High Flow Nasal Cannulae versus Nasal Continuous Positive Airway Pressure in Neonates with Respiratory Distress Syndrome Managed with INSURE Method: A Randomized Clinical Trial

Maliheh Kadivar, MD; Ziba Mosayebi, MD; Nosrat Razi, MD; Shahin Nariman, MD; Razieh Sangsari, MD

Department of Neonatology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Correspondence: Razieh Sangsari, MD; Children’s Medical Center, 62 Gharib Street Zip Code: 14197-33151, Tehran, Iran
Tel: +98 21 66920983
Fax: +98 21 66929235
Email: raz3532@yahoo.com
Received: 31 August 2015
Revised: 07 October 2015
Accepted: 01 November 2015

Abstract

Background: In recent years, various noninvasive respiratory support (NRS) of ventilation has been provided more in neonates. The aim of this study was to compare the effect of HFNC with NCPAP in post-extubation of preterm infants with RDS after INSURE method (intubation, surfactant, extubation).

Methods: A total of 54 preterm infants with RDS (respiratory distress syndrome) were enrolled in this study. Using a randomized sequence, they were assigned into two groups after INSURE method. The first group received HFNC while the second group received NCPAP for respiratory support after extubation. A comparison was made between these two groups by the rate of reintubation, air leak syndrome, duration of oxygen therapy, hospitalization, the rate of bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and mortality. Data were analyzed by using the SPSS version 18 software. The statistical analyses included Student’s t-test for continuous data and compared proportions using Chi-squared test and Fisher’s exact test for categorical data.

Result: The rate of reintubation was higher in the HFNC compared with the NCPAP group. The rate of either IVH or ROP had no significant differences between the two groups. In addition, duration of oxygen requirement and hospitalization were not statistically different. There was no case of BPD or mortality among these patients.

Conclusion: This study showed that preterm infants with RDS managed post extubation after intubation-surfactant-extubation (INSURE) method with either on nasal continuous positive airway pressure (NCPAP) or high-flow nasal cannulae (HFNC).

Trial Registration Number: IRCT201201228800N1

What’s Known

- Heated humidified high-flow nasal cannulae (HHHFNC) have been used to provide supplemental oxygen and positive end-expiratory pressure (PEEP).
- HHHFNC are easy to use and offer better tolerance, easier movement, and more attachment between infant and parents.
- Less nasal injury by HHHFNC has resulted in the use of this type of noninvasive respiratory support in neonates.
- Preterm infants with respiratory distress syndrome (RDS) can be managed post extubation after intubation-surfactant-extubation (INSURE) method with either on nasal continuous positive airway pressure (NCPAP) or high-flow nasal cannulae (HFNC).

What’s New

- Although preterm infants with RDS managed by the INSURE method were supported post extubation via either HFNC or NCPAP, the rate of reintubation was higher in HFNC. Higher level of flow rate in the HFNC group requires further multicenter studies for solid conclusions.

Keywords

- Oxygen inhalation therapy infant-newborn
- Premature birth
- Pulmonary surfactants
Introduction

In recent years, various noninvasive respiratory support (NRS) of ventilation has been provided more in neonates, especially preterm infants.\(^1\) The continuous positive airway pressure (CPAP) is one of the most common methods of NRS that has been used in neonatal period, especially via nasal prongs as NCPAP.\(^1,2\) Nowadays, it is generally practiced in neonates with RDS by INSURE method after surfactant administration via endotracheal tube, and then extubation to NCPAP.\(^2\) However, there are some concerns about NCPAP; such as nasal trauma, deformity of nostrils, and columellar necrosis, along with discomfort of infants and difficulty in nursing care.\(^3,4\) Therefore, heated humidified high-flow nasal cannulae (HHHFNC) has been used in some centers in the past decade to provide supplemental oxygen and positive end expiratory pressure (PEEP) by nasal cannulae (NC).\(^5,6\) On the other hand, the ease of use, better tolerance, easier movement, more attachment between infant and parents, less nasal injury of HHHFNC have recently resulted in a wide use of this type of NRS, especially in preterm infants in most centers.\(^2,7,8\)

The aim of this study was to compare the effect of HFNC and NCPAP in post-extubation of preterm infants with respiratory distress syndrome (RDS) after surfactant administration via INSURE method on the rate of reintubation, duration of oxygen therapy, hospitalization, BPD, IVH, ROP, and mortality in an inborn neonatal intensive care center.

Patients and Methods

This study was approved by the Ethics Committee of Tehran University of Medical Sciences and registered in IRCT. Written informed parental consent was obtained before the enrollment. This was a prospective block randomized pilot study conducted at the inborn neonatal intensive care unit (NICU) in Arash Hospital; affiliated with Tehran University of Medical Sciences in Tehran (Iran) from April 2011 to May 2012.

The sample size was estimated 54 (27 in each group) with a type I error less than 5% and power greater than 80%. Preterm infants with gestational age 28-34 weeks with severe RDS who had needed surfactant replacement therapy within 48 hours after birth were enrolled in this study. Maternal characteristics (e.g. age), medical problems (e.g. diabetes or hypertension during pregnancy, gestational age, mode of delivery, prenatal corticosteroid administrations), and neonatal characteristics (e.g. birth weight, and sex of infants) were included by block randomized pilot study. Otherwise, the differences between the two groups were not significant regarding the maternal and neonatal characteristics.

The inclusion criteria were RDS, had required surfactant replacement therapy within 48 hours after birth, and extubated in one hour of surfactant replacement therapy. The exclusion criteria were any signs of asphyxia (5 minute Apgar score ≤5), another respiratory disease other than RDS, major congenital anomalies, and had not needed surfactant replacement therapy within 48 hours after birth or had long intubation for more hours. To avoid maldistribution of GA and sex, the patients were blocked on these two variables by using four categories, namely 28-30 weeks males, 28-30 weeks females, 31-34 weeks males, and 31-34 weeks females (table 1).

Preterm infants with respiratory distress syndrome and RDS score >7 and/or fraction of inspired oxygen (FiO\(_2\)) requirement more than 0.4, who were candidate of exogenous surfactant administration by neonatologist,\(^9,10\) were intubated for surfactant replacement therapy (Survanta, Abbott Comp, USA; 4 ml/kg via endotracheal tube). Patients extubated within one hour after INSURE method according to the institutional guideline and the neonatologist’s assessment with the target pulse oximeter 90-92% were included. All infants were loaded with caffeine citrate prior to extubation. The patients assigned to group 1 and 2 post extubation in random order. In the first group, they received NCPAP (Dragger, Lubeck, Germany) after extubation, while group 2 received HFNC (Fisher & Paykel Healthcare, Auckland, New Zealand). HFNC group received flow according to the below formula\(^11,12\) and were titrated according to arterial blood gases of neonates and pulse oximeter.

\[
\text{Flow L/min}=0.92 + [0.68 \times \text{Weight (in kg)}]
\]

We were more cautious to use higher flow rate as this was a pilot study and we were

| Variable          | NCPAP (n=27) | HFNC (n=27) | P    |
|-------------------|--------------|-------------|------|
| Girl              | 13           | 13          | 0.99 |
| Boy               | 14           | 14          | 0.99 |
| 28-30 weeks       | 9            | 9           | 0.99 |
| 31-34 weeks       | 18           | 18          | 0.99 |
| Prenatal corticosteroid | 10       | 14          | 0.27 |
| Administration of caffeine | 27         | 27          | 0.99 |
| Gestational age   | 31.33        | 31.52       | 0.7  |
| Weight            | 1,601        | 1,642       | 0.7  |
dealing with a new device in our setting. Thus, we considered 4 L/min along with FiO<sub>2</sub>≤0.6 as the maximal acceptable flow. In the NCPAP group, the minimal starting pressure was a sustained PEEP of 5 cmH<sub>2</sub>O along with FiO<sub>2</sub>≤0.3 and were titrated according to arterial blood gases of neonates and pulse oximeter. Maximal acceptable distending pressure was 8 cmH<sub>2</sub>O if infants needed FiO<sub>2</sub>＞0.3.

The patient was reintubated if hypercapnea (pCO<sub>2</sub>≥60) with pH＜7.25 and/or paO<sub>2</sub>＜50 with FiO<sub>2</sub>＞0.6 had been detected. The primary outcome was remaining extubated for at least 3 days after INSURE method. The secondary outcomes were included as; duration of oxygen requirement and hospitalization (days), air leak syndrome, BPD, IVH, ROP, and mortality rate.

Data were analyzed using SPSS version 18 software. The statistical analyses included Student's t-test for continuous data and compared proportions using Chi-squared test, and Fisher’s exact test for categorical data. P values ＜0.05 were considered statistically significant.

**Results**

A total of 42 infants with the same GA were admitted during the study period, but did not meet the inclusion criteria. This was due to either congenital anomalies, another respiratory disease other than RDS, asphyxia, extubated after one hour of INSURE method, or needed surfactant replacement therapy after 48 hours birth. As shown in figure 1, 18 out of 54 included infants (33%) failed and required reintubation in INSURE method, which was higher in the HFNC group (14 vs. 4, P＜0.004). Reintubation was higher in the HFNC group among preterm infants with gestational age of 28-30 weeks and 31-34 weeks compared with the NCPAP group. Reintubation was higher in the HFNC group that received partial prenatal corticosteroid too (delivery occurred more than 24 hours after starting, at least, one dose of betamethasone). Five of the 14 neonates who received partial prenatal course of corticosteroid in the HFNC group, were reintubated compared to none of the 10 neonates of NCPAP with the same situation. Neonates of 31-34 weeks gestation were likely to benefit from INSURE method in both groups, 27 of 36 neonates of this gestation were not reintubated compared with the 9 out of 18 neonates of the 28-30 weeks GA who were not reintubated in both groups (table 2).

Secondary outcome included either IVH or ROP, had no significant differences in these

---

**Figure 1:** Participants’ CONSORT flow diagram.

- **Enrollment**: Assessed for eligibility (n=150)
  - Excluded (n=42)
    - Not meeting inclusion criteria (n=42)
    - Declined to participate (n=0)
    - Other reasons (n=0)
- **Randomized (n=108)**
  - Allocated to intervention HFNC (n=54)
    - Received allocated intervention (n=54)
    - Did not receive allocated intervention (give reasons) (n=0)
  - Allocated to intervention NCPAP (n=54)
    - Received allocated intervention (n=54)
    - Did not receive allocated intervention (give reasons) (n=0)
- **Follow-Up**: Lost to follow-up (n=0)
  - Discontinued intervention (n=14): required reintubation
- **Analysis**: Analyzed (n=40)
  - Excluded from analysis (give reasons) (n=0)
Compare HFNC with NCPAP using the INSURE method

Also, duration of oxygen therapy and hospitalization in NICU were not statistically different between the groups. However, the mean duration of oxygen requirement were 5.07 days and 4.56 days in the HFNC and NCPAP groups, respectively. In addition, the mean duration of hospitalization in NICU was 11.6 days in the HFNC group compared with 13.11 days in the NCPAP group. There were no cases of BPD or mortality among these patients in both groups (table 3). We did not have deformity of nostrils, columellar necrosis, or other complications among the groups in this study.

**Discussion**

Sreenan et al. compared standard HFNC with NCPAP in preventing apnea of prematurity, which had detected the effectiveness of HFNC in the management of neonates with apnea and bradycardia. However, Campbell and Wilkinson suggested that HFNC probably should not be used as an equivalent form of CPAP in preterm infants compared with NCPAP. They found that HFNC was associated with increases in the number of extubation failures and a higher level of oxygen requirement. Yoder et al. showed that among infants ≥28 weeks of GA, HHHFNC appeared to have similar efficacy and safety to NCPAP when applied immediately post extubation or as early as initial noninvasive support for respiratory dysfunction. Shoemaker et al. compared HHHFNC with NCPAP for neonatal respiratory disease. They reported that premature infants less than 30 weeks of gestational age well tolerated HHHFNC without apparent differences in adverse outcomes comparable with NCPAP, and HFNC has largely replaced NCPAP as the preferred mode of NRS. Lampland et al. found that HFNC can produce continuous distending pressure, but having a pressure-limiting valve within a HFNC system appears to be necessary to limit the potential for inadvertent delivery of very high distending pressures.
pressures to the preterm lung.\textsuperscript{15} Saslow et al. compared the work of breathing (WOB) with HFNC and NCPAP in premature neonates. They reported that HFNC can provide CPAP and replace NCPAP in preterm infants with mild respiratory disease.\textsuperscript{6} Collin showed that with a flow rate of 8 L/min, there was no difference in the rates of extubation failure between infants randomly placed on either NCPAP or HFNC in the first 7 days after extubation. However, nasal trauma was significantly less in HHHFNC group compared with NCPAP.\textsuperscript{3} Iranpour and his colleagues compared NCPAP and HFNC in preterm infant (30–35 weeks gestation) with RDS, who had received NCPAP for the first 24 hours after birth. They showed HFNC was as effective as NCPAP in the management of RDS in premature neonates more than 30 gestational weeks. In addition, HFNC performed easier than NCPAP by maintaining a normal nasal mucosa.\textsuperscript{16} Holleman-Duray et al. showed that HFNC is a safe and well-tolerated device for extubated neonates and decreased the duration of invasive respiratory therapy, especially in preterm infants. Therefore, it can decrease the rate of ventilator associated with pneumonia and ventilator induced lung injury due to less duration of mechanical ventilation.\textsuperscript{17} Spence et al. studied intrapharyngeal pressure generated by HFNC at varying flow rates. They showed that HFNC could deliver significant intrapharyngeal pressure and replace NCPAP at flow rate 3 min/L or more in respiratory care of infants.\textsuperscript{18}

In this study, we compared NCPAP with HFNC in preterm infants with RDS who received surfactant prior to extubation after INSURE approach and randomly placed on either NCPAP or HFNC. According to our study, the rate of reintubation was higher in the HFNC group (14 vs. 4, \textit{P}<0.004) which is the same as Campbell’s findings (12 vs. 3, \textit{P}<0.003).\textsuperscript{12} However, the finding of Shoemaker were different to ours (18\% vs. 40\%, \textit{P}<0.03). There were no statistically significant differences noted in the incidence of secondary outcomes between the two groups in either Campbell’s or our study (IVH, ROP, BPD, air leak, duration of oxygen therapy, and hospitalization).

We used a maximum flow rate of 4 L/min, thus, it is possible that the rate of failure and reintubation would be lower if we had used higher flow rate.\textsuperscript{19} Shoemaker used a wide flow rate (2.5–8 L/min),\textsuperscript{14} but Collins and his colleagues used a much higher starting flow rate (8 L/min).\textsuperscript{3} They showed that using a flow rate of 8 L/min, there was no difference in the rates of extubation failure. A study by Spence showed that HFNC could be replaced by NCPAP at a flow rate of 3 min/L or more in respiratory care of infants.\textsuperscript{18} We were more cautious to use higher flow rate as this was a pilot study and we were dealing with a new device in our setting. The pressure generated is varied in infants treated with HFNC and is dependent on the flow rate and infant’s weight.\textsuperscript{13} Therefore, differences between flow rates for HHHFNC were considered a possible source of heterogeneity for extubation failure.\textsuperscript{19}

Based on the results of this study, there is insufficient evidence to determine whether HFNC is safe or as effective as a form of respiratory support in preterm infants.

The main limitation of our study was the small number of patients from a single center. Further randomized multicenter studies, including a larger group of patients in multiple centers are necessary for a better evaluation of HFNC as a noninvasive device.

Clinicians are using HFNC for respiratory treatment of RDS infants after extubation and replaced NCPAP instead of HFNC for respiratory care of neonates with apnea. Although, in the absence of sufficient clinical trial studies, there have been some concerns about the widespread use of these devices.\textsuperscript{6} The airway pressure delivered using a HFNC will vary with flow rate and the presence of leaks within the airway is according to cannulae size and infants weight. However, the operators generally have no knowledge of the actual level of airway pressure delivered to the infant via HFNC.\textsuperscript{13,19,20} It is hoped that adequate randomized trial studies in the future would define a safe and effective flow rate of HFNC and clarify guidelines for respiratory care via HFNC instead of NCPAP for non-invasive respiratory support in neonates for more attachment between infant and parents.

**Conclusion**

According to this study, preterm infants with RDS who had received surfactant by INSURE method could be managed post extubation via either HFNC or NCPAP. The ease of use of this device for nurses, better tolerance of infants, and more attachment between infant and parents may justify this replacement. Although, in this short study, the rate of reintubation was higher in the HFNC group, but it seems that higher level of maximum flow rate would be necessary for a better evaluation of this modality. We were more cautious to use higher flow rate as this was a pilot study and we were dealing with a new device in our setting. Therefore, we restricted ourselves to a maximum flow rate of 4 L/min. The pressure generated in infants treated with HFNC is dependent on the flow rate.
Consequently, lower flow rates for HFNC were considered as a possible source of extubation failure. Probably, the rate of failure and reintubation would have been lower if we had used a higher flow rate in our study. In addition, as a limitation of this study, the number of infants was too few. Therefore, we recommend further randomized multicenter studies, including larger group of patients and higher level of maximum flow rate for a better evaluation of HFNC as noninvasive device in preterm infants with RDS who received surfactant via INSURE approach instead of NCPAP.

Acknowledgement

This project was supported by “Maternal, Fetal, and Neonatal” Research Center at Tehran University of Medical Sciences. The authors would like to thank all patients who participated in this study, the personnel of NICU at Arash Hospital, and Dr. Alireza Ahmadvand for his excellent support with the statistical analysis.

Conflict of Interest: None declared.

References

1. LeVan JM, Brion LP, Wrage LA, Gantz MG, Wyckoff MH, Sanchez PJ, et al. Change in practice after the Surfactant, Positive Pressure and Oxygenation Randomised Trial. Arch Dis Child Fetal Neonatal Ed. 2014;99:F386-90. doi: 10.1136/archdischild-2014-306057. PubMed PMID: 24876196; PubMed Central PMCID: PMC4134421.
2. Dani C, Corsini I, Bertini G, Fontanelli G, Pratesi S, Rubaltelli FF. The INSURE method in preterm infants of less than 30 weeks’ gestation. J Matern Fetal Neonatal Med. 2010;23:1024-9. doi: 10.3109/14767050903572174. PubMed PMID: 20180736.
3. Collins CL, Holberton JR, Barfield C, Davis PG. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. J Pediatr. 2013;162:949-54 e1. doi: 10.1016/j.jpeds.2012.11.016. PubMed PMID: 23260098.
4. Ramanathan R. Nasal respiratory support through the nares: its time has come. J Perinatol. 2010;30 Suppl: S67-72. doi: 10.1038/jpeds.2010.99. PubMed PMID: 20877411.
5. Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? Pediatrics. 2008;121:82-8. doi: 10.1542/peds.2007-0957. PubMed PMID: 18166560.
6. de Klerk A. Humidified high-flow nasal cannula: is it the new and improved CPAP? Adv Neonatal Care. 2008;8:98-106. doi: 10.1097/01.ANC.0000317258.53330.18. PubMed PMID: 18418207.
7. Yoder BA, Stoddard RA, Li M, King J, Dimberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics. 2013;131:e1482-90. doi: 10.1542/peds.2012-2742. PubMed PMID: 23610207.
8. Saslow JG, Aghai ZH, Nakhta TA, Hart JJ, Lawrysh R, Stahl GE, et al. Work of breathing using high-flow nasal cannula in preterm infants. J Perinatol. 2006;26:476-80. doi: 10.1038/sj.jp.7211530. PubMed PMID: 16688202.
9. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Neonatology. 2013;103:353-68. doi: 10.1159/000349928. PubMed PMID: 23736015.
10. Polin RA, Carlo WA, Committee on F, Newborn, American Academy of P. Surfactant replacement therapy for preterm and term neonates with respiratory distress. Pediatrics. 2014;133:156-63. doi: 10.1542/peds.2013-3443. PubMed PMID: 24379227.
11. Sreenan C, Lemke RP, Hudson-Mason A, Osovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. Pediatrics. 2001;107:1081-3. doi: 10.1542/peds.107.5.1081 PubMed PMID: 11331690.
12. Campbell DM, Shah PS, Shah V, Kelly EN. Nasal continuous positive airway pressure from high flow cannula versus Infant Flow for Preterm infants. J Perinatol. 2006;26:546-9. doi: 10.1038/sj.jp.7211561. PubMed PMID: 16837929.
13. Wilkinson D, Andersen C, O’Donnell CP, De Paoli AG. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev. 2011;CD006405. doi: 10.1002/14651858. CD006405.pub2. PubMed PMID: 21563154.
14. Shoemaker MT, Pierce MR, Yoder BA, DiGeromino RJ. High flow nasal cannula versus nasal CPAP for neonatal respiratory
disease: a retrospective study. J Perinatol. 2007;27:85-91. doi: 10.1038/sj.jp.7211647. PubMed PMID: 17262040.

15. Lampland AL, Plumm B, Meyers PA, Worwa CT, Mammel MC. Observational study of humidified high-flow nasal cannula compared with nasal continuous positive airway pressure. J Pediatr. 2009;154:177-82. doi: 10.1016/j.jpeds.2008.07.021. PubMed PMID: 18760803.

16. Iranpour R, Sadeghnia A, Hesaraki M. High-Flow Nasal Cannula Versus Nasal Continuous Positive Airway Pressure in the Management of Respiratory Distress Syndrome. Archives of Disease in Childhood. 2012;97:A115-A6. doi: 10.1136/archdischild-2012-302724.0393.

17. Holleman-Duray D, Kaupie D, Weiss MG. Heated humidified high-flow nasal cannula: use and a neonatal early extubation protocol. J Perinatol. 2007;27:776-81. doi: 10.1038/sj.jp.7211825. PubMed PMID: 17855805.

18. Spence KL, Murphy D, Kilian C, McGonigle R, Kilani RA. High-flow nasal cannula as a device to provide continuous positive airway pressure in infants. J Perinatol. 2007;27:772-5. doi: 10.1038/sj.jp.7211828. PubMed PMID: 17762844.

19. Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, et al. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2013;369:1425-33. doi: 10.1056/NEJMoa1300071. PubMed PMID: 24106935.

20. Finer NN, Mannino FL. High-flow nasal cannula: a kinder, gentler CPAP? J Pediatr. 2009;154:160-2. doi: 10.1016/j.jpeds.2008.08.021. PubMed PMID: 19150670.