

Comparison of Nasal Non-invasive Ventilation Methods in Preterm Neonates with Respiratory Distress Syndrome

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ABSTRACT

Background: Humidified heated high flow nasal cannula (HHHFNC), nasal continuous positive airway pressure (NCPAP), and nasal intermittent positive pressure ventilation (NIPPV) are three nasal non-invasive ventilation methods. The purpose of this study was to compare these three methods in decreasing intubation and mechanical ventilation rate in preterm neonates with respiratory distress syndrome (RDS).

Methods: This study was a randomized controlled study conducted on 160 neonates. The inclusion criteria for intubation in this study were persistent respiratory acidosis (arterial pH<7/2 or PCO₂>60), hypoxemia, severe and repeated apnea episodes which did not respond to increasing respiratory rate and therefore required ventilation. Cranial Ultrasound was performed on the third day after birth. The data of all neonates were collected until the day of discharge and analyzed by SPSS (version 20) and statistical methods.

Results: Based on the results, there was no significant difference among the three randomized methods. Out of all the cases, 72% of the neonates with NIPPV had successful non-invasive ventilation (35/53), compared to 73/6% in NCPAP (39/53) and 72/2% in HHHFNC (P=0/999). Similarly, there was no significant difference among the three methods in total ventilation time and the need for supplemental oxygen.

Conclusion: The use of HHHFNC at birth in preterm neonates with RDS is safer than the other two methods. However, it is not more effective than the other two methods in the reduction of intubation rate.

Keywords: Humidified heated high flow nasal cannula (HHHFNC), Nasal continuous positive airway pressure (NCPAP), Nasal intermittent positive pressure ventilation (NIPPV), Preterm neonates, Respiratory distress (RDS)

Introduction

Currently, the use of surfactant and mechanical ventilation through intubation are the standard care in respiratory support in preterm infants with respiratory failure. However, the role of some other non-invasive respiratory support is increasing rapidly. Definitely, none of these non-invasive favorable options is superior comparing to intubation and surfactant administration, but these methods have been applied due to less morbidity and cost, and desired outcome (1).

Many disorders can decrease the respiratory support especially in preterm neonates, such as neonatal apnea, hypoventilation, atelectasis, lung hemorrhage, aspiration syndrome, delivery asphyxia, infection, and air leak syndrome. Despite

the fact that the introduction of invasive mechanical ventilation in neonatal intensive care cause to improve in the premature neonatal surveillance, but it has resulted in the occurrence of some complications.

One of the most important complications of neonates with very low birth weight (i.e., less than 1500 g), is bronchopulmonary dysplasia (BPD) that leads to neonatal death. In the present study the risk factors that can increase the BPD incidence (up to 35-60%) among the study population were endotracheal positive pressure ventilation, complementary oxygenation, perinatal inflammation (e.g., chorioamnionitis), PDA neuro-developmental problems, and re-admission during

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the first year (2, 3).

Endotracheal intubation and mechanical ventilation cause airway and lung inflammation and impaired lung development, and eventually bring about BPD. The most sensitivity rate of lung tissue in premature neonates was in transitional phase when stiff collapsed lung of premature neonate should be inflated with the air for the proper function (ventilation and oxygenation) (2, 4).

These concerns have encouraged neonatologists to use non-invasive modes of ventilation. Non-invasive ventilation (NIV) in neonates has already been used only to maintain effective breathing after a period of intubation and avoid extubation failure for the reduction of the total intubation time. A recent trend has begun to use NIV not only as a secondary-assisted method after intubation, but also as a primary mode of ventilation as an alternative for intubation regarding early management of respiratory distress syndrome (RDS).

NIV in neonates has been used for almost over half a century. However, First forms of NIV (applied through facial mask) had severe complications, such as head molding, cerebral hemorrhage, and gastric perforation, that restricted its use. During the time, the development of interfaces and more modern devices reduced these complications and the neonatologists were again more interested in applying new methods of NIV (1).

Respiratory failure in premature neonates is common for at least two reasons, including the immaturity of respiratory system and unstable chest wall, which makes the airways easy to collapse. The exact mechanism of how NIV affects preterm neonates is not clear, but several theories have been postulated, for instance stimulating the upper airways that could be helpful in obstructive sleep apneas and make extubation easier after invasive ventilation. Increasing respiratory efforts in preterm neonate may lead to increasing surfactant production and as a result, functional residual capacity may improve. However, it has not yet been proved in large controlled trials that the main potential advantage of non-invasive ventilation is the prevention of ventilator-induced lung injury, BPD, and ultimately some side effects of endotracheal intubation.

High flow nasal cannula (HFNC) was small, thin, and tapered cannula used to deliver blended oxygen and air at flow rates higher than 1 L/min (more than patients inspiratory flow rate). The use of high flow rates in preterm newborns might provide positive end-expiratory pressure (PEEP)

(2). In this method, oxygen was supplied through nasal cannula that flowed just inside the nostrils without occluding them (5, 6). Oxygen administered via HFNC was usually blended with air, heated, and humidified (2) use of un-humidified. Unheated HFNC has been associated with mucosal irritation, nasal obstruction or bleeding, as well as a possible increase in the risk of nosocomial infection (3).

When HFNC was used following the extubation, it might be associated with a higher rate of reintubation than nasal continuous positive airway pressure (NCPAP). There was not enough evidence to tell if HFNC were safe or effective compared to other ways of supporting premature neonates with breathing problems. The main problem with HFNC was that the generated-pressure was not measurable and could not be regulated.

Other probable problems with HFNC include (in few case reports) the contamination of the units used for administration of HFNC with gram negative or positive organisms, pneumocephalus, pneumo-orbitis, scalp emphysema, possibility of lung overdistension and trauma from unmeasured and variable PEEP with high flow nasal cannula, and gastric distension or perforation (2). The advantages of HFNC were ease of use and less nasal trauma; therefore, it was more popular among neonatal nurses.

NCPAP was commonly used in term or preterm neonates as an effective and safe alternative to endotracheal intubation. It may minimize extubation failure, apnea treatment, or RDS, and decrease chronic lung diseases by the reduction of mechanical ventilation time (1, 2). Methods for delivering NCPAP or NIPPV to the nose include binasal prongs, single nasal prongs, and nasal masks. Binasal prongs were the most effective and popular methods for administration of CPAP. These prongs fit completely into the neonate's nostrils in a way that the air leak is minimal. The main disadvantage of binasal prongs is nasal trauma and distortion of the nares.

Similar to HHHFNC, the Oxygen administered by NCPAP should be blended, humidified, and heated. However, in contrast to HFNC, the generated pressure in NCPAP was measured and directly regulated (2). Even though, NCPAP was accepted as standard method of respiratory support for preterm neonates in delivery room, this method was failed in 40% of neonates, so they need mechanical ventilation in first week of their life.(2)

Today NIPPV is widely used but its exact role

in neonatal respiratory support has not fully been perceived. Current belief in very premature neonates is that if NIPPV is used after extubation it may reduce the need for reintubation. In addition, it may increase tidal volume and minute ventilation and marginally improve gas exchange by reducing breathing work and thoraco-abdominal asynchrony. Consequently, it can decrease extubation failure and apnea rates. Nonetheless, it has not yet proved that this method can reduce BPD or not. NIPPV has complications similar to CPAP, such as gastric distension, nasal trauma, pneumothorax, gastric distention, and other theoretical complications due to high nasopharynx pressure similar to middle ear infection, hearing impairment, chronic mucosal inflammation, necrotizing enterocolitis or Intraventricular hemorrhage (2, 3).

The Main goal of any form of supportive ventilation is to maintain physiologic respiratory condition and acceptable blood gas parameters while minimizing the side effects. Although there has been useful progression over last 20 years in understanding of NIV use in neonates, further research is still needed for the best ways of using this approach. In this study

The purpose of this study was to compare three nasal non-invasive ventilation methods, namely HHHFNC, NCPAP, and NIPPV, in decreasing intubation and mechanical ventilation rate in preterm neonates with RDS in a tertiary referral neonatal intensive care unit (NICU) center.

Methods

This study was conducted on preterm neonates with gestational age of 28-34 weeks and birth weight of 800-2500 g, admitted to intensive care unit of Imam Reza hospital due to respiratory distress syndrome. If parental consent was obtained, oxygen therapy was randomly performed on the neonate via appropriate size of nasal cannula for HHHFNC method, or a nasal prong for two other methods. The study population was 160 neonates and the data were collected through randomized convenience sampling method. All the neonates entering the study were randomized groups matched for birth weight and gestational age. Each group received oxygen via one of the following methods using nasal cannula or nasal prong:

- Humidified high flow nasal cannula (HHFNV) method: primary flow was based on patient weight (equal to or more than 2 lit/min) and increased with patient's needs (up to 5

lit/min).

- Nasal continuous positive airway pressure (NCPAP) method: primary CPAP pressure was set to 6 cmH₂O (up to 8cmH₂O).
- Nasal intermittent positive pressure ventilation (NIPPV) method's set up onset was, pick inspiratory pressure of less than 18 cmH₂O and positive end expiratory pressure (PEEP) of 4-5cmH₂O, then increased by 1cmH₂O to the stabilization of patient. Oxygen concentration (FiO₂) that delivered to newborns, was variable (up to 50%) according to patients' needs in each method.

Orogastric tube was laid and fixed for all neonates to reduce gastric distention. Neonatal monitoring was performed via continuous pulse oximetry and obtaining intermittent blood gases to ensure that the patient was stable and did not need endotracheal mechanical ventilation. The intubation criteria were severe apnea, PCO₂>60 and pH<7.25, and refractory hypoxia despite receiving FiO₂>50%. Surfactant therapy was performed with INSURE method (intubation surfactant extubation) via temporary intubation and immediate extubation after the surfactant administration to nasal method. In this study methylxanthine therapy was used since the first day of birth of the neonate.

The primary outcome was obtained, if the endotracheal intubation and invasive ventilation was not necessary, within the first 72 h after birth.. If the cases were clinically suspected, chest X-ray was taken, to exclude complications, such as pneumothorax, collapse, or pneumonia. Cranial ultrasound was performed for all the cases on the third day after birth for the detection of possible intraventricular hemorrhage. Neonates were observed and evaluated in terms of nasal injury, patent ductus arteriosus (PDA) signs (i.e., new cardiac murmur, banding pulse) or abdominal distension. Echocardiography was performed for suspected PDAs. Furthermore, abdominal X-ray was performed for the exclusion of necrotizing enterocolitis (NEC).

Full sepsis workup was carried out, if clinical symptoms and signs of sepsis or laboratory suspicious, such as C-reactive protein more than 10mg/ lit appeared. BPD was considered if the cases needed supplemental oxygen more than 28 days. The exclusion criteria were the neonates with severe asphyxia (umbilical vein pH<7.0 and 5 min APGAR<5), major anomalies, birth weight less than 800g or more than 2500 g, gestational age less than 28 weeks or more than 34 weeks, congenital pneumonia, positive primary blood

culture, and parental dissatisfaction.

Data Analysis method

Appropriate statistical tables and indexes were used for data analysis. Kolmogorov-Smirnov test and Lilliefors test were used if it was necessary. Suitable parameters method for example variance analysis was used for data analysis. Kruskal-Wallis test was alternatively utilized for non-normal curves. Pearson Chi-Square test was employed for the analysis of nominal variables. Fisher's exact test was applied when more than 20% of expected frequency was less than 5. Linear models for the simultaneous evaluation of results were used. SPSS Software (version 20) was utilized and meaningful levels in statistical tests were considered less than 5%. The present study was approved by Mashhad Medical University Ethics Committee with (Code: 139380) and parental informed consent was obtained.

Results

From April 2014 to November 2014, 160 infants that met the study criteria were randomly categorized into three separate groups to receive NCPAP (53 patients), NIPPV (53 patients), or HHFNV (54 patients) instantly after birth. There were no significant differences in intercurrent variables, namely birth weight, gestational age, C-section, antenatal steroid, Apgar score, prenatal problems, and RDS grade, among the three groups.

The mean scores of gestational age and birth weight were $31.4 \pm$ weeks (SD: 1.9 w) and $1632 \pm$ (SD: 447.9), respectively. P-value was considered 0.262 and 0.937 without statistically significant differences among three groups. Out of all the cases, 55% and 43% of the patients were male and female, respectively. Type of delivery in 71% of the newborns was C-section and in other cases was normal vaginal delivery. Only 13.8% of the neonates did not receive antenatal steroid therapy.

Prolonged premature rupture of membrane

more than 18, maternal diabetes, and hypertension were reported in 25%, 7.5%, and 18% of the subjects, respectively. In addition, P-value was considered 0.566, 0.706, and 0.579 with no significant differences among the three groups (table1). The neonates ventilated noninvasively through NCPAP, IPPV, or HHFNV immediately after birth and surfactant was prescribed if needed via INSURE technique (intubation surfactant administration, and extubation to nasal ventilation). Surfactant was administered in 50.6% of all the cases with no significant differences among the three groups ($P=0.763$).

Out of all the neonates, 27% of patients in the first 72 h of life and 14.4% after that time needed mechanical ventilation via endotracheal tube. Significant differences for intubation need or even the time of first intubation were not observed among the three groups ($P=0.99, 0.675$). Mean duration of oxygen and nasal ventilation were 7.3 and 3.7 days, respectively ($P=0.333, 0.205$). The problems that lead to neonatal intubation were severe apnea, hypercapnia, and refractory hypoxia in 38.4%, 26.9%, and 34.7% of the patients.

Complications during nasal ventilation, such as PDA, pulmonary hemorrhage, sepsis, NEC, and collapse were not significantly different between the three groups. Only nasal damage occurred less significantly in HHHFNC group ($P=0.001$). Intraventricular hemorrhage (IVH) happened in 20.6% of the neonates with any significant differences among the three groups ($P=0.252$). However, based on the pairwise comparison, NIPPV group had more severe IVH grades than HHHFNC ($P=0.008$) and NCPAP group ($P=0.026$). The BPD, which was defined as the duration of oxygen therapy for more than 28 days occurred as an important complication in 3.8% of patients and P-values was considered 0.086. Mean duration of patients' hospitalization were 14.5 days and 12.5% during this period, and there was no significant difference among the three groups ($P=0.287, 0.913$) (table2).

Table 1. Demographic characteristics of the neonates in three groups

	NCPAP	NIPPV	HHFNC	P-value	
Number of patients	53	53	54		
Gestational age (week)	31.1(2)	31.8(1.7)	31.3(1.9)	0.262	
Birth weight (gr)	1650(486)	1622(437)	1624(425)	0.937	
Male	64.2%	45.3%	61.1%	0.114	
Cesarean section delivery	77.6%	66%	70.4%	0.440	
Prenatal steroid	83%	86.8%	88.9%	0.655	
APGAR 1min (Mean)	6.4	6.4	6.9	0.149	
APGAR 5min (Mean)	7.7	7.8	8	0.452	
Maternal problems	PPROM	20.8%	24.5%	29.6%	0.566
	DM	9.4%	7.5%	5.6%	0.706
	HTN	17%	22.6%	14.8%	0.579

Table 2. Outcomes in three groups

		NCPAP	NIPPV	HHFNC	P-value
Intubation	<72 h after birth	26.4%	28.3%	27.8%	0.999
	>72 h after birth	11.3%	20.8%	11.1%	0.312
Duration of mechanical ventilation (day)		3.1	4.5	3.5	0.660
Time of first intubation (h)		30.5	36	24.4	0.670
Duration of nasal ventilation (day)		3.4	4.2	3.5	0.205
Duration of oxygen therapy (day)		7.4	8.5	6.3	0.532
Surfactant		49.1%	54.7%	48.1%	0.763
Complications during nasal ventilation	IVH	17%	28.3%	16.7%	0.252
	Apnea	17%	24.5%	18.5%	0.641
	Hypercapnia	11.3%	13.2%	13%	0.999
	Sepsis	11.3%	13.2%	5.6%	0.339
	Air leak	9.4%	17%	13%	0.517
	pneumonia	5.7%	5.7%	5.6%	1
	collapse	6.7%	7.5%	7.4%	0.999
	GI complications	7.5%	9.4%	5.6%	0.706
	Pulmonary hemorrhage	3.8%	5.7%	7.4%	0.750
	Nasal damage	24.5%	39.6%	9.2%	0.001*
PDA		9.4%	11.3%	7.4%	0.750
Bronchopulmonary dysplasia		3.8%	7.5%	0%	0.086
Death		13.2%	13.2%	11.1%	0.913
Duration of hospitalization (day)		15.8	14.8	12.8	0.287

Discussion

In this randomized controlled trial preterm neonates between 28 and 34 weeks of gestational age, which needed oxygen therapy at birth time received ventilation support via one of the non-invasive ventilation methods (NCPAP, HHHFNC, or NIPPV). As primary object of this study, there is no difference among the three methods in necessity for intubation during the first 72 h. As secondary objects, for instance BPD incidence, total admission time, or total duration in which neonates needed supplemental oxygen therapy, there were no significant differences among the methods. Therefore, despite worrying about inability to measure airway pressure in HHHFNC; this method is safe and useful compared to other NIV methods.

Gas conditioning is important for the appropriate function of upper and lower airways for instance the reduction of metabolic load, maintenance of ciliary function, prevention of airway mucus injury, reduction of respiratory work (with the reduction of nasal resistance to airflow) and lung improvement mechanism (6). In HHHFNC method, the humidity of approximately 100% and temperature of 37° should be applied. In recent decades, it is possible to apply more humid and warmer airflow to patient for instance 2-8 lit per min for neonates and up to 50 lit per min for adults (6).

The first study performed by Fray (2003) demonstrated that 2 lit of airflow per min can cause up to 10 cm H₂O positive pressure. However, recent studies carried out in animal and

human models showed that the provided pressure measurements through pharynx and esophagi and even trachea in HHHFNC method is less than what was expressed by Fray in 2003 (7-9). Certainly, nasal cannula size is an important factor in HHHFNC since Lock et al. in 1993 revealed that if external cannula size was larger than 3 mm (completely packed the nares), it can provided pressure increase uncontrollably. However, this uncontrollable pressure was not observed less than 2 mm in cannula size (6). Accordingly, the nasal cannula with external diameter less than 3 mm was utilized in this study.

HHHFNC is a safe and useful method for preterm neonates with respiratory distress especially after extubation based on the following studies: Woodhead in 2006, Holman Duray in 2007, Shoemaker in 2007, and Miller in 2010 (10-12). However, Abdel-hady (2011) showed that changing from NCPAP to HHHFNC in comparison with direct changing from NCPAP to room air in 60 patients, did not improve oxygen therapy weaning, and consequently increased needed time for oxygen therapy.

However, in this study, the flow rate was less than 2 lit per min and appropriate temperature and enough humidity were not provided (13). Similarly, Campbell (2006) claimed that using high flow CPAP with continuous positive air pressure through nasal cannula, compared with NCPAP through nasal prong or endotracheal tube was considered less useful in extubation success. The use of nasal cannula was accompanied by

increased apnea experience and bradycardia after infant extubation. Furthermore, the flow rate in this study was less than 2 lit per min (14).

Although there is not any investigation to compare the three methods, namely NCPAP, NIPPV, and HHHFNC, simultaneously the results of the present study were compared with other studies, which were conducted on two of the mentioned methods(6)

Collins (2013) investigated 132 neonates with less than 32 weeks of gestational age and reported that reintubation chance during first week after extubation (in contrast to the present study) was similar in both HHHFNC and NCPAP methods while nasal trauma in HHHFNC was clearly less than NCPAP (15).

Although in the present study, newborns' mean of birth weight was lower and 10% of the subjects were less than 1 kg at birth, the need for intubation and duration of nasal ventilation were similar between the two groups. In this study similar to Ronald's study, HHHFNC method reduced nasal damage significantly. Therefore, nasal cannula with appropriate size along with gas conditioning can decrease nasal damage and with easier nursing consider HHHFNC as the preferred method.

In a retrospective study (2007), Pierce claimed that using high flow cannula in NICU centers increased up to 65% and contrastively using NCPAP decreased up to 20%. However, the mortality rate or severe complications for instance BPD did not changed and need for intubation decreased up to 18% in neonates that first received high nasal flow, as an alternative for NCPAP (5).

The NIPPV is recommended after extubation as a treatment for preterm neonate apnea. In contrast to NCPAP, in this method tidal volume and minute ventilation is higher and breathing work is lower (3). In comparison with NCPAP the majority of randomized controlled trials claimed that NIPPV as a post-extubation mode of assisted ventilation in preterm neonates has higher extubation success rate and lower chance of BPD incidence (4).

Many studies have been performed on these two NIV methods as a primary mode of oxygen therapy. Although most of the studies have demonstrated that temporary benefits in the use of NIPPV; nonetheless, there is not similar long-term outcome among the studies. Kugelaman et al. (2007) investigated NIPPV and NCPAP in preterm neonates with RDS. In contrast with the present study, their results showed that NIPPV group needed less intubation (25% versus 49%, $P<0.05$),

and there is not any significant difference in the incidence of Intraventricular hemorrhage, duration of Total parenteral nutrition, or admission.

Moreover, Ramantan et al. (2012) demonstrated that when NIPPV was used as primary assisted ventilation method only 17% of the patients needed intubation during the first seven days while in NCPAP method as principal assisted ventilation method 40% of the patients needed intubation during the first seven days (16). Hyeon-Soo Lee (2014) in a study conducted on 30 neonates showed more advantages of NIPPV (e.g., reducing intubation, apnea spells, duration of receiving full feeding, and duration of admission) after surfactant therapy in preterm neonates (17).

In another review article (2012), it was concluded that the risk of intubation in first 72 h of assisted ventilation is dramatically lower in NIPPV compared to NCPAP. However, controversies exist about the BPD incidence rate and further investigation is needed (18). In a study performed by Armanian, similar to the present study, NIPPV did not decrease endotracheal intubation (4.5% versus 1.5%, $P=0.23$); nonetheless, earlier receiving full feeding in this method, was obtained (19).

In another study, Harsh Kirpalani et al. investigated 1007 preterm neonates with birth weight less than 1 kg and gestational age of 30 weeks from 34 NICU centers of 10 countries that needed non-invasive assisted ventilation during the first seven days of life as the primary mode or after extubation, compared with NIPPV and NCPAP method. Out of all the cases, 49.8% of the neonates involved in this study did not need any ventilation mode before NIV. The results revealed that NIPPV did not reduce intubation rate and there was no difference between the two methods in BPD incidence, other complications (e.g., IVH, PDA, NEC, and pneumothorax), any mortality rate difference, and independence in synchronization (2).

Comparing the study population among the different researches conducted in this field, the present study mean birth weight and gestational age was more than those in studies performed by Kirpalani and Armanian; however, they were similar to those in a study carried out by Kugelaman and less than those in a study conducted by Bradley. The primary outcome of the present study was the success of NIV during the neonate's first 72 h of life. Although this duration was similar to that in a study performed by Kugelaman; nonetheless, there was some differences among other studies (2-7 days). Consequently, the results cannot be aggregated or extended.

In the present study, NIPPV did not have any significant advantages compared with the other methods (unlike the results of a study by Kugelman). Furthermore, there was no difference among the three non-invasive assisted ventilation methods in mortality rate or other complications, such as BPD, pneumothorax, and intestinal complications, or even in intubation need during the first three days or later.

Based on the results, NIPPV increased IVH severity. In addition, IVH severity had significant association with intubation need and death. The increased incidence of IVH was also observed in some previous studies, for instance in an investigation performed by Anne Greenough and Moretti on the use of NIV methods as post-extubation support for the neonates (20). However, the reason is unclear; its possibility can be reduced, with the appropriate use of synchronization or analgesic agents to decrease cerebral fluctuations in blood flow during NIPPV.

The limitations of the present study were budget lack, no further follow-up for neonates and nervous and audial side effects were not investigated. Based on the results, HHHFNC can be used as a safe and efficient method for primary choice in non-invasive assisted ventilation due to its easier nursing care and less cost and complications, as it is known in this study the same result were obtained for NIPPV and NCPAP.

Conclusion

It was concluded that that HHHFNC is a safe respiratory method that should be considered in preterm neonates with respiratory distress at birth. However, there were some differences in investigation methods between the present study and other studies, which were previously mentioned.

Acknowledgments

This study was approved by ethical committee with the code of IR MUMS.REC.1393.80.

Conflicts of interests

The authors declare that there is no conflict of interest.

References

1. Manley BJ, Dold SK, Davis PG, Roehr CC. High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence. *Neonatology*. 2012; 102(4):300-8.
2. Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS, et al. A trial comparing noninvasive ventilation strategies in preterm infants. *N Engl J Med*. 2013; 369(7):611-20.
3. Ramanathan R. Nasal respiratory support through the nares: its time has come. *J Perinatol*. 2010; 30:S67-72.
4. Rangasamy R, Paz P, Binwal M. Non-invasive ventilation and surfactant therapy. *J Pulmon Resp Med*. 2013; 13:161-72.
5. Shoemaker MT, Pierce MR, Yoder BA, DiGeronimo RJ. High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. *J Perinatol*. 2007; 27(2):85-91.
6. Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated humidified high flow nasal cannula versus nasal CPAP for respiratory support in neonates. *Pediatrics*. 2013; 131(5):1482-90.
7. Frizzole M, Miller TL, Rodriguez ME, Zhu Y, Rojas J, Heseck A, et al. High flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. *Pediatr Pulmonol*. 2011; 46(1):67-74.
8. 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(1):82-8.
9. Frey B, Shann F. Oxygen administration in infants. *Arch Dis Child Fetal Neonatal Ed*. 2003; 88(2):84-8.
10. Woodhead DD, Lambert DK, Clark JM, Christensen RD. Comparing two methods of delivering high flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomized, masked, crossover trial. *J Perinatol*. 2006; 26(8):481-5.
11. Holleman-Duray D, Kuapie D, Weiss MG. Heated humidified high flow nasal cannula: use and a neonatal early extubation protocol. *J Perinatol*. 2007; 27(12):776-81.
12. Shoemaker MT, Pierce MR, Yoder BA, Digernomio RJ. High flow nasal cannula versus nasal CPAP for neonatal respiratory distress: a retrospective study. *J Perinatol*. 2007; 27(2):85-91.
13. Abdel Hady H, Shouman B, Aly H. Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: a randomized control trial. *Early Hum Dev*. 2011; 87(3):205-8.
14. Compbell DM, Shah PS, Shah V, Kelly N. Nasal continuous positive airway pressure from high flow cannula versus infant flow for preterm infants. *J Perinatol*. 2006; 26(9):546-9.
15. Collins CL, Holberton JR, Bafield C, Davis PG. A randomized control trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in preterm infants. *J Pediatr*. 2013; 162(5):949-54.
16. Ramanathan R, Sekar KC, Rasmussen L, Bhatia J, Soll RF. Nasal intermittent positive pressure ventilation after surfactant treatment for respiratory distress syndrome in preterm infants <30 weeks' gestation: a randomized, controlled trial. *J Perinatol*. 2012; 32(5):336-43.
17. Lee HS, Min SR. Comparison of effectiveness of nasal continuous positive airway pressure and nasal intermittent positive pressure ventilation for the

- initial treatment of preterm respiratory distress syndrome: a prospective pilot study. *Neonatal Med.* 2014; 21(3):158-65.
18. Menses J, Bhandari V, Alves JG. Nasal intermittent positive pressure ventilation vs nasal continuous positive airway pressure for preterm infants with respiratory distress syndrome. *Arch Pediatr Adolesc Med.* 2012; 166(4):372-6.
19. Armanian AM, Badiee Z, Heidari G, Feizi A, Salehimehr N. Initial treatment of respiratory distress syndrome with nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure: a randomized controlled trial. *Int J Prev Med.* 2014; 5(12):1543-51.
20. Moretti C, Luigi G, Fassi C, Gizzi C, Papoff P, Colarizi P. Nasal flow synchronized intermittent positive pressure ventilation to facilitate weaning in very low-birthweight infants: unmasked randomized controlled trial. *Pediatr Int.* 2008; 50(1):85-91.