ORIGINAL ARTICLE

Heated Humidified High Flow Nasal Cannula (HHHFNC) is not an effective method for initial treatment of Respiratory Distress Syndrome (RDS) versus nasal intermittent mandatory ventilation (NIMV) and nasal continuous positive airway pressure (NCPAP)

Amir-Mohammad Armanian[1], Ramin Iranpour[1], Mehdi Parvaneh[2], Nima Salehimehr[3], Awat Feizi[4], Mostafa Hajirezaei[5]

[1]Department of Pediatrics, Division of Neonatology, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Pediatrics, Division of Neonatology, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Psychology, Almahdi Mehr Higher Education Institute, Isfahan, Iran, [4]Department of Epidemiology and Biostatistics, Endocrinology and Metabolism Research Center, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran, [5]Infectious Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran

Background: Noninvasive respiratory support techniques are widely used to treat respiratory distress syndrome (RDS) in preterm infants, and the effectiveness of these methods should be compared. In the current study, nasal continuous positive airway pressure (NCPAP), nasal intermittent mandatory ventilation (NIMV), and heated humidified high-flow nasal cannula (HHHFNC) were compared. **Materials and Methods:** In the current bicenter clinical trial, 109 preterm infants with RDS not treated with surfactant were randomly assigned to three groups: NCPAP, NIMV, and HHHFNC. The initial outcomes including the failure of treatment within the first initial 72 h, and the duration of RDS treatment, and the secondary outcomes including the need for intubation, the need for surfactants, the duration of oxygen dependency, the incidence of pneumothorax, the patent ductus arteriosus, intraventricular hemorrhage, length of stay, and mortality were compared among the groups. **Results:** The frequency of HHHFNC treatment failure (54.3%) was significantly higher compared with those of NIMV (21.6%) ($P < 0.001$, hazard ratio [HR] = 9.12, 95% confidence interval [CI] = 2.59 – 32.07) and NCPAP (35.1%) ($P = 0.004$, HR = 21.25, 95% CI = 2.51–180.08). The median duration of RDS treatment was longer (40 h) in the HHHFNC group, although it was not significantly different from those of NIMV (31.16 h) and NCPAP (38.91 h). **Conclusion:** Based on the high prevalence of failure of HHHFNC treatment than the other two methods (NCPAP and NIMV), HHHFNC is not recommended as the initial treatment of RDS.

Key words: Noninvasive ventilation, premature infants, respiratory distress syndrome

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INTRODUCTION

Respiratory distress syndrome (RDS) is one of the most common respiratory diseases in newborns, especially preterm ones, and also the most common cause of mortality and morbidity in such patients during the 1st month of life.[1,2] In spite of advanced preventive and therapeutic measures, about 30%–50% of premature neonates develop this disorder.[3-5] Surfactant therapy and mechanical ventilation (MV) are two standard measures to treat neonatal RDS,

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Address for correspondence: Dr. Ramin Iranpour, Department of Pediatrics, Division of Neonatology, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: iranpour@med.mui.ac.ir

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but significant complications such as bronchopulmonary dysplasia (BPD) impede the use of MV in neonates with RDS.[6,7] Noninvasive respiratory support techniques that are performed without the need for an endotracheal tube are widely used as a primary treatment in infants with RDS and significantly reduce the need for MV.[8-10] Nasal continuous positive airway pressure (NCPAP) is one of the noninvasive techniques for the early treatment of RDS; it is used in many centers as an accepted standard treatment for RDS disease.[11] Various studies indicated the effectiveness of this technique in reducing infant mortality as well as the risk of BPD. Furthermore, improved neurodevelopmental outcomes on the reduction of respiratory morbidity and death are a long-term positive effect of this technique.[12-14] Based on some cases of treatment failure in the NCPAP, other noninvasive respiratory management techniques are also investigated. One of these methods is nasal intermittent mandatory ventilation (NIMV), MV without intubation and through the placement of nasal prongs, which is used as another noninvasive technique to treat RDS, transient neonatal tachypnea, and as a postextubation treatment for infants with RDS.[6,15,16] Heated humidified high-flow nasal cannula (HHHFNC) is another technique of respiratory support in neonates with RDS, which is recently considered due to its ease of use, better tolerance, improved nutrition, increased maternal–infant bonding, and less iatrogenic injury.[17,18] However, based on the results of the current study, there is still no study on its efficacy as a primary treatment for neonates with RDS. Therefore, the current study aimed at comparing the strength of HHHFNC respiratory management with the standard treatment of RDS disease (NCPAP), as well as noninvasive NIMV technique, and also other primary and secondary clinical outcomes of the three mentioned techniques.

MATERIALS AND METHODS

Subjects

The current randomized, clinical trial was conducted on 109 neonates born from February 2015 to March 2016 in Alzahra or Shahid Beheshti Hospitals in Isfahan, Iran. The current study is a pilot one and we did not do power calculation in the stage of study design, and we recruited, based on common approach in pilot randomized trials studies, at least 30 patients in each study group. In the current study, premature infants with a birth weight of <1500 g evaluated and diagnosed with RSD based on clinical examinations and chest X-ray radiographic evidence (based on the Makinen classification) were enrolled in the study.[19] Infants with asphyxia, major congenital anomalies, cyanotic congenital heart diseases, and orofacial and respiratory anomalies, and the ones in need of intubation at the beginning of treatment were excluded from the study and replaced with other infants.

Study interventions

The neonates were randomly assigned into the study groups. Due to the gradual enrollment of patients into the study, the randomized assignment was performed using envelopes containing names of the therapy group using permuted block randomization of size 6. Premature infants weighing < 1500 g after initial resuscitation were evaluated in neonatal intensive care unit. If they had the symptoms of RDS, such as chest retraction, grunting, tachypnea, or loss of arterial oxygen saturation (SO_2), a sealed envelope was randomly selected to assign the patient to one of 3 groups: NCPAP, NIMV, or HHHFNC. After determining the RDS score, an orogastric tube was used to decompress the stomach in all newborns, and pulse oximeter saturation and heart rate (HR) were continuously monitored by a digital monitoring system (Saadat-Iran). The ambulatory blood pressure monitoring was performed every 6 h, and the results were recorded. Intravenous aminophylline was administered to all neonates to neutralize the possible confounding effect of apnea of prematurity with an initial dose of 8 mg/kg and a maintenance dose of 1.5 mg/kg every 8 h. NIMV-treated neonates underwent nasal MV with peak inspiratory pressure = 16–20 cm H_2O, positive end expiratory pressure = 5–6 cm H_2O, flow = 8–10 L/min, rate = 50/min, inspiratory time (Ti = 0.4) second after placement of the nasal prong, supportive caps, and nasal tubes.

Neonates of the NCPAP group were treated with a continuous pressure of 5–6 cm H_2O at a flow rate of 8–10 L/min using the underwater bubble CPAP system after placement of nasal prongs and joints. In the HHHFNC group, the incubated neonates underwent the oxygen therapy after instillation of nasal cannula with external diameter of 2 mm, using connecting oxygen tubes and its joints at 37°C and 2.5°C L/min for infants weighing <1000 g and 3 L/min for infants weighing 1000–1500 g after placement of the nasal cannula with an external diameter of 2 mm, oxygen interface tubes, and associated fittings using a warm and moisturizer (Fisher and Paykel-New Zealand). Atrial blood gas (ABG) of all neonates was measured 60 min after the initiation of treatment. Furthermore, ABG was prepared again if some changes were made to the settings of the devices or after administration of surfactant. The device settings were adjusted based on the results of ABG and clinical findings. If patients were required to maintain a SpO_2 content of more than 91%, a fraction of inspirational oxygen (FiO_2) >30%, a normal surfactant (Curosurf® or Survanta®) at a dose of 100 mg/kg using intubation-surfactant-extubation was prescribed.

Clinical outcomes

Clinical outcomes were evaluated in the two primary and secondary groups. The primary outcomes included the

frequency of primary treatment failure and the duration of RDS treatment. Neonates with blood pH <7.2 and PCO_2 >60 mmHg, repeated apnea more than 6 times/h with bradycardia or cyanosis, severe apnea requiring bag and mask ventilation, O_2 saturation <90% despite FiO_2 more than 40%–60%, or requiring emergency intubation in the blood gas analysis were considered as cases of treatment failure. The treatment process for neonates that experienced primary treatment failure continued on the basis of clinical status using one of the NIMV, NCPAP, or MV techniques. The need for surfactant and the frequency of surfactant prescriptions, intraventricular hemorrhage (IVH), and severity (confirmed by ultrasound based on the Papile classification), patent ductus arteriosus (PDA) (based on transthoracic echocardiogram results), pneumothorax, duration of oxygen dependency, length of hospital stay, and mortality were considered as secondary clinical outcomes. Information on the primary and secondary outcomes of the treatment and basic information about the patients such as gender, gestational age, birth weight, 1st and 5th min APGARs, and RDS score were taken from clinical records and recorded in a questionnaire.

Ethical considerations

All stages of the design and implementation of the current study were monitored and approved by the Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran. All ethical principles were observed according to the 196/96 resolution on research involving human subjects at all stages of the current study. The informed written consent was obtained from a legal guardian of the newborn. The current study was registered in the Iranian Registry of Clinical Trials (IRCT2016052510026N7).

Statistical analysis

The data analysis was carried out using IBM SPSS version 24.0 (SPSS, Chicago, IL, USA). The normal distribution of data was investigated using the Kolmogorov–Smirnov test. One-way ANOVA, Kruskal–Wallis H, and Mann–Whitney U-tests were used to compare the continuous normal and nonnormal variables. Categorical variables were compared between groups using Chi-square and Fisher's exact tests. Hazard ratio and 95% confidence intervals (CIs) were calculated using the Cox regression for investigating the effects of interventions on primary and secondary binary clinical outcomes, and confounding effect of gestational age and birth weight as the confounder factors were adjusted. The quantitative variables with normal and nonnormal distribution were presented as mean ± standard deviation and median (range: minimum–maximum), respectively, and categorical variables were reported as frequency (percentage). All tests were of two-tailed structure, and $P < 0.05$ was considered as the significant level.

RESULTS

A total of 271 neonates were investigated in terms of possessing the inclusion criteria and 162 neonates were excluded due to lack of the same. Finally, 109 neonates were divided into three groups: NIMV ($n = 37$), HHHFNC ($n = 35$), and NCPAP ($n = 37$) [Figure 1]. There was no significant difference between male and female ratio in the studied groups ($P = 0.87$). Mean gestational age in the neonates of the HHHFNC group was significantly higher than those of the other two groups ($P = 0.02$). Furthermore, the birth weight of neonates treated with HHHFNC was higher than those of the other two groups ($P = 0.02$). Baseline characteristics of patients are shown in Table 1.

After comparing the primary clinical outcomes, it was found that despite the higher gestational age and birth weight of the neonates in the HHHFNC group [Table 1], the frequency of early treatment failure of RDS was significantly higher than those of the neonates in the NIMV and NCPAP groups (54.3% in the HHHFNC group compared with 21.6% in the NIMV [HR = 9.12, 95% CI = 2.59–32.07, $P < 0.001$] and 35.1% in the NCPAP groups [HR = 21.25, 95% CI = 2.51–180.08, $P = 0.004$]) [Tables 2 and 3]. The most common cause of treatment failure in all three groups, especially the HHHFNC group, was hypoxia, i.e., the need for FIO_2 above 40% to maintain SO_2 above 90% [Table 4]. On the other hand, the median duration of RDS treatment in the HHHFNC group was longer than that of the other two groups, although it was not statistically significant (40 h in the HHHFNC group compared with 31.16 h in the NIMV group [$P = 0.2$] and 38.91 h in the NCPAP group [$P = 0.66$] [Tables 2 and 3]). To provide a better and more analytical representation of results, the primary and secondary outcomes obtained in the groups are provided two by two.

Table 1: Patients' baseline characteristics

Variables	Groups			*P**
	NIMV (*n*=37)	NCPAP (*n*=37)	HHHFNC (*n*=35)	
Gender[a]				
Female	22 (59.5)	20 (54.1)	19 (54.3)	0.87
Male	15 (40.5)	17 (45.7)	16 (45.7)	
Gestational age[b]	29.29±1.7	29.92±2.99	30.781.89	0.02
Birth weight[b]	1151.13±236.08	1153.38±226.3	1282.86±184.43	0.02
Apgar of 1st min[c]	5 (3)	5 (3.5)	6 (2)	0.005
Apgar of 5th min[c]	7 (2)	8 (2.5)	8 (1)	0.002
RDS score[c]	6 (0.5)	6 (1)	6 (1)	0.62

[a]Values have been presented as *n* (%); [b]Values have been presented as mean±SD; [c]Values have been presented as median (range). *Resulted from ANOVA and Kruskal-Wallis test for normal and nonnormal quantitative and Chi-square test for categorical variables. NIMV=Nasal intermittent mandatory ventilation; NCPAP=Nasal continuous positive airway pressure; HHHFNC=Heated humidified high-flow nasal cannula; RDS=Respiratory distress syndrome; SD=Standard deviation

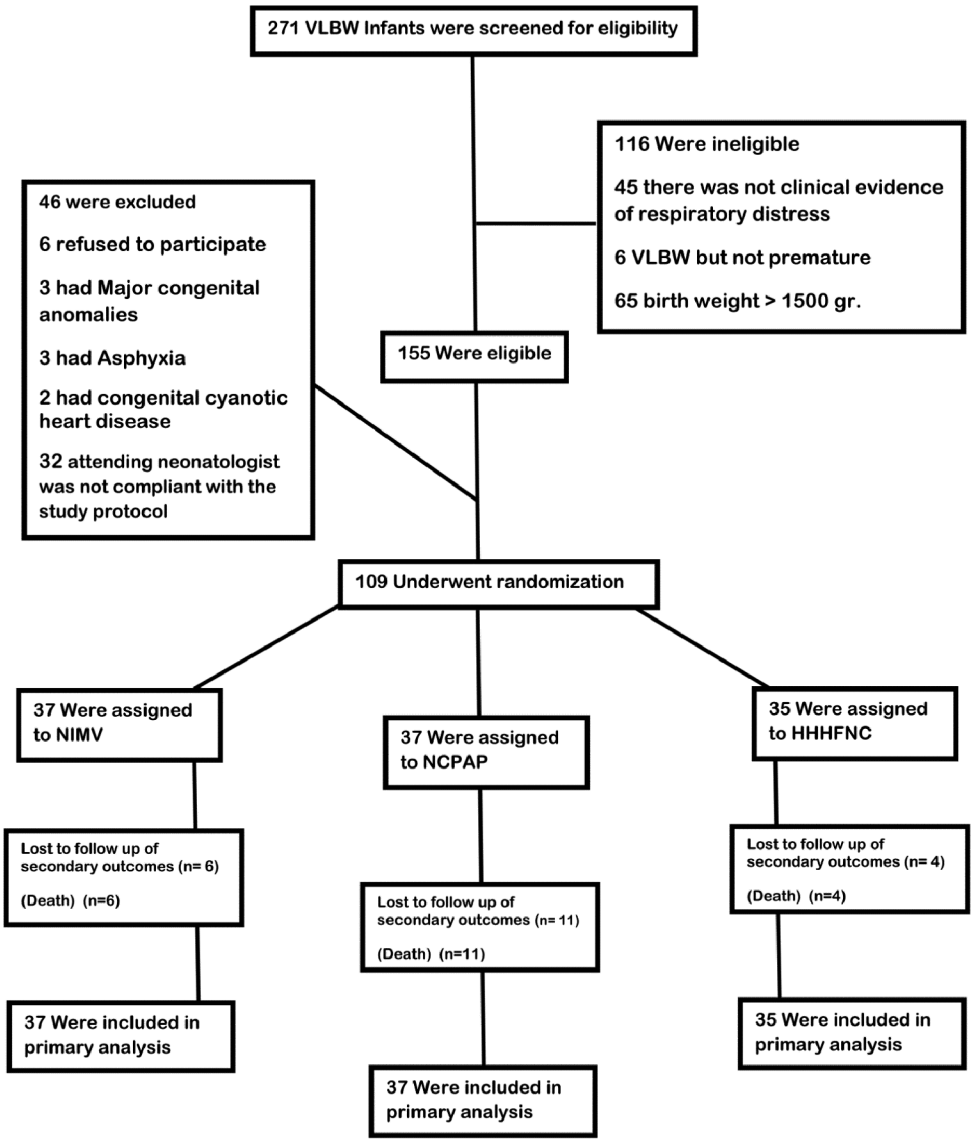

Figure 1: CONSORT diagram showing the flow of individuals through each stage of study

Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure

The results of comparing the primary clinical outcomes showed similar prevalence for failure rate of initial treatment of RDS in the NIMV and NCPAP groups (P = 0.59, HR = 1.35, 95% CI = 0.13–13.72), and there was also no significant difference between the two groups in terms of the median duration of RDS treatment (P = 0.29). In addition, although the frequency of need for intubation and treatment with surfactant, pneumothorax, and death cases in the NCPAP group was higher than those of the NIMV, there was no significant difference between the two groups in this regard. Although the majority of IVH and PDA cases were observed in the NIMV group, the difference was not statistically significant. The primary and secondary clinical outcomes of patients treated with NIMV and NCPAP are shown in Table 5.

Nasal intermittent mandatory ventilation versus heated humidified high-flow nasal cannula

The failure rate of initial treatment of RDS was observed in 19 of 35 patients in the HHHFNC group and 8 of 37 patients in the NIMV group, indicating a significant increase in the treatment failure using HHHFNC technique (P < 0.001, HR = 9.12, 95% CI = 2.59–32.07). Furthermore, the median duration of treatment of RDS, as another primary outcome of treatment, was significantly higher in the HHHFNC group, but it did not differ significantly between the two groups (P = 0.2). The results of comparing the secondary clinical outcomes in the two groups showed that the duration of the oxygen dependency, hospitalization duration, and IVH severity in the HHHFNC group was significantly lower than those of the NIMV group, but other outcomes including the need for MV and surfactant and the frequency of IVH, PDA, pneumothorax, and mortality were

Table 2: Comparison clinical outcomes in nasal intermittent mandatory ventilation and heated humidified high-flow nasal cannula patients

Clinical outcomes	Groups		HR (95% CI)[c]	*P**
	NIMV (*n*=37)	HHHFNC (*n*=35)		
Initial treatment failure[a]	8 (21.6)	19 (54.3)	9.12 (2.59-32.07)	<0.001
RDS treatment duration (hours)[b]	31.16 (5.92-130.92)	40.0 (13.66-630.0)	-	0.2
Intubation requirement[a]	8 (21.6)	5 (14.3)	0.07 (0-1667.75)	0.31
Surfactant therapy[a]	25 (67.6)	22 (62.9)	1.63 (1.06-2.5)	0.67
Times of surfactant therapy[b]	1 (0-4)	1 (0-4)	-	0.69
Oxygen dependency duration (hours)[b]	235.66 (21-1502)	94.25 (21.16-503.16)	-	0.001
IVH[a]	10 (27.0)	1 (2.9)	0.004 (0-6.82)	0.12
IVH severity[a]				
0	27 (73.0)	34 (97.1)	-	0.02
I	2 (5.4)	0 (0)		
II	8 (21.6)	1 (2.9)		
PDA[a]	10 (27.0)	10 (28.6)	2.17 (0.9-4.28)	0.07
Pneumothorax[a]	4 (10.8)	2 (5.7)	1.73 (0.39-7.64)	0.88
Hospitalization duration (day)[b]	29 (10-65)	26.0 (10-57)	-	0.04
Death[a]	6 (16.2)	4 (11.4)	N/A	0.56

[a]Values have been presented as *n* (%); [b]Values have been presented as median (range); [c]HR adjusted for gestational age and birth weight; *Resulted from Kruskal-Wallis test for nonnormal quantitative and Chi-square test for categorical variables. NIMV=Nasal intermittent mandatory ventilation; RDS=Respiratory distress syndrome; IVH=Intraventricular hemorrhage; PDA=Patent ductus arteriosus; HR=Hazard ratio; CI=Confidence interval; HHHFNC=Heated humidified high-flow nasal cannula

Table 3: Comparison clinical outcomes in nasal continuous positive airway pressure and heated humidified high-flow nasal cannula patients

Clinical outcomes	Groups		HR (95% CI)[c]	*P**
	NCPAP (*n*=37)	HHHFNC (*n*=35)		
Initial treatment failure[a]	13 (35.1)	19 (54.3)	21.25 (2.51-180.08	0.004
RDS treatment duration (hours)[b]	38.91 (10.16-416.42)	40.0 (13.66-630.0)	-	0.66
Intubation requirement[a]	12 (32.4)	5 (14.3)	2.94 (0.008-1040.91)	0.69
Surfactant therapy[a]	26 (70.3)	22 (62.9)	0.51 (0.23-1.11)	0.87
Times of surfactant therapy[b]	1 (0-4)	1 (0-4)	-	0.88
Oxygen dependency duration (hours)[b]	150.62 (23.25-1571.92	94.25 (21.16-503.16)	-	0.06
IVH[a]	5 (13.5)	1 (2.9)	0 (0-1.52)	0.17
IVH severity[a]				
0	32 (86.5)	34 (97.1)	-	0.34
I	2 (5.4)	0 (0)		
II	2 (5.4)	1 (2.9)		
III	1 (2.7)	0 (0)		
PDA[a]	8 (21.6)	10 (28.6)	1.01 (0.22-4.62)	0.36
Pneumothorax[a]	5 (13.5)	2 (5.7)	0.16 (0.007-3.92)	0.53
Hospitalization duration (day)[b]	24.5 (8-82)	26.0 (10-57)	-	0.53
Death[a]	11 (29.7)	4 (11.4)	0.25 (0.12-0.52)	0.05

[a]Values have been presented as *n* (%); [b]Values have been presented as median (range); [c]Hazard ratio adjusted for gestational age and birth weight; *Resulted from Kruskal-Wallis test for nonnormal quantitative and Chi-square test for categorical variables. NCPAP=Nasal continuous positive airway pressure; RDS=Respiratory distress syndrome; IVH=Intraventricular hemorrhage; PDA=Patent ductus arteriosus; HR=Hazard ratio; CI=Confidence interval; HHHFNC=Heated humidified high-flow nasal cannula

similar in the three groups. Clinical outcomes of HHHFNC and NIMV techniques are compared in Table 2.

Nasal continuous positive airway pressure versus heated humidified high-flow nasal cannula

Treatment failure frequency of RDS in neonates treated with HHHFNC and NCPAP was observed in 54.3% and 35.1% of the cases, respectively, and the difference between the two groups was significant ($P = 0.004$, HR = 21.25, 95% CI = 2.51–180.08). The median RDS treatment duration in the HHHFNC group was higher than that of the NIMV group, but not statistically significant ($P = 0.66$). No significant differences were also observed between the two groups in terms of secondary clinical outcomes. Table 3 shows the results of comparing the clinical outcomes of the groups.

DISCUSSION

The current clinical trial was designed and evaluated to compare the clinical outcomes of noninvasive respiratory support techniques in neonates with RDS. The results of the study showed that despite the higher gestational age and birth weight of neonates in the HHHFNC group, the treatment failure rate in HHHFNC-treated neonates was significantly higher than the ones treated with NIMV or NCPAP techniques, and the HHHFNC technique showed no appropriate efficacy in the treatment of infants with RDS; therefore, it cannot be recommended as the primary treatment for neonates with RDS based on the results of the current study. Although HHHFNC is widely used to treat neonates with RDS, studies in this area merely examined the efficacy of this technique, and there is limited evidence of comparing the effects of this technique with those of other noninvasive respiratory support techniques. Various studies also presented different definitions for the failure of primary treatment that makes it difficult to compare the results.[20] In a clinical trial, Roberts *et al*. investigated the efficacy of HHHFNC, as the initial treatment of RDS, on 543 premature infants. The case finding was stopped early in the study due to a significant difference in clinical outcomes. Consistent with the results of the current study, it was observed that the rate of treatment failure within the first 72 h was significantly higher in patients treated with HHFNC than the NCPAP-treated neonates (25.5% vs. 13.3%, risk difference 95% CI = 5.8–18.7, $P < 0.001$).[21] Shin *et al*. investigated the failure rate of HHHFNC and NCPAP in a clinical trial performed on neonates with RDS aged 35–30 weeks. In their study where the treatment failure criteria were similar to those of the current study, the frequency of treatment failure in HHHFNC-treated neonates was higher than that of NCPAP neonates, although there was no statistically significant difference (38.1% vs. 20.9%, risk difference 95% CI = −1.9–36.23, $P = 0.1$).[22] It seems that the lack of significant differences between HHHFNC failures compared with that of NCPAP in the study by Shin *et al*. can be attributed to differences in the baseline characteristics of the studied

Table 4: Reasons of treatment failure for infants assigned to receive either heated humidified high-flow nasal cannula or nasal continuous positive airway pressure or nasal intermittent mandatory ventilation

Treatment failure reasons	Groups, *n* (%)			*P**
	NIMV (*n*=8)	NCPAP (*n*=13)	HHHFNC (*n*=19)	
Hypoxia (need to FiO_2 ≥40%)	4 (50.0)	5 (38.4)	14 (73.6)	0.67[a] 0.37[b] 0.07[c]
Respiratory acidosis	1 (12.5)	2 (15.4)	1 (5.3)	>0.99[a] 0.51[b] 0.55[c]
Urgent need for intubation	1 (12.5)	0	1 (5.3)	0.38[a] 0.51[b] >0.99[c]
Sever apnea	2 (25.0)	3 (23.1)	0 (0)	>0.99[a] 0.08[b] 0.06[c]
Frequent apnea	0	3 (23.1)	3 (15.8)	0.26[a] 0.53[b] 0.47[c]

[a]NIMV versus NCPAP; [b]NIMV versus HHHFNC; [c]NCPAP versus HHHFNC; *Resulted from Chi-square or Fisher's exact test. NIMV=Nasal intermittent mandatory ventilation; NCPAP=Nasal continuous positive airway pressure; HHHFNC=Heated humidified high-flow nasal cannula

Table 5: Comparison clinical outcomes in nasal intermittent mandatory ventilation and nasal continuous positive airway pressure patients

Clinical outcomes	Groups		HR (95% CI)[c]	*P**
	NIMV (*n*=37)	NCPAP (*n*=37)		
Initial treatment failure[a]	8 (21.6)	13 (35.1)	1.35 (0.13-13.72)	0.59
RDS treatment duration (hours)[b]	31.16 (5.92-130.92)	38.91 (10.16-416.42)	-	0.29
Intubation requirement[a]	8 (21.6)	12 (32.4)	1.35 (0.13-13.72)	0.59
Surfactant therapy[a]	25 (67.6)	26 (70.3)	1.94 (0.97-3.87)	0.19
Times of surfactant therapy[b]	1 (0-4)	1 (0-4)	-	0.51
Oxygen dependency duration (hours)[b]	235.66 (21-1502)	150.62 (23.25-1571.92	-	0.18
IVH[a]	10 (27.0)	5 (13.5)	1.02 (0.21-4.83)	0.65
IVH severity[a]				
0	27 (73.0)	32 (86.5)	-	0.44
I	2 (5.4)	2 (5.4)		
II	8 (21.6)	2 (5.4)		
III	0 (0)	1 (2.7)		
PDA[a]	10 (27.0)	8 (21.6)	1.34 (0.45-3.99)	0.85
Pneumothorax[a]	4 (10.8)	5 (13.5)	8.1 (0.43-152.57)	0.47
Hospitalization duration (days)[b]	29 (10-65)	24.5 (8-82)	-	0.38
Death[a]	6 (16.2)	11 (29.7)	1.22 (0-6.07)	0.14

[a]Values have been presented as *n* (%); [b]Values have been presented as median (range); [c]Hazard ratio adjusted for gestational age and birth weight; *Resulted from Kruskal-Wallis test for nonnormal quantitative and Chi-square test for categorical variables. NIMV=Nasal intermittent mandatory ventilation; NCPAP=Nasal continuous positive airway pressure; RDS=Respiratory distress syndrome; IVH=Intraventricular hemorrhage; PDA=Patent ductus arteriosus; HR=Hazard ratio; CI=Confidence interval

neonates; for example, the mean gestational age and birth weight of the neonates in the study by Shin *et al*. was much higher than those of the study by Robert and the current study.[21,22] In the current study, the need for intubation in the first 72 h after starting treatment was considered as a secondary outcome, and it was found that the need for intubation was lower in HHHFNC-treated neonates than the NCPAP-treated ones, though the difference was not statistically significant between the two groups. Many previous studies, which compared these two methods, considered the need for intubation as a primary outcome, and their results were consistent with those of the current study. In a large clinical trial that compared HHHFNC with NCPAP, Lavizzari *et al*. investigated 316 infants with mild to moderate RDS. They observed that the frequency of need for intubation in the HHHFNC and NCPAP groups was 10.8% and 9.5%, respectively, and there was no significant difference between the two groups (risk difference 95% CI = −6.0%, 8.6%, P = 0.71).[23] In another comparative study, Yoder *et al*. compared the effect of HHHFNC, as a primary treatment or postextubation treatment of neonates requiring respiratory support, with NCPAP. The results of their study also indicated the similarity of therapeutic outcomes including the need for intubation in both techniques.[24] Zheng *et al*. investigated the primary and secondary clinical outcomes of HHHFNC and NCPAP as the primary treatment of mild to moderate RDS in a cross-sectional study. A total of 13 of 65 HHHFNC-treated patients and 11 out of 63 NCPAP-treated patients needed intubation within 72 h after initiation of the treatment, which did not show a significant difference between the two groups (risk difference 95% CI = 0.5–2.9, P = 0.7).[25] In another study on very low birth weight (VLBW) infants with RDS, Chen *et al*. found no significant difference between the two groups treated with HHHFNC and NCPAP in terms of the need for intubation.[26] Based on the results of current and aforementioned studies, it seems that the need for intubation is not a suitable factor to assess the success rate of treatment in neonates treated with different ventilation techniques. Therefore, considering the adverse effects of hypoxia, it is more logical to consider this factor as a treatment failure criterion, especially in neonates with lower birth weight and gestational age, which requires further studies.

Based on the results of the search in various databases, the current study was the first one that compared the clinical outcomes of the initial treatment of RDS with HHHFNC versus NIMV and NCPAP methods. It was found that NCPAP and NIMV were more reliable techniques for respiratory support in neonates with RDS. In the HHHFNC method, patient's personal factors (such as weight) and technical issues (such as the increased airflow leak) cause heterogeneity in the pressure applied to the airways. These factors were reviewed and confirmed in previous studies.[27,28] Therefore, it seems that HHHFNC is less efficient than NIMV and NCPAP techniques to open microatelectasis and optimize the use of alveolar space.[29,30]

The results of comparing the secondary clinical outcomes in the current study showed that HHHFNC-treated patients had a better status than patients treated with NIMV and NCPAP. However, previous studies showed no significant difference between the secondary outcomes of HHHFNC and CPAP techniques regardless of the primary outcomes.[21-26] The issue seems to be due to high rate of treatment failure and the mandatory use of the second line of treatment rather than higher efficiency of the HHHFNC technique, i.e., MV or NCPAP. Comparison of the secondary clinical outcomes between the two groups of NIMV and NCPAP indicated that these two groups were similar in all of the studied variables.

The current study showed no significant difference between the NIMV and NCPAP-treated neonates in terms of the primary and secondary outcomes, which was inconsistent with the results of authors' previous study in 2014, which showed that the preventive effect of NIMV supportive strength was greater than that of NCPAP to avoid intubation. Furthermore, the duration of RDS treatment in the NIMV group was much shorter than that of the NCPAP group. However, it seems that a significant higher gestational age and birth weight in the NIMV group, as a confounder, caused false results. In the current study, the gestational age and birth weight were not different in the groups, and the confounding effect of these factors was adjusted. Therefore, the current study did not show any significant differences between treatment failures, protective strength of NIMV for intubation prevention, and duration of RDS treatment.[31]

Finally, it seems that making decisions about the efficacy of HHHFNC in comparison with other noninvasive respiratory support techniques in infants with RDS requires further studies on larger populations. Furthermore, further considerations of long-term implications such as neurodevelopmental outcomes and respiratory morbidities in subsequent studies facilitate the selection of the preferred technique as the initial treatment of RDS.

CONCLUSION

The use of HHHFNC as the initial treatment for VLBW preterm infants with RDS is significantly associated with higher failure rates compared with the employment of NIMV and NCPAP techniques. Despite the fact that some secondary treatment outcomes are better in HHHFNC

technique, it is not safe to select this technique as a primary treatment.

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Conflicts of interest
There are no conflicts of interest.

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