IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Continuous Positive Airway Pressure or Humidified High Flow Nasal Cannula for Respiratory Distress Syndrome: A Randomized Control Trial among Premature Neonates

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ABSTRACT

Background: Respiratory distress syndrome (RDS) is a common lung problem in neonates born before 28 weeks of pregnancy. The current study aimed to assess the clinical outcomes of Nasal Continuous Positive Airway Pressure (NCPAP), as compared to humidified high flow nasal cannula (HHFNC) in the treatment of premature neonates with RDS.

Methods: This randomized control trial was conducted on 60 preterm neonates (gestation <34 weeks and birth weight <2,000 g) with mild to moderate RDS (respiratory severity score of 4 to 7) and oxygen requirement 60% or less. They were randomly assigned to either NCPAP or HHFNC groups. Treatment failure in the first 72 h after birth was the primary outcome. Secondary outcomes included Pneumothorax, patent ductus arteriosus (PDA), chronic lung disease, surfactant injection, tracheal intubation, necrotizing enterocolitis (NEC), several days of delay in establishing full enteral feeds, extended length of hospital stay and oxygen therapy days, and death. Data were analyzed in SPSS software (version 16) using independent t-test, chi-square, and logistic regression statistical tests at 95% significant level.

Results: There were no significant differences in primary and secondary outcomes, including pneumothorax, patent ductus arteriosus (PDA), chronic lung disease, surfactant injection, tracheal intubation, death, necrotizing enterocolitis (NEC), days of delay in establishing full enteral feeds, duration of hospitalization, and the number of the days for oxygen requirement between NCPAP and HHFNC groups.

Conclusion: HHFNC and NCPAP techniques have the same efficacy in the treatment of RDS in neonates, and there was no difference between the two techniques in terms of treatment failure and clinical outcomes. Since HHFNC is less invasive with the same efficacy compared to CPAP, we recommend that it can be used as a primary modality in preterm neonates with RDS.

Keywords: HHFNC, NCPAP, Premature neonate, Respiratory Distress Syndrome

Introduction

Respiratory distress syndrome (RDS) is a common lung problem in neonates born before 28 weeks of pregnancy (1). This disease can be followed by several complications, such as chronic lung disease (2), and increased neonatal mortality (3). Moreover, RDS imposes a high economic burden on patients and society. For instance, the cost of respiratory care for newborns with RDS has been reported at $ 4.4 billion a year in the United States (4). Although Mechanical ventilation

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Please cite this paper as:
Eslaminia Shirvani T, Nayeri FS, Shariat M, Nik Nafas N, Mirjalili MR, Hosseini SN, Ghorbansabagh V. Continuous Positive Airway Pressure or Humidified High Flow Nasal Cannula for Respiratory Distress Syndrome: A Randomized Control Trial among Premature Neonates. Iranian Journal of Neonatology. 2020 Dec: 11(4). DOI: 10.22038/ijn.2020.46421.1783

(MV) is one of the main RDS treatment methods, neonates under MV are always at risk for lung injury, and about up to 30% have the chronic pulmonary disease, and sometimes lung damage is so severe that it impairs the growth and development of neonates (5). Therefore, therapeutic approaches should be sought with minimal clinical complications. Based on studies, the use of nasal Continuous Positive Airway Pressure (NCPAP) in the first minutes after birth, accompanied by a reduction in the use of mechanical ventilation, can reduce the chance of death, brain hemorrhage, and complications of the RDS (7-9). The NCPAP is designed to deliver a predetermined oxygen concentration to breathe airborne neonatal airways. The main objective of this method is the application of minimum relaxation pressure during the respiratory cycle to prevent alveolar and airway collapse (especially when exhaling) (10). The NCPAP is non-invasive respiratory support in the treatment of preterm neonates which can be performed without endotracheal intubation. Consequently, continuous airway positive pressure distends the lungs which led to the promotion of ventilation (11). The positive effects of NCAPA on premature infants include the stabilization of breathing patterns, as well as the reduction of respiratory apnea and airway resistance (12). Nevertheless, it should be noted that unnecessary use of NCPAP can be followed by several complications, such as air leak syndromes, intraventricular hemorrhage (IVH), decreased cardiac output, as well as adverse effects on the digestive system and abdominal distension (13, 14).

The humidified high-flow nasal cannula (HHFNC) is another widely used method for the treatment of infant RDS (15-17). The use of lighter and easier cannula in HHFNC may be followed by positive outcomes, such as less nasal injury and ease of care, in comparison to the NCPAP (18, 19).

Several studies have indicated the efficacy of HHFNC in the early treatment of RDS among premature infants (19). However, today's challenge is to choose the best method to achieve Positive End-Expiratory Pressure (PEEP) in the neonate, with the least side-effect and the best clinical outcome for the treatment of newborns with RDS. In this regard, the main goal is to choose the most non-invasive and effective method of respiratory support (20).

The current study assessed the outcomes of NCPAP, compared to HHFNC, in the treatment of premature neonates with RDS. Treatment failure in the first 72 h after birth was the primary outcome.

Methods

Participants

This randomized control trial was conducted on 60 newborns suffering from RDS in the neonatal intensive care unit (NICU) of Imam Khomeini Hospital Complex, Valiasr Hospital, Tehran, in 2018. The sample size was calculated at 60 cases according to the results of a previous study (21). Thereafter, the newborns were randomly assigned to two NCPAP and HHFNC groups (n=340). They entered one of the NCPAP and HHNFC treatment groups at birth without receiving any specific treatment. The allocated treatment, HHFNC or NCPAP, was started immediately. The assigned mode of support was continued until the improvement of respiratory distress. The design of the study population is presented in Figure 1.

Inclusion and exclusion criteria

Neonates with mild to moderate RDS, birth weight <2000 grams, gestational age <34 weeks, respiratory severity score within 4-7, and oxygen requirement< 60% were eligible to participate in the current study.

On the other hand, d cardiac, gastrointestinal, and respiratory anomalies, intraventricular hemorrhage (IVH) at birth, positive blood culture when admitted to NICU, and 5-minute Apgar score <5 were regarded as exclusion criteria. Moreover, the neonates whose parents did not provide consent or refused to allow their participation were excluded before randomization.

RDS was classified according to Downes et al. scoring system (22). Accordingly, mild, moderate, and severe RDS were defined as respiratory score <4, 4-7, and >7, respectively (Table 1).

Procedure

Before the admission of the newborns, informed consent was obtained from their parents. Initially, these parameters were studied: mother's age, newborns' weight, length, head circumference, gestational age, APGAR score at 1 and 5 min after birth, and need of oxygen. A chest X-ray was used to reject another differential diagnosis of respiratory distress. Brain sonography was also used to diagnose ventricular hemorrhage. Both treatment methods were performed by one pediatrician or neonatologist. If

persistent respiratory distress occurred in spite of NCPAP/HHFNC, surfactant (Curosurf®/Survanta®) was administered in the first two h after birth. This was performed via INSURE method (intubation, surfactant administration, rapid extubation). Thereafter, the previous treatment method (NCPAP/HHFNC) was continued.

NCPAP was delivered by the Infant Flow CPAP system or ventilator using short single nasal prong with different sizes pursuant to weight. This group initially received positive end-expiratory pressure (PEEP) of 5 cmH_2O which was adjusted between 4-6 cmH_2O according to the neonate's respiratory condition. A fraction of inspired oxygen (FiO_2) of 0.4 was initiated, and it was adjusted until SpO_2 of 92-6% was maintained. Weaning was started with a progressive reduction of the set FiO_2 to 0.25 and PEEP to 4 cmH_2O.

HHFNC support was delivered using the Medin© blender System. We used the short binasal cannula as an interface with different sizes according to weight. The neonates on HHFNC received a flow of 5 L/min initially, and it was adjusted between 3-7 L/min according to the newborn's respiratory condition (to ensure blood gas analysis results within normal ranges). FiO2 of 0.4 was initiated, and it was adjusted until SpO2 of 92–96% was maintained. Weaning was started with a progressive reduction of FiO2 to 25% and flow to 3 L/min. Oxygen was heated with a blender unit at a temperature of 32-35°C.

Weaning

Respiratory supports were stopped when the neonates showed no signs of respiratory distress and SpO2 > 92%, PCO2 < 60 mmHg with FiO2 of 0.25 and HHFNC flow rate of 3 L/min or NCPAP PEEP of 4 cmH2O. The newborns then received oxygen by Head box or free-flow oxygen.

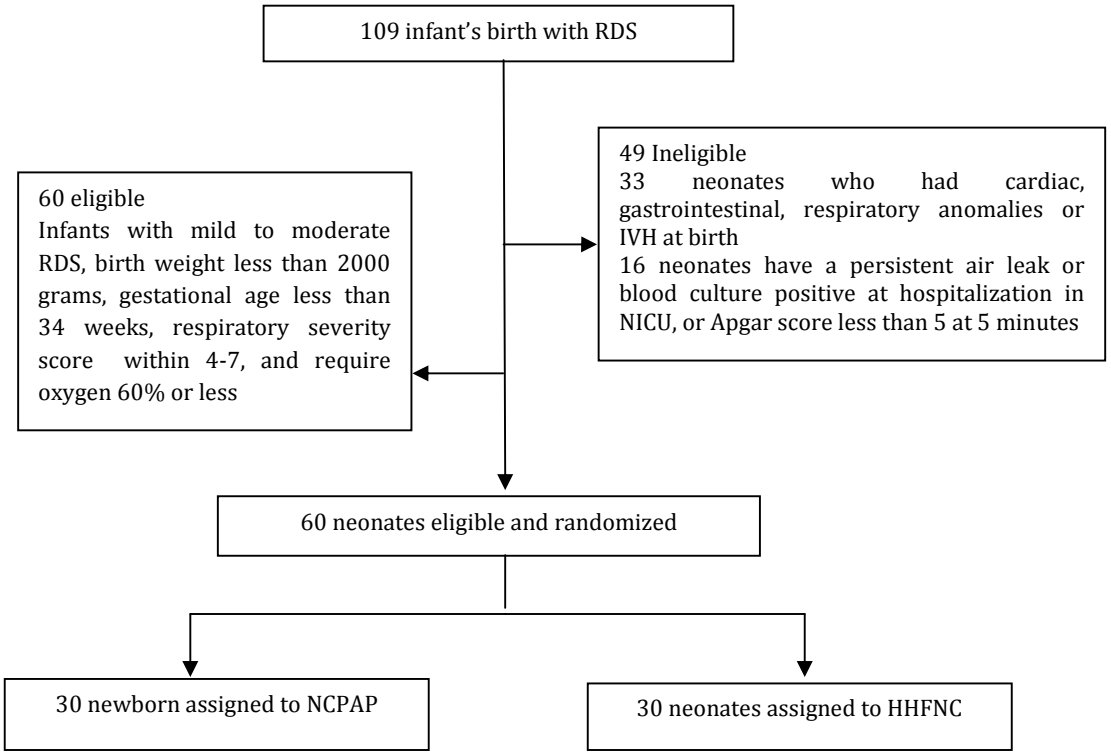

Figure 1. Design of the study population

Table 1. Modified Downes et al. scoring system (24)

Score	0	1	2
Cyanosis	room air (21%) in	FIO2≤%40	FIO2 >40%
Retraction	No	Mild	Moderate to severe
Grunting	No	Audible with Stethoscope	Audible without Stethoscope
Air Entry (crying)	Clear	Delayed or decreased	Barely audible
Respiratory Rate (breaths/min)	<60	60-80	>80
Gestational age (weeks)	>34	30-34	<30

Treatment failure

Respiratory acidosis (PaCO2 > 65 mmHg with pH < 7.2) at the maximum setting of the allocated device, flow 7 L/min or PEEP 6 cmH2O, hypoxia (FiO2 > 0.6 to maintain SpO2 92-96%) or apnea (>2–3 episodes of apnea/hour requiring repeated stimulation or bag-and-mask ventilation) despite adequate prong fixation and flow or PEEP delivery, were considered as the criteria for treatment failure.

Outcomes

The primary outcome was treatment failure in both NCPAP and HHFNC group. Secondary outcomes included pneumothorax, patent ductus arteriosus (PDA), chronic lung disease, surfactant injection, tracheal intubation, necrotizing enterocolitis (NEC), several days of delay in establishing full enteral feeds, extended length of hospital stay and oxygen therapy days, and death.

Measures

The data which were collected by trained nurses included mother age (years), the gender of neonates (male, female), gestational age (week), weight (gram), length (centimeter), head circumference (centimeter), Apgar at 1 and 5 min after birth (score). Primary and secondary outcomes were recorded by participating neonatologists.

Ethical approval

Ethical approval was obtained from the Research Ethics Board of Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1395.1477). Written informed consent was obtained from neonates' parents.

Data analysis

Age of mothers, weight, length, head circumference, gestational age, Apgar at 1 and 5 min after birth, number of days to full enteral feeding, the length of hospital stay, and number of oxygen therapy days between two groups were analyzed using Student's t-test. Comparisons between neonates' gender and treatment failure among groups were conducted using the chi-square test. Multivariable logistic regression models were performed to predict secondary outcomes between groups. The obtained data were analyzed in SPSS software (version 16.0) (SPSS Inc., Chicago, IL, USA). A p-value less than 0.05 was considered Statistically significant.

Results

The mean age of mothers was reported as 32.16 years [SD: 5.73] ranging from 18-years. CPAP group included 15 (50%) female newborns and 15 (50%) male neonates, while the HHFNC group consisted of 17 (56.7%) female neonates and 13 (43.3%) male cases. There were no significant differences in gender between the two groups (P=0.605). In addition, Table 2 depicts the frequency of demographic data in NCPAP and HHFNC groups.

Treatment failure rates are displayed in Table 3. Based on the obtained results, there was no significant difference in treatment failure between the two groups. Results revealed a total of 11.7% (7.60) of treatment failure in both groups.

The comparison of full feeding days, length of hospital stay, and oxygen therapy days between NCPAP and HHFNC groups is reported in Table 4. Our findings indicated no significant differences in the number of days to full enteral feeding, length of hospital stay, and the number of oxygen

Table 2. Demographic Data in NCPAP (n=30) and HHFNC groups (n=30)

Variables	NCPAP Group Mean (±SD)	HHFNC Group Mean (±SD)	*P*-value
Mothers' Age (years)	31.57 (4.72)	32.79 (6.69)	0.424
Weight (g)	1315.67 (417.49)	1181.17 (306.31)	0.160
Length (cm)	39.17 (4.99)	39.00 (4.89)	0.897
Neonates' head circumference (cm)	27.71 (2.73)	26.82 (2.63)	0.199
Gestational age (week)	29.50 (2.09)	30.40 (2.08)	0.065
Apgar at 1 min after birth	6.80 (1.99)	6.14 (2.91)	0.863
Apgar at 5 min after birth	8.40 (1.22)	8.17 (1.34)	0.638

Table 3. Primary outcome for neonates assigned to receive either HHFNC or NCPAP for the initial respiratory support

Outcomes	NCPAP (n=30)	HHFNC (n=30)	P-value
Treatment failure	5 (16.7 %)	2 (6.7 %)	0.228
Reasons			
Hypoxia	4 (13.3 %)	2 (6.7 %)	0.389
Respiratory acidosis	1(3.3 %)	0 (0 %)	0.313

Table 4. Comparison of days to full enteral feeding, length of hospital stay, and oxygen therapy days between NCPAP and HHFNC groups

Variables	NCPAP Group Mean (±SD)	HHFNC Group Mean (±SD)	*P*-value
Days to full enteral feeding	18.50 (10.57)	18.73 (8.05)	0.930
Duration of hospitalization	32.53 (19.86)	41.27 (22.46)	0.116
Oxygen therapy days	10.34 (15.62)	14.76 (22.81)	0.839

Table 5. Multiple logistic regression analysis for clinical conditions related to NCPAP and HHFNC groups

Clinical Conditions	Odds Ratio (95% CI)	P-value
Pneumothorax		
NCPAP	1.00	0.561
HFNC	2.071 (0.178- 24.148)	
PDA		
NCPAP	1.00	0.775
HHFNC	1.179 (0.383- 3.629)	
Chronic lung disease		
NCPAP	1.00	1.000
HHFNC	1. 00 (0.302- 3.308)	
Surfactant injection		
NCPAP	1.00	0.837
HHFNC	0.837 (0.260- 2.699)	
Tracheal intubation		
NCPAP	1.00	0.505
HHFNC	0.322 (0.131- 1.951)	
Death		
NCPAP	1.00	0.728
HHFNC	0.781 (0.195- 3.137)	
NEC		
NCPAP	1.00	0.452
HHFNC	0.556 (0.120-2.569)	

therapy days between the NCPAP and HHFNC groups.

Finally, the assessment of secondary outcomes with "treatment method" was performed using logistic regression analyses (Table 5). There were no significant differences in Pneumothorax, PDA, chronic lung disease, surfactant administration, tracheal intubation, NEC, and death between NCPAP and HHFNC groups.

Discussion

As previously described, NCPAP and HHFNC as new methods for RDS support in neonates carry some strengths and limitations. The present study aimed to compare the efficacy of NCPAP and HHFNC methods in the treatment of Iranian premature neonates with RDS. The results of the study indicated there was no difference in treatment failure rate and clinical conditions between NCPAP and HHFNC groups. This finding is similar to the results reported in other studies which suggested that both NCPAP and HHFNC techniques have the same therapeutic effects (23-26). Evidence from other studies supports our findings. However, some studies have pointed to some differences in the efficacy of these two methods in the treatment of RDS among premature neonates. For instance, Vitaliti et al. carried out a study to identify the most efficient treatment of RDS (NCPAP or HHFNC) in neonates and revealed that both NCPAP and HHFNC techniques were efficient to improve the clinical conditions, although NCPAP was superior to HHFNC (24). Sreenan et al. found no significant differences between NCPAP and HHFNC in the treatment of apnea and bradycardia among neonates (19). In addition, Fernandez-Alvarez et al. reported that the clinical outcomes of the HHFNC and NCPAP did not show a significant difference. Nonetheless, in contrast to NCPAP, the HHFNC does not cause nasal trauma and this could be considered an advantage of HHFNC (18). Contrary to our findings, Yoder et al. reported that the length of hospital stay among the neonates in the HHFNC treatment group was significantly higher than that of newborns in the CPAP treatment group (25). Along the same lines, Milési et al. in French university hospital centers recommended that NCPAP could be more efficient than HFNC for initial RDS support (26).

However, due to the lack of any significant difference between the two techniques in terms of therapeutic outcomes, the use of any technique depends on the expert's opinion. In this regard, the initial conditions of the neonate, the experience of the physician, the access to technical tools, and the cost-effectiveness of the selected

technique are important in prioritizing the therapeutic approach.

Furthermore, it should be noted that our findings indicated that the odds ratio for the clinical outcomes, such as tracheal intubation, death, surfactant injection, and NEC in the HHFNC method was lower, compared to the NCPAP method. Moreover, previous studies (19) denoted that HHFNC is less invasive, in comparison to NCPAP. Therefore, considering the same efficacy, this method is recommended for the improvement of respiratory distress in newborns. However, neonates' initial conditions, the physician's experience, access to method tools, and cost-effectiveness of the selected method should be considered in prioritizing the therapeutic approach. Shoemaker et al. reported that the main reason to use HHFNC was the ease of use and minimal nasal trauma, compared to the NCPAP (4).

Limitations and strengths

Every study has some limitations which must be addressed in the paper. Firstly, the small sample size does not provide enough study power. Secondly, some underlying variables were not assessed, including the level of physician experience in performing the NCPAP and HHFNC methods or maternal disorders during pregnancy. Finally, the long-term follow-up of neonates treated with these two methods is recommended in a larger sample size.

Conclusion

Based on the insight gained in the current study, both NCPAP and HHFNC techniques have the same efficacy in the treatment of RDS in neonates, and there is no difference between the two techniques in terms of in-hospital clinical outcomes. However, considering the same efficacy of two methods and less invasiveness of HHFNC, compared to NCPAP, it can be concluded that HHFNC can be recommended for the improvement of respiratory distress in preterm neonates.

Acknowledgments

The authors would like to extend their gratitude to Imam Khomeini Hospital Complex, Valiasr Hospital, Tehran, Iran.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of the current article.

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