FACTORS ASSOCIATED WITH THE OCCURRENCE OF DEATH OUTCOME IN CHILDREN WITH NEONATAL RESPIRATORY DISTRESS SYNDROME

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FAKTORI UDRUŽENI SA POJAVOM SMRTNOG ISHODA KOD DECE SA NEONATALNIM RESPIRATORNIM DISTRES SINDROMOM

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ABSTRACT

Neonatal respiratory distress syndrome (NRDS) is a consequence of immaturity at birth and it is still associated with relatively high mortality rate. The aim of this study was to identify the factors associated with the occurrence of fatal outcome in newborns with neonatal respiratory distress syndrome.The research was designed as a case-control study nested in a retrospective cohort, and it enrolled newborns treated during 2015 at Pediatric Clinic of Clinical Center in Kragujevac. Diagnosis of NRDS and decision about the treatment were left at the discretion of attending pediatricians. The cases were patients with fatal outcome, while controls were randomly selected from the pool of survivors and matched with each case by gender in a ratio of 4:1. The study included 371 newborns, of whom 201 (54.2%) were male and 170 (45.8%) female. Lethal outcome occurred in 36 newborns (9,7%). Significant association was found between death and APGAR score ($OR_{adjusted}$: 0.516, 95% CI: 0.322-0.827), weight on delivery ($OR_{adjusted}$: 0.996, 95% CI: 0.993-0.999), duration of hospitalization ($OR_{adjusted}$: 0.901, 95% CI: 0.835-0.972) and mechanical ventilation ($OR_{adjusted}$: 165.256, 95% CI: 7.616-3585.714). Higher gestational age, higher birth weight, higher APGAR score and longer duration of hospitalization were singled out as protective factors, while use of mechanical ventilation increased the risk of death. Major limitations of the study were retrospective nature and relatively small number of identified cases. Postponing delivery and delivery in institution with neonatal intensive care unit are crucial for survival of newborns with NRDS.

Keywords: *neonatal respiratory distress syndrome, risk factors, mechanical ventilation.*

SAŽETAK

Neonatalni respiratorni distres sindrom se javlja kao posledica nedovoljne zrelosti deteta na rođenju i još uvek se često završava smrtnim ishodom. Cilj rada je bio da se identifikuju faktori koji su udruženi sa pojavom smrtnog ishoda kod novorođenčadi sa neonatalnim respiratornim distres sindromom.

Istraživanje je dizajnirano kaostudija tipa slučaj-kontrola u retrospektivnom kohortu, a sprovedeno je na novorođenčadi koja su tokom 2015. godine lečena na Pedijatrijskoj klinici Kliničkog centra u Kragujevcu. Postavljanje dijagnoze neonatalnog respiratornog distres sindroma, kao i odluke o terapijskim procedurama bili su u nadležnosti dežurnog pedijatra. Slučajevi su bili pacijenti sa letalnim ishodom, dok su kontrole nasumično odabrane iz grupe preživelih pacijenata, a povezivane sa svakim od slučajeva po polu u odnosu 4:1. U studiju je uključeno 371 novorođenče od čega je 201 (54,2%) novorođenče bilo muškog pola, a 170 (45,8%) ženskog pola. Kod 36 (9,7%) novorođenčadi nastupio je smrtni ishod. Značajna povezanost u prilagođenom regresionom modelu uočena je između smrtnog ishoda i APGAR skora (OR: 0.516, 95% CI: 0.322-0.827), telesne težine na porođaju (OR: 0.996, 95% CI: 0.993-0.999), trajanja hospitalizacije (OR: 0.901, 95% CI: 0.835-0.972) i primene mehaničke ventilacije (OR: 165.256, 95% CI: 7.616-3585.714). Veća gestacijska starost, veća telesna masa na rođenju, veća vrednost APGAR skora i duža hospitalizacija su se izdvojili kao protektivni faktori, dok je primena mehaničke ventilacije fakor rizika za smrtni ishod. Glavna ograničenja studije su retrospektivni karakter istraživanja i relativno mali broj identifikovanih slučajeva. Odlaganje porođaja i porođaj u ustanovi koja poseduje jedinicu neonatalne intenzivne nege su ključni faktori za preživljvanje dece sa neonatalnim respiratornim distres sindromom.

Ključne reči: *Neonatalni respiratorni distres sindrom, faktori rizika, mehanička ventilacija.*

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INTRODUCTION

Neonatal respiratory distress syndrome (NRDS), also known as the disease of the hyaline membranes, is characterized by respiratory failure that occurs after the birth or during the next 48 hours. This syndrome is potentially life-threatening and difficult to treat, with sudden onset and progressive course during the first hours after birth (1). It could be also associated with serious acute and chronic complications, which may further contribute to deterioration of the infants' health and their quality of life (2-4).

Main reason for occurrence of NRDS is lack of surfactant, which occurs as a result of the immaturity of the enzymatic systems necessary for its synthesis (5-7). However, some authors suggest that development of NRDS has a genetic foundation (8). Based on previous studies, the most important risk factor for the occurrence of NRDS is a premature birth. The other risk factors include maternal diabetes mellitus, perinatal asphyxia, history of NRDS occurrences in the family and delivery by caesarean section (9-10).

In recent years, progress was made in understanding pathophysiology as well as in the treatment of this condition, which led to certain reduction in morbidity and mortality rates (11). However, an emerging problem is an increasing number of premature newborns, especially those with gestational age between 34 and 37 weeks (12). Although risk factors for neonatal respiratory distress syndrome were well documented, the data linking certain factors with the occurrence of fatal outcome in these patients are still scarce.

The aim of this study is to identify factors associated with the occurrence of death in newborns with NRDS, and to analyze the degree of their relative impact on the observed outcome.

PATIENTS AND METHODS

A total of 371 newborns with NRDS treated in Center for Neonatology at Pediatric Clinic of Clinical Center Kragujevac between January 1st and December 31st, 2015, were enrolled in a retrospective cohort. Relevant demographic and clinical data were extracted from the patients' histories. The diagnosis of NRDS and decision about the treatment were left at discretion of attending pediatricians. The newborns with incomplete files as well as those referred from other hospitals (where they have been previously diagnosed and treated) to Neonatal Intensive Unit of Pediatric Clinic in Kragujevac were excluded from the study. This study was approved by Ethics Committee of Clinical Centre Kragujevac.

Based on outcome of interest, i.e. death due to NRDS, a case-control study was nested in aforementioned retrospective cohort. Cases (n=36) were patients with fatal outcome, while controls (n=144) were participants who survived and whose treatment was successfully completed. These two groups were individually matched by gender, and for each case there were four matched controls randomly selected from survived patients enrolled in the cohort study, as previously mentioned. Cases and controls were then compared in terms of factors assumed to have an important association with death, such as gestational age (in weeks), type of birth (vaginal delivery or caesarean section), APGAR score, weight on delivery, duration of hospitalization, mechanical ventilation, duration of mechanical ventilation, oxygen therapy, surfactant therapy and the development of acute complications of NRDS such as pneumonia, pneumothorax and pulmonary hemorrhage.

Sample size calculation

In order to determine required sample size for this research, a following calculation for categorical/dichotomous variables were performed (13):

$$N = 4 \cdot (z_{1-\frac{\alpha}{2}})^2 \cdot \frac{p(1-p)}{GP^2}$$

Where N stands for– number of patients in the sample; p – is the proportion of characteristic in the sample; GP – Confidence interval width; $(z_{1-\frac{\alpha}{2}})$ – 1.96 (with probability of 95%). The effect size was taken from the study by Smolarova et al. (14), who had found the incidence of lethal outcome in 27% of newborns with NRDS with 95% confidence interval of 20-35%. According to previously mentioned parameters, minimum necessary sample size was 134 newborns.

Statistical analysis

The baseline characteristics of the patients were summarized by descriptive statistics. Means ± standard deviations were used for presenting continuous data, and frequencies (percentages) for presenting categorical variables. After the normality of the data distribution for continuous variables had been checked by Kolmogorov-Smirnov test, an appropriate parametric or nonparametric test (i.e. Student's T test for independent samples or Mann-Whitney U test) was used to evaluate the observed differences. Significance of differences in the rates of categorical variables were tested by the Chi-square test with Yates continuity correction in 2*2 contingency tables, or in a case of low prevalence of particular categories by Fisher's test. The influence of independent variables on the dichotomous outcome (i.e. patient was dead or alive) was tested using univariate and a stepwise backwards conditional multivariate logistic regression analysis. The results were shown as crude and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CI). The level of significance was 0,05 in all analyses, while stepwise regression model removed all variables with an additional probability (p value) of 0.1 and above. The association between observed risk/protective factors and death was considered significant if 95% CI of adjusted OR did not include the value of 1. All calculations were performed by statistical program for social sciences (SPSS version 18).

RESULTS

The study included 371 newborns in total, of whom 201 were male (54.1%) and 170 female (45.8%). In total, 36 newborns died (9,7%), 13 male (36.1%) and 23 female (63.9%). Average gestational age was 35.3±4.6 weeks and average birth weight was 2500.8±1039.8 grams. Complications (pneumonia, pneumothorax and pulmonary hemorrhage) were identified in 82 newborns (22.1%) and a total number of complications was 89. There were 60 cases of pneumonia, 18 cases of pneumothorax and 11 cases of pulmonary hemorrhage. Seven newborns (1.9%) had two complications.

Baseline characteristics of cases and controls are shown in Table 1. Highly significant differences between cases and controls were observed in the following features: gestational age ($p<0.001$), APGAR score ($p<0.001$), weight on delivery ($p<0.001$), duration of hospitalization ($p<0.001$), mechanical ventilation ($p<0.001$), duration of mechanical ventilation ($p<0.001$), surfactant therapy ($p<0.001$), presence of pneumonia ($p=0.010$) or pulmonary hemorrhage ($p=0.001$).

Table 1. Baseline characteristics of cases and controls.

Variable	Cases (n=36)	Controls (n=144)	Test value and probability of null hypothesis
Gestational age (weeks)	28.4±5.2	37.1±3.4	U=604.000 p=0.000*
Type of birth - vaginal delivery - cesarean section	 24 (66.7%) 12 (33.3%)	 80 (55.6%) 64 (44.4%)	χ^2=1.457 p=0.227
APGAR score	3.9±2.6	8.0±1.7	U=622.500 p=0.000*
Weight on delivery (grams)	1242.8±929.2	2918.5±826.1	U=531.500 p=0.000*
Duration of hospitalization (days)	6.8±12.6	15.3±9.1	U=750.500 p=0.000*
Mechanical ventilation	35 (97.2%)	45 (31.3%)	χ^2=50.766 p=0.000*
Duration of mechanical ventilation (days)	6.8±12.6	2.4±5.8	U=1131.500 p=0.000*
Oxygen therapy	34 (94.4%)	303 (84.0%)	χ^2=2.613 p=0.106
Surfactant therapy	27 (75.0%)	63 (16.0%)	χ^2=50.019 p=0.000*
Pneumonia	0 (0.0%)	23 (16.0%)	χ^2=6.592 p=0.010*
Pneumothorax	5 (13.9%)	13 (6.9%)	χ^2=1.818 p=0.178
Pulmonary hemorrhage	4 (11.1%)	1 (0.7%)	χ^2=11.571 p=0.001*
Results are presented as mean ± standard deviation, or n (%); *Significant difference			

The results of the both univariate and multivariate binary logistic regression with a model of acceptable quality (Cox & Snell R square 0.527 Nagelkerke R square 0.833, Hosmer-Lemeshow Chi square 2.148, df = 8, p = 0.976) are shown in Tables 2 and 3. After adjustment for potential confounders and other independent variables it was shown that death was more likely in patients with lower APGAR score and weight on delivery, shorter period of hospitalization and use of mechanical ventilation support (Table 2). Although crude ORs for gestational age, surfactant therapy and the development of acute complications such as pneumothorax and pulmonary hemorrhage pointed out on an important association with death, after adjustment, their influence did not reach a level of statistical significance.

Table 2. Crude and adjusted odds ratios (OR) of the risk factors for death in neonates due to NRDS

Risk factors	**Univariate model Crude OR (95% CI)**	**Multivariate model Adjusted# OR (95% CI)**
Gestational age (weeks)	0.685 (0.609-0.771)	1.870 (0.942-3.715)
Type of birth (referent category vaginal delivery)	0.591 (0.275-1.272)	0.101 (0.009-1.181)
APGAR score	0.465 (0.369-0.584)	0.516 (0.322-0.827)
Weight on delivery (grams)	0.998 (0.998-0.999)	0.996 (0.993-0.999)
Duration of hospitalization (days)	0.830 (0.774-0.890)	0.901 (0.835-0.972)
Mechanical ventilation	105.000 (13.884-794.091)	165.256 (7.616-3585.714)
Duration of mechanical ventilation (days)	1.042 (1.004-1.081)	0.000 (0.000-/)
Oxygen therapy	1.795 (0.431-9.065)	0.000 (0.000-/)
Surfactant therapy	14.280 (5.989-34.049)	0.173 (0.009-3.299)
Pneumonia	0.000 (0.000-/)	0.000 (0.000-/)
Pneumothorax	3.710 (1.064-12.937)	0.863 (0.040-18.544)
Pulmonary hemorrhage	5.875 (1.253-27.552)	4.865 (0.232-102.024)
p – Statistical significance; CI – Confidence interval; * Statistically significant # Adjusted for gestational age, type of birth, APGAR score, weight on delivery, duration of hospitalization, mechanical ventilation and surfactant therapy.		

Table 3. Multivariate model quality characteristics

Parameter	**Value**	**df**	**p**
Cox & Snell R square	0.527	8	0.976
Nagelkerke R square	0.833		
Hosmer-Lemeshow Chi square	2.148		
df – Degrees of freedom; p – Statistical significance			

DISSCUSION

Our study identified higher gestational age, higher birth weight, higher APGAR score and longer duration of hospitalization as protective factors for death outcome in newborns with NRDS, while the use of mechanical ventilation increased the risk of death.

Respiratory distress syndrome is one of the most common causes of infant death worldwide. Incidence data vary from country to country, but it is common for incidence rates to be higher when gestational age is lower (1). In our study, of the 371 patients, 36 patients died, which makes about 10%. This result is consistent with the data provided by the World Health Organization and the European Neonatology Association (15-16).

The results of this study indicate a statistically significant difference in gestational age in children who suffered from respiratory distress syndrome in comparison with those who did not, which is consistent with previous studies and data obtained in the last extensive study in which the incidence ranged from 92% when the gestational age was around 24-25 weeks and gradually decreased to 57% at gestational age of 30-31 weeks (1, 17). It should also be noted that gestational age loses significance as a protective factor when viewed in combination with other observed factors. Possible cause of this phenomenon is that gestational age was not determined precisely in all pregnant women, as observed in other studies (12).

Higher APGAR score and longer hospitalization were identified as protective factors, like in other similar studies (18-20). In general, the APGAR score over 7 is associated with better survival. Duration of hospitalization ranges between 10 and 32 days, depending on a study sample (21-22). A longer stay in intensive care units and more frequent survival are associated with the fact that severe patients' fatal outcomes occur within 48 hours, while the patients with a milder clinical picture require longer treatment, and consequently there is much greater chance of survival. Average number of hospitalization days in our cases was 6.8±12.6.

Regarding decreased death rate in patients who were not treated by surfactants, care should be taken when drawing conclusions. It is important to note that the surfactant is administered in patients with the severe clinical picture who initially have greater likelihood of fatal outcome. Besides, studies examining possibilities of less invasive use of surfactants (via nasal cannula or aerosol), which would reduce the probability of lung injury, are underway, but none of these techniques entered routine clinical practice (23-25).

In most cases, mechanical ventilation is necessary to increase chances of survival of patients with respiratory distress syndrome. Although we had information about the number of days that a patient spent on mechanical ventilation, the details about characteristics of the procedure itself were not available (whether the pressure was positive or negative, what modality was used, what was the number of respirations, complications, etc.) (26-28), which makes explanation of the impact of mechanical ventilation on lethal outcome very difficult. Respiratory complications of respiratory distress syndrome occur either as a result of the primary respiratory disorder or more often as a result of therapy, and in most cases as a result of intubation and mechanical ventilation (1). The patients who developed pneumonia were treated by antibiotics (29-31), and those who experienced pneumothorax by surgical drainage. Pulmonary hemorrhage occurred only in a few cases, which is consistent with other studies. Treatment of pulmonary hemorrhage implied theuse of antifibrinolytics such as a tranexamic and aminocaproic acid (32-33). Other acute complications in this study were not monitored.

Evidence of a chronic complications of respiratory distress syndrome (34-37) was not found in the patients' files, although ophthalmologists (due to retinopathy) and child's neurologists (due to neurological disorders) were regularly consulted, which was in line with current treatment guidelines for respiratory distress syndrome (1). A possible reason why these complications were not observed was that the patient's follow-up period was too short, or that the data from the control visit were not available.

One of major limitations of this study was its retrospective nature, so certain details were missing for some patients and the data about follow-up after discharge were not available. Also, data concerning maternal health and course of pregnancy were not always adequately noted. Small number of cases is another important limitation, which decreased number of factors that could have been included in the regression model. In future research, more attention should be paid to acute complications not covered by this study and treatment procedures themselves. Besides, overall maternal health and occurrence of hypertension and diabetes in pregnancy should be taken into account. A prospective study should also be considered, which would reduce the amount of missing data in patients and enable identification of currently unknown risk factors.

CONCLUSION

In conclusion, higher gestational age, higher birth weight, higher APGAR score and longer duration of hospitalization are protective factors, while use of mechanical ventilation increases the risk of death. Postponing delivery as much as possible and conducting delivery in an institution with neonatal intensive care unit are crucial for ensuring survival of newborns with neonatal respiratory distress syndrome.

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