Clinical features of neonates treated in the intensive care unit for respiratory distress

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The aim of this study was to determine the indications for hospitalization, clinical features, and risk factors in neonates treated in the intensive care unit (ICU) for respiratory distress.

Patients who were treated in the neonatal intensive care unit (NICU) for respiratory distress between 1 January 2008 and 31 December 2008 were included in the study. The indications for hospitalization, duration of hospitalization, clinical features, risk factors, maternal age, number of pregnancies, duration of antibiotic treatment, and mortality rate were retrospectively obtained from hospital records and evaluated.

The medical records of 240 neonates treated in the ICU during a one-year period were evaluated. Of the neonates, 64.6% were boys, 20.4% were premature, and 71.7% were born by cesarean section. The most frequent indication for hospitalization was tachypnea of the newborn (76.7%). Meconium aspiration syndrome and respiratory distress syndrome were also among the frequent indications for admission to the NICU. Recognition of risk factors for respiratory distress in neonates is crucial for development of prevention and early treatment strategies, and correct timing of elective cesarean sections is important for reduction in morbidity and mortality.

Key words: neonatal intensive care unit, respiratory distress, risk factors, mortality.

Respiratory distress is observed in nearly 7% of newborns. Respiratory distress is caused by transient tachypnea of the newborn (TTN) in >40% of the cases[1]. Other causes of respiratory distress include respiratory distress syndrome (RDS), meconium aspiration syndrome (MAS), pneumonia, sepsis, pneumothorax, persistent pulmonary hypertension of the newborn (PPHN), and non-pulmonary causes (i.e. anemia, congenital heart disease, congenital malformations, medications, neurologic or metabolic abnormalities, and polycythemia)[1]. TTN is a benign condition that occurs due to the presence of residual fluid in the lung tissue after birth, and often improves spontaneously. Tachypnea appears in the newborn right after or within two hours after birth. Risk factors for TTN include maternal asthma, male gender, macrosomia, maternal diabetes, and birth by cesarean section (C/S)[1]. RDS, also called as "hyaline membrane disease," is the most frequent cause of respiratory distress in premature infants, especially neonates <28 weeks gestation[1]. The reason for respiratory distress in premature infants is lack of surfactant and inadequate development of the lungs. RDS is more common in boys and babies of diabetic mothers[1]. Compared to term infants, preterm infants are at increased risk for several complications, such as TTN, PPHN, respiratory failure, temperature instability, jaundice, hypoglycemia, and feeding difficulties[2,3]. MAS occurs in term and post-term infants. Although meconium is sterile, meconium aspiration is significant because it leads to local irritation and obstruction and creates a suitable environment for bacterial

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growth. MAS leads to respiratory distress immediately after birth[1].

Bacterial infections, such as pneumonia and sepsis, are also potential causes of respiratory distress. Prenatal screening and treatment for group B streptococcal infections have proven effective in the reduction of neonatal infections[1]. Management of neonatal respiratory distress includes treatment of causative disorders, in addition to general measures. An increase in oxygenation, surfactant treatment and use of antibiotics may be required, and oral nutrition may have to be postponed[1]. In infants born by elective C/S, presence of labor, and the timing of delivery significantly affect morbidity[4]. The aim of this study was to determine the clinical features, causes, risk factors, and mortality rate of infants treated in a neonatal intensive care unit (NICU) for respiratory distress.

Material and Methods

Patients who were treated in the NICU for respiratory distress between 1 January 2008 and 31 December 2008 were included in the study. Information regarding indications for hospitalization, duration of hospitalization, clinical features, risk factors, maternal age, number of pregnancies, and duration of antibiotic treatment was examined retrospectively from hospital records.

The Number Cruncher Statistical System (NCSS) 2007 and PASS 2008 statistical software (UT, USA) were used for the statistical analysis of data. For quantitative variables, in addition to descriptive statistical methods (mean and standard deviation), Student's t-test was used for the comparison of normally distributed parameters and the Mann-Whitney U test was used to compare non-normally distributed parameters. A chi-square test was used for comparison of qualitative variables. P values <0.05 were considered statistically significant.

Results

During a one-year period, 1772 live births were recorded in our hospital. Among 390 patients admitted to the ICU, 240 had respiratory distress.

Among the neonates treated for respiratory distress, 191 (79.6%) were delivered at term and 49 (20.4%) were premature. One hundred fifty-five neonates (64.6%) were boys and 85 (35.4%) were girls. One hundred seventy-two (71.7%) were born by C/S and 68 (28.3%) were born vaginally. The lowest birth weight was 950 g and the highest birth weight was 5000 g (mean, 3039±728.6 g). The mean duration of hospitalization in the ICU was 4.3±6.9 days (range, 1-49 days). TTN was the most frequent indication for hospitalization (76.7%), followed by MAS and RDS. The indications for hospitalization are summarized in Table I.

Among potential risk factors for neonatal respiratory distress, large-for-gestational age (LGA), small-for-gestational age (SGA) and cord knots were the most frequent. The distribution of risk factors is presented in Table II.

The mean maternal age was 28.0±4.7 years (range, 18-43 years) and the mean number of pregnancies was 2.3±1.3 (range, 1-8). At the time of hospitalization, hypoglycemia

Table I. Indications for Hospitalization in Patients Treated for Respiratory Distress

Diagnosis	n	(%)
Transient tachypnea of the newborn (TTN)	184	(76.7)
Meconium aspiration syndrome (MAS)	20	(8.3)
Respiratory distress syndrome (RDS)	15	(6.3)
Asphyxia	9	(3.8)
Sepsis	5	(2.1)
Pneumonia	4	(1.7)
Multiple congenital anomalies	1	(0.4)
Inborn metabolic disease	1	(0.4)
Aspiration pneumonia	1	(0.4)

Table II. Distribution of Potential Risk Factors for Respiratory Distress in the Neonates

Risk factor	n	(%)
Large-for-gestational age (LGA)	20	(8.3)
Entanglement of the umbilical cord	15	(6.3)
Small-for-gestational age (SGA)	9	(3.8)
Preeclampsia	8	(3.3)
Placental detachment	7	(2.9)
Diabetes	7	(2.9)
Twin newborn	6	(2.5)
Premature rupture of the membranes	3	(1.3)
Maternal infection	3	(1.3)
Prolonged labor	2	(0.8)
Maternal smoking	1	(0.4)

was present in 10 patients, elevated aspartate aminotransferase (AST) + alanine aminotransferase (ALT) levels in 7 patients, hypocalcaemia in 4 patients, anemia in 3 patients, thrombocytopenia in 1 patient, and hyperglycemia in 1 patient. Other laboratory and clinical features of the patients are presented in Table III.

Patients were grouped according to the duration of tachypnea (<72 hours or ≥72 hours), and a comparison of these groups in terms of clinical characteristics is summarized in Table IV.

The birth weight of infants with tachypnea ≥72 hours of duration was significantly higher than of those with tachypnea <72 hours of duration (p=0.001; Fig. 1).

No statistically significant difference was noted between the two groups in terms of mean breaths per minute (p=0.177). While the duration of tachypnea was not significantly correlated with type of birth, gender or presence of prenatal risk (p=0.523, p=0.561, and p=0.171, respectively), there was a significant correlation between the duration of tachypnea and pregnancy (p=0.002). The rate of tachypnea >72 hours of duration was significantly higher in preterm newborns compared to term newborns.

Transient tachypnea of the newborn was present in 75.3% of the boys and 73.5% of the girls. There was no statistically significant correlation between gender and the presence of TTN (p=0.768).

Transient tachypnea of the newborn was present in 80.2% of those born by C/S, and in 58.8% of those who were born vaginally. The rate of TTN was significantly higher in those born by C/S compared to vaginal deliveries (p=0.001).

The mean duration of hospitalization in the ICU was 10.17±11.24 days in SGA infants (n=46), and 2.75±1.80 days in LGA infants (n=20); the difference was highly significant (p=0.001). The mean duration of oxygen administration was 6.35±6.42 days in SGA infants and 2.50±1.63 days in LGA infants,

Table III. Laboratory and Clinical Features

Feature	Mean±SD
Blood pH	7.18±0.91
pCO_2 (mmHg)	52.4±8.1
Breaths per minute	71.5±11.9
Beats per minute (BPM)	127.0±10.9
Tachypnea duration (days)	2.8±4.2

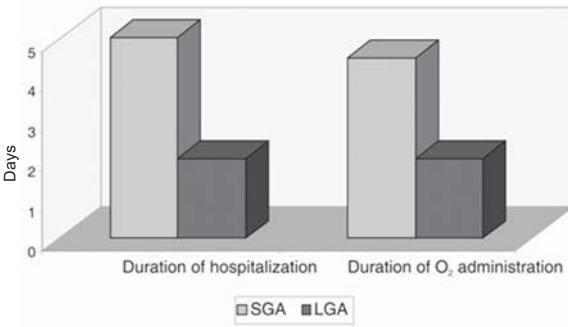

Fig. 1. Duration of hospitalization and duration of O_2 administration in small- (SGA) and large-for-gestational age (LGA) newborns.

and the difference was highly significant (p=0.005; Fig. 1).

The mean time to start nutrition was significantly higher in the term delivery group (27.13±28.49 hours) than the preterm group (47.48±40.10 hours; p=0.001). The duration of antibiotic administration was significantly longer in preterm infants compared to term infants (p=0.042; Fig. 2).

There was no significant difference between infants with or without MAS in terms of time to start nutrition and duration of antibiotic administration (p=0.747 and p=0.115, respectively; Table V).

Echocardiography was performed in 19 patients (7.9%) with respiratory distress who had murmurs and persistent tachypnea despite treatment. Patent ductus arteriosus (PDA) and atrial septal defect (ASD) were noted in 6 patients, PDA in 5 patients, hypertrophic cardiomyopathy in 4 patients, aortic failure in 2 patients, ASD in 1 patient, and aortic coarctation in 1 patient. PDA was closed by indomethacin in 3 patients and by ibuprofen in 8 of 11 patients with PDA.

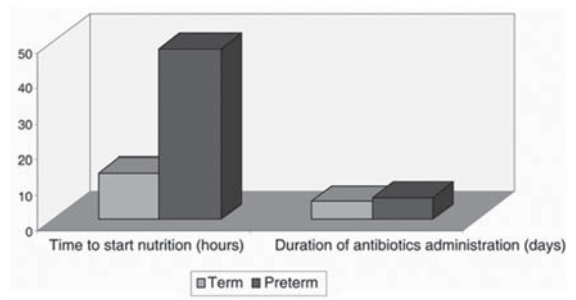

Fig. 2. Time to start nutrition and duration of antibiotic administration according to time of birth.

Oxygen treatment was administered by hood in 144 patients (60%), nasal continuous positive airway pressure (CPAP) in 73 patients (30.4%), synchronized intermittent mandatory ventilation (*SIMV*) in 18 patients (7.5%), and as nasal O_2 in 5 patients (2%). Pneumothorax developed in 1 patient. Antibiotic treatment was initiated in 210 patients according to clinical and posteroanterior chest X-ray findings. The mean duration of antibiotic administration was 5.8±2.4 days (range, 3-18 days). One patient died due to asphyxia, 1 due to congenital heart disease, and 1 due to multiple congenital anomalies. The mortality rate in neonates treated in the ICU due to respiratory distress was 1.2%.

Discussion

Approximately two-thirds of the deaths during the first year of life occur in the neonatal period, and 98% of neonatal deaths occur in developing countries. The leading causes of neonatal deaths include infections, birth asphyxia, injuries, consequences of prematurity, low birth weight, and congenital anomalies[5]. Determining causes and risk factors for neonatal deaths is essential for planning prevention strategies and reducing mortality.

Respiratory distress due to medical or surgical reasons is common in the neonatal period and is among the most frequent indications for hospitalizations in ICUs[6]. TTN, RDS, pulmonary air leaks, and pneumothoraces are the major medical causes of respiratory distress. Surgical causes of respiratory distress include airway obstruction, various congenital anomalies and disorders that lead to pulmonary collapse or displacement and parenchymal disease or insufficiency[6]. Although the mortality rate is low in TTN, it is associated with an increased economic burden because it requires hospitalization of the infant in intensive care, detachment from the mother, numerous differential diagnostic interventions, and longer duration of hospital stay[4].

Several causes of respiratory distress in neonates have been reported. Agrawal et al.[7] evaluated 2824 births prospectively in order to determine the prevalence of respiratory disorders. One or more respiratory symptoms were noted in the first day of life in 21% of the

Table IV. Patient Characteristics According to Duration of Tachypnea

	Tachypnea Duration		
	<72 hours (n=151)	≥72 hours (n=87)	
	Mean±SD	Mean±SD	[a]p
Birth weight (g)	3185.03±589.76	2787.46±871.50	[b]0.001
Breaths per minute	70.87±11.84	73.03±11.85	0.177
	n (%)	n (%)	[c]p
Type of birth			
C/S	110 (64.7)	60 (35.3)	0.523
NSD	41 (60.3)	27 (39.7)	
Gender			
Girl	56 (65.9)	29 (34.1)	0.561
Boy	95 (62.1)	58 (37.9)	
Pregnancy duration			
Term	124 (68.9)	56 (31.1)	[b]0.002
Preterm	27 (46.6)	31 (53.4)	
Prenatal risk			
Present	30 (55.6)	24 (44.4)	0.171
Absent	121 (65.8)	63 (34.2)	

C/S: Cesarean section. NSD: Normal spontaneous delivery. *[a]Student t test, [b]Chi-square test, [c]p<0.01*

infants, and 400 infants were admitted to the ICU in that study. They evaluated respiratory symptoms according to classic criteria and reported that RDS was most frequent, followed by TTN, MAS, pneumonia, and other reasons. The risk for RDS is increased with decreasing gestational age. Maternal diabetes, race, male gender, asphyxia, and sepsis increase RDS risk. The possibility of developing RDS is about 60% in infants born before 29 weeks[8]. Although MAS occurs less and less frequently, it is still among the major causes of morbidity in term infants[8]. Mathur et al.[9] evaluated all neonates with respiratory symptoms and found that the most frequent cause of respiratory distress was neonatal pneumonia (68.6%). Hyaline membrane disease (HMD), TTN, birth asphyxia with hypoxic ischemic encephalopathy (HIE), and MAS were reported among other causes.

We found that the most frequent cause of hospitalization in the ICU for respiratory distress was TTN (76.7%), followed by MAS and RDS.

We found that the mean duration of hospitalization in the ICU for respiratory distress was 4.3±6.9 days (range, 1-49 days). Riskin et al.[10] reported the mean duration of hospitalization in neonates due to TTN to be 7.2±5.6 days.

In the current study, the mortality rate in neonates treated in the ICU for respiratory distress was 1.2%. Agrawal et al.[7] reported the five-day mortality rate in 400 infants admitted to the neonatal ICU for respiratory distress as 3.2%.

Identification of risk factors for respiratory distress is crucial for timely prevention and early treatment. Risk factors for respiratory distress reported in previous studies include male gender, preterm birth, C/S, young gestational age, macrosomia, assisted birth, and low Apgar score. The risk factors for TTN, which is one of the most frequent causes of respiratory distress, have been reported as C/S, male gender, family history of asthma (especially maternal), maternal diabetes, lower gestational age, and macrosomia[4]. Riskin et al.[10] compared 67 infants with TTN and controls all born at ≥35 weeks gestation, and found that the rate was higher in the TTN group

Table V. Time to Start Nutrition and Duration of Antibiotic Administration According to the Presence of MAS

	Meconium aspiration syndrome (MAS)				
	Present		Absent		
	n	Mean±SD (Median)	n	Mean±SD (Median)	[a]p
Time to start nutrition (hours)	16	37.62±40.09 (12)	217	31.61±32.22 (15)	0.747
Duration of antibiotic administration (days)	9	5.89±1.05 (5)	123	5.53±2.30 (5)	0.115

[a] Mann-Whitney U test

compared to controls (50.7% vs. 22.4%). C/S and young gestational age were determined to be risk factors for TTN. TTN was associated with a longer hospital length of stay. In a controlled study evaluating 100 TTN cases, Rawlings and Smith[11] found that male gender, macrosomia, prolonged labor interval, and requirement of C/S after labor was initiated were major risk factors. Takaya et al.[12] reported risk factors associated with TTN in infants born ≥37 weeks by vaginal delivery as nulliparity, history of infertility treatment, assisted birth, use of vacuum or forceps, and Apgar score <7. Levine et al.[13] evaluated 29,669 births within 7 years and found that the incidence of PPHN was 0.37% for elective C/S and 0.08% for vaginal delivery. In infants treated in the ICU due to respiratory distress, Agrawal et al.[7] reported that 55% were boys, the mean weight was 2613 g, the mean gestational age was 36 weeks, 63% of the births were natural spontaneous delivery (NSD), 19% were assisted vaginal delivery (forceps or vacuum), and 18% were C/S.

Most of the infants in our study were boys (64.6%) and the C/S rate was 71.7%. The mean birth weight was 3039 g and 20.4% were premature. LGA and cord knots were the most frequent risk factors for respiratory distress.

Tachypnea in TTN often resolves within 72 hours in most cases; however, tachypnea may also persist for a long period of time in some. When groups with a duration of tachypnea ≤72 hours were compared, the duration of tachypnea was significantly longer in infants with low birth weight and those who were preterm. Kasap et al.[14] retrospectively determined the predictive factors for prolonged tachypnea (>72 hours) in TTN in 95 cases. Male gender, prematurity and C/S were noted as risk factors. In the same study, prolonged TTN was associated with a lower white blood cell count and hematocrit values, longer hospitalization and antibiotic treatment.

Cardiovascular disorders may also cause respiratory distress. Respiratory symptoms, such as dyspnea and tachypnea, have been reported to be common in neonates with congenital heart disease[15]. Echocardiography is recommended to exclude congenital heart diseases, especially when prolonged tachypnea duration (>5 days) is present[4]. We found in our study that congenital heart disease was noted by echocardiography in 19 patients (7.9%) who had murmurs and persistent tachypnea despite treatment. Risk factors should be noted in neonates with respiratory distress, and cardiac causes should also be considered in cases with persistent tachypnea unresponsive to therapy. We recommend cardiologic consultation in cases of unexplained tachypnea and the presence of murmurs.

Elective C/S is one of the significant causes of increased respiratory distress in post-term and term neonates. The rate of C/S was quite high (71.6%) in our study. The proportion of elective C/S deliveries is reported to have increased by approximately 43.6% in recent years (19.7% in 1994 and 28.3% in 2001) [16]. Infants with a gestational age <35 weeks and those weighing <2300 g should be closely monitored to reduce morbidity and mortality[2]. While the incidence of respiratory morbidity in infants delivered by C/S before the onset of labor is 35.5 per 1000, the incidence is 12.2 per 1000 in those delivered by C/S during labor. Morbidity is around 5.3 per 1000 in vaginal deliveries[4]. Not performing an elective C/S before 38 weeks is a preventive measure to reduce the risk for TTN. It has been estimated that approximately 2.5-18% of all live births

are performed by C/S in accordance with the mother's preference[2]. Since a history of C/S is an indication for C/S for following deliveries, a decision for elective C/S should be made more selectively.

In conclusion, respiratory distress is the most frequent cause of hospitalization in the ICU in neonates, and TTN, which is its most frequent cause, often resolves spontaneously and is associated with high morbidity and cost. Recognition of risk factors and attention to correct timing of elective C/S are crucial for reducing morbidity and economic burden.

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