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ORIGINAL ARTICLE

Comparison of heated humidified high flow nasal cannula and nasal continuous positive airway pressure after surfactant administration in preterm neonates with respiratory distress syndrome

Zahra Akbarian-rad[1,2] | **Avishan Mohammadi**[3] | **Soraya Khafri**[4] | **Mousa Ahmadpour-kacho**[1] | **Yadollah Zahed-pasha**[1] | **Mohsen Haghshenas-Mojaveri**[1,2]

[1]Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

[2]Clinical Research Development Unite of Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran

[3]Student Committee Research, Department of Obstetrics and Gynecology, Babol University of Medical Sciences, Babol, Iran

[4]Infertility and Reproductive Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

Correspondence
Mohsen Haghshenas Mojaveri, Department of Pediatrics, Babol University of Medical Sciences, Amirkola Pediatrics Hospital-Amirkola, Babol, Mazandaran, Iran.
Email: matia.mojaveri@yahoo.com

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Babol University of Medical Sciences

Abstract

Background and objective: The aim of this study was to evaluate the effect of humidified high-flow nasal cannula (HHHFNC) therapy, and compare it with the effect of nasal Continuous Positive Airway Pressure (NCPAP) in neonates with respiratory distress syndrome (RDS).

Method: In this clinical study, consecutively admitted 27-32 weeks preterm infants with RDS who received surfactant through a brief intubation (INSURE method) were randomly assigned immediately after extubation to HHHFNC or NCPAP. Primary outcomes were oxygen saturation values and oxygen need at 6, 12 and 24 h after surfactant administration as well as duration of oxygen and respiratory support, need for intubation and mechanical ventilation and incidence of apnea. Secondary outcomes were duration of hospitalization and incidence of complications such as pneumothorax.

Results: Sixty-four infants met the inclusion criteria and were enrolled in the study, 32 per arm. Two cases in HHFNC group dropped due to congenital pneumonia/sepsis. No differences were seen between groups in primary and secondary outcomes except for arterial oxygen saturation values (SaO2) 24 h after surfactant administration that were significantly higher in the NCPAP group [95.97% ± 1.96% vs. 95.00% ± 1.80% ($P = .04$)] with similar oxygen needs. The treatment failure was observed in four (11.8%) infants of the NCPAP group compared to five (16.7%) cases of the HHHFNC group ($P = .57$).

Conclusion: Based on the results of the present study, the HHHFNC can be as effective as NCPAP to treat the neonates with RDS after surfactant administration.

KEYWORDS

HHHFNC, NCPAP, Preterm infant, Respiratory distress, Surfactant

1 | INTRODUCTION

The Respiratory distress syndrome (RDS) or hyaline membrane disease (HMD) is the most prevalent respiratory disease in premature infants and is one of the most important causes of their mortality, so that 60% of infants with a gestational age less than 30 weeks and 45% of them with a birth weight less than 1500 g suffer from this disease.[1]

In recent years, antenatal corticosteroid use for accelerating the fetal lung maturity, postnatal surfactant therapy and the use of various mechanical ventilation and continuous positive airway pressure (CPAP) techniques have improved the outcome of RDS.[2]

The early weaning from ventilator and removal of ETT with an approach to reduction of risks (damage to the larynx and trachea, reducing hospital-acquired pneumonia (HAP), sepsis and reducing the severe chronic pulmonary disease) are taken into consideration, nowadays. CPAP is a type of noninvasive respiratory support (NIRS) that is increasingly used in sick neonates.[2]

The preventive use of nasal CPAP (NCPAP) in preterm infants declines the need for mechanical ventilation and ultimately, reduces the rate of pneumothorax and mortality, especially accompanied with surfactant administration.[3-5]

Humidified high-flow nasal cannula (HHHFNC) has been widely applied as a NIRS method in preterm infants.[6-11] HHHFNC is used in clinical situations including respiratory support in newborns with RDS, apnea in preterm infants, prevention from treatment failure after the ETT removal.[6,11-13]

Nasal cannula has been used to oxygenate the preterm neonates in NICU. The apparatus of HHHFNC comprises an air/oxygen blender and humidifier, which is much cheaper and more accessible compared to that of NCPAP.[14]

Over the past decade, the HHHFNC has been applied throughout the academic and non-academic NICU in the United States as well as world.[15] Recently, the use of HHHFNC has been increasing, but there are few studies on its use in the preterm and low birth weight (LBW) infants.[1]

In fact, the results of the HHHFNC use have not been well reported in the clinical setting, and few structured studies have been found about the benefits of its use.[15] Despite the popularity of using this method, there are still precautions regarding the use of HHHFNC due to its safety and efficacy compared to other noninvasive methods.[15]

The aim of this study was to evaluate the effect of HHHFNC in comparison with NCPAP after the surfactant administration on O_2 saturation and required FiO_2 and on treatment failure in the preterm neonates with RDS.

2 | MATERIALS AND METHODS

This clinical trial was done from September 2017 to April 2018. All preterm infants admitted to the NICU of Ayatollah Rohani Hospital affiliated by medical university of Babol, IRAN were entered into study based on the inclusion criteria. On baby admission in NICU a consent form was completed by parents. Preterm neonates with 27-34 weeks of gestational age, who required the INSURE (intubation, surfactant, extubation) procedure during the first 2 h after birth due to the respiratory distress were entered into the study. We have done bedside echocardiography on age 48-72 h for excluding PDA (Patent Ductus Arteriosus) cases. By WBC count blood culture and CRP, we excluded cases with congenital sepsis/pneumonia. Other exclusion criteria were the infants with asphyxiated baby, the obvious anomalies, arrhythmia in heart rate, any cardiovascular problem (such as PDA) or diagnosed congenital heart disease and history of sever oligohydramnios (AFI <5 percentile for gestational age) as well as the neonates who after receiving surfactants, for any reason, required respiratory support as mechanical ventilation (more than 30 minutes) and the INSURE procedure could not be performed.

The sample size was determined as 32 neonates for each groups using the reintubation rate in HHHFNC and CPAP groups with the frequency 40% and 18%, respectively,[16] considering 95% confidence level and 80% power and drop-out rate (10% of samples).

All preterm infants with respiratory distress received NCPAP in delivery room, at least 5 cm. H_2O, fraction of inspired oxygen (FiO_2) 30% via face mask (CPAP device, Neopuff model, made by Fisher Company in New Zealand in 2011). They were transferred from delivery room to NICU. According to the intra-unit protocol (based on ACORN scoring, score ≥5 and/or needed Fio_2 >40%) the CPAP (Sindhi model, Median mark, made in Germany in 2010) was applied for neonates (maximum of FiO_2 = 40% and Pressure 5-7 cm H2O).

Score	0	1	2
Respiratory rate	40-60/min	60-80/min	>80/min
Oxygen requirement	None	≤50%	>50%
Retractions	None	Mild to moderate	Severe
Grunting	None	With stimulation	Continuous at rest
Breath sounds on auscultation	Easily heard throughout	Decreased	Barely heard
Prematurity	>34 wk	30-34 wk	<30 wk

2.1 | Acute care of at-risk newborns (ACoRN) respiratory score

If the respiratory distress was exacerbated (score ACORN 5-8), the neonates would receive intubation and surfactant (Curosurf, 200 mg/kg), and at most up to half-hour later, they were extubated in the case of acceptable arterial blood gas (ABG) (PCO2 <60, PO2 ≥50, PH ≥7.25). Few babies needed a short time respiratory support after surfactant by ventilator not longer than 30 minutes. All of them were randomly (simple random allocation) divided into HHHFNC (blender device, Median mark, made in Germany in 2009) and NCPAP groups. Randomization was based on simple computer-generated lists, which were placed in sealed envelopes. After extubation, Pressure 5-7 cm H2O and FiO2 = 40% were applied in the NCPAP group, and heated humidified oxygen with maximum FiO2 = 40% and flow = 3-5 lit/min via nasal cannula (short binasal prongs, Made in Germany) with size 0 for the infants ≤ 1000 g and size 0.5 for the infants >1000 g was used in the HHHFNC group.

In both groups, when the needed FiO2 for keeping saturation O2 between 90% and 95% within 6 h after the surfactant administration was more than 30%, the patient was reintubated and the second dose of surfactant was administered.

HHHFNC failure was defined as the infant on HHHFNC could not maintain SpO2 between 90% and 95% despite receiving flow = 3-5 lit/min and maximum of FiO2 = 40%. In these infants, prior to the next dose of surfactant, the patient was replaced on NCPAP based on the protocol.

After 30-60 minutes, if the NCPAP was failed, the patient was intubated and then, the next dose of surfactant was administered. Information for each baby was recorded through observation and checklist.

At the time of data interpretation, the two groups were similarly matched for the variables of receiving antenatal steroid, weight, intrauterine age, gender and maternal risk factors.

Primary outcomes included the concentration of FIO2 received oxygen saturation values assessed by pulse oximetry, the secondary outcomes were duration of oxygen demand and respiratory support, apnea, need for endotracheal intubation and mechanical ventilation, the duration of hospitalization and the incidence of complications such as pneumothorax.

2.2 | Statistics

Data were analyzed using SPSS 22. Chi-square and *t* test were used for quantitative and qualitative variables, $P < .05$ was considered as significant level.

3 | RESULTS

Sixty-four premature infants with respiratory distress were enrolled and after surfactant administration and ETT removal, 32 neonates were received NCPAP and HHHFNC in each group for continuing respiratory support. Two babies in HHHFNC group were excluded of study because of PDA (Patent ductus arteriosus) and congenital pneumonia/sepsis (Figure 1).

No significant difference was found between the two groups in the study of confounding variables such as infant's gender, receiving antenatal steroids and magnesium sulfate, type of delivery and multiple pregnancies. Comparison of underlying and confounding variables and maternal factors in both groups are listed in (Table 1).

Comparison of the incidence of apnea, need for resuscitation including positive pressure ventilation (PPV) with a bag and mask, cardiac massage, need for intubation and continuation of mechanical ventilation indicated no significant difference between HHHFNC and NCPAP groups.

The Mean ± SD of SpO2 (assessed by pulse oximetry) at the time of admission was 84.85 ± 6.52 and 85.27 ± 5.67 in the NCPAP and HHHFNC groups, respectively ($P = .79$).

The arterial SpO2 increased from admission to 24 h after treatment in both groups ($P < .001$). (Figure 2).

At 6, 12 and 24 h after INSURE, the Mean ± SD of SpO2 (%) in the NCPAP and HHHFNC groups was 92.82 ± 1.80 versus 91.90 ± 3.25 ($P = .15$), 94.70 ± 1.78 versus 94.46 ± 2.22 ($P = .63$) and 95.97 ± 1.96 versus 95.00 ± 1.80 ($P = .04$), respectively. (Figure 2).

At 6, 12 and 24 h after INSURE, the Mean ± SD of FiO2 percent in the NCPAP and HHHFNC groups was 33.67 ± 10.83 vs. 35.50 ± 8.38 ($P = .39$), 26.38 ± 9.82 vs. 29.53 ± 7.78 ($P = .45$) and 24.70 ± 10.69 vs. 24.70 ± 6.31, respectively ($P = .99$) (Figure 3).

Treatment failure in NCPAP and HHHFNC groups were four (11.8%) and five (16.7%) cases, respectively ($P = .57$).

In the study of the causes of failure, the pneumothorax was found in four babies, two cases in each groups and intraventricular hemorrhage (IVH) in five babies, two cases in the NCPAP and three in the HHHFNC groups. There were no significant difference between the two groups ($P = .81$) (Table 2).

4 | DISCUSSION

Based on the findings of the current study, it was found that FIO2 values did not differ in two groups. In other words, the NCPAP and HHHFNC methods do not have priority over each other in terms of FIO2 required for 24 h. Shin et al in 2017 compared the HHHFNC with NCPAP methods. They suggested that in the initial treatment of respiratory distress,

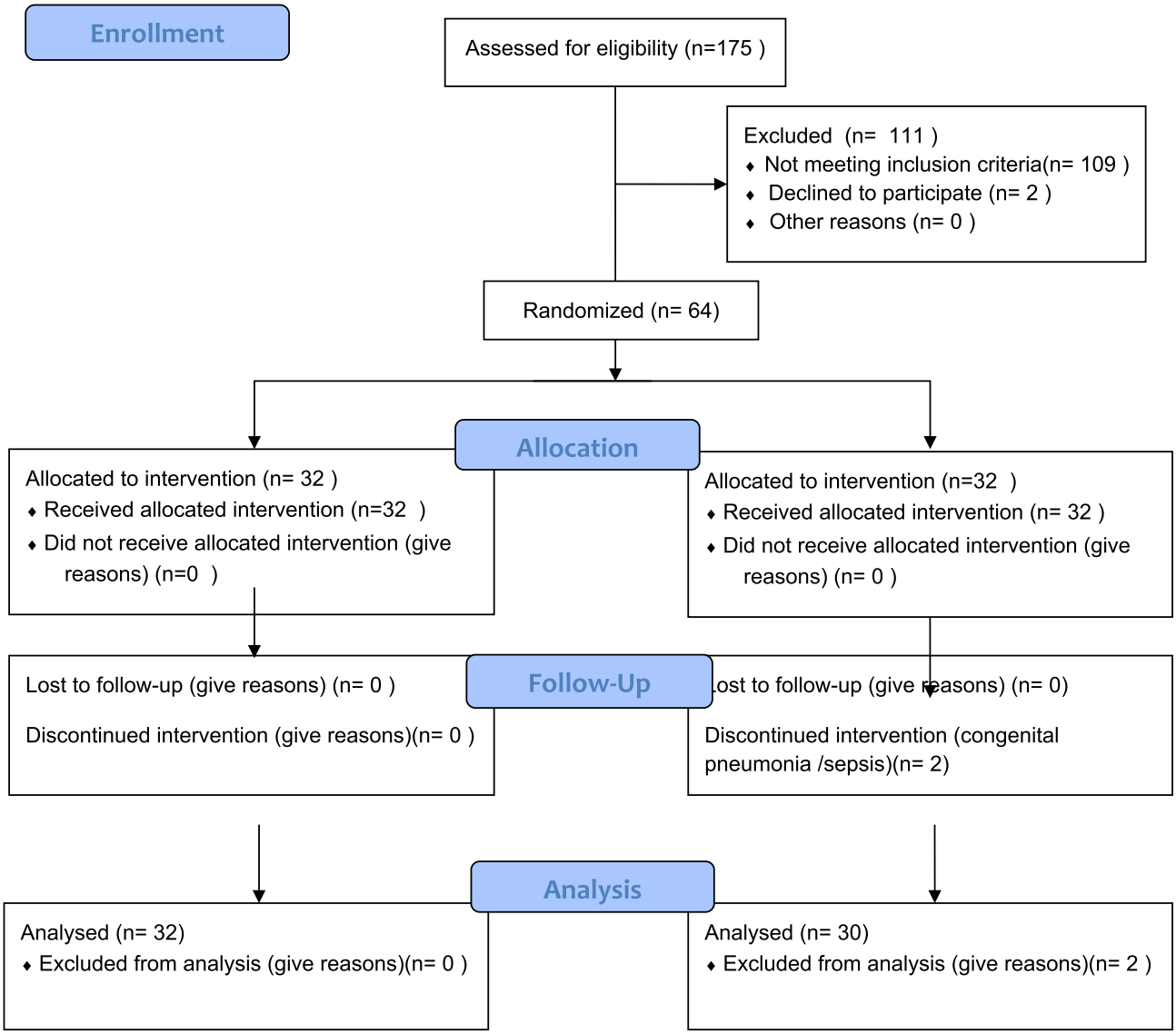

FIGURE 1 Consort flow diagram

both HHHFNC and NCPAP had similar performance on the preterm neonates with a gestational age of 30-35 weeks.[3] Their results were similar to present study.

Regarding the second aim of the current study, the SPO2 values 24 h after treatment in NCPAP group statistically were higher than HHHFNC group, however the two values were in acceptable amount for premature babies (90%-95%). Shoemaker et al compared HHHFNC with NCPAP in preterm infants less than 30 weeks with respiratory distress. As the present study, the results of their study have indicated that the HHHFNC method is as effective as NCPAP in respiratory support of neonates with respiratory distress.[4]

Furthermore, Garg et al in 2017 studied on neonates with gestational age ≤32 weeks and birth weight <1500 g and concluded that HHHFNC and NCPAP had similar efficacy after extubation,[5] which is consistent with the present study.

In line with the current study, the study of Ramanathan et al on preterm infants represented no complications such as damage to nasal mucosa, necrotizing enterocolitis and abdominal distension. Finally, they reported that HHHFNC could be safely used for infants.[6] However, in the present study, pneumothorax and IVH occurred in the two groups with no significant difference. Sreenan et al stated that the efficacy of HHHFNC and NCPAP was the same.[7]

Regarding the investigation of complications and failure in treatment using NCPAP and HHHFNC methods, it can be stated that the HHHFNC method is as reliable and safe as the NCPAP method. Campbell et al observed that the NCPAP compared to HHHFNC had less chance of reintubation in preterm infants with respiratory distress.[9]

Nevertheless, in our study, there was no significant difference in the need for reintubation between the two groups. This disparity between two studies can be due to the weight

TABLE 1 Comparison of underlying and confounding variables and effective maternal factors in HHFNC and NCPAP groups in infants with respiratory distress

Variables	Group NCPAP N (%)	Group HHHFNC N (%)	*P* value
Gender			
Female	19 (55.9)	17 (56.7)	0.95
Male	15 (44.1)	13 (43.3)	
Birth weight (g) (mean ± SD)	334.71 ± 1348.97	493.26 ± 1416.00	0.52
Gestational age (week) (mean ± SD)	1.83 ± 30.98	2.00 ± 30.45	0.26
Type of delivery			
NVD	7 (20.6)	7 (23.3)	0.79
Cesarean	27 (79.4)	23 (76.7)	
Antenatal steroids			
Yes	19 (55.9)	23 (76.7)	0.08
Maternal magnesium sulfate			
Yes	7 (20.6)	6 (20.0)	0.95
Betamethasone dose			
No	15 (44.1)	7 (23.3)	0.26
Single	5 (14.7)	5 (16.7)	
Double	14 (41.2)	17 (56.7)	
Triple	—	1 (3.3)	
Multiple pregnancy			
Singleton	28 (82.4)	19 (63.3)	0.14
Multiple pregnancy	6 (17.6)	11 (36.7)	
History of infertility			
Yes	10 (29.4)	5 (16.7)	0.33
Preeclampsia			
Yes	9 (26.5)	6 (20.0)	0.54
Diabetes			
Yes	1 (2.9)	1 (3.3)	0.92
Oligohydramnios			
Yes	3 (8.8)	6 (20.0)	0.19
PPROM			
Yes	9 (26.5)	13 (43.3)	0.15
Antepartum hemorrhage			
Yes	3 (8.8)	5 (16.7)	0.34
Placenta previa			
Yes	2 (5.9)	1 (3.3)	0.63
Abruption			
Yes	1 (2.9)	4 (13.3)	0.12
Chorioamnionitis			
Yes	2 (5.9)	5 (16.7)	0.16

of the infants, which is different in the study of Campbell et al and ours.

Lower weight and gestational age in the study of Campbell et al compared with the present study represented that in the former study, the clinical condition of newborns was worse and the neonates had more severe RDS. Moreover, Kadivar et al evaluated 54 preterm neonates with gestational age of 28-34 weeks suffered from RDS. The preterm infants were divided into two groups of HHHFNC and NCPAP after INSURE method. They reported that HHHFNC could be replaced by NCPAP.[10]

NCPAP is considered as one of the non-invasive methods of respiratory cares. As noted, its beneficial effects have been proven, but the use of this method has clinical limitations such

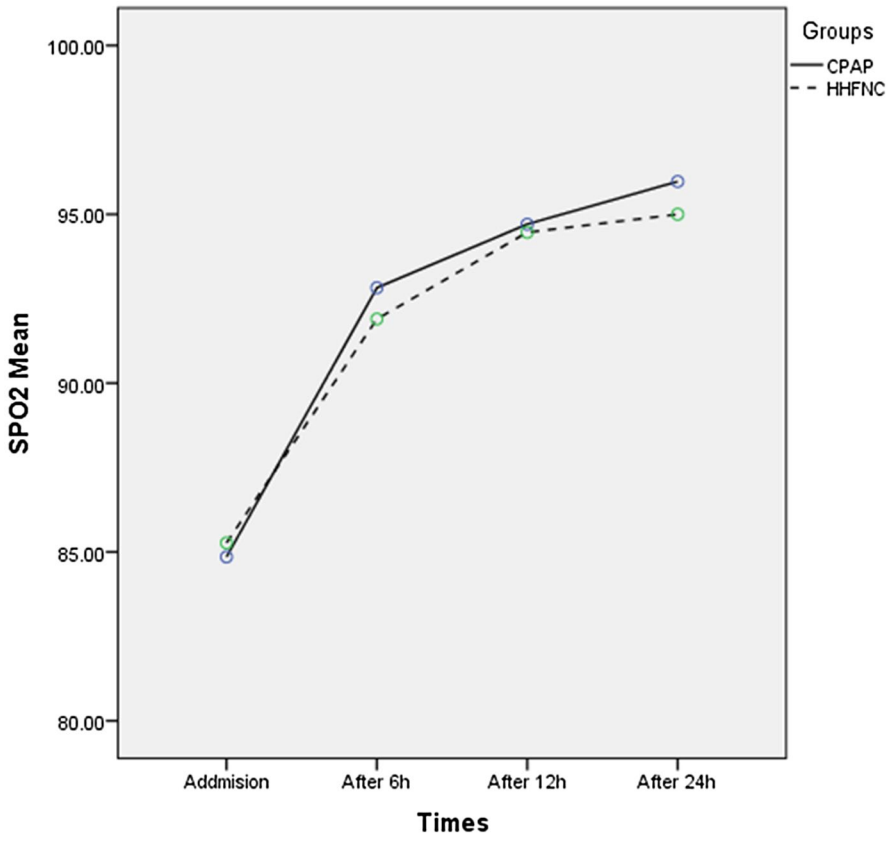

FIGURE 2 SpO2 percentage in the NCPAP and HHHFNC groups at different time intervals

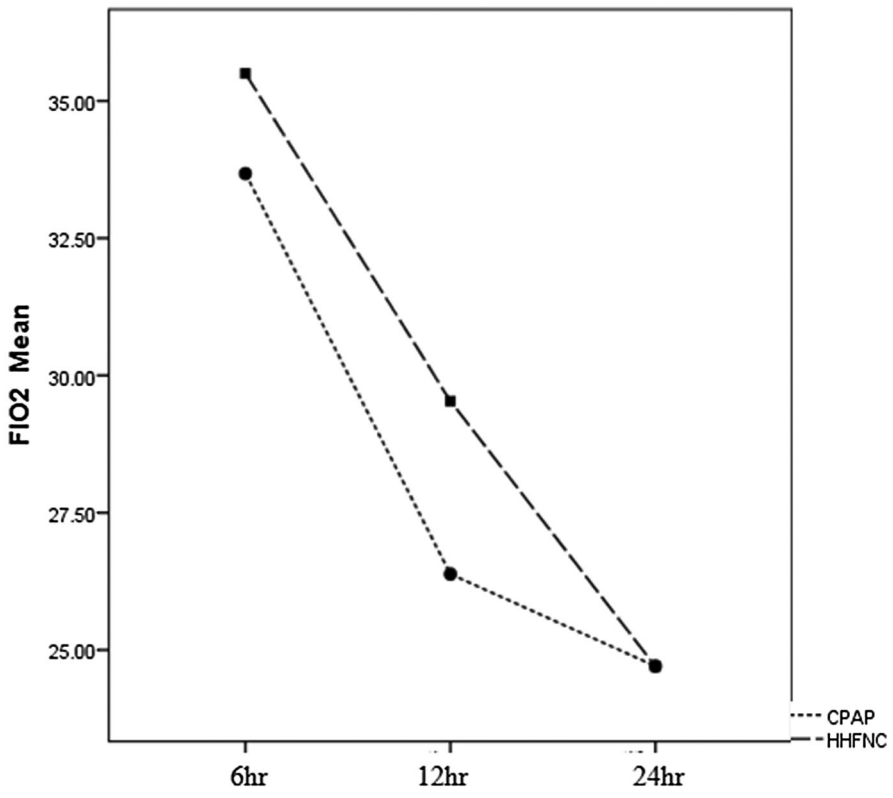

FIGURE 3 FIO2 percentage in both NCPAP and HHHFNC groups at different time intervals

as mechanical problems in inserting the nasal prongs to the small nares of the preterm infant and fitting them in the appropriate place, nasal septum trauma caused from nasal prongs and intolerance for the establishment of NCPAP by infants.[11,12]

The limitations of this study were small sample size, conclusions not extendible to infants with a GA <27 weeks and the other limitation was this study specifically has been done on babies with RDS and no other respiratory problem.

TABLE 2 Secondary outcome in two groups

Secondary outcome	Group NCPAP N = 32	Group HHHFNC N = 30	*P* value
Duration of hospitalization	33.9 ± 22.6	34.6 ± 25.2	0.9
Complication			
Pneumothorax	2	2	0.81
IVH	2	3	
Treatment failure	4 (11.8%)	5 (16.7%)	0.57

5 | CONCLUSION

The results of this study indicated that the values of FiO2 needed at 6, 12 and 24 h after treatment were not different between NCPAP and HHHFNC groups. Therefore, the HHHFNC in preterm infants with respiratory distress may be as effective as NCPAP to treat the neonates with RDS after surfactant administration, similar failure rate and desirable respiratory care method if the NCPAP is not available and an appropriate alternative one.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

ZA and MH conceived the research question, designed the protocol, and were involved in the literature search, study selection, and data extraction. ZA, MH, SKH and AM contributed to data acquisition, analysis, and interpretation. MA and YZP created the tables and figures.

ETHICS

This research project was approved by the research committee of the Babol University of Medical Sciences and by the ethics committee of this university (ethic code: MUBABOL.REC.1396.58). Clinical trial registry and registration number IRCT2018022603865N1.

ORCID

Zahra Akbarian-rad https://orcid.org/0000-0003-0668-1137
Avishan Mohammadi https://orcid.org/0000-0002-1567-7319
Soraya Khafri https://orcid.org/0000-0002-2398-7560
Mousa Ahmadpour-kacho https://orcid.org/0000-0001-8572-2026
Yadollah Zahed-pasha https://orcid.org/0000-0002-3011-0361
Mohsen Haghshenas-Mojaveri https://orcid.org/0000-0001-7427-2576

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