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RESPIRATORY DISTRESS SYNDROME (RDS) IN NEWBORNS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

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ABSTRACT

Respiratory distress syndrome (RDS) and hypoxic-ischemic encephalopathy (HIE) are frequent causes of death and disability in neonates. This study included newborns between January 2021 and July 2022 at the University Clinic for Gynecology and Obstetrics, Skopje. Up to date criteria for HIE/RDS for term and for preterm infants as well for the severity of HIE/RDS were used in a comprehensive analysis of cranial ultrasonography, neurological status, neonatal infections, Apgar score, bradycardia and hypotension, X-ray of the lungs, FiO2, acid-base status, assisted ventilation and use of surfactant.

Three groups were created: HIE with RDS (42 babies), HIE without RDS (30 babies) and RDS without HIE in 38 neonates. All newborns with severe (third) degree of HIE died. Intracranial bleeding was found in 35.7% in the first group and 30% in the second group, and in the third group in 53.3%. The need for surfactant in the HIE group with RDS is 59.5%, and in the RDS group without HIE 84.2%. DIC associated with sepsis was found in 13.1-50% in those groups. In newborns with HIE and bradycardia, the probability of having RDS was on average 3.2 times higher than in those without bradycardia.

The application of the surfactant significantly improved the pH, pO2, pCO2, BE and chest X-ray in children with RDS. An Apgar score less than 6 at the fifth minute increases the risk of RDS by 3 times. The metabolic acidosis in the first 24 hours increases the risk of death by 23.6 times. The combination of HIE/RDS significantly worsens the disease outcome. The use of scoring systems improved the early detection of high risk babies and initiation of early treatment increased the chances for survival without disabilities.

Keywords: respiratory distress syndrome, hypoxic-ischemic encephalopathy, premature neonates, term neonates, surfactant

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) occurs when the brain does not receive enough oxygen, or the blood flow is reduced for a period of time. These changes occur most often in perinatal asphyxia, where besides the brain, other organs and organ systems may be affected, leading to the development of multisystem organ failure (MOF).

There is a significant correlation between the involvement of other organs and the severity of HIE, and the knowledge of the incidence of such complications may allow for early intervention [1]. The degree of damage to other organs and organ systems is different: heart (43-78%), lungs (71-86%), kidneys (46-72%), liver (80-85%), hematological system (32 -54%) [2].

Common respiratory manifestations in neonates with HIE are apnea, persistent pulmonary hypertension of the newborn (PPHN), respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), and pulmonary hemorrhage. The respiratory management in these neonates is challenging, as the hypoxic-ischemic event has an impact on the lung and respiratory function [3].

Hypoxia at birth modifies the physiology of the newborn's transition from intra- to extra uterine life. It affects the increase in the pulmonary vascular resistance, a decreased pulmonary flow and persistence of the right-left shunt through the foramen ovale. In conditions of severe hypoxia, spontaneous breathing is compromised, causing apnea and bradycardia [4, 5]. If these long-term and severe hypoxic-ischemic changes affect the brain stem directly, it leads to respiratory center injury and subsequently to respiratory depression [6].

The pathophysiological mechanism of RDS in newborns with HIE is associated with metabolic acidosis and increased capillary permeability of plasma proteins, which leads to surfactant inactivation [7-9]. The alveolar surfactant deficiency increases the surface tension in the alveoli, leading to microatelectases, reduced lung volume, and reduced gas exchange [10]. Atelectasis damages the respiratory epithelium, causing a cytokine-mediated inflammatory response. Pulmonary edema develops because of the inflammation [11, 12]. This explains the main reason for the development of RDS in newborns with HIE.

The clinical signs and symptoms in the newborn are tachypnea, nasal flutter, grunting, subcostal, intercostal and substernal circulation, cyanosis, increased need for oxygen and development of acidosis.

Although this condition is more common in premature infants, it is also found in term infants. The frequency of RDS increases with the decreasing of the gestational week. 15–30% of preterm infants between 32–36 weeks of gestation and 60–80% of infants <28 weeks of gestation have RDS [13]. In term or near-term newborns, RDS occurs in 6.8% [14]. A recent study reported that RDS occurred in up to 75% of asphyxiated, preterm infants [15].

AIM

The aim of this study is to analyze the RDS in newborns with HIE and to compare the same condition in a group of newborns without HIE and in those who only have HIE.

PATIENTS AND METHODS

This is a retrospective observational cross-sectional study analyzing newborns with HIE born at the University Clinic for Gynecology and Obstetrics in Skopje, hospitalized at the Neonatal Intensive Care Unit (NICU). The cohort includes newborns between January 2021 and July 2022. Premature (≥25-36 gestational weeks) and term (≥37 gestational weeks) infants with HIE and RDS, HIE without RDS and only RDS without HIE were included in the study. Newborns with congenital anomalies, chromosomal abnormalities, and premature newborns <24 weeks of gestation were excluded from the study. The newborns were grouped into three groups: the first group HIE with RDS, the second group HIE without RDS and the third group RDS without HIE.

The criteria we used are in accordance with the American College of Obstetricians and Gynecologists (2019) [16] for HIE in acute peripartum or intrapartum changes, as well as the criteria for term newborns proposed by Gillam-Krakauer M et al. (2021) [17]. The diagnostic criteria for HIE in premature infants we used to include infants in this study were proposed by Gopagondanahalli KR et al. (2016) [18]. A modified scale of Sarnat & Sarnat for the severity of HIE (2019) [19] and the Thompson score system for the severity of HIE (1997) [20] were used to grade the severity of HIE.

The neurological status (reflexes, tone and convulsions), bradycardia and hypotension in newborns were monitored. Through cranial ultrasound examination in newborns, intracranial hemorrhages were detected and classified from grade I-IV, according to the classification set forth by Papile (1978) [21].

RDS was analyzed in newborns with and without HIE. The following criteria were used to determine RDS in newborns: Silverman-Andersen Score (1956) for premature newborns [22] and Downe's Score (1970) for term newborns [23], lungs X-ray, FiO2 in the first hour of birth, the need for mechanical ventilation, the need for surfactant.

The Apgar score (1952) [24] values in the first and fifth minutes were monitored in the first and third groups.

The classification for the RDS severity after the X-ray findings was made according to the Giedion scale [25]: stage I-reticulogranular appearance of lungs; stage II-reticulogranular appearance with air bronchograms; stage III- reticulogranular ground-glass appearance with air bronchograms; stage IV- "white lung".

Natural surfactant (poractant-alfa) in a dose of 200mg/kg was used for newborns who needed surfactant, administered endotracheally after previous intubation through an endotracheal tube or by the LISA (less invasive surfactant administration) method.

Neonatal infections (non-specific neonatal infection, sepsis, pneumonia) were considered as comorbidity in the examined newborns. Disseminated intravascular coagulation (DIC) accompanied by thrombocytopenia and hemorrhagic diathesis were analyzed in newborns with sepsis.

Through non-invasive monitoring, the vital functions of all newborns were monitored. The length of hospitalization in the three groups of newborns was analyzed. A comparison was made of the parameters of the blood gas analysis (pH, pO2, pCO2, HCO3, BE, sO2, lactate) from the peripheral blood of newborns, before and after the administration of the surfactant. A RAPID Point 500 Siemens biochemical device was used for the biochemical analysis of the blood gas analysis.

The data obtained from the medical history of the newborns were grouped and distributed accordingly in a database in Microsoft Excel. The data were processed with the statistical software programs Microsoft Excel and SSPS 26. A descriptive analysis was carried out and certain conclusions were obtained. Part of these results are the basis for the calculation of further statistical research. Student's t-test for two dependent samples and Student's t-test for two independent samples were used to determine the significance for testing the alternative hypothesis. With a non-parametric Fisher's Exact Test, the statistical significance/insignificance of the differences between the frequencies of the dependent samples was determined. A p-value less than 0.05 was considered statistically significant. The calculation of the correlation between variables was performed with binomial logistic regression and multiple linear regression.

RESULTS

The studied cohort of newborns in the period from January 2021 to July 2022 at the University Clinic for Gynecology and Obstetrics, at the Neonatal Intensive Care Unit. The study, included 110 newborns divided into three groups. In the first group there were 42 newborns with HIE and RDS. 4 of them were term (≥37 weeks of gestation), and 38 were premature (≥25-36 weeks of gestation). The second group included 30 newborns with HIE, but without RDS. In this group, 6 were term and 24 were premature newborns. There were 38 premature newborns with RDS without HIE in the third group. The birth weight for the newborns of the first group is 1715.7 ± 762.037g, and the gestational age is 31.55 ± 3.54 gestational weeks. The second group of newborns has a birth weight of 2228.2 ± 685.32g, and a gestational age of 34.87 ± 2.33 gestational weeks. In the third group, the birth weight of the newborns is 1461.71 ± 418.09g, and the gestational age is 30 ± 1.88 gestational weeks. The stratification of the weeks of gestation [26], the gender distribution and the delivery mode of the newborns from the three groups are shown in Table 1. Diabetes mellitus gestations in mothers of newborns with RDS from the first group (HIE with RDS) was found in 4.7%, and in the third group (RDS without HIE) is 5.2%.

Table 1. *Gestational weeks, gender distribution and delivery mode of the newborns in the three groups*

Gestational weeks	**Group I (HIE with RDS) (n=42)**	**Group II (HIE without RDS) (n=30)**	**Group III (RDS without HIE) (n=38)**
Extremely preterm (<28 weeks), n (%)	5 (11.9%)	/	2 (5.2%)
Very preterm (28–<32 weeks), n (%)	18 (42.8%)	/	20 (52.6%)
Moderate or late preterm (32–<36weeks), n (%)	15 (35.7%)	24 (80%)	16 (42.1%)
Term newborn (≥37 weeks), n (%)	4 (9.5%)	6 (20%)	/
Gender			
Male, n (%)	14 (33.3%)	12 (40%)	22 (57.9%)
Female, n (%)	28 (66.6%)	18 (60%)	16 (42.1%)
Delivery mode			
Sectio Caesarea, n (%)	35 (83.3%)	26 (86.7%)	27 (71.1%)
Vaginal, n (%)	7 (16.6%)	4 (13.3%)	11 (28.9%)

The severity of HIE, according to the modified Sarnat & Sarnat scale, has the same values of 1.40 ± 0.627 in the first group (HIE with RDS) and in the second group (HIE without RDS). In the first group, there are 66.6% with first degree HIE, 26.1% with second degree HIE and 7.1% with third degree HIE. Newborns from the second group have the following distribution of the weight of HIE: 66.6% first degree, 26.6% second degree and 6.6% third degree.

According to the Thompson Score, the following results were obtained for the severity of HIE in the first group of newborns: mild degree (0-10) in 66.6%, moderate degree (11-14) in 26.1%, severe degree (≥15) in 7.1%. In the second group, according to the Thompson Score, there are 83.3% with mild degree (0-10), 10% with moderate degree (11-14), 6.6% with severe degree (≥15).

The binomial logistic regression predicted the probability of RDS occurrence and the severity of HIE according to the modified scale of Sarnat & Sarnat and the Thompson Score. At the same time, the probability of occurrence of RDS in newborns increases by 2,046 times, with each unit increase in the value of the Thompson Score for the severity of HIE (mild degree 0-10). For the Sarnat & Sarnat severity scale of HIE, on the other hand, the Odds Ratio value is 0.059, signifying that the probability of occurrence of RDS in newborns decreases by 0.06 times with each unit increase in the Sarnat & Sarnat score. The association of the Thompson Score (moderate grade 11-14) with the occurrence of RDS was examined Fisher's Exact Test and it was found to be statistically insignificant (r = 374, which is greater than 0.05).

From the available data of neurological symptoms, convulsions are found in 4.8% of newborns in the first group (HIE with RDS). Hypotonia dominates in this group with 92.9%, and weakened reflexes are present in 57.1%. In the newborns of the second group (HIE without RDS), convulsions were found in 20%, hypotonia in 86.7% and weakened reflexes in 40%. In the third group (RDS without HIE) convulsions were found in 6.6%.

Through non-invasive monitoring of the vital parameters of the cardiovascular system, bradycardia was observed in 40% in the second group (HIE without RDS) and hypotension in 20%. In the first group, bradycardia is present in 14.3% of newborns, and hypotension in 21.4%. No bradycardia with hypotension was found in the second group of newborns, while in the newborns from the first group, the combination of bradycardia with hypotension was found in 4.72%.

From the neurological symptoms (convulsions, hypotonia, weakened reflexes), bradycardia and hypotension in newborns with HIE, through binomial logistic regression, it is confirmed that only bradycardia has an impact on the occurrence of RDS. That is, if bradycardia occurs, the probability of getting RDS is on average 3.2 times higher than if it does not occur. However, this effect is borderline statistically significant (p = 0.053).

Intracranial hemorrhages were detected through cranial ultrasonography, and in the newborns of the first group (HIE with RDS) they were found in 35.7%, where grade I in 4.7%, grade II in 28.5%, and grade III in 8.3%. In the second group of newborns (HIE without RDS) the intracranial hemorrhages are present in 30%, and grade I in 6.6%, grade II in 16.6%, and grade III in 6.6%. In the newborns from the third group (RDS without HIE) intracranial hemorrhages was found in 53.3%, and grade I in 16.6%, grade II in 30% and grade III in 6.6%.

38 newborns from the first group (HIE with RDS), 27 from the second group of newborns (HIE without RDS) and 35 newborns from the third group (RDS without HIE) needed respiratory support. Table 2 shows the need for invasive and non-invasive respiratory support in the three groups.

Table 2. *The need for invasive and non-invasive respiratory support among the newborns in the three groups*

	Group I (HIE with RDS)	Group II (HIE without RDS)	Group III (RDS without HIE)
Invasive respiratory support (SIPPV, SIMV, PSV), n (%)	30 (71.4%)	19 (63.3%)	29 (76.3%)
Non-invasive respiratory support (nCPAP, SNIPPV), n (%)	8 (19%)	8 (26.7%)	6 (15.8%)

There were no deaths in the newborns who needed non-invasive mechanical ventilation, but the mortality rate among newborns from the first group (HIE with RDS) on invasive mechanical ventilation was 9.5% (n=4), and among newborns from the second group (HIE without RDS) it was 3.3% (n=1), and the third group has no deaths.

Surfactant in the newborns of the first group (HIE with RDS) was applied in 25 (59.5%) newborns, 23 (92%) premature and 2 (8%) term newborns. In the group of 25 infants who received surfactant, there were 2 deaths, and in the group of 17 infants who did not receive surfactant, 3 infants died. An odds ratio value of 2.2 indicates that among children with RDS who did not receive surfactant, the risk of a fatal outcome was 2.2 times higher (120%) than those who did.

Determining the severity of RDS in newborns was performed with the Respiratory Severity Score, Silverman-Andersen for premature neonates and the Downe's Score for term neonates. The average Silverman-Andersen Score for the first group (HIE with RDS) is 5.63± 1.53 SD, and the average Downe's Score is 6 ± 1 SD. In the third group (RDS with HIE) the average Silverman-Andersen Score is 5.39 ± 1.22 SD.

Using multiple linear regression to determine the correlation between the Silverman-Andersen Score and the parameters from the blood gas analyzes (pH, pO2, pCO2, HCO3, BE, sO2, lactate) before the surfactant application, it was shown that with an increase of one unit at pO2, the Silverman-Andersen Score decreases by 0.084 times, and with an increase of one unit of sO2, the Silverman-Andersen Score increases by 0.055 times. The correlation analysis between the Silverman-Andersen Score and the blood gas analysis parameters (pH, pO2, pCO2, HCO3, BE, sO2, lactate) after surfactant application showed that, with the increase of pH, the Silverman-Andersen Score decreases.

When analyzing the association between the need for mechanical ventilation and a high Silverman-Andersen Score (≥5), it was found that there is no statistically significant association between the invasive mechanical ventilation and the Silverman-Anderson Score ≥5, (Fisher's Exact Test = 2.757, p = 0.675, which is greater than 0.05), as well as between the non-invasive mechanical ventilation and the Silverman-Anderson Score ≥5, (Fisher's Exact Test = 2.757, p = 0.763, which is greater than 0.05).

The difference of the arithmetic means of the blood gas parameters before and after the administration of surfactant was tested in the first group of newborns (HIE with RDS) and in the third group (RDS without HIE) by applying the Student's t-test for two dependent variables. The difference between the arithmetic means, before and after the surfactant administration, in the first

group is statistically significant for all parameters of the blood gas analyses, except for the lactates (r = 0.657, which is greater than 0.05). The difference between the arithmetic means of the blood gas parameters, before and after the surfactant administration, in the third group is statistically significant for pH (p = 0.000), pO2 (p = 0.001), pCO2 (p = 0.000) and BE (p = 0.004). It is not significant for HCO3 (p = 0.255), lactates (p = 0.183) and sO2 (p = 0.561). Table 3 summarizes the arithmetic means and standard deviations (SD) of the blood gas parameters before and after the administration of surfactant in the first and in the third group.

Table 3. *Arithmetic means and standard deviations (SD) of blood gas analysis before and after surfactant application in the first and third groups*

	Group I (HIE with RDS)			Group III (RDS without HIE)		
	Before surfactant mean±SDS	**After surfactant mean±SDS**	**p**	**Before surfactant mean±SDS**	**After surfactant mean±SDS**	**p**
pH	7.19±0.80	7.29±0.87	p=0.00 S	7.25±0.79	7.34±0.52	p=0.00 S
pO2	42.14±11.82	55.87±15.08	p=0.00 S	39.62±13.52	57.13±22.13	p=0.01 S
pCO2	57.75±10.36	44.54±9.2	p=0.00 S	56.52±11.27	41.22±6.25	p=0.00 S
HCO3	19.21±3.00	20.36±2.22	p=0.044 S	23.19±3.31	22.50±1.90	p=0.255 NS
BE	-8.82±5.95	-6.82±5.73	p=0.00 S	-4.76±3.44	-2.96±2.07	p=0.04 S
Lactate	6.038±3.61	5.80±4.09	p=0.657 NS	3.16±3.1	9.07±23.0	p=0.183 NS
sO2	75.0±19.71	87.53±10.02	p=0.00 S	79.92±15.99	83.47±27.26	p=0.561 NS

Comparing the blood gas parameters for the significance of the difference between the arithmetic means before the surfactant application, with the Student's t-test for two independent samples between the first and the third group, it was determined that the differences between the arithmetic means are statistically significant for the pH (p = 0.008), HCO3 (p = 0.000), BE (p = 0.000) and lactates (p = 0.003). The same blood gas parameters after the application of surfactant between the first and third groups, show that the differences between the arithmetic means are statistically significant for the pH (p = 0.019), HCO3 (p = 0.000) and BE (p = 0.001).

The lung X-rays of the newborns with RDS (first and third group) were analyzed before and after the surfactant application. The distributions of lung X-ray before and after the surfactant application are statistically significantly different (Fisher's Exact Test=37.732; p=0.000), which indicates that after the surfactant administration, the lung X-rays significantly improved.

The arithmetic mean value of FiO2 requirement in the first hour of birth in newborns with HIE and RDS (first group) is 52.88 ± 26.47 SD, for newborns with HIE without RDS (second group) 50.62 ± 21.19SD and for newborns with RDS without HIE (third group) 38.47 ± 9.91 SD.

The average duration of hospitalization of the newborns in the first group is 41.01 ± 26.3 days, in the second group 22.23 ± 11.96 days, and in the third group it is 42.74 ± 16.304 days. Based on these subsections, a statistically significant difference was found for the average duration of hospitalization between the infants with RDS and the infants without RDS (r = 0.000). In other words, the hospitalization lasted significantly longer for infants with RDS compared to those without RDS.

The risk of the occurrence of RDS at a low Apgar score in the first and the fifth minute was determined by binomial logistic regression. The value of the odds ratio (Odds Ratio) of 3.011 shows that if the Apgar score is less than 6 at the fifth minute, the risk of RDS in newborns increases by 3 times, than if the Apgar score would be greater than 6. Also, the odds ratio showed that the risk of RDS in newborns will be 2.73 times higher if the Apgar score is less than 6 in the first minute than if it is greater than 6.

During the analysis of the metabolic acidosis and the outcome in newborns from the first and the second group, it was found that the odds ratio

is 23.6250, meaning that the probability of death in newborns, who will have acidosis in the first 24 hours after birth, is 23.6 times higher, compared to the newborns without acidosis. This result is statistically significant (r = 0.0026).

The number of neonatal infections is high. Infections in newborns from the first group (HIE with RDS) are represented in 90% (non-specific neonatal infection 47.6%, sepsis 38.1%, pneumonia 4.8%). The disseminated intravascular coagulation (DIC) in sepsis, followed by thrombocytopenia and hemorrhagic diathesis was found in 43.7% of newborns in this group. In the newborns of the second group (HIE without RDS), the rate of infections is 83.3% (non-specific neonatal infection 53.3%, sepsis 26.7%, pneumonia 3.3%). In this group, DIC in combination with sepsis was found in 50% of the newborns. In the third group (RDS without HIE), 50% of the newborns had a non-specific neonatal infection, 36.8% had sepsis, 2.6% pneumonia. DIC in combination with sepsis in this group was found in 13.1%.

In the cohort of 42 newborns with HIE and RDS, the mortality rate is 9.5%, and in 30 newborns with HIE without RDS, it is 3.3%. All infants with a fatal outcome had severe (third) degree of HIE, according to the modified classification of Sarnat & Sarnat. Only 2 dead newborns with HIE and RDS from the first group had a non-specific neonatal infection. There were no deaths from sepsis and pneumonia. But if we consider all infections together (sepsis, pneumonia and non-specific neonatal infections) and children without infections, the Fisher's Exact Test shows that, statistically, the infections are significantly associated with the death outcome (p = 0.012). The cranial ultrasonography in term newborns with HIE and RDS showed signs of periventricular hypoxic zones and cerebral edema in 50%, but there were no signs of intracranial hemorrhage.

DISCUSSION

Worldwide, 13 million infants are born preterm, and almost one million die within 1 month [27]. Neonatal mortality in North Macedonia for the year 2020 was 4.7 per 1,000 live births [28], which is higher than in the developed countries and in some countries in the region. According to the WHO, the most common causes of neonatal mortality in 2020 were prematurity (34%), respiratory and cardiovascular diseases (11%), infections (8%), congenital anomalies (6%) and perineal asphyxia (5%) [29].

In developed countries, the incidence of HIE is 1.5 per 1000 live births [30]. Newborns suffering from HIE have complications in other organs as well [31]. HIE was observed in 9.4% of the total treated newborns at our NICU in the period from January 2021 to July 2022.

From a pathophysiological point of view, pulmonary manifestations in neonates with HIE include increased pulmonary vascular resistance, pulmonary hemorrhage, pulmonary edema followed by secondary heart failure, and decreased surfactant production with development of RDS (hyaline membrane disease) [32].

Risk factors for the development of RDS are premature birth, white race, male gender, late-preterm infants, diabetes in the mother, perinatal hypoxia-ischemia and delivery by provocation [33, 34]. Also, cesarean delivery may favor the onset of RDS [35]. In this study the first group of newborns with HIE and RDS, preterms (90.5%) are dominant, of which 35.7% are late-preterm. Female newborns (66.6%) are predominant (boys 33.3%). In the third group (RDS without HIE) 42.1% are late-preterm. In this group, the male gender dominates with 57.9%. All newborns of the first group have perinatal hypoxia-ischemia. Cesarean delivery is a more common way of delivery in the first (HIE with RDS) and third group (RDS without HIE) of newborns. Diabetes mellitus gestations among mothers in the first group (HIE with RDS) was found in only 4.7%, and in the third group (RDS without HIE) it was 5.2%.

An equal risk was observed in newborns with moderate and severe form of HIE, in terms of respiratory complications [36]. According to the Sarnat & Sarnat score system for severity of HIE, respiratory disorders are common in moderate and severe form of HIE [37]. In this study in the first group of newborns, RDS is the least represented (7.1%) in the severe form of HIE according to the scale of severity of HIE by Sarnat & Sarnat. It is of note that the Sarnat & Sarnat severity scale of the HIE calculated that the probability of RDS decreases by 0.06 times, with each unit.

The Thompson Score for the severity of HIE in the first 4 days provides predictive information on mortality, respiratory disorders and feeding problems [38]. In this study, the probability of RDS in newborns increases 2,046-fold with each

unit increase in the Thompson Score for the severity of HIE.

When comparing the two used scales for the severity of HIE, Sarnat & Sarnat and Thompson score, it was found that the representation of newborns with mild, moderate, and severe degrees of HIE, according to the modified scale for the severity of HIE by Sarnat & Sarnat, is identical to the Thompson score of light (0- 10), moderate (11-14), severe (≥15) HIE.

Intracranial hemorrhages are the most common type of brain injury in neonates, especially in neonates with RDS [39]. Helwich E et al. (2017) provide data on intracranial bleeding in newborns with RDS of 49.4% [39], whereas in the study by Kinikar U, Dhanawade S. (2018) the incidence of intracranial bleeding is 22% [40]. In this study, intracranial hemorrhages had an incidence of 35.7% in the first group (HIE with RDS), which is nearly identical to the incidence of a recent study published by Arkin N et al. (2023) which is 38.2% [41]. Grade II intracranial hemorrhages is dominant in all three groups.

Bradycardia without apnea is always associated with changes in respiratory function and may precede severe respiratory symptoms [42]. Binomial logistic regression confirms that only bradycardia has an impact on the occurrence of RDS. This means that if bradycardia occurs, the probability of getting RDS is on average 3.2 times higher than if it does not occur. However, this effect is only borderline statistically significant ($p = 0.053$).

FiO2 is a parameter for assessing the severity of respiratory insufficiency and monitoring the dynamics of RDS [43]. Dargaville P et al. (2013) and Gulczyńska E et al. (2019) confirmed that increased capacity demand above 30% in the first hours of life is associated with numerous negative effects. [44, 45]. The need for oxygen in the first hour is higher in newborns with HIE and RDS (first group) compared to the rest, which has an impact on the overall further treatment of these newborns.

Hospitalization of newborns with RDS in the USA averages 31.3 days, and the costs are about $55,000 for insured patients [46]. In the studied groups, it has been shown that infants with RDS have a longer hospitalization, more than 40 days, compared to infants without RDS, and the treatment burden is higher. This study confirmed the lengthier hospital stay in babies with RDS.

Infections are frequent in the three studied groups: 90% of the newborns from the first group (HIE with RDS) and 83.3% in the second group (HIE without RDS). Sepsis is dominant among newborns from the first group with 38.1%. Recent studies have reported that neonates with perinatal asphyxia have a 17,308-fold higher risk of early neonatal sepsis compared to neonates without perinatal asphyxia [47].

Sepsis/infections and hypoxic-ischemic encephalopathy are dominant risk factors for DIC in the neonatal population. Although there is a lack of data confirming the incidence of DIC in term and preterm infants, the prevalence is concerning among hospitalized patients in neonatal intensive care units [48]. In this study, DIC in association with sepsis was found in 43.7% of newborns in the first group (HIE with RDS), 50% in the second group (HIE without RDS) and 13.1% in the third group (RDS without HIE).

Newborns with an Apgar score ≤7 at the fifth minute have a high probability of developing RDS [49]. An Apgar score, less than 6 at the fifth minute in this study was found to increase the risk of RDS by 3 times.

The Silverman-Andersen Score is an easy and simple tool to determine the severity of respiratory distress in newborns. The arithmetic mean value of the Silverman-Andersen Score in premature infants of the first group in this study is 5.63 ± 1.53 SD, which indicates a moderate degree of RDS. A strong association with the need for respiratory support in infants with a high Silverman-Andersen Score (≥5) has been confirmed [50], but this study found no statistically significant association between invasive/non-invasive mechanical ventilation and a Silverman-Anderson Score ≥5. On the other hand, analyzing the correlation between the Silverman-Andersen Score and the parameter from the gas analyses (pH, pO2, pCO2, HCO3, BE, sO2, lactati) after surfactant application, it was shown that by improving the pH value, the Silverman-Andersen Score decreases.

Management and treatment of infants with RDS includes the monitoring of oxygenation and ventilation, respiratory support, exogenous surfactant, and supportive care. Approximately 50–70% of asphyxiated infants without pulmonary effects require mechanical ventilation [51]. The need for mechanical ventilation due to RDS is 52.77%, and due to HIE is 12.5% [52]. In this study, 71.4% of newborns with HIE and RDS needed invasive

respiratory support, and 19% needed non-invasive ventilation. In contrast, in newborns with HIE without RDS, the need for invasive respiratory treatment is represented by 63.3%, and non-invasive ventilation in 26.7%. Mortality was also noted in these two groups only in neonates on invasive mechanical ventilation of 9.5% in the first group and 3.3% in the second group, which is higher (1.8%) compared to the study by Raha BK et al. (2020) [53], but lower compared to less developed countries (100%) [54].

In this study 59.5% (n=25) babies from the first group (HIE with RDS) were treated with exogenous natural surfactant 200mg/kg. In this group, the risk of a fatal outcome is 2.2 times higher (120%) among those who did not receive surfactant. There is also an improvement in gas analysis parameters (pH, pO2, pCO2, HCO3, BE and sO2) after surfactant application in the first group (HIE with RDS). In the third group there is an improvement in pH, pO2, pCO2, BE before and after the surfactant application, as well as an improvement in radiographic findings in both groups. This is confirmed by several studies and a systematic review of 13 randomized controlled trials associated with the surfactant application derived from animal origin in newborns with RDS, with a significant improvement in oxygenation, the need for ventilation and a reduction in pneumothorax, mortality and bronchopulmonary dysplasia at 28 days, compared to a placebo group [55, 56].

In this study, the probability of death in newborns with metabolic acidosis in the first 24 hours after birth is 23.6 times higher, compared to newborns without acidosis. De Bernardo G et al. (2020) gives similar results. Neonatal acidosis was correlated with an increased risk of admission to neonatal intensive care units, hypoxic ischemic encephalopathy, respiratory distress syndrome, multiple organ dysfunction, and neonatal death [57]. In addition, Ma H et al. (2021) reported that neonatal metabolic acidosis is associated with poor clinical outcomes [58].

Martín-Ancel A. et al. (1995) have published that 6% of the newborns died due to respiratory system involvement [59]. Shankaran S et al. (1991) reported a mortality rate of 7% with pulmonary involvement [60], while in the study of Rohit V et al. (2018) the mortality of asphyxiated newborns with respiratory complications is 50% [32]. In the studied cohort of HIE newborns with RDS (first group) the mortality rate is 9.5%, with all dead newborns having a severe degree of HIE. In diseased babies with HIE and RDS, periventricular hypoxic zones and cerebral edema were found in 50%. The frequency of infection among the newborns in this study is high. Comparing children with infections (sepsis, pneumonia and non-specific neonatal infections) and children without infections, this study showed that infections were statistically significantly associated with mortality.

Despite the recent advances in the understanding of the pathogenesis of HIE, it remains difficult to predict which infants will develop further respiratory complications. Appropriate pregnancy control and lowering the number of preterm births will reduce the general incidence of RDS. Apparently, early detection and appropriate treatment of RDS in newborns with HIE will reduce the damage to the lungs and the consequences of lung affection. The use of scales for the severity of HIE (Sarnat & Sarnat and Thompson scores) is helpful for early detection of severe HIE/RDS and their timely treatment. Neonatal infections are still unacceptably frequent. Hence, reducing premature births and neonatal infections is essential to reduce the number of children with HIE/RDS and lower the general neonatal mortality.

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Резиме

РЕСПИРАТОРЕН ДИСТРЕС СИНДРОМ (РДС) КАЈ НОВОРОДЕНЧИЊАТА СО ХИПОКСИЧНО-ИСХЕМИЧНАТА ЕНЦЕФАЛОПАТИЈА (ХИЕ)

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Респираторниот дистрес синдром (РДС) и хипоксично-исхемичната енцефалопатија (ХИЕ) се честа причина за смрт и инвалидитет кај новороденчињата. Оваа студија опфаќа новороденчиња родени меѓу јануари 2021 и јули 2022 година на Универзитетската клиника за гинекологија и акушерство, Скопје. Во сеопфатна анализа на кранијалната ултрасонографија, невролошкиот статус, неонаталните инфекции, Апгар-скорот, брадикардијата и хипотензијата, рендген на белите дробови, FiO2, ацидо-базниот статус, механичката вентилација и употребата на сурфактант, беа користени најновите критериуми за ХИЕ/РДС за термински и за недоносени новороденчиња, како и скалите за тежината на ХИЕ/РДС .

Креирани се три групи: ХИЕ со РДС (42 новороденчиња), ХИЕ без РДС (30 новороденчиња) и РДС без ХИЕ кај 38 новороденчиња. Сите новороденчиња со тежок (трет) степен на ХИЕ починаа. Интракранијално крвавење е откриено кај 35,7 % во првата група, 30 % кај втората група и во третата група кај 53,3 %. Потребата од сурфактант во групата ХИЕ со РДС е 59,5 %, а во групата РДС без ХИЕ – 84,2 %. ДИК поврзан со сепса е пронајден кај 13,1–50 % во овие групи. Кај новороденчињата со ХИЕ и брадикардија, веројатноста за добивање на РДС би била 3,2 пати поголема отколку кај оние без брадикардија.

Примената на сурфактантот значително ги подобри pH, pO2, pCO2, BE и рендген-графиите на белите дробови кај новороденчињата со РДС. Апгар-скорот помал од 6 во петтата минута го зголемува ризикот за РДС за 3 пати. Метаболната ацидоза во првите 24 часа го зголемува ризикот од смртност за 23,6 пати. Комбинацијата на ХИЕ/РДС значително го влошува исходот на болеста. Употребата на скоринг-системи за тежината на ХИЕ го подобруваат раното откривање на новороденчињата со висок ризик и започнувањето на ран третман, со што се зголемуваат шансите за преживување без попреченост.

Клучни зборови: респираторен дистрес синдром, хипоксично-исхемична енцефалопатија, прематурни новороденчиња, доносени новороденчиња, сурфактант