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Original Article

Effect of different modalities of noninvasive respiratory support in preterm infants with respiratory distress syndrome: A prospective multicenter study

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Abstract

Background

The first few hours after birth are very critical for newborns to adapt to the extrauterine environment. However, respiratory distress syndrome (RDS) is very common in newborns, particularly in those with shorter gestation ages, sepsis, and fewer platelet counts. The evaluation of respiratory management with current noninvasive ventilation (NIV) support strategies in preterm infants present within the neonatal intensive care unit, as well as drawbacks of NIV modes including nasal continuous positive airway pressure, nasal intermittent positive pressure ventilation, and high-flow nasal cannula, is also critical for those patients. This study aimed to compare different modes of NIV to highlight the preferred respiratory support model for preterm infants with RDS and to assess the advantages of NIV such as decreasing ventilator-induced lung injury to highlight the best model for NIV.

Patients and methods

A total of 120 babies were randomly divided into three equal groups in four neonatal intensive care units. Each group was treated with one type of NIV immediately after birth. Demographic data and clinical, laboratory, and radiographic measures were collected. Moreover, the use of surfactant/caffeine, optimum humidification, and appropriate nasal interface were recorded.

Results

The nasal intermittent positive pressure ventilation mode revealed a higher preference with different risk factors; however, a significant association between better survival and heated humidified high-flow nasal cannula mode was also revealed. Moreover, intubation decreased in neonates with feeding intolerance, abdominal distention, and pressure necrosis by about 27, 87, and 13%, respectively ($P > 0.05$).

Keywords: High-flow nasal cannula, nasal continuous positive airway pressure, nasal intermittent positive pressure ventilation, noninvasive ventilation, preterm neonates

Introduction

Respiratory distress syndrome (RDS) is still considered a significant problem for premature infants. However, its management has developed gradually over the years, leading to improved survival for young infants but with unacceptable rates of bronchopulmonary dysplasia (BPD).

The first hours and days of life are very important for a newborn baby as he/she adapts to the extrauterine environment. The

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newborn infant is susceptible to a range of respiratory illnesses. Therefore, when evaluating newborns with unexplained lung disease, neonatologists should have a high index of suspicion for interstitial lung disease, including surfactant protein mutations [1].

The cascading events that characterize RDS and its long-term sequelae, for example, chronic lung disease, are rooted in intrinsic early lung disability as well as exacerbation by mechanical ventilation (MV) [2].

Urgent management in cases of neonatal respiratory distress is to reverse any hypoxia with supplemental oxygen and to prevent or reverse any respiratory acidosis by ensuring adequate ventilation of the lungs. This may require noninvasive respiratory support, such as continuous positive airway pressure (CPAP), high-flow therapy or endotracheal intubation, and MV in the most affected cases [3].

The backbone of the management of severe neonatal respiratory failure is MV supportive care. However, MV by itself may cause stress to the lung. Ventilator-induced lung injury is an important risk factor in extremely low birth weight (ELBW) infants for developing BPD. Consequently, the use of MV as a primary method for alleviating respiratory failure in ELBW infants has decreased significantly over the past decade [4].

Recently, it has been highlighted that preterm infants should be managed without MV when possible, and if ventilation is mandatory to reduce the time, an endotracheal tube is used. The use of noninvasive respiratory support has increased as noninvasive ventilation (NIV) procedures have been developed to achieve this. Still, there is often a lack of evidence to determine which method is the most effective [5].

Noninvasive respiratory support refers to the support provided to open the upper airway of infants who are spontaneously breathing in the absence of an endotracheal tube. This support consists of CPAP, mandatory noninvasive intermittent ventilation (NIMV), also known as noninvasive intermittent positive pressure ventilation (NIPPV), noninvasive high-frequency ventilation, and modified neurally adjusted ventilatory assist. Although not usually classified as noninvasive respiratory support, humidified high-flow nasal cannula (HHFNC) may give positive pressure and respiratory assistance as well [5,6].

Premature infants should be stabilized on nasal continuous positive airway pressure (NCPAP) in the delivery room. Additionally, NCPAP is generally indicated in infants with increased work of breathing, substernal and suprasternal retractions, grunting, and nasal flaring. The chest radiograph may show poorly expanded and/or high lung opacification. Ongoing management for optimal NCPAP levels is based on the adequacy of lung inflation without distending over the lung parenchyma. Blood gases and chest radiography can be helpful in determining patient response to NCPAP. The goal is to keep the fraction of inspired oxygen (FiO_2) from 0.3 to 0.4 or less than 0.3 by increasing the NCPAP level stepwise up to 8 cm H_2O, if necessary [7].

CPAP helps in achieving better lung or pulmonary ventilation (V), and perfusion (Q) scans (V/Q) matching and ensures maintenance of functional residual capacity. CPAP is not associated with adverse effects of invasive MV, like excessive use of sedation and adverse effects of positive pressure ventilation (volutrauma and barotrauma). In the inpatient setting, it should be monitored very closely with vital signs, blood gases, and clinical profiles. If there is any sign of deterioration, MV should be considered [8].

The possible mechanisms by which NIPPV works are by increasing mean airway pressure, allowing recruitment of alveoli by lowering the work of breathing. It is also possible that higher mean airway pressure delivered at the nasal interface during NIPPV may have resulted in maintaining optimal lung expansion than during NCPAP. Besides, the most essential effect of NIPPV might be stimulating breathing. The apparent advantage of NIPPV over NCPAP in stimulating breathing to avoid apnea and hypercapnia could play an important role in avoiding failure of NIV and resolving RDS. However, NIPPV was not found to be superior to NCPAP for decreasing the need for IMV in the handling of preterm infants with RDS [9].

Although NCPAP is the current model of NIV, it has been widely used in complications [such as nasal injury and necrotizing enterocolitis (NEC)] that cause a significant effect on clinical outcomes. Heated humidified high-flow nasal cannula (HHHFNC) is another globally noninvasive respiratory support model for the management of RDS in preterm infants. The use of HHHFNC may be associated with improvement of respiratory function, increased ventilation efficiency, and reduced intubation necessities in neonates with poor respiratory function [10].

As primary respiratory support for preterm infants with respiratory distress, HHHFNC and NCPAP were associated with a lower incidence of nasal trauma [9]. In this respect, a pilot study suggested that HHHFNC may be as effective as NCPAP in preventing endotracheal ventilation in premature infants in the primary management of RDS [10].

Our objectives in this study were to investigate the clinical efficiency of HHHFNC compared with NCPAP and NIPPV for premature babies, aiming to explore a more effective mode of NIV for ELBWI.

Aim

This study aimed at comparing different modes of NIV to highlight the preferred respiratory support model for preterm infants with RDS and to assure the advantages of NIV as decreasing ventilator-induced lung injury and to detect the possible complications associated with each NIV modes with different clinical risk factors.

Study design and patient selection

This study was a multicenter, three-arms, parallel, randomized trial conducted on four Egyptian neonatal intensive care units (NICUs). A prospective study on preterm neonates with RDS was performed. The neonates were admitted to the NICU at Mataria Teaching Hospital, Misr Qadema Mabarra Hospital, Maadi Mabarra Hospital, and Gameya Shareya Hospital in the 6th of October City. This study was done in the period from the January 1, 2021 to the end of June 2022. A total of 120 neonates from NICUs were included in this study. The primary outcome was the intubation requirement during noninvasive respiratory support, whereas the secondary outcome assessed the association between mortality and clinical characteristics of neonates

Inclusion criteria were as follows: all preterm neonates presented with RDS since birth who needed respiratory support were included.

Exclusion criteria were as follows:

(1) Presence of congenital heart diseases.
(2) Presence of other congenital anomalies that required surgical interventions (gastrointestinal tract, central nervous system, or renal anomalies).
(3) Presence of symptoms and signs suggesting metabolic diseases of newborn or intrauterine Toxoplasmosis, Others (Syphilis, Hepatitis B), Rubella, Cytomegalovirus, Herpes Simplex (TORCH) infections.

Group classification

A total of 120 neonates were assigned into the following groups:

(1) The first group was composed of 40 preterm neonates with RDS who were on NIPPV as the primary mode.
(2) The second group was composed of 40 preterm neonates with RDS who were on NCPAP as the primary mode.
(3) The third group was composed of 40 preterm neonates with RDS who were on HHHFNC as the primary mode.

Full clinical and demographic data were obtained for each included neonate.

Full clinical examination and routine neonatal care included the following:

(1) Assessment of Apgar scores at 1 and 5 min [11].
(2) Assessment of gestational age through maternal dates, antenatal ultrasound, and the New Ballard score [12].

Respiratory support methods and monitoring

All included neonates were provided respiratory support by NIV through either NCPAP, NIPPV, or HHHFNC, according to the availability of the machine.

The following machines were used for respiratory support:

First group (nasal intermittent positive pressure ventilation mode)

(1) CARESCAPE R860 Ventilator: model G1500197 GE *P*/N M1229957, Datex–Ohmeda, Inc., Chicago, Illinois, USA (Mabara Misr El Qadema Hospital).
(2) Puritan Bennett840 Ventilator: Puritan Bennett Corporation Pleasanton, California, USA (Mabara Misr El Qadema Hospital).
(3) Drager: Babylog 8000 plus Ventilator. Manufacturer: Drägerwerk AG & Co. K GaA Moislinger Allee 53–55 23542, Lubeck, Germany (Mabara Maadi Hospital and El Mataria Teaching Hospital).
(4) The Covidien Newport e360 ventilator, Soma Tech Intl-166 Highland Park Dr, Bloomfield, Connecticut, USA (El Mataria Teaching Hospital and Gameya Shareya Hospital).

Second group (nasal continuous positive airway pressure mode)

(1) MedinCNO. Medin low flow Blender, Air/Oxygen. Medical Innovations GmbH, Adam-Geisler-Str, Olching, Germany (Mabara Maadi Hospital and El Mataria Teaching Hospital).
(2) Mediset, Bio-Med device low flow Blender, Air/Oxygen, SN/BX1953210, Biomed Tech Australia (Mabara Maadi Hospital, El Mataria Teaching Hospital, and Gameya Shareya Hospital).
(3) SLE1000 Adaptive nasal CPAP Therapy System, an Inspiration Healthcare Group Company, Croydon, UK.

Third group (heated humidified high-flow nasal cannula mode)

Sechrist Products. Model 3600 High Flow Precise Mixing of Air and Oxygen. COMEN NV8, Sechrist Industries, Inc., Anaheim, California, USA (El Mataria Teaching Hospital and Gameya Shareya Hospital).

The following data were recorded:

(1) Arterial blood gases.
(2) Settings of the respiratory support methods and its direction (↑↑ or ↓↓) and age of weaning from respiratory support,
(3) Intubation was needed or not and if yes, demonstrate its indication.

The following investigations were done:

(1) Laboratory: complete blood count with differential leukocyte count and venous blood gases.
(2) Radiological: chest radiography.
(3) Any other investigations as needed according to the case for complete assessment and diagnosis.

Administrative design

(1) Informed consent was obtained from the parents of each neonate participating with full details about the study procedure and the benefits.
(2) Approval from ethical committee was obtained.

Statistical analysis

All data were fed to the computer for statistical analysis using R Software, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria. 2018-12-20) – 'Eggshell Igloo.' Descriptive analysis for quantitative data included mean and SD. For qualitative categorical variables, count and percentage

were applied. Comparative analysis for the baseline patients' demographics, clinical, and biochemical characteristics was done using the χ^2 test or Fisher exact test for categorical data and analysis of variance or Kruskal–Wallis test for continuous data. Binomial logistic regression model was used to investigate the need for intubation following three different NIV modes considering potential risk factors. Univariate and multivariate binomial logistic regression models were used to investigate the association between the improvement and the different NIV modes considering the potential risk factors that were significant at the baseline comparison. Two-way repeated measures analysis of variance was used to compare between the three different NIV modes regarding saturation, pH, $PaCo_2$, and HCO_3 at different time points (initial, before, and after). Kaplan–Meier curve was used to investigate the overall survival for the three different NIV modes, followed by detecting the difference in the median survival time using the log-rank test. Cox proportional hazard regression models were used to predict the hazard of death between the different NIV modes, considering the potential risk factors that were significant at the baseline comparison. *P* values less than equal to 0.05 were considered statistically significant.

Results

The baseline demographics for the study population are shown in Table 1.

The binomial logistic regression model for predicting the odds of intubation associated with different NIV modes showed that the adjusted odds of intubation increased but nonsignificantly among neonates on HHHFNC mode by about 17% and also decreased nonsignificantly among neonates on NIPPV mode by ~6% compared with neonates on NCPAP taking in consideration the possible postventilation complications and risk factors [odds ratio (OR)=1.17, 95% confidence interval (CI): 0.04–53.50, *P* = 0.929, and OR = 0.94, 95% CI: 0.04–35.79, *P* = 0.972, respectively]. Moreover, the adjusted odds of intubation increased nonsignificantly in neonates with intraventricular hemorrhage (IVH), hypoventilation, and sepsis, whereas increased significantly in neonates with

Table 1: Comparative analysis for the baseline patients' demographics and clinical and biochemical characteristics

Patients' characteristics*	HHHFNC (*n*=40) (33.3%)	NCPAP (*n*=40) (33.3%)	NIPPV (*n*=40) (33.3%)	*P*
Weight (grams)				
Mean±SD	2254.5±373.6	2197.6±582.2	1938.9±496.2	0.009**
Gestational age (weeks)				
Mean±SD	35.2±1.2	34.6±2.2	33.6±2.0	<0.001***
Sex				
Males	28 (70.0)	22 (55.0)	22 (55.0)	0.29
Females	12 (30.0)	18 (45.0)	18 (45.0)	
Mode of delivery				
Cesarean	39 (97.5)	36 (90.0)	35 (87.5)	0.339
Vaginal	1 (2.5)	4 (10.0)	5 (12.5)	
Apgar score (1 min)				
Mean±SD	4.9±1.5	5.0±1.5	4.7±1.2	0.411
Apgar score (5 min)				
Mean±SD	8.3±0.7	7.8±1.0	7.7±0.8	0.0024**
Hemoglobin				
Mean±SD	14.6±2.2	14.8±2.2	16.1±2.3	0.005**
Hematocrit				
Mean±SD	42.7±6.3	43.6±6.9	47.3±6.3	0.005**
Total leukocyte count				
Mean±SD	13 353.0±4235.0	12 732.2±4325.3	11 910.2±5659.2	0.118
Platelet				
Mean±SD	261 750.0±64 440.7	246 000.0±99194.4	210 475.0±51 162.4	0.008**
Cultures				
Negative	38 (95.0)	35 (87.5)	40 (100.0)	0.068
Positive	2 (5.0)	5 (12.5)	0	
C reactive protein				
Negative	31 (77.5)	30 (75.0)	35 (87.5)	0.335
Positive	9 (22.5)	10 (25.0)	5 (12.5)	
Use of surfactant				
No	30 (75.0)	30 (75.0)	24 (60.0)	0.24
Yes	10 (25.0)	10 (25.0)	16 (40.0)	

HHHFNC, heated humidified high-flow nasal cannula; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation. *Data are represented as mean±SD and count (%). ** Data <0.05 indicates significant results. *** Data < 0.001 indicates highly significant results.

apnea by about 5.5 folds, 13.8 folds, 96%, and 36.4 folds, respectively (OR = 5.48, 95% CI: 0.03–1156.59, $P = 0.988$; OR = 13.76, 95% CI: 0.45–614.97, $P = 0.128$; OR = 1.96, 95% CI: 0.09–52.86, $P = 0.662$; and OR = 36.36, 95% CI: 1.07–1563.63, $P = 0.046$, respectively).

However, the adjusted odds of intubation decreased nonsignificantly among neonates with feeding intolerance, abdominal distention, and pressure necrosis by ~27, 87, and 13%, respectively (OR = 0.73, 95% CI: 0.00–73.19, $P = 0.903$; OR = 0.13, 95% CI: 0.00–49.35, $P = 0.501$; and OR = 0.87, 95% CI: 0.00–157.34, $P = 0.967$, respectively) (Table 2 and Fig. 1).

However, the odds of improvement increased but nonsignificantly among neonates on HHHFNC and NIPPV modes by about 65% and two folds, respectively, when compared with neonates on the NCPAP mode (OR = 1.65, 95% CI: 0.53–5.41, $P = 0.393$, and OR = 2.03, 95% CI: 0.63–7.22, $P = 0.245$, respectively). After adjustment for the weight, the gestational age, Apgar score (5 min), time after current mode (hours), and hospital stay (days), the adjusted odds of improvement decreased but nonsignificantly among neonates on NIPPV and HHHFNC modes by ~61 and 66%, respectively, compared with neonates on the NCPAP mode (OR = 0.39, 95% CI: 0.04–4.43, $P = 0.421$; $P = 0.035$; and OR = 0.34, 95% CI: 0.02–3.72, $P = 0.387$, respectively) (Table 3 and Fig. 2). Moreover, the adjusted OR of improvement decreased significantly by about 5% for each 1-h increase in the time after the current mode (adjusted OR = 0.95, 95% CI: 0.92–0.97, $P < 0.001$), whereas the unadjusted odds of improvement

Table 2: Binomial logistic regression model to investigate the need for intubation following to the three different noninvasive ventilation modes

Predictors*	Need for intubation		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	No	Yes		
NIV mode				
NCPAP	29 (72.5)	11 (27.5)	Reference	
HHHFNC	29 (72.5)	11 (27.5)	1.00 (0.37-2.69, *P*=1.000)	1.17 (0.04-53.50, *P*=0.929)
NIPPV	31 (77.5)	9 (22.5)	0.77 (0.27-2.11, *P*=0.606)	0.94 (0.04-35.79, *P*=0.972)
IVH				
No	88 (75.9)	28 (24.1)	Reference	
Yes	1 (25.0)	3 (75.0)	9.43 (1.16-194.81, *P*=0.056)	5.48 (0.03-1156.59, *P*=0.988)
Apnea				
No	83 (93.3)	6 (6.7)	Reference	
Yes	6 (19.4)	25 (80.6)	57.64 (18.47-215.41, *P*<0.001)	36.36 (1.07-1563.63, *P*=0.046)
Feeding intolerance				
No	51 (65.4)	27 (34.6)	Reference	
Yes	38 (90.5)	4 (9.5)	0.20 (0.06-0.56, *P*=0.005)	0.73 (0.00-73.19, *P*=0.903)
Abdominal distension				
No	52 (65.8)	27 (34.2)	Reference	
Yes	37 (90.2)	4 (9.8)	0.21 (0.06-0.59, *P*=0.007)	0.13 (0.00-49.35, *P*=0.501)
Hypoventilation				
No	85 (94.4)	5 (5.6)	Reference	
Yes	4 (13.3)	26 (86.7)	110.50 (30.93-513.05, *P*<0.001)	13.76 (0.45-614.97, *P*=0.128)
Sepsis				
No	71 (78.0)	20 (22.0)	Reference	
Yes	18 (62.1)	11 (37.9)	2.17 (0.87-5.32, *P*=0.091)	1.96 (0.09-52.86, *P*=0.662)
Pressure necrosis				
No	86 (74.8)	29 (25.2)	Reference	
Yes	3 (60.0)	2 (40.0)	1.98 (0.25-12.50, *P*=0.467)	0.87 (0.00-157.34, *P*=0.967)
Weight (grams)				
Mean (SD)	2225.1 (398.1)	1858.4 (670.7)	1.00 (1.00-1.00, *P*=0.001)	1.00 (0.99-1.00, *P*=0.098)
Gestational age (weeks)				
Mean (SD)	34.9 (1.6)	33.2 (2.5)	0.67 (0.53-0.82, *P*<0.001)	0.43 (0.09-1.53, *P*=0.212)
Time after current mode (hours)				
Mean (SD)	49.1 (28.0)	162.2 (192.4)	1.02 (1.01-1.04, *P*<0.001)	1.03 (1.01-1.06, *P*=0.050)
Hospital stay (days)				
Mean (SD)	10.4 (7.0)	10.2 (9.0)	1.00 (0.94-1.05, *P*=0.882)	0.79 (0.56-0.99, *P*=0.077)

CI, confidence interval; HHHFNC, heated humidified high-flow nasal cannula; IVH, intraventricular hemorrhage; NCPAP, nasal continuous positive airway pressure; NIV, noninvasive ventilation; NIPPV, nasal intermittent positive pressure ventilation; OR, odds ratio. *Data are represented as count (%), mean (SD), odds ratio (95% confidence interval).

Table 3: Univariate and multivariate binomial logistic regression models to investigate the association between the improvement and the different noninvasive ventilation modes considering the potential risk factors that were significant at the baseline comparison

ü Potential risk factors*	Died	Improved	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
NIV mode [*n* (%)]				
NCPAP	9 (22.5)	31 (77.5)	-	-
HHHFNC	6 (15.0)	34 (85.0)	1.65 (0.53-5.41, *P*=0.393)	0.34 (0.02-3.72, *P*=0.387)
NIPPV	5 (12.5)	35 (87.5)	2.03 (0.63-7.22, *P*=0.245)	0.39 (0.04-4.43, *P*=0.421)
Weight (grams)				
Mean±SD	1886.0±785.4	2179.2±419.0	1.00 (1.00-1.00, *P*=0.022)	1.00 (0.99-1.00, *P*=0.136)
Gestational age (weeks)				
Mean±SD	33.2±2.8	34.7±1.7	1.37 (1.10-1.72, *P*=0.005)	2.93 (1.21-8.53, *P*=0.026)
Apgar score (5 min)				
Mean±SD	7.5±1.0	8.1±0.9	1.88 (1.14-3.21, *P*=0.015)	3.59 (1.43-11.35, *P*=0.012)
Time after current mode (hours)				
Mean±SD	129.3±136.6	68.1±103.3	1.00 (0.99-1.00, *P*=0.056)	0.95 (0.92-0.97, *P*<0.001)
Hospital stay (days)				
Mean±SD	6.3±4.4	11.2±7.8	1.19 (1.06-1.38, *P*=0.011)	3.12 (1.83-6.73, *P*<0.001)

CI, confidence interval; HHHFNC, heated humidified high-flow nasal cannula; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; NIV, noninvasive ventilation; OR, odds ratio. *Data are represented as count (%), mean±SD, odds ratio (95% confidence interval).

Table 4: Two-way repeated measures analysis of variance to compare between the three different noninvasive ventilation modes regarding saturation at different time points (initial-after)

NIV modes	Initial saturation		Saturation after		Adjusted *P*
	Mean	SD	Mean	SD	
HHHFNC	90.325	1.542	93.375	3.295	<0.001***
NCPAP	90.675	1.591	93.125	3.291	<0.001***
NIPPV	89.975	2.537	93.375	3.271	<0.001***
Adjusted *P*	0.556		1.0		-

HHHFNC, heated humidified high-flow nasal cannula; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; NIV, noninvasive ventilation. ***Data < 0.001 indicates highly significant results.

Table 5: Two-way repeated measures analysis of variance to compare between the three different noninvasive ventilation modes regarding pH at different time points (initial-after)

NIV modes	Initial pH		pH after		Adjusted *P*
	Mean	SD	Mean	SD	
HHHFNC	7.342	0.074	7.357	0.077	1.0
NCPAP	7.334	0.079	7.35	0.079	1.0
NIPPV	7.292	0.083	7.335	0.065	0.033*
Adjusted *P*	0.022*		0.790		-

HHHFNC, heated humidified high-flow nasal cannula; NCPAP, nasal continuous positive airway pressure; NIV, noninvasive ventilation; NIPPV, nasal intermittent positive pressure ventilation. *Data <0.05 indicates significant results.

increased significantly by about 19%, and after adjustment, the adjusted odds increased also significantly by about 3.1 folds for each 1-day increase in hospital stay (unadjusted OR = 1.19, 95% CI: 1.06–1.38, *P* = 0.011, and adjusted OR = 3.12 95% CI: 1.83–6.73, *P* < 0.001) (Table 3 and Fig. 2).

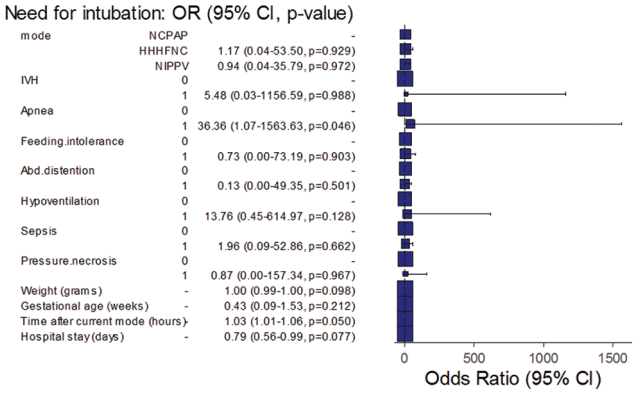

Figure 1: Risk of intubation after different NIV modes considering potential risk factors. NIV, noninvasive ventilation.

Table 4 shows that there is no statistically significant difference between the three NIV modes regarding the saturation in all time points (initial and after) (*P* > 0.05) (Fig. 3). However, the overall comparative analysis between the two time points shows a statistically significant difference within each NIV mode (*P* < 0.001), and the pairwise comparison showed that the saturation after each NIV mode is significantly higher than the initial saturation (Fig. 4).

Table 5 shows a statistically significant difference among the three NIV modes regarding the initial pH (*P* = 0.022), whereas the pH after the NIV mode does not show any significant difference among the three modes (*P* = 0.790). Moreover, pairwise comparison shows the initial pH in neonates on NIPPV mode is significantly lower than the initial pH in neonates on HHHFNC

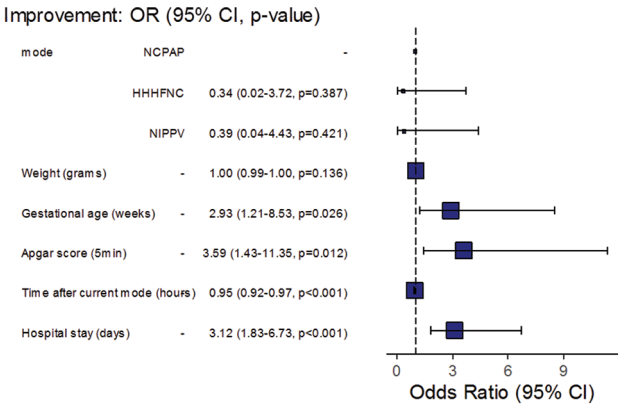

Figure 2: Odds of improvement among different NIV modes considering potential risk factors. NIV, noninvasive ventilation.

and on NCPAP (Fig. 5). However, the overall comparison between the two time points (initial pH and pH after) does not show any significant difference within HHHFNC and NCPAP modes ($P > 0.05$) but shows a statistically significant difference at NIPPV mode ($P = 0.033$), and the pairwise comparison showed that the pH after NIPPV mode is significantly higher than the initial pH for the same mode (Fig. 6).

Table 6 shows the initial $PaCo_2$ in neonates on NIPPV mode is significantly higher than the initial $PaCo_2$ in those on both HHHFNC and NCPAP modes. Moreover, the $PaCo_2$ level after the NIPPV mode is significantly higher than $PaCo_2$ after both HHHFNC and NCPAP modes (Fig. 7).

The overall comparison between $PaCo_2$ levels at the two time points did not show any significant difference within HHHFNC and NCPAP modes ($P > 0.05$) but shows a statistically significant difference in NIPPV ($P = 0.027$), and the pairwise comparison indicates that the $PaCo_2$ level after NIPPV mode is significantly lower than the initial $PaCo_2$ at the same mode (Fig. 8).

In Table 7, a statistically significant difference among the three NIV modes regarding HCO_3 levels at the two time points (initial and after) ($P < 0.001$) is seen. Moreover, the pairwise comparison shows that the initial HCO_3 in neonates on NIPPV mode is significantly higher than the initial HCO_3 in those on both HHHFNC and NCPAP modes. HCO_3 level after NIPPV mode is significantly higher than HCO_3 after both HHHFNC and NCPAP modes (Figs. 9 and 10).

Kaplan–Meier estimate shows that the median survival time (50% survived) in the case of HHHFNC mode is 318 h, which is shorter than the median survival time in the case of NCPAP mode, that is, 360 h, whereas the neonates on NIPPV mode does not reach the median survival (meaning that it was the highest overall survival rate) but the log-rank test did not show any statistically significant difference ($P = 0.6$, log-rank = 1.2) (Fig. 11).

Table 8 shows that the adjusted hazard of death decreased but nonsignificantly among the neonates on NIPPV mode by about

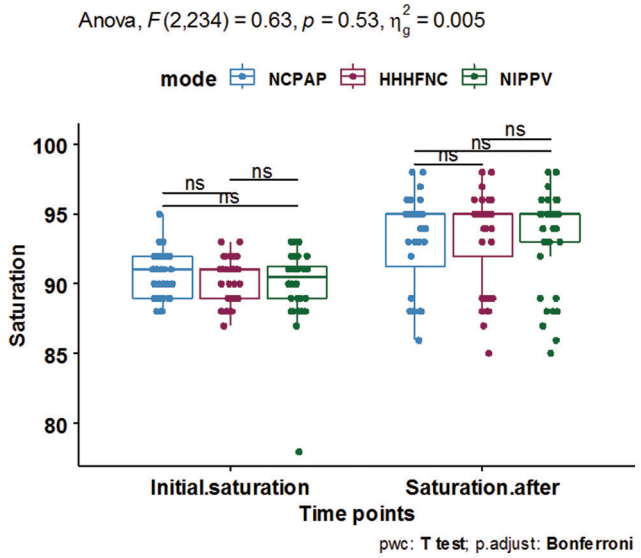

Figure 3: Comparative analysis for saturation at different time points between three NIV modes showing the pairwise significance. NIV, noninvasive ventilation.

Table 6: Two-way repeated measures analysis of variance to compare between the three different noninvasive ventilation modes regarding $PaCo_2$ at different time points (initial-after)

NIV modes	Initial $PaCo_2$		$PaCo_2$ after		Adjusted *P*
	Mean	SD	Mean	SD	
HHHFNC	27.59	12.314	27.28	9.669	0.881
NCPAP	27.515	9.72	30.75	11.509	0.165
NIPPV	46.52	15.403	40.215	13.56	0.027**
Adjusted *P*	<0.001***		<0.001***		-

HHHFNC, heated humidified high-flow nasal cannula; NCPAP, nasal continuous positive airway pressure; NIV, noninvasive ventilation; NIPPV, nasal intermittent positive pressure ventilation. **Data <0.05 indicates significant results. ***Data < 0.001 indicates highly significant results

Table 7: Two-way repeated measures analysis of variance to compare among the three different noninvasive ventilation modes regarding HCO_3 at different time points (initial-after)

NIV modes	Initial HCO_3		HCO_3 after		Adjusted *P*
	Mean	SD	Mean	SD	
HHHFNC	14.557	4.278	15.13	4.329	1.0
NCPAP	14.835	4.372	15.957	4.481	0.78
NIPPV	20.457	6.782	19.925	4.89	1.0
Adjusted *P*	<0.001***		<0.001***		-

HHHFNC, heated humidified high-flow nasal cannula; NCPAP, nasal continuous positive airway pressure; NIV, noninvasive ventilation; NIPPV, nasal intermittent positive pressure ventilation. ***Data < 0.001 indicates highly significant results.

54%. In comparison, it increased also nonsignificantly by about 19% among neonates on HHHFNC mode when compared with

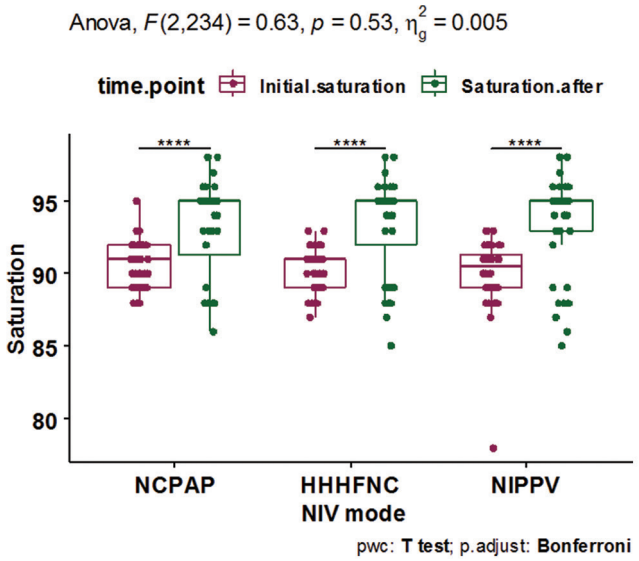

Figure 4: Comparative analysis for saturation at three NIV modes between different time points showing the pairwise significance. NIV, noninvasive ventilation.

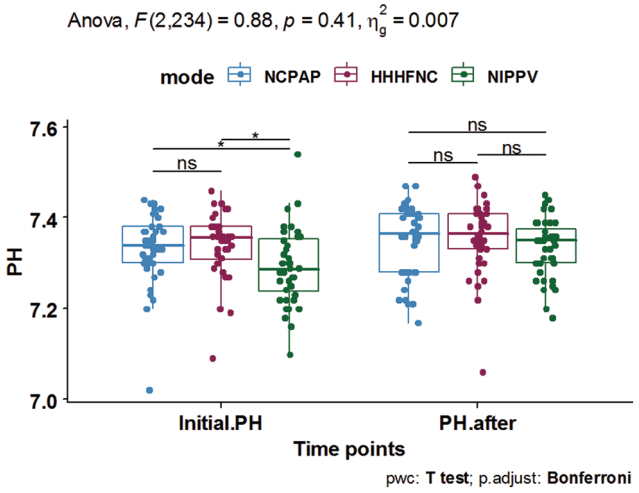

Figure 6: Comparative analysis for pH at three NIV modes between different time points showing the pairwise significance. NIV, noninvasive ventilation.

the neonates on NCPAP mode [adjusted hazard ratio (HR)=0.46, 95% CI: 0.15–1.44, *P* = 0.184, and Adjusted HR = 1.19, 95% CI: 0.34–4.16, *P* = 0.791, respectively] taking into consideration the gestational age and the use of surfactant. Moreover, the adjusted hazard of death decreased insignificantly by about 22% for each 1-week increase in the neonate gestational age (adjusted HR = 0.78, 95% CI: 0.54–1.14, *P* = 0.207).

Regarding surfactant use, neonates who used surfactant had an insignificant decrease in the adjusted hazard of death by about 6% when compared with the neonates who did not use it, taking in consideration the NIV mode used and the neonatal gestational age (adjusted HR = 0.94, 95% CI: 0.19–4.66, *P* = 0.939) (Table 8 and Fig. 12).

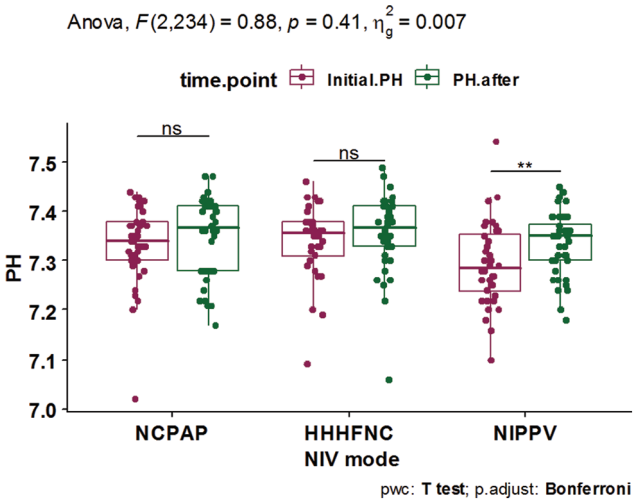

Figure 5: Comparative analysis for pH at different time points between three NIV modes showing the pairwise significance. NIV, noninvasive ventilation.

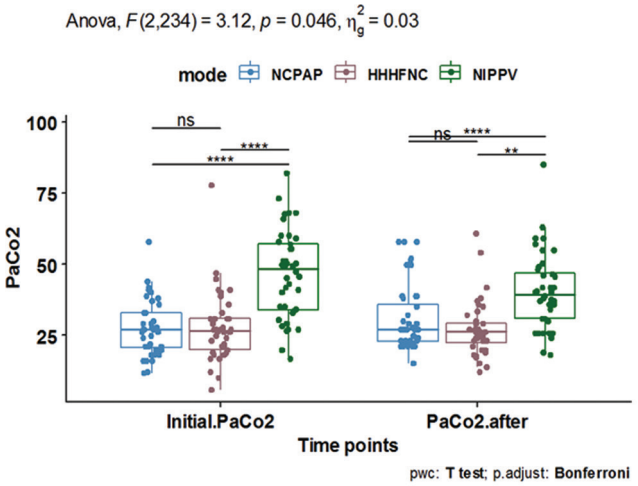

Figure 7: Comparative analysis for $PaCo_2$ at different time points among three NIV modes showing the pairwise significance. NIV, noninvasive ventilation.

Discussion

Monitoring neonatal vital signs after birth is essential to avoid the consequences of inappropriate breathing. In the current practice, it is preferred to use NIV and limit the use of oxygen exposure. Consequently, the primary use of nasal NCPAP either instantly or after surfactant administration has been strongly recommended through the last 20 years. However, HFNC was introduced in the last decade as an alternative NIV. It was used to enhance spontaneous breathing through the decrease in dead space and the creation of positive inflating airway pressure [10,13]. Furthermore, NIPPV was used extensively in adults as well as in older children as an effective mode for respiratory support; however, in neonates, cases of gastrointestinal perforations have been reported in apnea of preterm infants, which limited its use [14].

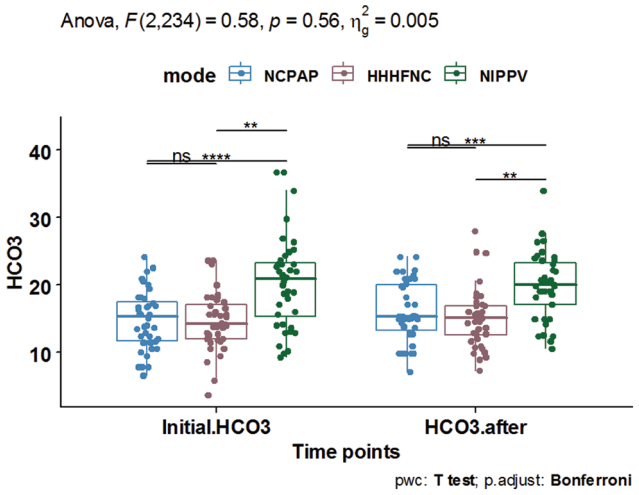

Figure 8: Comparative analysis for $PaCo_2$ at three NIV modes between different time points showing the pairwise significance. NIV, noninvasive ventilation.

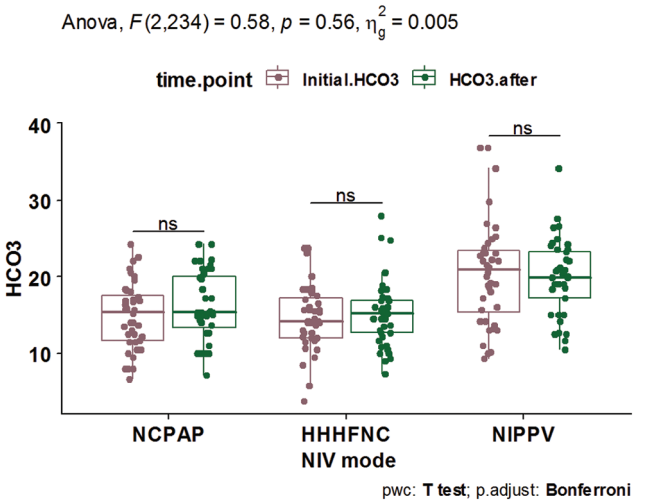

Figure 9: Comparative analysis for HCO_3 at different time points among three NIV modes showing the pairwise significance. NIV, noninvasive ventilation.

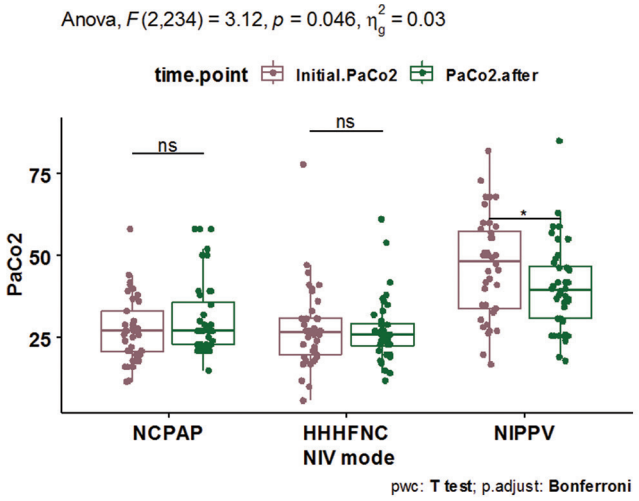

Figure 10: Comparative analysis for HCO_3 in three NIV modes between different time points showing the pairwise significance. NIV, noninvasive ventilation.

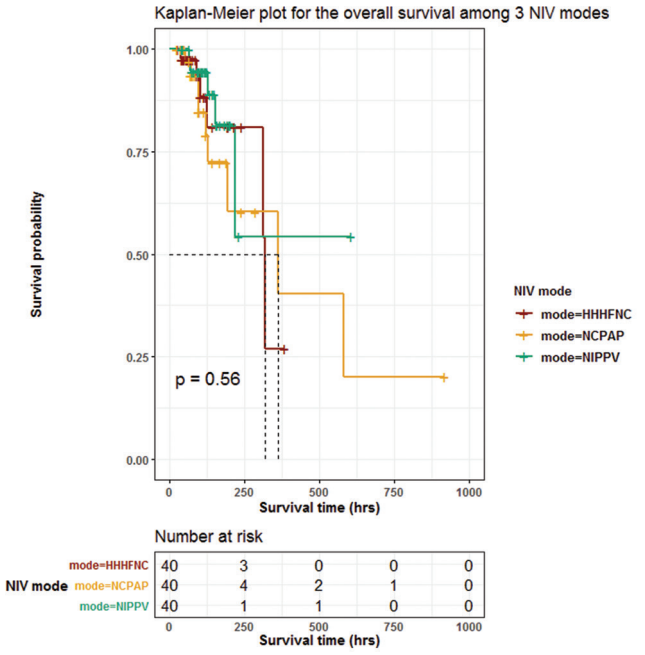

Figure 11: Kaplan–Meier curve to investigate the overall survival for the three different NIV modes. NIV, noninvasive ventilation.

In this study, the odds of intubation showed an insignificant decrease among neonates on NIPPV by about 6%, whereas it increased among neonates on HHHFNC by 17% compared with neonates on NCPAP taking into consideration the possible postventilation complications. In the contrary, one study compared the NIPPV with NCPAP in 497 preterm neonates. Similarly, ~50–67% of very low birth weight (VLBW) premature neonates showed initial support using NCPAP and then developed severe respiratory failure necessitating intubation and invasive ventilation [15].

Furthermore, in this study, the adjusted odds of intubation in HHHFNC increased in neonates with IVH and sepsis insignificantly whereas increased significantly in neonates with apnea and hypoventilation by about 5.5 folds, 13.8 folds, 96%, and 36.4 folds, respectively. Similarly, Sauer *et al.* [16] revealed that higher rates of intubation were associated with elevated frequency of severe IVH in infants less than 750 g and in infants less than 1500 g who were intubated only in the delivery room. Furthermore, sepsis was considered among the risk factors associated with the pathogenesis of IVH [17]. In addition, apnea was considered as a warning sign for NEC, systemic inflammation, and infections, including sepsis [18].

Moreover, in our study, the adjusted odds of intubation decreased insignificantly among neonates with feeding intolerance, abdominal distention, and pressure necrosis by about 27, 87, and 13%, respectively. It is well established that

Table 8: Cox proportional hazard regression models to predict the hazard of death between the different noninvasive ventilation modes considering the potential risk factors

Risk factors*	All	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
NIV modes			
NCPAP	40 (33.3)	-	-
HHHFNC	40 (33.3)	0.78 (0.27-2.23, *P*=0.639)	1.19 (0.34-4.16, *P*=0.791)
NIPPV	40 (33.3)	0.54 (0.18-1.66, *P*=0.285)	0.46 (0.15-1.44, *P*=0.184)
Gestational age (weeks)			
Mean±SD	34.5±2.0	0.84 (0.69-1.02, *P*=0.081)	0.78 (0.54-1.14, *P*=0.207)
Surfactant			
No	84 (70.0)	-	
Yes	36 (30.0)	2.05 (0.82-5.14, *P*=0.124)	0.94 (0.19-4.66, *P*=0.939)

CI, confidence interval; HHHFNC, heated humidified high-flow nasal cannula; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; NIV, noninvasive ventilation. *Data are represented as count (%), mean±SD, and hazard ratio (95% confidence interval).

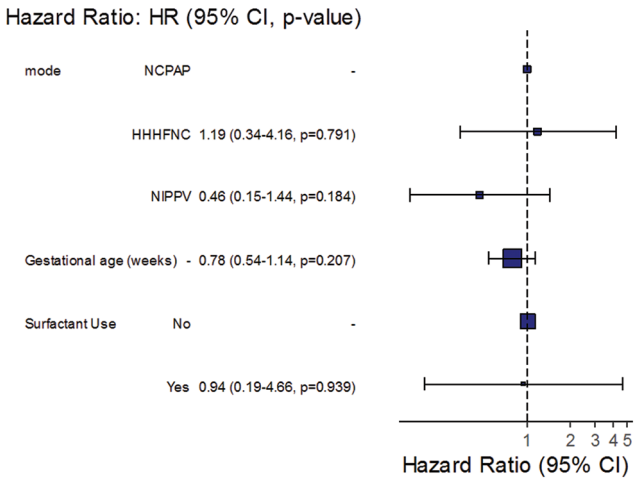

Figure 12: Forest plot for the hazard of death in different NIV modes. NIV, noninvasive ventilation.

gastric residuals are a potential consequence of delayed gut maturation and motility in VLBW infants. Gastric residual is considered a serious sign if accompanied by other warning signs, including severe vomiting, abdominal distension, apnea, bradycardia, and temperature instability [19]. In fact, the study confirmed that abdominal distension and NEC were leading factors for NIV failure in preterm newborns, which necessitated reintubation. Moreover, the frequency of NEC in the NCPAP group was significantly higher compared with those in the HHHFNC group ($P < 0.05$), which led to a significant extended time to reach full enteral feeding in the NCPAP group than in the HHHFNC group ($P < 0.05$). In addition, HHHFNC showed a significant improvement in average weight gain rate as well as lower hospitalization days with decreased cost of hospitalization (all $P < 0.05$) [10].

On the contrary, in infants older than 28 weeks of gestational age, HHHFNC showed equal efficacy and safety to NCPAP when applied immediately after extubation or as initial NI therapy for respiratory dysfunction. Furthermore, no difference was detected in early failure for HHHFNC [23/212 (10.8%)] vs. NCPAP [18/220 (8.2%); $P = 0.344$], succeeding need for any intubation [32/212 (15.1%) vs. 25/220 (11.4%); $P = 0.252$]. The study revealed 191 died or survived with BPD (38.4%) compared with 36.7% on NCPAP (adjusted odds ratio, 1.09; 95% CI: 0.83–1.43; $P = 0.56$). Approximately 25–38% of infants showed a failure to NCPAP following surfactant administration, resulting in reintubation and invasive ventilation [20].

In our study, the unadjusted odds of improvement increased significantly by 88% whereas increased significantly after adjustment by 3.6 folds for each 1 U increase in Apgar score (5 min). On the contrary, one study revealed that among 8288 neonatal ICU admissions, a significant upsurge in the use of NIV was seen (2.8%/year) with a decline in intubation rates (1.9%/year), and only 16.8% failed and consequently needed intubation [21]. Another has demonstrated that NIV was more effective than NCPAP in infants with apnea in dropping the need for intubation in mild to moderate RDS and in enhancing the success of extubation. In this study, NIV has not been established to confer significant advantages on the long term on respiratory outcomes; nevertheless, there is no evidence that NIPPV is accompanied by an increased risk of adverse events [22]. However, adjusting for weight, gestational age, Apgar score (5 min), and platelet count, the odds of improvement among neonates on NIPPV mode increased significantly by about seven folds when compared with neonates on HHHFNC mode. This contradicts the conclusion by Chen *et al.* [10] that HHHFNC proved efficacy in preventing extubation failure in MV preterm ELBW. Similarly, a pilot study revealed that comparing NIPPV and HHHFNC showed no significant difference in the need for endotracheal ventilation (28.9 vs. 34.2%) between HHHFNC and NIPPV groups [23].

However, infants on HHHFNC showed higher hospital stay compared with those on NCPAP (median: 4 vs. 2 days, respectively; $P < 0.01$), with no difference detected between studied groups for days on supplemental oxygen (median: 10 vs. 8 days), BPD (20 vs. 16%), or discharge from the hospital on oxygen (19 vs. 18%) [24]. On the contrary, in comparison with NCPAP, HHHFNC showed prevention in extubation failure in VLBW. HHHFNC has significantly decreased the frequency

of nasal injury and NEC; furthermore, it lowers the length of stay and the hospitalization cost. The study by Chen *et al.* [10] showed that on comparison between HHHFNC and NCPAP, HHHFNC shortened the oxygen exposure time and efficiently decreased the incidence of nasal injury and NEC (10.42 vs. 28.26%) ($P < 0.05$). Nevertheless, our study revealed that odds of improvement increased but insignificantly in HHHFNC and NIPPV modes by about 65% and two folds, respectively, when compared with those on the NCPAP mode.

Moreover, a study comparing HHHFNC and NIPPV showed that neonatal morbidities, including pneumothorax, BPD, IVH, NEC, patent ductus arteriosus, and nasal trauma, were similar in NIPPV and HHHHFNC groups. However, the duration of nasal support was longer in HHHFNC in comparison with NIPPV ($P = 0.006$). Nevertheless, the duration of endotracheal ventilation, time to complete feeds, and length of stay were comparable. This can predict comparable efficacy of HHHFNC to NIPPV in premature infants (<35 weeks of GA and weight of more than 1000 g), which could explain the controversial results with ours, where HHHFNC seems to be more effective in infants with borderline risks such as low birth weight or low gestational age [23]. This also comes in the line with our study, where there was an insignificant increase in the unadjusted odds of improvement by about 88% and the adjusted odds increased significantly by about 3.6 folds for each one unit increase in Apgar score (5 min). Additionally, it agrees with the fact that low scores of Apgar at 5 min indicate higher mortality and may lead to an increased risk of cerebral palsy [25]. Another study has revealed that HHHFNC, in comparison with NCPAP, does not increase the risk of treatment failure or need for MV compared with NCPAP; however, HHHFNC has demonstrated an upsurge in treatment failure compared with NIPPV as well as risk for MV [respiratory rate (RR)=2.34 95% CI: 1.59–3.33] and needs for MV (RR = 1.54; 95% CI: 1.04–2.31) [26].

Furthermore, a comparison between NIV modes in our study has revealed a statistically significant difference within each NIV mode ($P < 0.001$) as well as the pairwise comparison regarding higher saturation after in each NIV mode in comparison with initial saturation. In addition, a significant difference in initial vs. pH after in neonates on HHHFNC and on NCPAP was detected. At the same time, the overall comparison showed no significant difference within HHHFNC and NCPAP modes ($P > 0.05$). A statistically significant difference at the NIPPV mode ($P = 0.033$) and the pH after NIPPV mode were significantly higher than the initial pH for the same mode. It was mentioned that NIPPV use does not necessitate intubation, and the RR and gas exchange improved rapidly. In the same line, NIPPV was linked with a low required invasive MV, reduced mortality, and shorter hospital stay [27]. Thus, it was encouraged to use NIPPV in patients with respiratory failure [28]. Consequently, patients with acute respiratory failure who suffer disturbance in arterial blood gases and acid–base status (pH) require the use of NIPPV [29]. On the contrary, in comparison with NCPAP, HHFNC demonstrated a significantly longer duration of oxygen supplementation, according to the study by Anne and Murki [30]. Similarly, among 303 infants, 152 have been assigned to HHHFNC and 151 to the NCPAP group. The study revealed that the efficacy of HHHFNC was equal to that of NCPAP as a respiratory support for VLBI after extubation. Nevertheless, neonates with a gestational age lower than 26 weeks have not been established its safety [33]. This comes in the line with our study, where the $PaCo_2$ level after the NIPPV mode was significantly higher than $PaCo_2$ after both HHHFNC and NCPAP modes. Nevertheless, there was a statistically significant difference in NIPPV ($P = 0.027$), and the pairwise comparison indicated that the $PaCo_2$ level after NIPPV mode was significantly lower than the initial $PaCo_2$ at the same mode. However, the overall comparison between $PaCo_2$ levels at the two time points did not show any significant difference within HHHFNC and NCPAP modes ($P > 0.05$), indicating the efficacy of NIPPV over other modes and disagreeing with our initial HCO_3 in neonates on NIPPV mode where significantly higher results than the initial HCO_3 in those on both HHHFNC and NCPAP modes were detected. Moreover, the HCO_3 level after the NIPPV mode was significantly higher than HCO_3 after both HHHFNC and NCPAP modes. This also comes in the line with our results, where NIPPV showed the highest survival with the lowest hours of intubation, followed by HHHFNC, and then lastly NCPAP. On the contrary, HHHFNC use resulted in a longer duration of respiratory support with no differences in other secondary outcomes. Moreover, a difference was detected between HHHFNC and NCPAP in their intubation in preterm infants in infants with different gestational ages [32].

Regarding mortality rate in the three different NIV modes, in VLBW infants, the rate of survival to 36 weeks did not significantly differ between NIPPV and NCPAP [33]. This contradicts our results, where the use of surfactant decreased death by 6% in comparison with those who did not use it, taking in consideration the NIV mode used and the neonatal gestational age (adjusted HR = 0.94, 95% CI: 0.19–4.66, $P = 0.939$).

Conclusion

Although our study showed HHHFNC efficacy in neonates, NIPPV showed superiority in neonates with respiratory failure and better survival rates.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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