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Risk factors for noninvasive ventilation failure in preterm infants at less than 30 weeks of gestation with respiratory distress syndrome

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ABSTRACT

This study aimed to identify risk factors for noninvasive ventilation (NIV) failure in <30 weeks' gestation preterm neonates and compare morbidity in patients with and without NIV failure. This study included preterm neonates <30 weeks' gestation who received NIV support for respiratory distress syndrome (RDS). Demographic and clinical characteristics were compared between infants with and without NIV failure within the first 72 hours after birth. Of 443 preterm neonates, NIV failure occurred in 101 (22.8%). Of these, initial respiratory support was nasal continuous positive airway pressure (nCPAP) in 76 infants (75.2%) and nasal intermittent positive pressure ventilation (NIPPV) or bilevel positive airway pressure (BiPAP) in 25 infants (24.8%). Gestational age, birth weight, and antenatal steroid exposure were significantly lower in patients with NIV failure. Grade III-IV intraventricular hemorrhage, moderate/severe bronchopulmonary dysplasia, and retinopathy of prematurity requiring laser photocoagulation were significantly more common in the NIV failure group. Multivariate logistic regression analysis showed that antenatal steroid therapy reduced NIV failure [odds ratio (OR): 0.53, 95% confidence interval (CI): 0.29–0.94; $P = .03$], while nCPAP (OR: 2.61, 95% CI: 1.53–4.48; $P < .001$), surfactant requirement (OR: 2.40, 95% CI: 1.36–4.25; $P = .003$), and ≥2 doses of surfactant need (OR: 3.57, 95% CI: 1.89–6.74; $P < .001$) were associated with greater NIV failure. The results of this study indicated that administering antenatal steroids and using NIPPV or BiPAP instead of nCPAP as initial respiratory support reduced the likelihood of NIV failure in preterm infants with RDS.

KEYWORDS: BiPAP; noninvasive ventilation failure; nCPAP; NIPPV; prematurity; respiratory distress syndrome

INTRODUCTION

There is considerable evidence supporting the use of noninvasive ventilation (NIV) as the first option for very low birth weight (VLBW) preterm infants with respiratory distress syndrome (RDS). NIV provided immediately after birth reduces ventilator-associated lung injury and bronchopulmonary dysplasia (BPD) in preterm infants with RDS [1]. Inappropriate postnatal respiratory support leads to pulmonary injury in preterm neonates [2].

Nasal continuous positive airway pressure (nCPAP) was first used in 1968 to maintain airway patency, prevent atelectasis, and support preterm infants' weak respiratory muscles. Nasal intermittent positive pressure ventilation (NIPPV), bilevel positive airway pressure (BiPAP), and nasal high-flow oxygen therapy have been used instead of nCPAP to reduce the need for mechanical ventilation in preterm infants with recurrent apnea. Subsequent studies have presented the different

effects of these NIV methods in various diseases and their outcomes in preterm infants [3].

Interventions such as antenatal steroid prophylaxis, early nCPAP in the delivery room and for early respiratory support, and providing surfactant in the early phase of RDS have reduced the need for mechanical ventilation in neonatal RDS [4]. Early detection of NIV failure prevents delay of surfactant therapy, decreases pulmonary damage, and leads to better outcomes [5]. This reduces length of hospital stay and hospital costs, which is particularly important for low-middle income countries. As length of hospital stay of patients with BPD increases, need for hospital staff to care for these patients also increases, which creates additional costs for low- and middle-income countries. In addition, these patients are more likely to be rehospitalized after discharge compared to other patients, which is an issue that should be evaluated in terms of cost.

The aim of this study was to determine the risk factors for NIV failure in preterm neonates <30 weeks of gestational age and compare morbidity in those with and without NIV failure.

METHODS

This retrospective study included preterm infants <30 weeks of gestational age who received noninvasive respiratory support for RDS.

Inclusion criteria were: having signs of respiratory distress (wheezing, tachypnea, retraction, nasal wing respiration, and cyanosis), not requiring intubation in the delivery room, and receiving nCPAP, BiPAP, or NIPPV as initial respiratory support in the neonatal intensive care unit (NICU). Exclusion criteria were: having any major congenital abnormalities or perinatal asphyxia and being intubated in the delivery room. All infants were stabilized with nCPAP (Neopuff; Fisher and Paykel, Auckland, New Zealand) in the delivery room and during transfer to the NICU and were admitted to the NICU with nCPAP. The initial NIV mode was decided by the attending NICU physician. Infants receiving nCPAP respiratory support who were switched to BiPAP or NIPPV within 72 hours were also excluded from the study. NIV failure was defined as the need for intubation while receiving NIV within the first 72 hours postnatally.

Surfactant was administered as rescue therapy if 30% fraction of inspired oxygen (FiO_2) was needed to maintain a target oxygen saturation (SpO_2) level of 90%–95%. The first dose of surfactant was 200 mg/kg porcant alfa (Curosurf, Chiesi, Parma, Italy) delivered using the less invasive surfactant administration (LISA) method. Ventilation support remained unchanged during the LISA procedure. If 30% FiO_2 was still needed to maintain target saturation, additional surfactant doses of 100 mg/kg were administered [6]. Prophylactic caffeine was initiated in all infants within the first day.

Nasal CPAP support was provided using infant flow-driver device (Infant Flow System, Viasys Corp., Yorba Linda, CA, USA) with short binasal prongs (INCA, Ackrad Labs/Cooper Surgical, Trumbull, Connecticut, USA and Care Fusion, Yorba Linda, USA). Positive end-expiratory pressure (PEEP) was adjusted to 5–6 cmH_2O. nCPAP was discontinued when PEEP was 5 cmH_2O, FiO_2 was <30%, and the infant showed no signs of respiratory distress.

BiPAP support was also provided using an infant flow-driver device (Infant Flow System, Viasys Corp.) and short binasal prongs (Carefusion, Yorba Linda, USA) as the interface. Initial lower and upper pressures were set to 5–6 cmH_2O and 8–9 cmH_2O (max: 11 cmH_2O), inspiration time was set to 0.7–1 second, and respiratory rate was set to 15–30/minute. Respiratory settings were adjusted to keep blood gas parameters within normal ranges. Weaning started when the lower pressure was 5 cmH_2O, upper pressure was 6 cmH_2O, and respiratory rate was <20/min. BiPAP was discontinued if FiO_2 was <30% and the infant showed no signs of respiratory distress.

NIPPV support was provided in non-synchronous mode using a neonatal ventilator (SLE) and short binasal prongs (INCA). Ventilator parameters were set to PEEP: 5–6 cmH_2O, peak inspiratory pressure (PIP): 15–20 cmH_2O, inspiration time: < 0.3–0.4 s, and respiratory rate: 30–40/min. Respiratory settings (PIP max. 25 cmH_2O, PEEP max. 7 cmH_2O, respiratory rate: 60/min). NIPPV was terminated when infants with no signs of respiratory success had PIP: 10–15 cmH_2O, PEEP: 5 cmH_2O, respiratory rate: 15/min, and FiO_2 <30%.

All three methods were adjusted to the lowest FiO_2 necessary to maintain 90%–95% SpO_2.

NIV failure was defined as the recurrence of one or more of the following criteria: hypoxemia (FiO_2 requirement >50% to achieve target SpO_2), respiratory acidosis (pH < 7.2 and carbon dioxide pressure [pCO_2] > 65 mmHg), and recurrent apneas [7]. In addition, the development of pneumothorax was classified as NIV failure.

The infants' oxygen requirement was evaluated on postnatal day 28, at 36 weeks of postmenstrual age, and at discharge. BPD was defined using the National Institutes of Health classification published by Jobe and Bancalari [8]. RDS was diagnosed according to clinical signs and direct chest X-ray findings [9]. Cranial ultrasound was performed on postnatal days 1, 3, and 7, and patients with signs of intraventricular hemorrhage

(IVH) were followed with weekly cranial ultrasound examinations. IVH was graded according to the Papile classification [10]. Patent ductus arteriosus was diagnosed according to echocardiography performed at postnatal 24–72 hours (left atrium/aortic root ratio ≥ 1.5 and/or ductus diameter ≥ 1.5 mm) [11] and treated with ibuprofen or paracetamol and surgical ductal ligation if medical treatment was ineffective or contraindicated. Retinopathy of prematurity (ROP) was graded according to the International Classification of Retinopathy of Prematurity after examination by an ophthalmologist [12]. Clinical sepsis was diagnosed in the presence of clinical and laboratory criteria. Cases diagnosed within the first 72 hours after birth were classified as early neonatal sepsis [13]. Ethics committee approval was obtained for this study (24-2018).

Statistical analysis

The data were analyzed using SPSS® for Windows version 22 software (IBM Corp, Armonk, NY). Chi-square test was used for comparisons of categorical variables. Continuous data were summarized as mean and standard deviation and compared using Student's *t* test. $P < .05$ was accepted as statistically significant. Multivariate analysis was used to identify factors associated with NIV failure.

RESULTS

The study included data from a total of 443 infants, 101 (22.8%) of which had NIV failure. The mean (±SD) gestational age was 28.2 ± 1.1 weeks in the NIV success group ($n = 342$) and 27.9 ± 1.2 weeks in the NIV failure group ($n = 101$) ($P < .05$). 21.8% of the patients were in NIPPV group and 22.7% were in BiPAP group. The mean birth weight in these groups was 1103 ± 205 and 1044 ± 220 g, respectively ($P < .05$). Antenatal steroid administration was more common in the NIV success group compared to the other group ($P < .05$) (Table 1). The infants' general characteristics are shown in Table 1.

In the NIV failure group, initial respiratory support was nCPAP in 76 patients (75.2%) and NIPPV or BiPAP in 25 patients (24.8%) ($P < .001$). Infants with NIV failure had higher frequency of surfactant requirement, need for repeated surfactant therapy (≥2 doses), ROP requiring laser treatment, mortality ($P < .001$ for all), IVH grade ≥2, and moderate to severe BPD ($P < .05$) when compared with the NIV success group. In contrast, the rate of survival without BPD at 36 weeks of postmenstrual age was significantly higher in the NIV success group ($P < .001$) (Table 2).

Table 1. Demographic characteristics of the study groups

	NIV failure ($n = 101$)	NIV success ($n = 342$)	*P*
Gestational age (weeks)[a]	27.9 ± 1.2	28.2 ± 1.1	.049
Birth weight (g)[a]	1044 ± 220	1103 ± 205	.019
Male sex, *n* (%)	47(46.5)	169 (49.4)	.61
Caesarean delivery, *n* (%)	87(86.1)	284 (83)	.45
PPROM, *n* (%)	14(13.9)	68(19.9)	.17
Preeclampsia, *n* (%)	27(26.7)	65(19)	.09
Multiple birth, *n* (%)	16 (15.8)	82 (24)	.08
Apgar score at 5 min[b]	8 (7–8)	8(7–8)	.06
Antenatal steroid, *n* (%)	73 (72.3)	281 (82.2)	.02

[a] Mean ± standard deviation.
[b] Median and interquartile range (25th–75th percentile).
NIV, noninvasive ventilation; PPROM, preterm premature rupture of membranes.

Table 2. Clinical characteristics of the study groups

	NIV failure ($n = 101$)	NIV success ($n = 342$)	*P*
Required surfactant, *n* (%)	74 (73.3)	134 (39.2)	<.001
Required ≥2 doses of surfactant, *n* (%)	37 (36.6)	31 (9.1)	<.001
ENS, *n* (%)	20 (19.8)	51 (14.9)	.23
PDA requiring medical treatment, *n* (%)	35 (34.7)	97 (28.4)	.22
IVH >grade II, *n* (%)	10 (9.9)	15 (4.4)	.03
BPD, moderate-severe, *n* (%)	18 (17.8)	26 (7.6)	.003
ROP requiring laser treatment, *n* (%)	13 (16.5)	12 (3.7)	<.001
Death, *n* (%)	25 (24.8)	19 (5.6)	<.001
Survival without BPD at 36 weeks PMA, *n* (%)	59 (58.4)	296 (86.5)	<.001

BPD, bronchopulmonary dysplasia; ENS, early neonatal sepsis; IVH, intraventricular hemorrhage; NIV, noninvasive ventilation; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; PMA, postmenstrual age.

In the multivariate logistic regression analysis, it was determined that antenatal steroid exposure reduced NIV failure [odds ratio (OR): 0.53, 95% confidence interval (CI): 0.29–0.94; $P = .03$], while nCPAP as initial respiratory support (OR: 2.61, 95% CI: 1.53–4.48; $P < .001$), surfactant requirement (OR: 2.40, 95% CI: 1.36–4.25; $P = .003$), and ≥2 doses of surfactant need (OR: 3.57, 95% CI: 1.89–6.74; $P < .001$) were associated with greater NIV failure (Table 3).

DISCUSSION

The results of this study showed that antenatal steroid therapy and initial respiratory support with NIPPV or

Table 3. Independent risk factors for NIV failure

	Relative risk	95% CI	*P*
Using nCPAP as primary respiratory support	2.61	1.53–4.48	<.001
Surfactant requirement	2.40	1.36–4.25	.003
Required ≥ 2 doses of surfactant	3.57	1.89–6.74	<.001
Antenatal steroid	0.53	0.29–0.94	.03

nCPAP, nasal continuous positive airway pressure; NIV, noninvasive ventilation.

BiPAP instead of nCPAP were associated with a lower likelihood of NIV failure in preterm patients with RDS.

The use of NIV techniques in preterm infants with RDS in recent years has reduced both the need for invasive mechanical ventilation and its adverse pulmonary outcomes [4]. Our study evaluated the results obtained with three NIV modes used to provide respiratory support in preterm infants <30 weeks of gestational age with RDS.

nCPAP creates a constant pressure in the upper airways via the interface during the infant's respiratory cycle. The increased nasopharyngeal pressure and diaphragmatic activity reduces apnea frequency, improves ventilation-perfusion, and increases functional residual capacity [3, 14]. In contrast, NIPPV provides respiratory support via the interface by adding intermittent positive pressure breaths to the basal PEEP in addition to the set respiratory rate, inspiration time, and PIP. Intermittent positive pressure corrects nasopharyngeal inflation, increases tidal volume and lower airway pressure, and facilitates alveolar recovery. These effects lead to greater carbon dioxide elimination and fewer apnea episodes. BiPAP is a form of NIPPV. BiPAP delivers two different pressures, a higher inspiratory pressure and lower expiratory pressure, whereas NIPPV involves a high pressure delivered at set intervals [3]. Although nCPAP is frequently used for NIV support in RDS, it does not fully correct ventilation in preterm patients with inadequate respiratory effort and results in failure in 30%–50% of cases. For this reason, different NIV techniques such as NIPPV/BiPAP are recommended to enhance respiratory support [4].

In a multicenter study evaluating factors associated with nCPAP failure in 131 neonates <30 weeks of gestational age, significant factors in nCPAP failure within the first 72 hours of life (20.6%) included the presence of RDS (51.8%), low gestational age and low birth weight, and male sex [2]. Of the 101 infants (22.8%) with NIV failure in our study, 76 (75.2%) received nCPAP. Although NIV failure was not associated with male sex in our study, it was more common among infants with lower gestational age and birth weight, similar to the cited study. Furthermore, we also found that NIV failure was more frequent in infants that needed surfactant. These two comparable results can be explained by the low gestational age and birth weight in both studies.

Fuchs *et al.* reported low success in the stabilization of immature neonates in the delivery room with nCPAP. They stated that prolonged nCPAP treatment should be terminated through the early detection and intubation of neonates with nCPAP failure. They also emphasized the potential serious negative consequences of delaying surfactant treatment for infants with nCPAP failure [15]. In another study, higher rates of mortality and BPD were detected as gestational age decreased in the group with nCPAP failure [16].

In a retrospective multicenter study, 191 VLBW preterm infants (gestational age <32 weeks, birth weight <1500 g) with RDS were treated with three different NIV methods, similar to our study. NIV failure was defined as failure within the first 5 days and occurred at an overall rate of 23% ($n = 44$). Failure was more frequent with nCPAP (22/66, 33%) than with synchronized NIPPV (11/62, 17.7%) and BiPAP (11/63, 17.5%) ($P < .05$). Therefore, the authors concluded that BiPAP and synchronized NIPPV increased the efficacy of nCPAP in the treatment of RDS and reduced the risk of failure. It was emphasized that using synchronized or non-synchronized NIPPV and BiPAP provided better results than nCPAP [4]. In our study, successful results were obtained despite using non-synchronized NIPPV and BiPAP. The rates of moderate/severe BPD, IVH, and ROP were found to be higher in the NIV failure group in this study, whereas the authors of the aforementioned study observed no difference in these morbidities between the three groups. We identified surfactant need as an independent risk factor for NIV failure, while early neonatal sepsis, hypoxia-hypercapnia, and necrotizing enterocolitis were found to be the main causes of NIV failure in the three groups in the aforementioned study. We attribute this difference in results to the lower gestational age and birth weight in our patient group.

Handoka *et al.* provided synchronized NIPPV to 85 VLBW preterm infants (gestational age <32 weeks, birth weight <1500 g) with RDS and reported failure in 14.1% of the patients. The group with failure had lower gestational age and birth weight and more severe RDS ($P < .001$), while the successful group had higher rates of antenatal steroid exposure and 5-minute

APGAR scores ($P < .001$) [1]. In our study, there was no difference in APGAR scores between neonates with and without NIV failure. Moreover, although gestational age and birth weight were found to differ between the two groups, they were not identified as risk factors in multivariate logistic regression analysis, as in our study. Their multivariate logistic regression analysis indicated that antenatal steroids and RDS stage were more significant in predicting NIV failure [1]. Kishore *et al.* also recommended NIPPV as the first choice for the management of RDS in preterm infants at gestational ages of 28–30 weeks because it reduces the need for intubation and mechanical ventilation [17].

In patients with nCPAP failure, the first surfactant treatment is delayed to ∼2 hours after birth. Late surfactant delivery is less effective in alleviating respiratory distress than early rescue therapy (<2 hours postpartum). Therefore, early detection of nCPAP failure (within the first 2 hours) will prevent delayed administration of surfactant therapy and improve outcomes. In a study by De Jaegere *et al.* including 182 infants <30 weeks of gestational age, 34% had nCPAP failure and 94% of those infants received surfactant, and rates of mortality and BPD were higher in the nCPAP failure group [18]. In our study, surfactant and repeated surfactant requirement, BPD, and mortality rates were higher in the NIV failure group compared to the other group. Neonatal morbidities increase and length of hospital stay is prolonged in preterm infants with nCPAP failure [19].

Strengths of our study are that we compared three NIV modes and included a large number of neonates, many of whom were low gestational age. Limitations of our study are that it was a single-center retrospective study and NIV support was determined by the attending physician.

In conclusion, the results of our study demonstrate that antenatal steroid therapy and NIPPV or BiPAP as initial respiratory support reduces NIV failure in preterm neonates with RDS. Using NIV techniques in preterm infants with RDS reduces both the need for invasive mechanical ventilation and its adverse pulmonary outcomes. Providing close follow-up and antenatal steroid therapy for pregnant women at risk of preterm delivery and selecting effective NIV support will further reduce NIV failure and prevent morbidities of prematurity. This reduces length of hospital stay and hospital costs, which is particularly important for low-middle income countries. As length of hospital stay of patients with BPD increases, need for hospital staff to care for these patients also increases, which creates additional costs for low- and middle-income countries. In addition, these patients are more likely to be rehospitalized after discharge compared to other patients, which is an issue that should be evaluated in terms of cost. This prolonged process can be prevented even with antenatal steroid treatment, which is a much less costly treatment.

AUTHOR CONTRIBUTIONS

Aybuke Yazici (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Software [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—original draft [equal], Writing—review & editing [equal]), Mehmet Buyuktiryaki (Data curation [equal], Formal analysis [equal]), Fatma Nur Sari (Data curation [equal], Formal analysis [equal]), and Evrim Alyamac Dizdar (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Funding acquisition [equal], Investigation [equal], Methodology [equal], Project administration [equal], Resources [equal], Software [equal], Supervision [equal], Validation [equal], Visualization [equal], Writing—original draft [equal], Writing—review & editing [equal])

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