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Efficacy and Complications of Humidified High-Flow Nasal Cannula Versus Nasal Continuous Positive Airway Pressure in Neonates with Respiratory Distress Syndrome After Surfactant Therapy

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Abstract

Background: Neonatal respiratory distress syndrome (RDS) is a problem that often occurs in preterm neonates.
Objectives: The present study was conducted to compare the efficacy and complications of humidified high flow nasal cannula (HFNC) with those of nasal continuous positive airway pressure (NCPAP) after surfactant therapy in neonates with RDS.
Methods: This clinical trial was conducted on 60 neonates with the gestational age of 28 - 36 weeks suffering from RDS and admitted to Fatemieh Hospital in Hamadan, Iran, during 2017. Initially, all newborns were administered with exogenous surfactant. Subsequently, the participants were randomly assigned into two groups of HFNC (group 1) and NCPAP (group 2) to receive respiratory support. The NCPAP group was managed with a mask or nasal prong. The HFNC group was given warm and humid oxygen through a short binasal cannula proportional to the weight of each neonate until the recovery of respiratory distress.
Results: The mean one-minute Apgar scores were obtained as 6.23 ± 1.55 and 6.60 ± 1.07 in the HFNC and NCPAP groups, respectively. Furthermore, the mean five-minute Apgar scores were 8.0 ± 1.11 and 8.17 ± 0.95 in these groups, respectively. The mothers and neonates in both groups were comparable in terms of demographic and clinical data, except for gestational age and neonatal gender ($P = 0.05$). Furthermore, there was no statistically significant difference between the HFNC and NCPAP groups regarding the respiratory outcomes ($P = 0.05$).
Conclusions: As the findings indicated, humidified high flow nasal cannula was as effective as nasal continuous positive airway pressure in the management of respiratory distress in premature neonates with the gestational age of 28 - 36 weeks. Consequently, these two interventions could be used interchangeably for the provision of respiratory support among these patients.

Keywords: Cannula, Continuous Positive Airway Pressure (NCPAP), Newborn, Premature, Respiratory Distress Syndrome, Surfactant

1. Background

Neonatal respiratory distress syndrome (RDS) is a problem that often occurs in preterm neonates. Despite the increased use of antenatal steroids and early nasal continuous positive airway pressure (NCPAP), RDS remains a major cause of mortality and morbidity in preterm neonates (1).

The majority of preterm newborns with a gestational age of less than 30 weeks have immature lungs, and nearly half of them still need to receive surfactant therapy (2). The advances in the prevention and treatment of RDS, such as the administration of agents to prevent prematurity or accelerate lung maturation, surfactant replacement, and implementation of new mechanical ventilation techniques, will further decrease the mortality and morbidity associated with this medical condition (3).

The intubation-surfactant-extubation (INSURE) method is an impressive technique for decreasing the need for mechanical ventilation, shortening the length of respiratory support, and performing surfactant replacement in preterm neonates with RDS (4). The INSURE protocol is followed by nasal continuous positive airway pressure (NCPAP) (5). Al-lawama et al. reported the success rate of the NCPAP method as 93.7%. They also stated that the absence of a protocol for monitoring newborns while on CPAP leads to a low trend of CPAP use as primary respiratory support in extremely premature neonates (6). Lemyre et al. reported that NCPAP provides steady

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pressure to the back of the nose that is transmitted to the lungs, thereby helping the neonate to breathe more comfortably (7). Provencher and Nuccio demonstrated that the enhancement of our knowledge regarding the limitations of high-flow nasal cannula (HFNC) therapy in the management of respiratory failure leads to the reduction of therapeutic costs and undesirable outcomes (8).

2. Objectives

With this background in mind, the present study was conducted to compare the efficacy and complications of humidified HFNC with those of NCPAP in neonates with RDS after receiving surfactant therapy (INSURE) in Fatemieh Hospital, Hamadan, Iran.

3. Methods

3.1. Study Population

A clinical trial was performed on 60 neonates with the clinical and radiological signs of RDS, who were admitted to the Neonatal Intensive Care Unit (NICU) of Fatemieh Hospital affiliated to Hamadan University of Medical Sciences, Hamadan, Iran, during 2017. The inclusion criteria were: (1) preterm birth, (2) 28 - 36 weeks of gestation, (3) RDS affliction, (4) NICU admission length of < 24 h, (5) oxygen requirement with the fraction of inspired oxygen (FiO_2) of more than 40 mmHg, and (6) five-minute Apgar score of > 5. On the other hand, the exclusion criteria included the diagnosis of congenital heart defects or other major congenital anomalies. Figure 1 depicts the CONSORT flow diagram of the study.

3.2. Sample Selection

The sample size was determined as 30 cases for each group using the mean comparison formula considering 80% power and 95% confidence level. The formula is as follows:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left[P_1\left(1-P_1\right) + P_2\left(1-P_2\right)\right]}{\left(P_1 - P_2\right)^2}$$

In this formula, P_1 and P_2 were determined as 0.15 and 0. 5 for HFNC and NCPAP, respectively, based on a study performed by Kadivar et al. (9).

3.3. Research Interventions

The neonates had the clinical symptoms of RDS, including tachypnea (i.e., neonatal respiratory rate of > 60 breaths per minute), chest wall muscle depression, cyanosis, and grunting. In the present study, based on the radiographic and clinical findings, the neonates requiring oxygen tension of more than 40 mmHg were subjected to surfactant therapy at a dose of 200 mg/kg through tracheal injection via INSURE method (Curosurf, Chiesi Farmaceutici, Italy).

Subsequently, they were randomly allocated into two groups of HFNC (group 1) and NCPAP (group 2) using the table of random numbers based on computer programs. The HFNC and NCPAP are the most commonly used modes of non-invasive respiratory support in premature infants and newborns. The devices used in the current study were made by Medin Company, Germany.

Group 2 was provided with the routine treatment of NCPAP of 4 cm H_2O pressure and inspired oxygen of 40% mmHg exerted through an oxygen mask or nasal cannula. According to the decision of the researchers of the NICU under investigation and based on the pulse oximetry and arterial blood gases, water pressure and oxygen volume could be increased up to a maximum of 8 cmH_2O and 100%, respectively. An orogastric tube was placed for the neonates to prevent the accumulation of gas in their stomach.

Upon the improvement of the oxygen status, nonoccurrence of apnea or bradycardia, and improvement of breath function, FiO_2 was reduced up to 40%. In addition, CPAP was decreased to 1 - 2 cmH_2O per 24 h. The CPAP was weaned when the neonates had the H_2O pressure of 4 cm, FiO_2 of < 30%, and oxygen saturation of 90% - 94%. On the other hand, group 1 received warm moist oxygen via dual HFNC proportional to their weight. The oxygen flow was measured according to the following formula:

Oxygen flow (L/min) = 0.92 + (0.68 + weight [kg])

Based on the pulse oximetry and arterial blood gas, the minimum and maximum doses of supplied oxygen were 2 and 8 L/min, respectively. The rate of received FiO_2 was regulated by an oxygen blender within the range of 21% -100%. Oxygen was warmed and moistened via Medin device manufactured by a German company.

3.4. Research Measurements

The variables measured in each neonate included FiO_2, positive end-expiratory pressure, arterial oxygen saturation (with pulse oximetry), Co_2 pressure, and pH in case of using arterial blood gas, apnea attacks, and requirement

of positive pressure ventilation. In addition, the complications and side effects in the two investigated methods of the nasal cannula (e.g., pneumothorax [PTX], intraventricular hemorrhage [IVH], Bronchopulmonary dysplasia [BPD], retinopathy of prematurity [ROP], patent ductus arteriosus [PDA], and nasal trauma) were recorded in both groups.

3.5. Statistical Analysis

All statistical analyses were performed in SPSS Statistics for Windows, version 16.0 (SPSS Inc., Chicago, Ill., USA). The data were presented as means, standard deviations, and/or percentages. The qualitative data were analyzed using Chi-square and Fisher's exact tests. The normality of the data was checked prior to data analysis through the one-sample Kolmogorov-Smirnov test. Furthermore, the Mann-Whitney U test and Student's *t*-test were run to analyze the abnormal and normal data, respectively. P values of less than 0.05 were considered statistically significant.

3.6. Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committees of Hamadan University of Medical Sciences, Hamadan, Iran (Number: IR.UMSHA.REC.1396.423). This study was registered at the Iranian Registry for Clinical Trials (Code: IRCT201709049014N181). All diagnostic and therapeutic procedures in this research, including history taking, physical examination, testing, and drug prescription, were in line with the ethical principles of research. However, in this study, no additional examinations or additional interventions were imposed on the patients.

4. Results

Out of the 184 neonates born at the NICU of Fatemieh Hospital with the gestational age of 28 - 36 weeks, 125 cases were candidates for surfactant (INSURE) therapy. However, out of the 125 subjects, 65 neonates were excluded from the study due to severe intrauterine growth restriction (n = 1), congenital heart defect (n = 2), congenital genetic abnormalities (n = 3), parental dissatisfaction (n = 2), perinatal asphyxia (n = 5), and administration of different kinds of surfactants (n = 52). Therefore, the study continued with 60 neonates, who were assigned into group 1 (n = 30) and group 2 (n = 30) after receiving surfactant.

The results of the Kolmogorov-Smirnov test showed that all variables were normally distributed. The investigation of maternal variables revealed that the mean gestational age was significantly higher in group 2 than in group 1. However, there was no statistically significant difference between the two groups in terms of other variables, such as maternal age, history of blood pressure, history of diabetes, delivery method, and administration of corticosteroids (Table 1). Regarding the neonates, the number of males in group 2 was significantly higher than that in group 1 (P = 0.035). However, the two groups showed no significant difference in terms of the Apgar scores at 1 and 5 min and birth weight (Table 2).

The results revealed no significant difference between the NCPAP and HFNC groups in terms of the mean duration of respiratory support, mean length of hospital stay, rate of unresponsiveness to treatment, re-intubation, mean time of the first nutrition, mean duration of reaching full feeding (Table 3), side effects of nasal cannula (e.g., pneumothorax, intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, and patent ductus arteriosus), and nasal trauma (P = 0.05; Table 4).

5. Discussion

The predominant therapy for treating RDS is CPAP; however, adherence to this treatment is reportedly low due to its invasiveness and patients' complaints of airway dryness (10). The HFNC is an alternative to conventional CPAP that uses a weak nasal cannula and flushes the nasopharynx with high-flow rates of heated and moistened air that is compatible with the body temperature and humidity (11). It was hypothesized that HFNC would be effective in decreasing the symptoms of RDS among preterm infants.

This trial intended to evaluate the efficacy of HFNC as an alternative to NCPAP for respiratory support in preterm neonates with a gestational age of 28 - 36 weeks. The noninferiority of HFNC to NCPAP is an issue that has remained indefinite yet (12). The main finding of our study showed that the two groups receiving HFNC and NCPAP as respiratory support techniques were not different in terms of respiratory outcomes.

Hawkins et al. demonstrated that HFNC was more efficient in the reduction of respiratory events and heart rate and improvement of oxygenation, compared to CPAP. The use of nasal cannula can be accompanied by several side effects. In this regard, Provencher and Nuccio reported that in the HFNC method, the delivery of gas through a nasal cannula leads to the elevation of respiratory demand in the patient (8). Fernandez-Alvarez et al. (13) and Lavizzari et al. reported that the use of the INSURE method after receiving surfactant resulted in no statistically significant difference between the HFNC and NCPAP groups. However, in

Table 1. Comparison of Maternal Variables Between the Study Groups[a]

Variable	Groups		P Value
	NCPAP	HFNC	
Maternal age at pregnancy, y	29.92 ± 5.29	27.95 ± 5.19	0.176[b]
Gestational age, wk	32.63 ± 1.61	31.80 ± 1.19	0.026[b]
Gestational diabetes	0 (0)	4 (13.3)	0.056[c]
High blood pressure	4 (13.3)	3 (10.0)	0.500[c]
Cesarean section	25 (47.16)	28 (52.83)	0.424
Administration of corticosteroids	11 (36.7)	14 (48.3)	0.435[d]

Abbreviations: HFNC, humidified high flow nasal cannula; NCPAP, nasal continuous positive airway pressure.
[a]Values are expressed as mean ± SD and No. (%).
[b]Student's *t*-test.
[c]Fisher's exact test.
[d]Chi-square test.

Table 2. Comparison of Neonatal Variables Between the Study Groups[a]

Variable	Groups		P Value
	NCPAP	HFNC	
Gender (male)	22 (73.3)	14 (46.7)	0.035[b]
1st-Minute Apgar score	6.23 ± 1.55	6.60 ± 1.07	0.290[c]
5th-Minute Apgar score	8.0 ± 1.11	8.17 ± 0.95	0.535[c]
Birth weight, g	1840.73 ± 637.92	1743.83 ± 317.35	0.459[c]

Abbreviations: HFNC, humidified high flow nasal cannula; NCPAP, nasal continuous positive airway pressure.
[a]Values are expressed as mean ± SD and No. (%).
[b]Fisher's exact test.
[c]Student's *t*-test.

the mentioned study, the HFNC group had a higher rate of re-intubation than the NCPAP group. On the contrary, in a study carried out by Yoder et al., neither of the groups required re-intubation until 72 h after intubation; however, the HFNC group needed to receive non-invasive respiratory support for a longer time than the NCPAP group (14).

Kadivar et al. showed that preterm neonates with RDS could be managed post-extubation with the implementation of the INSURE method using either NCPAP or HFNC. However, they observed a higher rate of reintubation in the HFNC group (9). de Klerk applied HFNC and NCPAP for the treatment of RDS infants after extubation and neonates with apnea, respectively. However, given the lack of sufficient clinical trials in this regard, there have been some concerns about the widespread use of these devices (15). Zivanovic et al. reported that the most frequently seen complication of CPAP was the incidence of physical facial injuries (16).

Wilkinson et al. (17), Manley et al. (18) and Finer and Mannino (19), demonstrated that the airway pressure delivered through HFNC would vary with the flow rate, the presence of leaks within the airway, neonate's weight, and cannula size. However, the operators usually have no information regarding the actual level of airway pressure transported to the neonate via HFNC.

Iranpour et al. demonstrated that the NCPAP group experienced more nasal trauma side effects as compared to the HFNC group. Furthermore, they reported no significant difference between the two groups in terms of neonatal infections and patent ductus arteriosus (20). In another study performed by Hegde et al., re-intubation, duration of non-invasive ventilation, number of days needed for oxygen therapy, and other side effects were not significantly different between the HFNC and NCPAP groups. Nonetheless, the HFNC group was observed to have fewer nasal traumas than the NCPAP group (21).

Mostafa-Gharehbaghi and Mojabi observed a significantly higher rate of damage to the nasal mucosa in the NCPAP than in the HFNC group (22). In line with our findings, Holleman-Duray et al. observed no statistically significant difference between the HFNC and NCPAP groups in terms of PTX, IVH, BPD, ROP, PDA, and nasal trauma (23).

Our findings regarding respiratory failure and the need for re-intubation were consistent with those of other

Table 3. Comparison of Treatment Variables Between the Study Groups

Variables/Groups	N	Mean ± SD	P Value
Mean duration of respiratory support			0.842
HFNC	30	3.31 ± 1.79	
NCPAP	30	4.31 ± 5.26	
Mean length of hospital stay			0.593
HFNC	30	11.10 ± 5.23	
NCPAP	30	13.43 ± 5.51	
Mean time of the first nutrition			0.072
HFNC	30	2.77 ± 2.35	
NCPAP	30	3.23 ± 1.63	
Mean duration of reaching full feeding nutrition			0.204
HFNC	30	7.60 ±2.81	
NCPAP	30	9.30 ± 4.51	
	Response (%)	**No response (%)**	
No response to treatment and re-intubation			1.00
HFNC	1 (3.3)	29 (96.7)	
NCPAP	2 (6.7)	28 (3.93)	

Abbreviations: HFNC, humidified high flow nasal cannula; NCPAP, nasal continuous positive airway pressure.

Table 4. Side Effects of the Nasal Cannula After Surfactant Therapy[a]

Side Effects of the Nasal Cannula	Groups		P Value[b]
	HFNC	NCPAP	
Pneumothorax	0 (0)	0 (0)	-
Intraventricular hemorrhage	1 (3.3)	0 (0)	1.00
Bronchopulmonary dysplasia	1 (3.3)	2 (6.7)	1.00
Retinopathy of prematurity	0 (0)	2 (6.7)	0.492
Patent ductus arteriosus	6 (20)	3 (10)	0.472
Nasal trauma	0 (0)	2 (6.7)	0.492

[z] Abbreviations: HFNC, humidified high flow nasal cannula; NCPAP, nasal continuous positive airway pressure.
[a] Values are expressed as No. (%).
[b] Fisher's exact test.

studies (11, 14, 21). In a study conducted by Shoemaker et al., the rate of failure in the NCPAP method was higher than that of the HFNC method among infants aged over 30 weeks (11). Consistent with our findings, Shin et al. observed no significant difference between the two groups in terms of respiratory and clinical outcomes and complications (24). The HFNC method is reported to be the first method of choice for respiratory support because of its high acceptance by parents and nurses, as well as easier administration (25).

Several studies showed that the main challenges in caring for premature neonates with respiratory distress syndrome needing surfactant therapy (6, 26) include feeding, supportive care, nasal injury, and kangaroo care (16). Therefore, more research is needed to overcome these challenges.

5.1. Research Limitations

One of the limitations of this study was that no variable related to the airway leak was incorporated into the model. Therefore, the delivered pressure oscillations might have been higher than what actually occurred in vivo. Another limitation of the current study was its small sample size

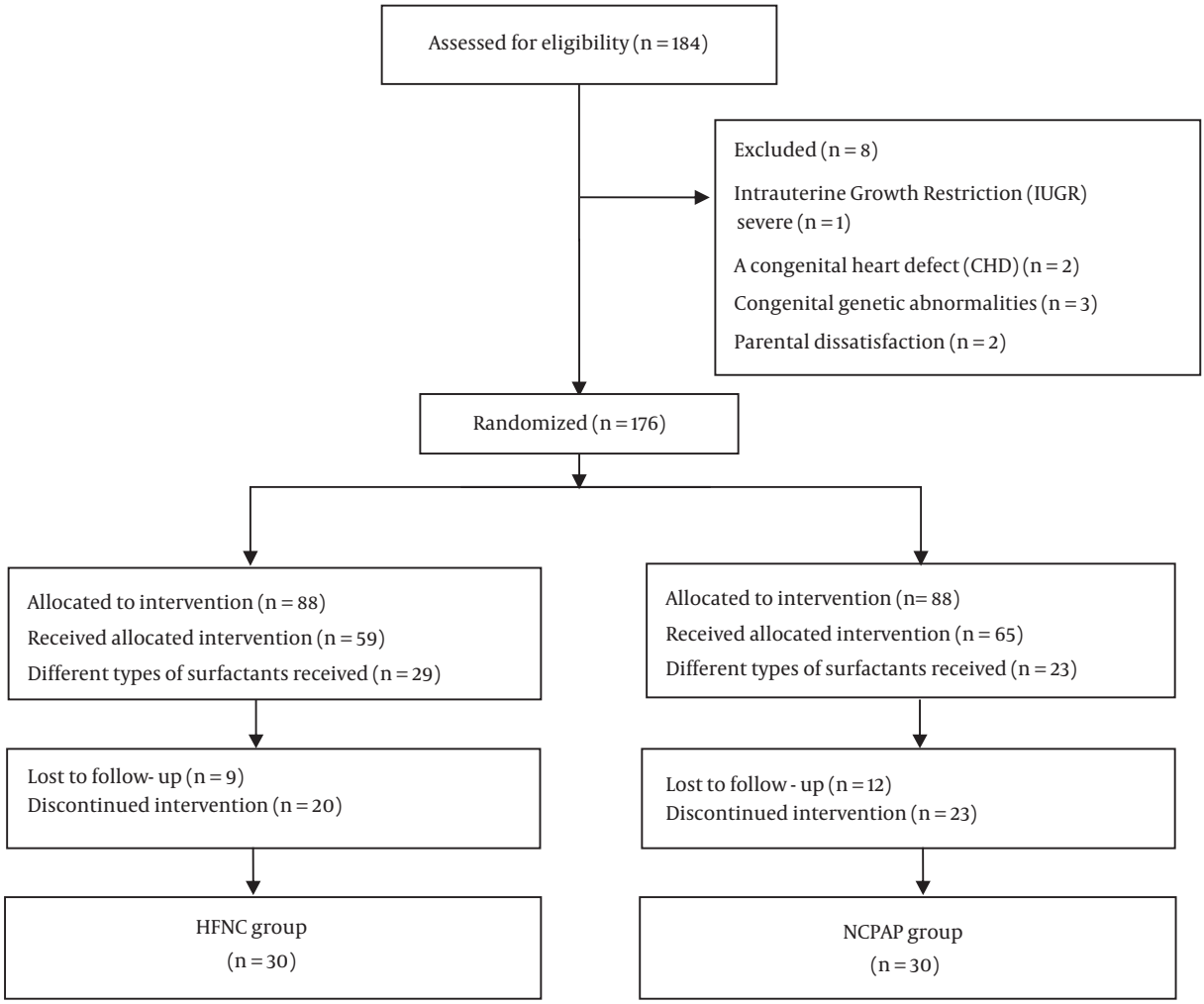

Figure 1. The flow diagram of the patients

that may explain the discrepancy between our results and those of some studies.

5.2. Conclusions

As the findings of the present study indicated, HFNC was as effective as NCPAP in preterm neonates with the gestational age of 28 - 36 weeks under respiratory support. Consequently, HFNC can be considered a good alternative to NCPAP due to its simplicity. Further studies are required to identify the additional outcome indices and determine the patient's responsiveness to HFNC.

Footnotes

Authors' Contribution: Maryam Shokouhi: Study design and manuscript writing; Behnaz Basiri: Data collection and manuscript editing; Mohammad Kazem Sabzehei: Data collection and analysis; Masoumeh Mahdiankhoo: Manuscript writing and editing; Azar Pirdehghan: Study design and data collection.

Conflict of Interests: None declared.

Ethical Considerations: The study protocol was reviewed and approved by the Ethics Committees of Hamadan University of Medical Sciences, Hamadan, Iran (Number: IR.UMSHA.REC.1396.423). This study was registered at the Iranian Registry for Clinical Trials (Code: IRCT201709049014N181). All diagnostic and therapeutic procedures, including history taking, physical examination, testing, and drug prescription, were in line with the ethical principles of research. However, in this study, no additional examinations or additional interventions were

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