Randomized Controlled Trial of High-Flow Nasal Cannula in Preterm Infants After Extubation

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abstract

OBJECTIVES: Our aim is to compare the efficacy and safety of high-flow nasal cannula (HFNC) against those of nasal continuous positive airway pressure (NCPAP) or nasal intermittent positive-pressure ventilation (NIPPV) after extubation in preterm infants.

METHODS: This prospective, randomized, noninferiority trial was conducted in 6 tertiary NICUs. Infants born at <34 weeks who needed noninvasive ventilation after extubation were enrolled. We randomly assigned infants to an HFNC group when HFNC was used or to an NCPAP/NIPPV group when NCPAP or NIPPV was used. The primary outcome was treatment failure within 7 days after extubation. We then examined clinical aspects of treatment failure with HFNC use.

RESULTS: In total, 176 and 196 infants were assigned to the HFNC and NCPAP/NIPPV groups, respectively. The HFNC group showed a significantly higher rate of treatment failure than that of the NCPAP/NIPPV group, with treatment failure occurring in 54 infants (31%) compared with 31 infants (16%) in the NCPAP/NIPPV group (risk difference, 14.9 percentage points; 95% confidence interval, 6.2–23.2). Histologic chorioamnionitis (P = .02), treated patent ductus arteriosus (P = .001), and corrected gestational age at the start of treatment (P = .007) were factors independently related to treatment failure with HFNC use.

CONCLUSIONS: We found HFNC revealed a significantly higher rate of treatment failure than NCPAP or NIPPV after extubation in preterm infants. The independent factors associated with treatment failure with HFNC use were histologic chorioamnionitis, treated patent ductus arteriosus, and a younger corrected gestational age at the start of treatment.

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WHAT'S KNOWN ON THIS SUBJECT: Meta-analyses strongly support the effectiveness and safety of HFNC compared with nasal continuous positive airway pressure for postextubation support of infants >28 weeks' gestation. Clinical aspects associated with treatment failure for HFNC therapy remain unknown.

WHAT THIS STUDY ADDS: In our study, we found HFNC showed a significantly higher rate of treatment failure than nasal continuous positive airway pressure or nasal intermittent positive-pressure ventilation after extubation. Histologic chorioamnionitis, treated patent ductus arteriosus, and younger corrected gestational age at the start of treatment were independent factors associated with treatment failure with HFNC use.

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Nasal continuous positive airway pressure (NCPAP) is a type of noninvasive ventilation (NIV) that is known to be effective for respiratory support after extubation in preterm infants.[1] Nasal intermittent positive-pressure ventilation (NIPPV) is another type of NIV that uses a nasal interface to deliver intermittent peak pressure during NCPAP to provide respiratory support.[2] Both NCPAP and NIPPV have been used widely for neonatal respiratory disorders because many respiratory devices have both NCPAP and NIPPV modes. The high-flow nasal cannula (HFNC) is a newer device for NIV that assists breathing by delivering a high flow of heated and humidified oxygen and air to the patients through the nose.[3] Recently, HFNC has gained popularity for use in newborn infants.[3,4] Although HFNC therapy has been studied clinically and its effectiveness and safety have been demonstrated in several articles, it remains unclear as to how HFNC therapy fits among the gamut of NIV therapeutic options, and its indications also remain unclear.[5–16]

We hypothesized that HFNC would be noninferior to CPAP or NIPPV in preventing treatment failure within 7 days of extubation. We conducted a multicenter, randomized trial of HFNC therapy by comparing HFNC with NCPAP or NIPPV therapy after extubation in preterm infants born <34 weeks' gestation. In addition, we examined clinical aspects of treatment failure on HFNC in these infants.

METHODS

Design

We conducted a prospective, open-label, randomized controlled trial in 6 tertiary NICUs belonging to the Non-Invasive Procedure for Premature Neonates Study Group. The units belonged to the following facilities: Tokyo Women's Medical University, Tokyo Metropolitan Children's Medical Center, Saitama Medical University, Nihon University School of Medicine, Nagaoka Red Cross Hospital, and the National Center for Child Health and Development. Hospital ethics committee approval was obtained from each hospital. We registered this study with the University Hospital Medical Information Network Clinical Trials Registry (identifier UMIN000013906).

Participants

Infants who met the following conditions were enrolled: (1) infants born at <34 weeks' gestation, (2) infants requiring NIV after extubation at <36 weeks' corrected gestational age, and (3) infants for whom written informed consent was provided from their legal guardians for participation in this study. The following infants were excluded: (1) infants with multiple malformation syndrome, (2) infants with a chromosomal abnormality, (3) infants with congenital airway diseases, and (4) infants for whom an attending physician judged inclusion to be inappropriate.

Device for HFNC, NCPAP, or NIPPV Therapy

We used Optiflow Junior (Fisher & Paykel Healthcare, Co Ltd, Irvine, CA) as a medical device for the HFNC group. On the other hand, we used several devices for the NCPAP/NIPPV group because each unit belonging to the Non-Invasive Procedure for Premature Neonates Study Group was different. These units were Infant Flow SiPAP (CareFusion, San Diego, CA); medinSindi (Medin Medical Innovations GmbH, Olching, Germany); medinCNO (Medin Medical Innovations GmbH); Babylog 8000 Plus (Dräger Medical AG & Co, Lübeck, Germany); Babylog VN500 (Dräger Medical AG & Co); and Bear Cub 750 (VIASYS Healthcare, Conshohocken, PA).

Randomization and Assignment

Infants were centrally randomly assigned by a computer-generated randomization sequence with 10 block sizes used to assign them to either an HFNC group or NCPAP/NIPPV group. The infants were stratified by each NICU. We allowed NIPPV as a first-line therapy after extubation because some recently developed respiratory devices for NIV have been equipped with both NCPAP and NIPPV modes and are easily switched from NCPAP to NIPPV or vice versa. On the basis of this clinical perspective, we included not only NCPAP but also NIPPV in the same control arm in this clinical trial. The choice of NCPAP therapy or NIPPV therapy depended on each physician's decision.

Interventions

Implementing HFNC Therapy

HFNC was started with a flow rate of >2 L/min and adjusted as appropriate according to the patient's respiratory condition. Maximum flow rate was up to 8 L/min according to the operating instructions. The fraction of inspired oxygen (F_{IO_2}) was determined according to the following target pulse oxygen saturation (Sp_{O_2}) levels. When supplemental oxygen was received, the target Sp_{O_2} levels were between 92% and 95%. If Sp_{O_2} levels became >95%, then F_{IO_2} was decreased. In case of room air, the target Sp_{O_2} levels were ≥92%. Weaning from HFNC therapy was performed when the infant's respiratory condition was stable at a flow rate of 2 L/min and F_{IO_2} <0.3 for 24 hours.

Implementing NCPAP or NIPPV Therapy

NCPAP therapy was performed to maintain a CPAP pressure of 4 to 5 cm H_2O. The F_{IO_2} with NCPAP therapy was determined in the same way as HFNC therapy. NIPPV therapy was performed to maintain a positive end-expiratory pressure (PEEP) of 4 to 5 cm H_2O and peak inspiratory

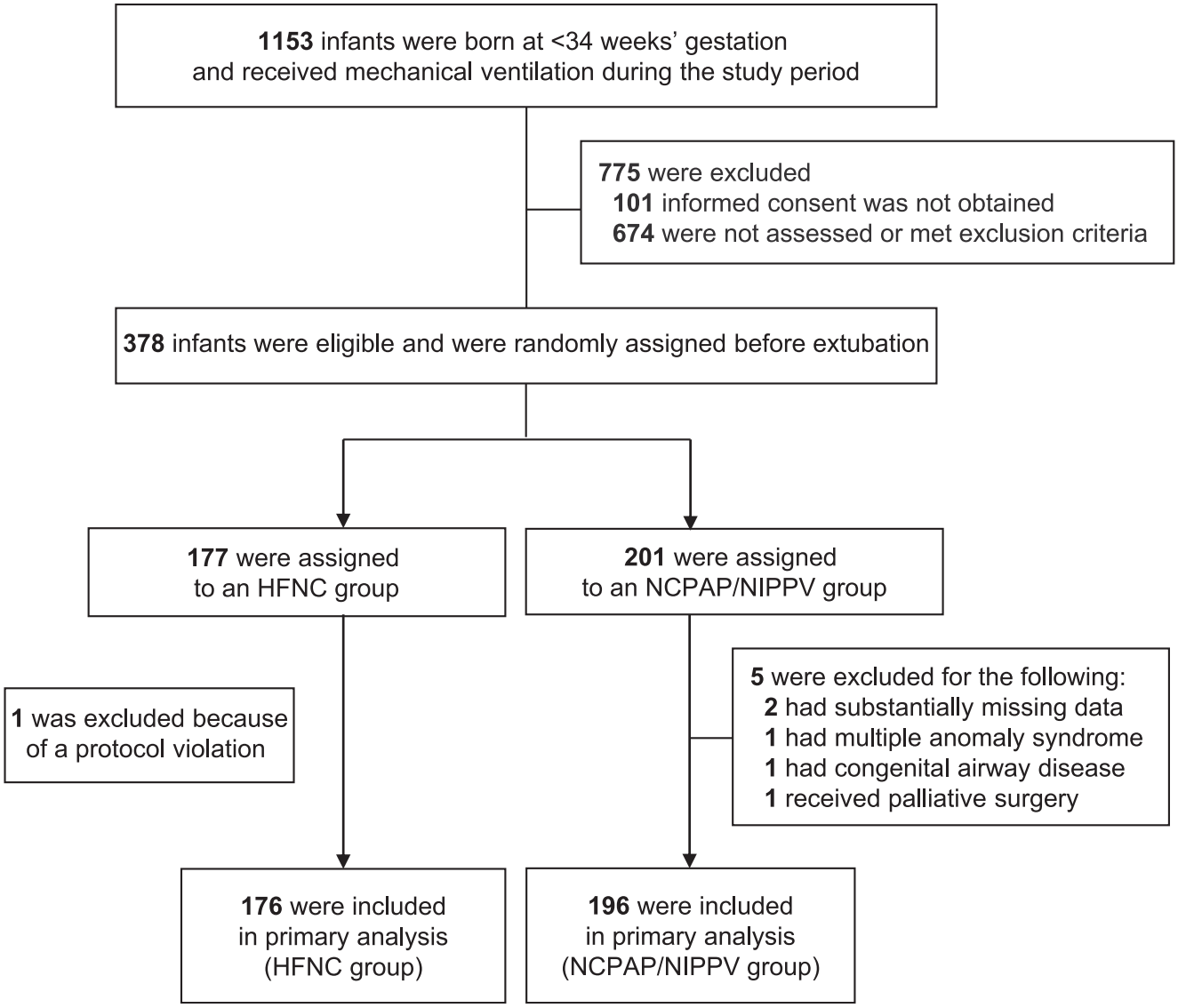

FIGURE 1

Numbers of study infants who were screened, assigned to the HFNC or NCPAP/NIPPV group, and included in the primary analysis. Infants were born at <34 weeks' gestational age who received mechanical ventilation were screened for eligibility.

pressure of 3 to 4 cm H_2O above PEEP.

Definition of Clinical Factors

Histologic chorioamnionitis was defined as a Branc[17] classification II or more. In terms of the use of antenatal steroids, an incomplete course was defined when infants received 1 dose, and a complete course was defined when infants received 2 doses. Respiratory distress syndrome was defined as the need for surfactant treatment by a chest radiographic finding. Treated patent ductus arteriosus (PDA) was defined as the need for indomethacin administration or surgical operation. Grade 3 or 4 cerebral hemorrhage was defined in accordance with Papile et al.[18] Blood gas analysis was performed by using capillary or venous samples. Nasal trauma was defined as the need for any treatments. We measured the modified COMFORT scale[19] to estimate the tolerability of NIV treatment. However, mean arterial pressure was not used as a parameter of the scale because no arterial line was inserted in the study infants.

Outcomes

The primary outcome was treatment failure, which was defined as a case in which the infant needed to be switched to another respiratory mode within 7 days (168 hours) after extubation. HFNC treatment failure criteria were as follows: (1) infant required a supplemental oxygen level of ≥40%, (2) infant showed sustained blood gas measurements of pH <7.20 and p_{CO_2} >60 mmol/L, (3)

TABLE 1 Baseline Clinical Characteristics in the HFNC and NCPAP/NIPPV Groups

Clinical Characteristics	HFNC Group (n = 176)	NCPAP Group (n = 196)
Prenatal factors, *n* (%)		
Histologic chorioamnionitis	51 (29)	41 (21)
Antenatal steroid administration		
Incomplete course/complete course, *n* (%)/*n* (%)	37 (21)/98 (56)	40 (20)/102 (52)
Cesarean delivery, *n* (%)	149 (85)	163 (83)
Multiple gestation, *n* (%)	55 (31)	53 (27)
Birth factors		
Gestational age,[a] wk	28.4 ± 3.0	28.2 ± 3.0
Birth wt,[a] g	1129 ± 426	1070 ± 455
Male sex, *n* (%)	91 (52)	97 (49)
1-min Apgar score[b]	5 (3–6)	4 (2–6)
5-min Apgar score[b]	7 (6–8)	7 (6–8)
Postnatal factors		
Respiratory distress syndrome, *n* (%)	122 (69)	148 (76)
Treated PDA, *n* (%)	67 (38)	67 (34)
Grade 3 or 4 cerebral hemorrhage, *n* (%)	5 (3)	3 (2)
Postnatal age at the start of treatment,[b] d	5 (2–30)	6 (1–33)
Corrected gestational age at the start of treatment,[a] wk	30.9 ± 2.2	30.7 ± 2.0
Body wt at the start of treatment,[a] g	1204 ± 329	1149 ± 380
F_{IO_2} before the start of treatment[b]	0.23 (0.21–0.28)	0.23 (0.21–0.26)
pH before the start of treatment[a]	7.36 ± 0.07	7.37 ± 0.07[c]
p_{CO_2} before the start of treatment,[a] mm Hg	43.9 ± 10.5	42.5 ± 9.74[c]
Base excess before the start of treatment[a]	−1.2 ± 3.8	−0.9 ± 3.6[c]
Modified COMFORT scale before the start of treatment[a]	13.9 ± 4.3[d]	13.9 ± 3.7[d]

There were no significant differences between groups.
[a] Data are expressed as mean ± SD values.
[b] Data are expressed as median (interquartile range) values.
[c] Data are not available for 1 infant in the NCPAP group.
[d] Data are not available for 32 infants in the HFNC group and for 44 in the NCPAP group.

infant presented with episodes of apnea requiring ≥1 bag mask ventilations within 24 hours or episodes of apnea requiring ≥1 stimulations within 1 hour that continued for 6 hours, and (4) attending physician determined that urgent reintubation is necessary. When HFNC treatment failure criteria were met, the infant was to be switched to ventilatory support with NCPAP, NIPPV, or mechanical ventilation after reintubation. NCPAP/NIPPV treatment failure was the same as for HFNC therapy. When NCPAP/NIPPV treatment failure criteria were met, the infant was switched to ventilatory support with HFNC, NIPPV (in the case with NCPAP), or mechanical ventilation after reintubation.

The secondary outcomes were reintubation within 7 days (168 hours), nasal skin or mucosal injury, chronic lung disease (CLD) at 36 weeks' corrected gestational age, death before hospital discharge, results of blood gas analysis such as pH and p_{CO_2}, and base excess. A modified COMFORT scale between 60 and 90 minutes after extubation was also evaluated. After that, we examined clinical aspects of treatment failure with HFNC therapy by comparing clinical characteristics between the high-flow nasal cannula success (HFNC-S) and high-flow nasal cannula failure (HFNC-F) groups.

Sample Size Definition

We designed this clinical study to determine if HFNC is noninferior to NCPAP or NIPPV in preventing treatment failure. Assuming a 15% intubation rate in the conventional NCPAP/NIPPV group, an expected treatment failure rate of 24% in the HFNC group, and with a 20% noninferiority margin whose value was determined in reference to the previous article,[10] the number of cases necessary for this study was calculated to be 155 patients in 1 group and 310 patients in both groups combined (α: .1; power: 0.8). After taking into account the dropouts from the study (eg, withdrawal of informed consent or exclusion from the study after allocation), a total of 340 patients was set as the target number of cases for this study.

Statistical Analysis

To clarify clinical aspects of treatment failure with HFNC, we also performed subgroup analysis. Namely, we divided the HFNC group into 2 subgroups as follows. Infants were assigned to an HFNC-F group if they had treatment failure with HFNC and to an HFNC-S group if they had treatment success with HFNC.

In performing a univariate analysis of group differences, we analyzed the continuous variables using either an unpaired Student's *t* test or Mann–Whitney *U* test and analyzed the categorical variables using either

a χ^2 test or Fisher's exact test. *P* values <.05 were considered significant. In performing a multivariate analysis to examine the clinical aspects of treatment failure with HFNC use, we used a multiple logistic regression analysis. We used variables that revealed a *P* value of <.05 in the univariate analysis. However, some of the variables that may have revealed multicollinearity were removed for the multiple logistic regression analysis. Statistical analyses were performed by using JMP Pro software (SAS Institute, Inc, Cary, NC) version 14.0 for Macintosh.

RESULTS

Study Population and Baseline Clinical Characteristics

Figure 1 shows the study population selection flowchart. A total of 1153 infants were born at <34 weeks' gestational age and received mechanical ventilation between April 2015 and September 2018. Among them, we did not obtain informed consent for 101 infants, and 674 infants were not assessed or did not meet the exclusion criteria.

A total of 378 infants were eligible in this study. Among these, 177 and 201 infants were assigned to the HFNC and NCPAP/NIPPV groups, respectively. We conducted a per-protocol analysis in this study, and among those in the HFNC group, 1 infant was excluded because of protocol violation caused by the use of a flow rate of 10 L/min. Among the NCPAP/NIPPV group, 5 infants were excluded: 2 were excluded because of substantially missing data, 1 because of multiple anomaly syndrome, 1 because of congenital airway disease, and 1 because of palliative surgery for midgut malrotation before receiving NCPAP therapy. Finally, 176 and 196 infants were assigned to the HFNC and NCPAP/NIPPV groups, respectively. Among the NCPAP/NIPPV group, the number of infants who received NCPAP and NIPPV therapies was 149 and 47, respectively.

Baseline clinical characteristics in the 2 groups are shown in Table 1. All prenatal, birth, and postnatal factors were not significantly different between the 2 groups.

TABLE 2 Treatment Failure, Changing the Ventilator Mode, and Other Secondary Outcomes

Outcome	HFNC Group, *n* = 176	NCPAP/NIPPV Group, *n* = 196	Risk Difference (95% CI) Percentage Points	*P*
Treatment failure <7 d after extubation, *n* (%)	54 (31)	31 (16)	14.9 (6.2 to 23.2)	.001
Treatment failure <72 h after extubation, *n* (%)	45 (26)	30 (15)	10.2 (1.9 to 18.3)	.008
Reintubation <7 d after extubation, *n* (%)	10 (6)	17 (9)	−3.0 (−8.3 to 2.4)	.29
Nasal trauma, *n* (%)	3 (2)	5 (3)	N/A	.42
CLD at 36 wk' corrected gestational age, *n* (%)	59 (34)	75 (38)	N/A	.34
Death before hospital discharge, *n* (%)	3 (2)	0 (0)	N/A	.10
pH between 60 and 90 min after the start of treatment[a]	7.35 ± 0.06[b]	7.36 ± 0.04[b]	N/A	.05
pco_2 between 60 and 90 min after the start of treatment,[a] mm Hg	44.6 ± 9.3[b]	43.6 ± 9.2[b]	N/A	.33
Base excess between 60 and 90 min after the start of treatment[a]	−1.2 ± 4.0[b]	−0.9 ± 3.8[b]	N/A	.41
Modified COMFORT scale between 60 and 90 min after the start of treatment[a]	12.9 ± 3.5[c]	12.9 ± 3.2[c]	N/A	.86

N/A, not applicable.
[a] Data are expressed as mean ± SD values.
[b] Data are not available for 8 infants in the HFNC group and for 1 in the NCPAP group.
[c] Data are not available for 33 infants in the HFNC group and for 42 in the NCPAP group.

Primary Outcome

Treatment failure within 7 days after extubation occurred in 54 of 176 infants (31%) in the HFNC group. On the other hand, it occurred in 31 of 196 (16%) in the NCPAP/NIPPV group. As a result, infants in the HFNC group had a significantly higher rate of treatment failure than infants in the NCPAP/NIPPV group (risk difference, 14.9 percentage points; 95% confidence interval [CI], 6.2–23.2). Among 54 infants with treatment failure in the HFNC group, 16 and 28 infants were successfully treated with NCPAP and NIPPV, respectively, without reintubation. Among 31 infants with treatment failure in the NCPAP/NIPPV group, 14 infants were successfully treated with NIPPV. Although one of the 31 infants was switched to HFNC, he experienced treatment failure again and needed reintubation. The rates of treatment failure, reintubation within 7 days after extubation, and CLD at 36 weeks' gestation stratified by gestational-age subgroup are provided in Supplemental Table 5.

Secondary Outcomes

Treatment failure within 72 hours after extubation occurred in 45 of 176 infants (26%) in the HFNC group. On the other hand, it occurred in 30 of 196 (15%) infants in the NCPAP/NIPPV group. The HFNC group showed a significantly higher rate in terms of treatment failure within 72 hours after extubation than the NCPAP/NIPPV group (risk difference, 10.2 percentage points; 95% CI, 1.9 to 18.3). Among those infants who had treatment failure within 7 days, treatment failure occurred within 72 hours after extubation in 83% (45 of 54) of the HFNC infants, and 97% (30 of 31) of the NCPAP/NIPPV infants. The rate of reintubation within 7 days after extubation did not show a significant difference between the 2 groups. The rate of nasal trauma, CLD at 36 weeks' corrected

gestational age, and death before discharge did not show significant differences between the 2 groups (Table 2). The pH, pco_2 between 60 and 90 minutes after the start of treatment, and base excess values did not show significant differences between the 2 groups. Modified COMFORT scale values between 60 and 90 minutes after the start of treatment also did not show significant differences between the 2 groups (Table 2).

We examined the clinical aspects of treatment failure with HFNC use by comparing clinical factors in the HFNC-F and HFNC-S groups. Table 3 shows the baseline clinical characteristics in the 2 groups.

Among the prenatal factors, the rate of histologic chorioamnionitis was significantly higher in the HFNC-F group than in the HFNC-S group. Among the birth factors, mean gestational age in the HFNC-F group was significantly lower than in the HFNC-S group. The mean birth weight in the HFNC-F group was also significantly lower than in the HFNC-S group. Among the postnatal factors, the rates of respiratory distress syndrome and treated PDA were significantly higher in the HFNC-F group than in the HFNC-S group (Table 3).

To identify factors related to treatment failure with HFNC use, a multivariate logistic regression analysis was performed. In the HFNC-F group, 2 infants had missing values for initial flow rate and body weight at the start of treatment and/or maximum flow rate and body weight at the start of treatment. Among the HFNC-S group, 3 infants had missing values for initial flow rate and body weight at the start of treatment and/or maximum flow rate and body weight at the start of treatment. Therefore, 5 infants were omitted from the multivariate logistic regression analysis. Namely, the data of 52 infants in the HFNC-F group and 119 infants in the HFNC-S group were used for the analysis. Variables used in the model were histologic chorioamnionitis, treated PDA, corrected gestational age at the start of treatment, gestational age, respiratory distress syndrome, pH before the start of treatment, initial flow rate and body weight at the start of treatment, and maximum flow rate and body weight at the start of treatment, which had P values of $<.05$ in the univariate analysis. We did not use birth weight as a variable for the analysis because gestational age and birth weight could show multicollinearity. Moreover, we did not use body weight at the start of treatment as a variable for the analysis because we thought it would show multicollinearity with initial flow rate and body weight at the start of treatment and maximum flow rate and body weight at the start of treatment. The results of the analysis revealed that histologic chorioamnionitis (adjusted odds ratio [aOR], 2.92; 95% CI, 1.17 to 7.31; P = .02), treated PDA (aOR, 3.61; 95% CI, 1.62 to 8.07; P = .002), and corrected gestational age at the start of treatment (aOR, 0.76; 95% CI, 0.61 to 0.94; P = .008) were independently associated with treatment failure with HFNC use (Table 4).

TABLE 3 Baseline Clinical Characteristics in the HFNC-F and the HFNC-S Groups

Clinical Characteristics	HFNC-F Group, n = 54	HFNC-S Group, n = 122	P
Prenatal factors, n (%)			
Histologic chorioamnionitis	19 (35)	20 (16)	.007
Antenatal steroid administration			.75
Incomplete	13 (24)	24 (20)	
Complete	28 (52)	70 (57)	
Cesarean delivery	48 (90)	101 (83)	.29
Multiple gestation	19 (35)	36 (30)	.46
Birth factors			
Gestational age,[a] wk	27.5 ± 2.3	28.8 ± 3.1	.006
Birth wt,[a] g	977 ± 349	1196 ± 441	.002
Male sex, n (%)	29 (54)	62 (51)	.72
1-min Apgar score[b]	4 (3–6)	5 (3–6)	.13
5-min Apgar score[b]	7 (6–8)	7 (6–8)	.24
Postnatal factors			
Respiratory distress syndrome, n (%)	43 (80)	79 (65)	.04
Treated PDA, n (%)	32 (59)	35 (29)	.0001
Grade 3 or 4 cerebral hemorrhage, n (%)	3 (6)	2 (2)	.17
Postnatal age at the start of treatment,[b] d	6.5 (3–27)	4 (2–31)	.25
Corrected gestational age at the start of treatment,[a] wk	29.8 ± 2.1	31.3 ± 2.0	<.0001
Body wt at start of treatment,[a] g	1044 ± 296	1275 ± 320	<.0001
Fio_2 before the start of treatment[b]	0.23 (0.21–0.30)	0.23 (0.21–0.27)	.51
pH before the start of treatment[a]	7.34 ± 0.06	7.37 ± 0.07	.0047
pco_2 before the start of treatment,[a] mm Hg	43.5 ± 8.8	42.7 ± 11.2	.65
Base excess before the start of treatment[a]	−2.0 ± 3.7	−0.9 ± 3.8	.067
Flow rate for HFNC			
Initial flow rate,[b] L/min	5.0 (3.5–6.0)[c]	5.0 (3.0–6.0)[c]	.35
Initial flow rate and body wt at the start of treatment,[b] L/min per kg	4.9 (2.2–7.3)[c]	3.7 (2.7–5.0)[c]	.006
Maximum flow rate,[b] L/min	7.0 (5.0–8.0)[d]	6.0 (5.0–8.0)[d]	.13
Maximum flow rate and body wt at the start of treatment,[b] L/min per kg	6.9 (4.7–8.1)[d]	5.0 (3.4–6.7)[d]	.0002

[a] Data are expressed as mean ± SD values.
[b] Data are expressed as median (interquartile range) values.
[c] Data are not available for 2 infants in the HFNC-S group and for 1 infant in the HFNC-F group.
[d] Data are not available for 3 infants in the HFNC-S group and for 2 infants in the HFNC-F group.

DISCUSSION

This study has suggested that HFNC use may be less effective than NCPAP

TABLE 4 Factors Associated With Treatment Failure With HFNC Use After Extubation

Clinical Characteristics	*P*	aOR (95% CI)
Histologic chorioamnionitis	.02	2.92 (1.17 to 7.31)
Treated PDA	.002	3.61 (1.62 to 8.07)
Corrected gestational age at the start of treatment, wk	.008	0.76 (0.61 to 0.94)
Gestational age, wk	.34	0.92 (0.77 to 1.10)
Respiratory distress syndrome	.58	1.28 (0.53 to 3.08)
pH before the start of treatment	.67	0.22 (0.02 to 2.04)
Initial flow rate and body wt at the start of treatment, L/min per kg	.54	1.08 (0.85 to 1.37)
Maximum flow rate and body wt at the start of treatment, L/min per kg	.44	1.12 (0.85 to 1.48)

Five infants with missing values in initial flow rate and body wt at the start of treatment or maximum flow rate and body wt at the start of treatment are omitted for the analysis.

or NIPPV for respiratory support in infants born at <34 weeks' gestation after extubation. Authors of several previous studies have reported that HFNC use reveals noninferiority compared with NCPAP in terms of treatment failure rates in preterm infants after extubation.[10,11] Our results were different from that of the previous reports. If our study had not included infants who received NIPPV, different results might have been observed. It is because meta-analysis reveals that NIPPV reduces the incidence of extubation failure within 48 hours to 1 week more effectively than NCPAP.[20] The median times of extubation for HFNC and NCPAP therapies in the previous study were 43.2 and 38.5 hours of age, respectively.[10] Those in our study were 5 and 6 days of age, respectively. Differences in the timing of extubation might have also produced different results. Flow rate at the start of treatment of HFNC in the study by Collins et al[11] was 8 L/min. The median maximum flow rate in our study was 7 L/min. In other words, half of the infants in our study did not receive a flow rate of 8 L/min. As a result, our study might have shown that HFNC revealed a significantly higher rate of treatment failure than NCPAP or NIPPV.

To evaluate the tolerability of HFNC or NCPAP therapy, we examined the modified COMFORT scale before and between 60 and 90 minutes after the start of treatment. It has been reported that infants <6 months of age with respiratory disorders who received HFNC were more comfortable than those who received NCPAP.[19] In our study, the scores did not differ significantly between the 2 groups. If the scale were measured not only once after extubation but also repeatedly over a longer period of treatment exposure, different results might have been shown.

This study clarifies the factors associated with treatment failure with HFNC use after extubation. Histologic chorioamnionitis, treated PDA, and corrected gestational age at the start of treatment were independently associated factors. It is well known that both histologic chorioamnionitis and treated PDA are risk factors for the development of CLD.[21–23] Many infants with CLD require positive-pressure respiratory support. Although HFNC use involves PEEP, it is thought that NCPAP is superior to HFNC for maintaining appropriate positive-pressure respiratory support.[24] Therefore, the use of NCPAP may be better than the use of HFNC in such infants.

The current study had several limitations. First, although medicines to stimulate the respiratory response such as caffeine citrate or aminophylline were used before and after extubation, we did not decide how to use the medicines in this study. If we had predetermined how to consistently use such medicines, results might have been different. The second limitation was that a variety of devices were used in the NCPAP/NIPPV group. We did not evaluate the differences of efficacy in each device.

Further studies are needed to establish the positioning of HFNC use among the various NIV therapies and to demonstrate the clinical aspects of HFNC therapy.

CONCLUSIONS

HFNC revealed a significantly higher rate of treatment failure than NCPAP or NIPPV within 7 days after extubation in preterm infants. Factors independently associated with treatment failure with HFNC use were histologic chorioamnionitis, treated PDA, and younger corrected gestational age at the start of treatment.

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ABBREVIATIONS

aOR: adjusted odds ratioCI, confidence interval
CLD: chronic lung disease
FIO_2: fraction of inspired oxygen
HFNC: high-flow nasal cannula
HFNC-F: high-flow nasal cannula failure
HFNC-S: high-flow nasal cannula success
NCPAP: nasal continuous positive airway pressure
NIPPV: nasal intermittent positive-pressure ventilation
NIV: noninvasive ventilation
PDA: patent ductus arteriosus
PEEP: positive end-expiratory pressure
Spo2: pulse oxygen saturation

Validade externa?

and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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