The Turkish Journal of Pediatrics 2021; 63: 23-30
https://doi.org/10.24953/turkjped.2021.01.003

Original Article

Comparison of four different non-invasive respiratory support techniques as primary respiratory support in preterm infants

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ABSTRACT

Background. The use of non-invasive ventilation methods in neonatal intensive care units has been increasing in recent years. Non-invasive ventilation techniques are lung preserving methods and they reduce the risk of volutrauma, barotrauma, and atelectotrauma.

Methods. The effect of heated humidified high-flow nasal cannula (HHHFNC), continuous positive airway pressure (CPAP), nasal intermittent positive-pressure ventilation (NIPPV), and nasal high-frequency oscillation ventilation (NHFOV) were compared in preterm infants with respiratory distress.

Results. Between December 2015 and February 2017, a total of 76 preterm infants (gestational age <32 weeks) with respiratory distress were enrolled in this study. Of the patients, 20 received HHHFNC, while 20 received nasal CPAP (NCPAP), 19 received NIPPV, and 17 received NHFOV for respiratory support. The primary outcome was intubation requirement during non-invasive respiratory support. The secondary outcome included duration of non-invasive ventilation, air leak syndrome, abdominal distension, intraventricular hemorrhage, necrotizing enterocolitis (NEC), nasal injury, increased secretions, agitation, and mortality rate. The intubation ratio was higher in the NCPAP (40%) and NHFOV (29.4%) groups when compared with the NIPPV (10.5%) and HHHFNC (11.8%) groups. More nasal injury had developed in the NIPPV (78.9%) and NHFOV (82.4%) groups when compared with the NCPAP (40%) and HHHFNC (35%) groups. Moreover, the viscous secretion that blocked the cannulas was higher in NIPPV (78.9%) and NHFOV (76.5%) groups than NCPAP (25%) and HHHFNC (40%) groups. There were no significant differences in the duration of non-invasive ventilation methods, abdominal distension, NEC, air leak syndrome or mortality in the 4 groups.

Conclusions. The NIPPV and HHHFNC methods can be useful as a primary mode of respiratory support for respiratory distress. However, doctors need to be careful with regard to the complications that may develop.

Key words: non-invasive ventilation, preterm, respiratory support, different techniques, efficiency.

New developments in neonatal intensive care units (NICUs) regarding ventilation techniques, antenatal steroid treatment, and surfactant therapy have decreased lung disease-related morbidity and mortality in newborns.[1-3] Despite the use of surfactant treatments with high-frequency oscillation or volume guarantee ventilation methods, bronchopulmonary dysplasia (BPD) is still the most important cause of pulmonary morbidity in preterm infants.[2,4] Invasive mechanical ventilation is an important environmental risk factor for BPD due to volutrauma, barotrauma, and atelectotrauma.[4] In recent years, various non-invasive respiratory support (NRS) techniques have been used in neonates.[5] The aim of this study was to compare the effects of heated humidified high-flow nasal cannula (HHHFNC), continuous positive airway pressure (CPAP), nasal intermittent

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Received 3rd February 2020, revised 6th October 2020, accepted 31st October 2020.

The study was presented at the UNEKO-25 National Neonatology Congress 12-16 April 2017, Antalya.

positive-pressure ventilation (NIPPV), and nasal high-frequency oscillation ventilation (NHFOV) in preterm infants with respiratory distress.

Material and Methods

This study was performed at Hacettepe University NICU between December 2015 and February 2017. Ethical approval was obtained from the institutional Hacettepe University, Clinical Research Ethics Committee (IRB number: 16969557-1327; GO 17/38-11) and participation involved informed consent. A total of 76 preterm infants (gestational age <32 weeks) with respiratory distress were enrolled in this study. All of the infants were supported with NCPAP (positive-end expiratory pressure (PEEP): 5 cm H_2O) in the delivery room and admitted to the NICU with CPAP. The newborns were randomly allocated into a nasal treatment mode of either HHHFNC, NCPAP, NIPPV, or NHFOV. During the study, 20 patients received HHHFNC, while 20 patients received NCPAP, 19 patients received NIPPV, and 17 patients received NHFOV for respiratory support. Newborns who required mechanical ventilation were excluded from the study. Moreover, newborns with congenital malformations or inherited metabolic diseases were also excluded.

All of the infants were loaded with caffeine citrate on their first day of life (10 mg/kg) and this continued each day. Data of the maternal characteristics (age, gestational age, mode of delivery, prenatal corticosteroid administrations, premature membrane rupture (PPROM), chorioamnionitis), and neonatal characteristics (birth weight, gender, 5-min Apgar score, etc.) of the patients were collected.

NCPAP

The NCPAP support was delivered via the bubble CPAP system (Fisher & Paykel Healthcare, Auckland, New Zealand), which generates continuous positive airway pressure, applied through short binasal prongs used as an interface (Optiflow Junior 2 nasal cannula). The respiratory pressure of the NCPAP was 5–6 cm H_2O.[6]

NIPPV

The NIPPV support was delivered via a conventional ventilator device (Drager Babylog 8000; Lübeck, Germany), which generates intermittent positive pressure ventilation, applied through short binasal prongs used as an interface (Optiflow Junior 2 nasal cannula). The initial ventilator parameters were PEEP: 5–6 cm H_2O; peak inspiratory pressure: 15–20 cm H_2O; inspiratory time 0.4–0.5 s; respiratory rate 25–30 breaths/min.

NHFOV

The NHFOV support was delivered via a high-frequency oscillation ventilator (Drager Babylog 8000), applied through short binasal prongs used as an interface (Optiflow Junior 2 nasal cannula). The initial ventilator parameters were mean arterial pressure: 6 cm H_2O; Delta P: 100% and rate: 10 Hz.

HHHFNC

The HHHFNC support was delivered via a precision flow device (Precision Flow, Vapotherm, Inc, Exeter, NH, USA), applied through the small bore cannula in the Vapotherm as an interface. The initial nasal flow parameters were: flow: 5 L/min, heat: 37 °C.

The fraction of inspired oxygen (FiO_2) was set in all of the NRS techniques with the target pulse oximeter rate of 90%–95%.

Non-invasive ventilation failure criteria included acidosis and hypercarbia (pH <7.20 and pCO2 >65 mmHg), apnea (≥2 episodes/h), and necrotizing enterocolitis (NEC) in the gastrointestinal tract. The criteria of surfactant administration included a FiO2 requirement higher than 0.4. The first dose of surfactant was 200 mg/kg (Curosurf, Chiesi, Parma, Italy) and an additional dose of 100 mg/kg was given at least 6 h after the previous administration. A

total of 54 patients had received minimally invasive surfactant therapy.

The primary outcome was the requirement of intubation during NRS. The secondary outcomes comprised the duration of non-invasive ventilation (days), air leak syndrome, abdominal distension, intraventricular hemorrhage (IVH), NEC, nasal injury, increased secretions, agitation, and mortality rate. N-PASS (Neonatal Pain Agitation and Sedation Scale) was used for diagnosis of pain and agitation and to determine the necessity of sedation.

Statistical analysis

For the calculation of the sample size, the rate of intubation requirement was used as the main primary outcome. A confidence level of α = 0.05 We used; the power level desired was 0.80, and consequently, 15 patients were needed for each group. Parameters of the 4 groups were compared using 1-way ANOVA for the continuous variables and the chi square test was performed for the categorical variables. Statistical significance was accepted as $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics for Windows (SPSS Inc., Chicago, IL, USA).

Results

The birth weight, gestational week (GW), maternal age, Apgar score, type of delivery, PPROM, and infection were evaluated as maternal and gestational properties. The median birth weight was 1190 g (600–2010) and the median GW was 28 weeks (26–32) in the HHHFNC group, while the median birth weight was 1240 g (580–2010) and the median GW was 28 (26–32) weeks in the NCPAP group. Moreover, the median birth weight was 1130 g (530–2550) and the median GW was 28 weeks (26–32) in the NIPPV group, while median birth weight was 1250 g (800–2240) and the median GW was 29 (27–32) weeks in the NHFOV group. There were no significant differences in the maternal and gestational features ($P > 0.05$) (Table I).

Of the patients, 54 needed surfactant therapy, but there were no significant differences in the surfactant necessity between the 4 groups ($P > 0.05$) (Table II).

The mean duration of NRS was 6.2 days in the HHHFNC group, 5 days in the NCPAP group, 3.4 days in the NIPPV group, and 4.2 days in the NHFOV group ($P > 0.05$). Additionally, there were no significant differences in the abdominal distension, NEC, air leak syndrome,

Table I. Maternal and gestational features of NRS groups.

	HHHFNC (n=20)	NCPAP (n=20)	NIPPV (n=19)	NHFOV (n=17)	p value
Birth weight (g) Median(min-max)	1190 (600-2010)	1240 (580-2010)	1130 (530-2550)	1250 (800-2240)	0.69
GW (week) Median(min-max)	28 weeks (26^2-32)	28 weeks (26^3-32)	28 weeks (26^2-32)	29 weeks (27-32)	0.58
Maternal age (year) mean ± SD	30.4 ± 5.8	29.9 ± 4.7	32.2 ± 4.4	30.2 ± 5.3	0.51
Apgar (5^{th} min)	9 (3-10)	9 (3-10)	8 (3-10)	9 (3-10)	0.48
C/S, n (%)	19 (95)	20 (100)	19 (100)	16 (94)	0.59
PPROM, n(%)	1 (5)	3 (15)	1 (5)	2 (12)	0.65
Chorioamnionitis, n(%)	1 (5)	1 (5)	0 (0)	0 (0)	1.0
Antenatal steroid, n(%)	6 (30)	5 (25)	7 (37)	11(65)	0.07

HHHFNC: Heated humidified high-flow nasal canula, NCPAP: Nasal continuous positive airway pressure, NIPPV: Nasal intermittent positive pressure ventilation, NHFOV: Nasal high-frequency oscillation ventilation, SD: Standart deviation, GW: Gestation week.
Apgar: Apgar score. C/S: Cesarian section. PPROM: Preterm premature rupture of membranes.

Table II. Surfactant necessity of infants in NRS groups

	HHHFNC	NCPAP	NIPPV	NHFOV	p value
Single dose surfactant	7	8	5	5	0.84
Two doses surfactant	2	3	2	4	0.67
Three doses surfactant	5	4	7	2	0.35

HHHFNC: Heated humidified high-flow nasal canula, NCPAP: Nasal continuous positive airway pressure, NIPPV: Nasal intermittent positive pressure ventilation, NHFOV: Nasal high-frequency oscillation ventilation.

Table III. Duration of ventilation and NRS related complications in NRS groups.

	HHHFNC (n=20)	NCPAP (n=20)	NIPPV (n=19)	NHFOV (n=17)	p value
NRS duration (day)	6.2 (2-25)	5 (2-15)	3.4 (2-12)	4.2 (2-8)	0.11
Air leak n(%)	0 (0)	0 (0)	1 (5.3)	1 (5.9)	0.22
Abdominal distension n(%)	8 (40.0)	7 (35.0)	5 (26.3)	8 (47.0)	0.62
NEC, n(%)	2 (10)	0 (0)	1 (5.3)	0 (0)	0.50
N-PASS score n(score>3)	5/20	5/20	5/19	4/17	0.54
Mortality, n(%)	0 (0)	1 (5.0)	0 (0)	0 (0)	1.0

HHHFNC: Heated humidified high-flow nasal canula, NCPAP: Nasal continuous positive airway pressure, NIPPV: Nasal intermittent positive pressure ventilation, NHFOV: Nasal high-frequency oscillation ventilation, NRS: Noninvasive respiratory support, NEC: Necrotizing enterocolitis, N-PASS: Neonatal pain agitation and sedation scale.

and mortality in the 4 groups (P > 0.05). Patients who had a N-PASS score of more than 3 required sedation. There were no significant differences between the groups (P > 0.05) (Table III).

The intubation ratio was higher in the NCPAP (40%) and NHFOV (29.4%) groups when compared with the NIPPV (10.5%) and HHHFNC (11.8%) groups (P < 0.05). Viscous secretion that blocked cannulas and required recurrent aspiration was present in the NIPPV (78.9%) and NHFOV (76.5%) groups when compared with the NCPAP (25%) and HHHFNC (40%) groups (P < 0.05). More nasal injury (nasal bleeding and ulceration) developed in the NIPPV (78.9%) and NHFOV (82.4%) groups when compared with the NCPAP (40%) and HHHFNC (35%) groups (P < 0.05). Moreover, more IVH was observed in the NIPPV (21.1%) and HHHFNC (10%) groups than in any of the other groups (P < 0.05) (Table IV).

We also separately evaluated small preterm infants whose gestational ages were below 28 weeks in the study group (Table V). The mean birth weight was not different between groups (P > 0.05). The intubation ratio was higher in the NCPAP (60%) and NHFOV (37%) groups when compared with the NIPPV (9%) and HHHFNC (15%) groups (P < 0.05). Viscous secretion was present in the NIPPV (90%) and NHFOV (80%) groups when compared with the NCPAP (30%) and HHHFNC (61%) groups (P < 0.05). There is no significant difference between the groups in terms of other morbidities (P > 0.05).

Discussion

In recent years, NRS methods have become the first respiratory support strategies in NICUs to prevent the development of BPD.[7,8] Hence, there are many studies comparing NRS methods and their results in the literature.[9-12] In this context, the use of different NRS methods has been proposed in different studies.

In this study, it was found that the HHHFNC and NIPPV groups had lower failure rates than the NCPAP and NHFOV groups. The intubation requirement was higher in the NCPAP and NHFOV groups. In a meta-analysis including 10 trials, NIPPV was stated as more efficient than NCPAP concerning the ratio of respiratory failure and intubation requirement.[13] Furthermore, in previous

Table IV. Non-invasive ventilation failure and procedure comorbid complications.

	HHHFNC (n=20)	NCPAP (n=20)	NIPPV (n=19)	NHFOV (n=17)	p value
Number of intubated infants after NIV n(%)	2(10)	8(40)	2(10.5)	5(29.4)	0.04
Viscous secretion n(%)	8(40)	5(25)	15(78.9)	13(76.5)	0.001
IVH n(%) (Grade 1)	2(10)	0(0)	4(21.1)	0(0)	0.04
Sepsis n(%)	7(35)	8(40)	9(47.3)	6(35.2)	0.85
PDA n(%)	3(15)	5(25)	5(26.3)	3(17.6)	0.81
Nasal injury n(%)	7(35)	8(40)	15(78.9)	14(82.4)	0.002
BPD n(%)	6(30)	3(15)	10(52.6)	6(35.2)	1.0

HHHFNC: Heated humidified high-flow nasal canula, NCPAP: Nasal continuous positive airway pressure, NIPPV: Nasal intermittent positive pressure ventilation, NHFOV: Nasal high-frequency oscillation ventilation, IVH: Intraventricular hemorrhage, PDA: Patent ductus arteriosus, BPD: Bronchopulmonary dysplasia.

Table V. Comparison of patient group findings under 28 weeks of gestation.

NRS Groups	GH: 28 weeks under cases(n=42)				
	HHHFNC (n=13)	NCPAP (n=10)	NIPPV (n=11)	NHFOV (n=8)	p value
NRS duration (day)(mean)	7.9	4.1	6.1	4.5	0.15
(min-max)	(5-25)	(3-15)	(2-12)	(3-8)	
GW (week)	27 weeks	27 weeks	27 weeks	27 weeks	0.79
Median(min-max)	(26^{2}-27^{4})	(26^{3}-27^{5})	(26^{2}-27^{4})	(27-27^{6})	
Birth weight (g)	1066.5± 328	1180 ± 396	1032.7 ± 370	1145 ± 265	0.59
mean ± SD	(600-1660)	(580-1770)	(530-1760)	(800-1510)	
Apgar (5th min)	8 (3-10)	7 (3-10)	7 (3-10)	8 (3-10)	0.95
C/S, n (%)	12(92)	10(100)	11(100)	8(100)	0.51
PPROM, n(%)	1(7)	3(30)	1(9)	1(12)	0.43
Antenatal steroid, n(%)	5(38)	4(40)	5(45)	5(63)	0.72
Abdominal distension, n(%)	6(46)	5(50)	3(27)	4(50)	0.67
N-PASS score n(score>3)	4 (30)	4(40)	3(27)	3(37)	0.23
Number of intubated infants after NIV n(%)	2(15)	6(60)	1(9)	3(37)	0.02
Viscous secretion, n(%)	8(61)	3(30)	10(90)	7(87)	0.01
Sepsis, n(%)	7(53)	6(60)	7(63)	4(50)	0.93
PDA, n(%)	3(23)	5(50)	5(45)	3(37)	0.55
Nasal injury, n(%)	7(53)	5(50)	10(90)	7(87)	0.08
BPD, n(%)	5(38)	3(30)	5(45)	3(37)	0.69

HHHFNC: Heated humidified high-flow nasal canula, NCPAP: Nasal continuous positive airway pressure, NIPPV: Nasal intermittent positive pressure ventilation, NHFOV: Nasal high-frequency oscillation ventilation, IVH: Intraventricular hemorrhage, PDA: Patent ductus arteriosus, BPD: Bronchopulmonary dysplasia.

studies with preterm infants, intubation rates were lower with NIPPV than with NCPAP.[14-16] Li et al.[17] compared NCPAP and NIPPV as the primary mode of respiratory support. They stated that there was a significant decrease in the intubation need and invasive ventilation in the NIPPV group, as in the current study. But we already know that synchronisation in NIPPV has much better results concerning the requirement for intubation and lung damage that will lead to the development of BPD.[18] One of the limitations in our study was that we could

not do synchronized NIPPV. However, there are studies in the literature showing that BPD, mortality, NEC and IVH rates do not change when synchronization is achieved.[19] Also no significant difference was found in the BPD and mortality in patients below 28 weeks GA.

According to previous studies, NHFOV does not require synchronization and caused less barotrauma.[20-22] However, similar to the current findings herein, Czernik et al.[23] determined a high risk of respiratory failure in extremely preterm babies. Moreover, a survey of 5 European countries described the side effects of NHFOV as agitation, viscous secretions, and upper airway obstruction associated efficiency problems. As a result of the higher mean pressures with NHFOV, abdominal distention becomes another side effect of this technique.[24] Viscous secretions and the need for very frequent aspiration was observed in the NHFOV group in the current study. It was also speculated that the use of a relatively low frequency at high amplitude with NHFOV causes excessive viscous secretion formation in the upper airway.[25] On the other hand, in babies below 28 weeks GA, nasal secretion rates were found to be high in all NRS groups except NCPAP group in the current study. Although ventilator-associated pneumonia and congenital pneumonia may cause increased secretion, pneumonia was not detected in our study cases. Pulmonary findings of our RDS cases regressed after surfactant treatment.

Additionally, the abdominal distension ratio was relatively higher in the NHFOV group than in the other groups herein, but it was not statistically significant.

In recent years, HHHFNC has been used in NICUs as a NRS.[26] Observed in the current study was a lower failure rate in the HHHFNC group when compared with the NCPAP group. Roberts et al.[27] compared NCPAP and HHHFNC as the primary mode of respiratory support and found a higher failure rate in the HHHFNC group. However, in their study, they used this method for early respiratory support without the use of a surfactant. Surfactant treatment was also given to the infants in the current study. Another randomized clinical trial found an increase rate of intubation in the HHHFNC group when compared with the NCPAP group.[28]

However, it was reported that flow levels higher than 4 L/min could solve this problem. In the present study, the initial nasal flow rate was 5 L/min. There were no differences observed in the efficacy and safety between the HHHFNC and NCPAP groups in a study involving 432 preterm babies.[29] Surfactant administration and higher flow rates might explain the success of HHHFNC in the current study. However, efficiency of HHHFNC is still controversial when compared with nasal NCPAP. HHHFNC generates pressure in the nasopharyngeal area, and there is not enough information about how much pressure is reflected into the respiratory tract. High flow rates lead to increase pharyngeal pressure.[30,31] Hence, the amount of pressure formed in the nasopharyngeal space is not exactly known.[32,33] The same failure rate was also found in the HHHFNC group when compared with the NIPPV group. When we evaluate our preterm patients below 28 weeks GA, the failure rate was high in the NCPAP and HFOV groups again.

On the other hand, the NRS methods, in terms of comorbid complications, were also evaluated herein. No significant differences in the sepsis, air leak, hemodynamically significant patent ductus arteriosus, NEC, BPD, or mortality were found. Similar results were found in preterm babies below 28 weeks GA. In the NIPPV group, 4 IVHs were observed, while 2 IVH were observed in the HHHFNC group. However, the IVHs in these patients were grade 1 and there were no neurological symptoms. Another complication investigated was the nasal injury between the groups. Nasal injury was followed-up as granulation tissue, ulceration, necrosis, and deformation of the nasal septum and edge of the nostril. Nasal injuries were higher in the NHFOV and NIPPV groups than in the NCPAP group. This may have occurred due

to viscous secretions and mucosal dryness. Moreover, the least nasal injury was observed in the HHHFNC group, special nasal cannula of HHHFNC might explain this situation. This nasal cannula allows air to leak from the nostril and this reduces nasal injury.[34] Although there was no statistical difference in our study, prolonged NRS duration is a risk factor for nasal injury. The N-PASS score was used to assess the comfort level of the patients, but no differences were found between the NRS groups.

In conclusion, this data suggested that the NIPPV and HHHFNC methods have beneficial effects on preterm infants in NICUs. These methods can be useful but they require more experience to use as a primary mode of respiratory support for RDS. NHFOV is thought to cause less barotrauma and damage to the lungs. However, doctors need to be careful with regards to its complications. Therefore, there is a need for further multicenter randomized controlled trials in a wider population.

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