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Comparing the Efficacy of Nasal Continuous Positive Airway Pressure and Nasal Intermittent Positive Pressure Ventilation in Early Management of Respiratory Distress Syndrome in Preterm Infants

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ABSTRACT

Objectives: There is a tendency to use noninvasive ventilation (NIV) as a substitute for mechanical ventilation in preterm infants who need respiratory support. Two important modes of NIV include nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive pressure ventilation (NIPPV). We sought to compare the efficacy of NCPAP and NIPPV as early respiratory support in preterm infants with respiratory distress syndrome in reducing the need for intubation, surfactant administration, and mechanical ventilation. ***Methods***: We conducted a randomized clinical trial. Sixty-one preterm infants with a gestational age of 28–32 weeks and a birth weight < 1500 g were randomly allocated to early NCPAP (n = 31) or NIPPV (n = 30) groups. The primary outcome was the need for intubation and mechanical ventilation in first 72 hours of life and the secondary outcome was oxygen dependency beyond day 28 post-birth. ***Results:*** Surfactant replacement therapy was done in 15 neonates (50.0%) in the NIPPV group and 19 neonates (61.3%) in the NCPAP group, odds ratio (OR) = 1.58 (95% confidence interval (CI): 0.57–4.37; $p = 0.370$). Intubation and mechanical ventilation in the first 72 hours of life were needed in five cases (16.7%) in the NIPPV group and two cases (6.5%) in the NCPAP group, OR = 2.90 (95% CI: 0.51–16.27; $p = 0.250$). The mean duration of hospitalization was 26.2±17.4 days in the NIPPV group and 38.4±19.2 days in the NCPAP group, $p = 0.009$. Bronchopulmonary dysplasia (BPD) occurred in two (6.7%) neonates in the NIPPV group and eight (25.8%) neonates in the NCPAP group, $p = 0.080$. ***Conclusions:*** NIPPV and NCPAP are similarly effective as initial respiratory support in preterm infants in reducing the need for mechanical ventilation and occurrence of BPD. The duration of hospitalization was significantly reduced using NIPPV in our study.

Respiratory distress syndrome (RDS) is a common problem in preterm infants. Advances in the management of RDS result in improved survival of very low birth weight infants.[1] Surfactant replacement therapy plays an important role in RDS management.[2] Initiation of nasal continuous positive airway pressure (NCPAP) from birth with early surfactant therapy in preterm infants with signs of RDS is recommended with the aim of avoiding mechanical ventilation using an endotracheal tube.[3] Since the airway of preterm infants has poor muscle tone with compliant structure, NCPAP opens it with less apnea and atelectasia.[4] Prolonged intubation and mechanical ventilation may be associated with bronchopulmonary dysplasia (BPD) because of barotrauma, volutrauma, and oxygen toxicity.[5]

Noninvasive ventilation (NIV) is considered the optimal method and a substitute for mechanical ventilation as it is less injurious to the lungs.[6–8] NIV includes various types of ventilation such as nasal intermittent positive pressure ventilation (NIPPV), NCPAP provided through soft nasal prongs or masks, and humidified oxygen delivered by high flow nasal cannula. NIPPV is a safe mode of NIV.[9] NIPPV in comparison with NCPAP appears

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to enhance the success rate of extubation from mechanical ventilation.[10–12] It is more effective than NCPAP in apnea of prematurity.[13] We hypothesized that the early use of NIPPV after birth reduces the need for surfactant replacement therapy and lowers the rate of intubation, mechanical ventilation, and BPD. However, there are a few studies that compared these two NIV methods as primary respiratory support after birth.[14–16] This study was conducted to compare two methods of NIV (NCPAP vs. NIPPV) as primary respiratory support in the management of RDS and its effect on the need for endotracheal intubation, surfactant replacement therapy, and mechanical ventilation.

METHODS

We conducted a randomized clinical trial of 61 inborn preterm infants admitted to the neonatal intensive care unit (NICU) in Al Zahra Hospital, a referral tertiary hospital, in Northwest Iran. Preterm infants with gestational age of 28–32 weeks and birth weight 1000–1500 g were eligible for inclusion in the study. The study was approved by the ethics committee of Tabriz University of Medical Sciences and registered in Iranian Registry of Clinical Trials (IRCT 201702063915N19). Written informed consent was obtained from infants' parents. Exclusion criteria were neonates with major congenital anomalies, severe cardiovascular instability and birth asphyxia (one-minute Apgar score ≤ 3), major cardiac diseases (not including patent ductus arteriosus), and parental refusal. Infants who needed endotracheal intubation at birth due to ineffective respiratory drive were also excluded from the study.

Our center policy is resuscitation according to the Neonatal Resuscitation Program (NRP)[17] and stabilization of the infant using NCPAP for preterm neonates in the delivery room and saving intubation only for those who have apnea or ineffective respiration.

Neonates who met the inclusion criteria were randomly allocated to either the NCPAP or NIPPV group upon arrival in NICU. NCPAP was administered through short bilateral nasal prongs, intermittently with a nasal mask. Distending pressure was generated by a variable flow NCPAP device and peak end expiratory pressure (PEEP) 5–6 cm H_2O and flow 6–7 L/min (Fisher & Paykel Health Care limited, New Zealand). Neonates in the NIPPV group received peak inspiratory pressure (PIP) 18–20 cm H_2O, PEEP 5–6 cm H_2O, and frequency 30–40/min, time inspiration 0.35–0.40 sec, flow rate 6–8 L/min, trigger sensitivity of 4 using Inspiration 5i ventilators (e Vent Medical Ltd, Ireland). Weaning strategy was PIP gradual reduction by decrements of 2 cm H_2O during weaning until it reached 14 cm H_2O. The rate adjusted by decrements of 5–10/min, while the neonate is hemodynamically stable, steadily increase spontaneous respiratory effort, and arterial blood gas values suggest that ventilator needs are decreasing.

We do not use prophylactic surfactants. Patients with evidence of respiratory compromise (tachypnea, retractions, and/or nasal flaring) shortly after delivery, a persistent oxygen requirement and radiographic findings of RDS received surfactant in both groups. Curosurf® (Poractant alfa, Chiesi Farmaceutici, Italy) 200 mg/kg/dose (2.5 mL/kg/dose intratracheally) with INtubation-SURfactant-Extubation (INSURE) technique was used. Caffeine citrate was administered at an initial dose of 20 mg/kg followed by 10 mg/kg as a maintenance dose. In all studied neonates, RDS score was recorded based on respiratory rate, retractions, presence of grunting and respiratory sounds, received fraction of inspired oxygen (FiO_2), and gestational age. All patients were monitored (Vectra, Sazgan Gostar co. Ltd, Tehran, Iran). The primary outcome was the need for surfactant replacement therapy or the failure of NIV and need for intubation during the first 72 hours of admission. Intubation was indicated either when the arterial oxygen saturation was less than 85%, partial pressure arterial oxygen (PaO_2) ≤ 50 mmHg while receiving FiO_2 ≥ 0.4, the partial pressure of carbon dioxide (PCO_2) was more than 65 mmHg with a pH < 7.2 on arterial blood gas analysis, or the occurrence of more than four apneic episodes in the first hours, more than two episodes of bagging per hour, clinical signs suggested necrotizing enterocolitis (NEC), or gastrointestinal perforation and hemodynamic instability. The secondary outcome was considered BPD or other complications of prematurity, duration of hospital stay, and mortality. BPD was defined as dependence on supplemental oxygen or mechanical respiratory support through day 28 post-birth. Intraventricular hemorrhage (IVH) was diagnosed by cranial ultrasound examination, which was performed for all infants at days 5–7 by a pediatric radiologist. The severity of IVH was

determined based on classic grading as follows: grade I, hemorrhage limited to subependymal matrix germinal; grade II, hemorrhage in subependymal matrix germinal with extension into the ventricular system without lateral ventricular dilation; grade III, hemorrhage in subependymal matrix germinal with extension into the ventricular system with lateral ventricular dilation; and grade IV, hemorrhage in subependymal matrix germinal with extension into the brain tissue.

Pneumothorax was determined by presence of air in the pleural space in chest X-ray. Retinopathy of prematurity was diagnosed by an expert ophthalmologist by indirect ophthalmoscopic eye examination initiated 4–6 weeks after birth. All data were recorded by an experienced nurse who was not aware of the study objectives and patient's groups.

Statistical analyses were performed using SPSS Statistics (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc). Quantitative data were presented as mean and standard deviation, and qualitative data as frequency and percentage. Independent t-test were used for testing continuous normally distributed data. Categorical data were compared between groups using chi-square or Fisher's exact test. Two tailed tests were used and a p-value < 0.005 was considered statistically significant. Odds ratio (OR) with 95% confidence interval (CI) were determined for predictors of complications in both groups.

RESULTS

A total of 110 preterm infants with RDS were admitted to NICU between January 2017 and September 2017. Seventy-four infants met the inclusion criteria. Thirteen patients were excluded from the study because of major congenital anomalies (three cases), no parental consent (two cases), and intubation before arrival to NICU (five cases). In three infants the same distending pressure was not continued after surfactant administration. A total of 61 neonates were enrolled in the study (30 patients in NIPPV group and 31 neonates in NCPAP group). The mean gestational age and birth weight of enrolled infants were 29.3±1.4 weeks and 1272.0±186.0 g, respectively [Table 1]. The most common risk factor in both groups was maternal pre-eclampsia, followed by premature rupture of membranes, multiple gestation, diabetes mellitus, and placenta abruption, p = 0.310 [Table 2]. The fraction of oxygen needed for maintaining oxygen saturation 90–95% and RDS score are shown in Table 3. The primary outcome was intubation and mechanical ventilation in seven patients (11.5%); five (16.7%) cases in the NIPPV group and two (6.5%) cases in the NCPAP group, OR = 2.90 (95% CI: 0.51–16.27, p = 0.250).

Table 1: Demographic characteristics of studied neonates receiving nasal continuous positive airway pressure (NCPAP) or nasal intermittent positive pressure ventilation (NIPPV).

Characteristics	NIPPV group n = 30	NCPAP group n = 31	*p-value*
Birth weight, g	1301.0 ± 167.0	1246.0 ± 201.0	0.240
Gestation age, weeks	30.4 ± 1.3	29.8 ± 1.7	0.130
Gender			
Male, n (%)	11 (36.7)	15 (48.4)	0.350
Delivery mode			
Cesarean section, n (%)	24 (80.0)	23 (74.2)	0.590
Antenatal steroids			
Not received	1 (3.3)	2 (6.5)	0.009
One dose	19 (63.3)	11 (35.5)	
Two doses	9 (30.0)	18 (58.1)	

Surfactant replacement therapy was done in 34 neonates (55.7%): 15 (44.1%) in the NIPPV group and 19 (55.8%) in the NCPAP group, OR = 1.58 (95% CI: 0.57–4.37, p = 0.370). A second dose of surfactant was needed in eight neonates (13.1%): five (16.6%) in the NIPPV group and three (9.6%) in NCPAP group, p = 0.370. One neonate in NCPAP group was treated with three doses of surfactant. The secondary outcome was complications of prematurity [Table 4]. No cases of NEC and severe IVH (grade III or IV) were determined in the NCPAP group.

The mean duration of hospitalization was 26.2±17.4 days in the NIPPV group and 38.4±19.2 days in the NCPAP group, p = 0.009. Ten neonates in NIPPV group (33.3%) and six in the NCPAP group (19.4%) had at least one apnea attack, OR = 2.08, (95% CI: 0.64–6.71, p = 0.21). Fifteen neonates (50.0%) in NIPPV group and 22 (71.0%) in NCPAP group were without complication, OR = 2.44, (95% CI: 0.85–7.02, p = 0.090). NIV failure was determined in seven neonates

Table 2: Maternal risk factors in studied neonates receiving nasal continuous positive airway pressure (NCPAP) or nasal intermittent positive pressure ventilation (NIPPV).

Risk factors	NIPPV group n = 30	Percent	NCPAP group n = 31	Percent	*p-value*
Pre-eclampsia	15	50.0	18	58.1	0.600
Multiple gestation	3	10.0	4	12.9	1.000
Diabetes mellitus	1	3.3	1	3.2	1.000
PROM	6	20.0	3	9.7	0.300
Placenta abruption	1	3.3	0	0.0	0.490
Hypothyroidism	1	3.3	0	0.0	0.490

PROM: premature rupture of membranes.

Table 3: Respiratory parameters at admission and six hours after management in neonates receiving nasal continuous positive airway pressure (NCPAP) or nasal intermittent positive pressure ventilation (NIPPV).

Parameters	NIPPV group n = 30	NCPAP group n = 31	*p*-value
RDS score	5.5 ± 0.7	6.5 ± 0.7	0.290
Needed FiO_2			
At admission	0.5 ± 0.1	0.4 ± 0.1	0.240
After six hours	0.3 ± 0.1	0.3 ± 0.1	0.710
pH			
At admission	7.0 ± 0.1	6.9 ± 0.1	0.320
After six hours	7.3 ± 0.3	7.3 ± 0.2	0.180
PCO_2			
At admission	48.2 ± 9.0	47.9 ± 12.1	0.910
After six hours	35.6 ± 8.1	38.0 ± 10.6	0.330

RDS: respiratory distress syndrome; PCO2: partial pressure of carbon dioxide.

[Table 5]. Surfactant replacement therapy was given to six neonates in the NIV failure group, twice in three patients. In the remaining neonates that had NIV without the need for mechanical ventilation, 29 did not receive surfactant. Twenty-one neonates were treated with surfactant once, three cases twice, and one case three-times, $p = 0.010$.

DISCUSSION

Use of NIPPV as primary respiratory support in comparison to early NCPAP decreases the duration of hospitalization significantly in preterm infants with a gestational age of 28–32 weeks who had RDS. Preterm neonates < 28 weeks gestation were not included in our study. A study of 76 preterm infants with similar gestational ages did not find a significant difference in hospitalization days

Table 4: Comparison of complications of prematurity in neonates receiving nasal continuous positive airway pressure (NCPAP) or nasal intermittent positive pressure ventilation (NIPPV).

Complications	NIPPV group n = 30	NCPAP group n = 31	*p*-value	Odds ratio	95% Confidence interval
Primary outcome					
NIV failure, n (%)	5 (16.7)	2 (6.5)	0.250	2.90	0.51–16.27
Surfactant therapy, n (%)	15 (50.0)	19 (61.3)	0.370	1.58	0.57–4.37
Secondary outcome					
NEC, n (%)	1 (3.3)	0 (0.0)	0.490		
ROP, n (%)	8 (26.7)	12 (38.7)	0.310	7.57	0.19–1.70
BPD, n (%)	2 (6.7)	8 (25.8)	0.080	0.20	0.04–1.06
IVH, n (%)	3 (10.0)	0 (0.0)	0.110		
PDA, n (%)	6 (20.0)	10 (32.3)	0.270	0.52	0.16–1.69
Pneumothorax, n (%)	1 (3.3)	0 (0.0)	0.490		
Mortality, n (%)	1 (3.3)	0 (0.0)	0.490		
Duration of hospital stay, days	26.2 ± 17.4	38.4 ± 19.2	0.009		

NIV: noninvasive ventilation; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; PDA: patent ductus arteriosus.

Table 5: Variables in neonates with noninvasive ventilation (NIV) failure.

Variables	NIV failure n = 7	NIV responsive n = 54	*p*-value
RDS score	6.5 ± 0.9	5.4 ± 0.6	< 0.001
Gestation age, week	29.2 ± 1.2	29.4 ± 1.4	0.350
Birth weight, g	1255.0 ± 206.0	1275.0 ± 186.0	0.770
Gender, male/ female	6/1	20/34	0.030
Antenatal steroids, n (%)			
Not received	2 (28.6)	11 (20.4)	0.620
One dose	3 (42.9)	17 (31.5)	
Two doses	2 (28.6)	26 (48.1)	

RDS: respiratory distress syndrome.

between these two modes of NIV.[15] On the other hand, another study showed significantly less duration of ventilation, oxygen supplementation, and hospitalization in preterm infants with gestation ages of 28–34 weeks supported by NIPPV.[18] It is suggested that NIPPV improves respiratory drive by increasing mean airway pressure, which allows recruitment of alveoli and decreases work of breathing.[19]

Studies that assessed NIPPV as a primary strategy to treat RDS reported improved carbon dioxide exchange. A study of 88 preterm infants randomly allocated to NIPPV and NCPAP groups as initial RDS treatment reported lower PCO_2 and fewer days of mechanical ventilation in the NIPPV group.[20] Consistent with present study, they did not find a decrease in the need for endotracheal intubation in the NIPPV group. They did not report the effect on mortality or BPD in their study.

On the other hand, a study of 84 preterm infants with 35 weeks gestational age who had clinical RDS randomized to NIPPV and NCPAP groups found a lesser rate of intubation in neonates that initially were stabilized by NIPPV.[21] In our study, although the need for intubation and mechanical ventilation was more common in the NIPPV group compared with the NCPAP group, the difference was not statistically significant. In one study,[22] the rate of NIPPV failure in the first 72 hours of life in 31 neonates with a gestational age of 24–32 weeks was 67%. It was 16.7% in our study. This low failure rate may be explained by the fact that the INSURE procedure for surfactant administration is routine in our center. In our study, neonates with NIV failure had higher RDS score than patients successfully managed by NIV.

A large randomized controlled trial consisting of more than 1000 neonates < 30 weeks gestational age and weighing < 1000 g at birth did not show any advantage of NIPPV over NCPAP either as a means of early respiratory support to treat RDS or to facilitate extubation.[22] This finding is supported by another multicenter study.[23]

The incidence of BPD in our study was 6.7% in the NIPPV group compared to 25.7% in NCPAP group, which is consistent with another study.[21] The different findings in various studies may be due to the heterogeneity of the study population with respect to wide range of gestational ages and birth weights, severity of RDS, the criteria for intubation and surfactant administration, weaning protocols, different devices used for NIV, and use of synchronization. We recommend future studies with larger number of patients with different gestational ages.

Only one neonate in the NIPPV group developed pneumothorax and needed a chest tube inserted. A neonate in the NIPPV group died due to pulmonary hemorrhage. Based on our findings, NIPPV and NCPAP are similarly effective as initial respiratory support in preterm infants in reducing the need for mechanical ventilation and surfactant replacement therapy.

CONCLUSION

The need for intubation and mechanical ventilation is similar among preterm infants supported by NIPPV and NCPAP within the first hours of life. NIPPV is a safe mode of NIV and is more effective in reducing the duration of hospitalization and occurrence of BPD than neonates supported by NCPAP. In neonates with high RDS score, NIV failure may be anticipated.

Disclosure
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