	B	SE	Wald	df	P	OR	95% CI
Resuscitation after birth	1.130	0.489	5.335	1	0.021	3.10	1.2-8.1
Surfactant administration	2.010	0.601	11.198	1	0.001	7.46	2.3-24.2
Severe respiratory distress syndrome	2.499	0.598	17.439	1	0.000	12.17	3.8 -39.3
Initial CPAP pressure (cm H_2O)	-0.973	0.488	3.968	1	0.046	0.38	0.15-0.99
Constant	1.938	2.582	0.564	1	0.045	6.95	
<29 weeks, *n* = 53							
Birth asphyxia	2.701	1.138	5.630	1	0.018	14.89	1.60-138.62
Severe respiratory distress syndrome	3.604	1.130	10.168	1	0.001	36.73	4.01-336.48
Initial CPAP pressure (cm H_2O)	-2.638	1.001	6.946	1	0.008	0.07	0.010-0.508
Constant	11.791	4.979	5.608	1	0.018	132083.21	
29–32 weeks, *n* = 98							
Maternal infectious risk factors	-2.428	1.177	4.251	1	0.039	0.09	0.01-0.89
Resuscitation after birth	2.110	0.774	7.432	1	0.006	8.25	1.81-37.59
Surfactant administration	2.193	0.779	7.919	1	0.005	8.96	1.95-41.29
Severe respiratory distress syndrome	2.005	0.748	7.179	1	0.007	7.43	1.71-32.19
Early sepsis	1.705	0.735	5.385	1	0.020	5.50	1.30-23.24
Constant	-3.732	.818	20.817	1	0.000	0.024	

wise inclusion of variables (inclusion of all important risk factors within 120 hours), the risk of CPAP failure was significantly associated with the need for resuscitation after birth, severe RDS, surfactant administration and initial CPAP pressure (Table 5).

Predictive value for CPAP failure is 82%.

For infants with GA <29 weeks, the most important factors associated with CPAP failure were birth asphyxia, severe RDS and initial CPAP pressure. For babies with GA 29–32 weeks, except severe RDS, were important other causes like maternal infectious risk factors, resuscitation after birth, surfactant administration and early sepsis.

Discussion

The frequency of CPAP failure remains a widespread and important problem among very preterm infants. The results of our study showed that 31% of newborns whose respiratory support was started with CPAP needed further intubation.

Results obtained by Dargaville et al. [8] in a large cohort of premature infants revealed considerable differences between the groups of infants 25–28 weeks and 29–32 weeks of gestation in the incidence of failed CPAP (43% vs. 21%, correspondingly). Although we did not estimate the prevalence of CPAP failure in infants of different GA groups due to the small number of patients, our results are comparable with this study.

In most cases, intubation was followed by administration of exogenous surfactant, which was too late (average age of five hours). Therefore, most of those infants could not be successfully extubated immediately after surfactant replacement therapy and still required mechanical ventilation for some period of time. The attempts to avoid intubation and mechanical ventilation delayed the administration of surfactant, which usually worsened the final outcomes in very premature neonates with RDS. Different investigators put forward a common finding –

the lower oxygen concentration under which tracheal intubation was performed and surfactant was mostly administered [10, 11] was indeed associated with better treatment outcomes in the most premature infants.

But since most studies, including ours, were retrospective, it was not possible to evaluate the real benefits of using lower concentrations primarily for administration of exogenous surfactant. Current recommendation for surfactant administration is the persistent need to use ≥30% oxygen in the first two hours after birth [1].

It is obvious that most risk factors of CPAP failure found by different researchers [8-11] and by us are actually related to the development of a more severe RDS (gestational age, male gender, higher oxygen and pressure demand on CPAP, etc.). Most infants who manage to avoid mechanical ventilation and stay on CPAP started after birth either do not need additional oxygen administration altogether or require a small amount of it. According to results of our research, CPAP failure was significantly associated only with exogenous surfactant therapy. Early selective administration of surfactant may improve the effectiveness of CPAP, reduce the likelihood of mechanical ventilation and prevent further lung damage.

Less invasive method of surfactant administration (LISA) for spontaneously breathing preterm is preferable [1]. A potential disadvantage of LISA might be the need for pre-trained, highly qualified personnel in the procedure who may not be on site to administer the surfactant as took place in our study; therefore, method LISA was substituted by INSURE in some cases.

Predicting an unsuccessful CPAP beyond the optimal time for surfactant treatment is still a dilemma.

In fact, oxygenation depends on several factors, such as peripheral perfusion, cardiac output, oxygen concentration in arterial blood, fetal hemoglobin level, temperature, degree of lung maturity and development, pressure used on the CPAP and the gas leakage through the open mouth, etc. [14, 15]. Respiratory support allows to control only a part of these indicators. Therefore, the need to use a certain concentration of oxygen on CPAP alone cannot reflect the severity of RDS and determine the need for exogenous surfactant administration.

Therefore, it is necessary to search for other criteria that would allow to distinguish infants who have not yet reached an oxygen demand of more than 30% on CPAP within the first 2–3 hours after birth when the administration of surfactant is most optimal but in whom RDS will progress.

Assessment of the available endogenous surfactant pool in preterm infants with RDS who are treated with CPAP after birth may provide important information for understanding the pathophysiology and course of the disease in each particular case.

Theoretically, if a study to determine the surfactant pool was carried out as soon as possible after birth, it would make it possible to predict unsuccessful CPAP and optimize the timing of exogenous surfactant administration.

Many researchers have studied the suitability for predicting the occurrence of RDS of various rapid and easy-to-use tests aimed at determining the amount and assessing the function of the newborn's own surfactant (stable microbubble test, lamellar body count, non-invasive surfactant adsorption test, etc.) [16]. However, the pronounced heterogeneity of the studies conducted and their results make it difficult to determine the most optimal threshold for assessing lung maturity. The search for the best test to predict CPAP failure is still ongoing and requires investigation in large and adequately designed studies.

Lung ultrasound can be a worthy alternative to laboratory tests to determine the need for exogenous surfactant administration. It is a simple, affordable and safe non-invasive method of lung imaging in real-time that is being widely implemented in the current practice of neonatal intensive care units. Lung ultrasound (LUS) may help to accurately estimate the lung volume available for gas exchange.

A significant correlation between the results of lung ultrasound performed in the first hours of life in infants who were treated with CPAP and oxygenation status/need for surfactant therapy has recently been identified by some authors [17, 18].

In particular, the use of the ESTHER (Echography-guided Surfactant Therapy) protocol in neonatal intensive care units increased the proportion of infants who received exogenous surfactant in the first three hours after birth by almost 20%, without an increase in the overall frequency of surfactant use in infants after the introduction of the protocol [19].

The quantitative approach to LUS, using appropriate scoring scales, makes this instrumental method suitable for monitoring the course of pulmonary disease and early identification of infants who will progress in severity of RDS despite the initial

administration of CPAP, which will allow to optimize the treatment of the most premature infants.

Our study has several limitations, firstly, retrospective study design and quite small size of CPAP failure group. In addition, higher concentration of oxygen was used as criteria for intubation and surfactant administration because there were other recommendations at the time of the study. Another limitation was a quite late administration of methylxanthines to stimulate self-breathing and improve lung function in preterm infants. Our patients received methylxanthines only after admission to the NICU, not immediately after birth as is currently recommended.

Since at the time of the study there were limitations with the state procurement of surfactant for hospitals, three infants from the CPAP failure group did not receive surfactant for the treatment of RDS. The principles of care for babies born in Lviv city and region did not differ. Infants who were on CPAP in a maternity hospital and demonstrated signs of severe respiratory distress (RD) were intubated before being transported to the NICU of Lviv Regional Clinical Hospital. Patients with mild and moderate RD were kept on CPAP. During transportation, infants received glucose infusion and vital signs were closely monitored. Although there was no significant difference in age at the time of admission between the groups, children transported from remote areas of the Lviv Region were admitted to the unit later than children from maternity hospitals in Lviv. During the study period, the approaches to the initial administration of CPAP, transportation, treatment (including the administration of exogenous surfactant) and indications for intubation did not change. It is important to note that, in contrast to current European guidelines for the treatment of RDS, the initial pressure on the CPAP in our study was 5 cm H2O and surfactant was administered when the oxygen demand reached more than 40% or the newborn was radiographically diagnosed with severe RDS.

Conclusions. CPAP failure in very low birth rate infants is related to severe acute disease of immature lungs and needs surfactant replacement therapy with more accurate instruments for ventilation like a high-flow nasal cannula (HFNC) are needed.

Early selective use of surfactant could be the key intervention to prevent CPAP failure along with the need to use mechanical ventilation in very preterm infants. Although, the need to use higher oxygen concentrations may be a marker of severe nRDS and predict ineffective CPAP.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ФАКТОРИ РИЗИКУ ІНТУБАЦІЇ ТА ШТУЧНОЇ ВЕНТИЛЯЦІЇ ЛЕГЕНЬ У НЕДОНОШЕНИХ НОВОНАРОДЖЕНИХ У РАЗІ ЗАСТОСУВАННЯ CPAP

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Раннє застосування постійного позитивного тиску в дихальних шляхах (CPAP) у новонароджених дітей з високим ризиком розвитку респіраторного дистрес-синдрому (РДС) прирівнюється за своєю ефективність до профілактичного призначення сурфактанту. Однак, в перші 72 год після народження майже половина немовлят все ж потребують інтубації та штучної вентиляції легень (ШВЛ), а неуспішне початкове застосування CPAP у цих дітей асоціюється з гіршим прогнозом. Тому пошук надійних прогностичних чинників ризику неефективності CPAP у глибоконедоношених новонароджених, дихальну підтримку в яких розпочинають зі CPAP, залишається актуальним і сьогодні. У ретроспективне когортне дослідження, що проводилось на базі КНП ЛОР «Львівська обласна клінічна лікарня» (Україна), було залучено 151 дитину з масою тіла <1500 г і гестаційним віком <32 тижнів, яким відразу після народження при-

значали CPAP. За отриманими результатами частота неефективного застосування CPAP в даній когорті становила 31%. Потреба в інтубації дитини виникала в середньому через п'ять годин після народження, при цьому середня концентрація кисню (FiO_2) становила 0,48 (0,15). Поширеність основних чинників ризику розвитку тяжкого РДС суттєво не відрізнялася між двома групами (успішне CPAP і неуспішне CPAP). Ризик неуспішного застосування CPAP був достовірно пов'язаний з лікуванням сурфактантом, при цьому коефіцієнт співвідношення шансів (КСШ) – 7,46; 95% довірчий інтервал (ДІ): 2,3-24,2, тяжким РДС (КСШ – 12,17; 95% ДІ: 3,8-39,3), потребою в реанімації після народження (КСШ – 3,10; 95% ДІ: 1,2-8,1), початковим тиском на CPAP (КСШ – 0,38; 95% ДІ: 0,15-0,99). Більш раннє введення екзогенного сурфактанту дітям високого ризику розвитку РДС могло б попередити необхідність застосовувати у них ШВЛ.

Ключові слова: недоношені діти, неефективне застосування CPAP, респіраторний дистрес-синдром новонароджених, штучна вентиляція легень, сурфактант.

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