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ORIGINAL ARTICLE

Noninvasive Positive Airway Pressure Management for Post-extubation Support in Preterm Infants: Observational Cohort Study with Overlap Weighting Analysis

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ABSTRACT

BACKGROUND

Nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV), and high-flow nasal cannula (HFNC) are often used after initial extubation in preterm infants. However, data regarding the choice between NCPAP/NIPPV and HFNC are limited. This study examined which therapy was more effective as post-extubation support.

METHODS

This is a retrospective, cohort study that used the Diagnosis Procedure Combination database in Japan, 2011–2021. Propensity score overlap weighting analyses were performed to compare the composite outcomes of in-hospital death and reintubation in preterm infants who received NCPAP/NIPPV and HFNC. We identified infants born at gestational age 22–36 weeks who were intubated within 1 day of birth. We included patients who underwent NCPAP/NIPPV or HFNC after initial extubation. Patients with airway obstruction or congenital airway abnormalities were excluded.

RESULTS

We identified 1,203 preterm infants treated with NCPAP/NIPPV (n = 525) or HFNC (n = 678). The median (interquartile range) gestational age at delivery was 30 (27–33) weeks, and birth weight was 1296 (884–1,802) g. Compared with the HFNC group, the NCPAP/NIPPV group had a significantly lower proportion of the composite outcome after the overlap weighting analysis (risk ratio, 0.62; 95% confidence interval, 0.47 to 0.83; p = 0.001). This significant difference was also observed in infants born at gestational age 22–31 weeks, whereas no significant difference was observed in infants born at gestational age 32–36 weeks.

CONCLUSIONS

NCPAP/NIPPV may be a superior post-extubation support than HFNC in preterm infants, especially in those born at gestational age of 22–31 weeks.

KEY WORDS

Airway Extubation, Cannula, Continuous Positive Airway Pressure/instrumentation, Infant, Premature, Observational study

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INTRODUCTION

Nasal continuous positive airway pressure (NCPAP) and high-flow nasal cannula (HFNC) are non-invasive positive airway pressure management methods for respiratory distress in neonates, especially in preterm infants [1]. NCPAP delivers continuous gas pressure through a nasal prong or mask. Some NCPAP devices also have a nasal intermittent positive pressure ventilation (NIPPV) mode, which delivers superimposed cycled intermittent peak inspiratory pressures. HFNC is a relatively new device that delivers gas at a high rate through a nasal cannula, instead of a nasal prong or mask. NCPAP, NIPPV, and HFNC are widely used for post-extubation respiratory support to prevent extubation failures, such as respiratory acidosis, apnea, and high oxygen demand.

Studies have investigated the use of NCPAP, NIPPV, and HFNC for post-extubation support [1–10]. A previous meta-analysis (n = 934) showed no significant differences between NCPAP and HFNC in mortality, the rate of reintubation, and the incident rate of bronchopulmonary dysplasia (BPD). In contrast, HFNC therapy was associated with a significantly lower risk of treatment-related nose trauma and pneumothorax [1]. Another meta-analysis (n = 2,072) showed the superiority of NIPPV over NCPAP in preventing reintubation [7]. When clinicians perform NCPAP and NIPPV, they sometimes switch respiratory support modes, such as from NCPAP to NIPPV mode, in the same device. However, the data are limited to the clinical choice between NCPAP/NIPPV and HFNC in a real-world clinical setting.

A previous randomized study on infants born before 34 gestational weeks (n = 372) showed that NCPAP devices, including both NCPAP and NIPPV modes, had a significantly lower rate of treatment failure than HFNC [5]. However, this study had a relatively small sample size and excluded patients with comorbidities. Thus, it remains unknown which treatment, NCPAP/NIPPV or HFNC, should be undertaken in preterm infants (including those with comorbidities).

This study aimed to clarify which therapy, NCPAP/NIPPV or HFNC, would be more effective as post-extubation support for preterm infants.

METHODS

DATA SOURCE

This retrospective cohort study used data from the Diagnosis Procedure Combination database, a national database of inpatients in acute care institutions in Japan. The details of this database have been described elsewhere [11].

Approximately 1,000 institutions in Japan, including 82 academic institutions, participate in the database and provide data on approximately eight million inpatient admissions annually, representing approximately 50% of all acute care inpatients in Japan [12]. A previous validation study reported that the sensitivity and specificity of the recorded primary diagnoses were 78.9% and 93.2%, respectively, whereas those of the recorded procedures exceeded 90% [13].

The database included the following information: infant's age in days, sex, diagnoses recorded with text data in the Japanese and International Classification of Diseases, Tenth Revision (ICD-10) codes (including main diagnosis, comorbidities present at admission, and conditions that arose after admission), procedures (including the dates of intubation, NCPAP/NIPPV, HFNC, and oxygen therapy), length of stay, and discharge status.

STUDY PARTICIPANTS

We identified all preterm infants born between April 2011 and March 2021 at gestational age 22–36 weeks. Newborns within 28 days of birth were included as infants. We included patients who were hospitalized at birth or on the following day, who underwent intubation within 1 day of admission and NCPAP/NIPPV or HFNC within 1 day of the initial extubation. We excluded preterm infants with airway obstruction or congenital airway abnormalities (ICD-10 codes: Q30–34.x) because they were not an appropriate indication for NCPAP/NIPPV or HFNC. In addition, we excluded preterm infants who underwent both NCPAP/NIPPV and HFNC simultaneously on the day or the day following the initial extubation because we were not able to clarify which therapy was performed first.

EXPOSURE AND OUTCOMES

The exposure variable of primary interest was the choice of NCPAP/NIPPV or HFNC after the initial extubation. We classified the included patients into NCPAP/NIPPV and HFNC groups. Our database contained data only on device choices, while we did not have data on respiratory support modes. Therefore, we could not distinguish between NCPAP and NIPPV.

The primary outcome of interest was the composite outcome of in-hospital death and reintubation within 7 days of the initial extubation. Secondary outcomes were

the incidence of BPD, length of stay, and duration of any respiratory support, including supplemental oxygen and/or mechanical ventilation. We defined BPD as the requirement for supplemental oxygen and/or respiratory support at corrected 36-week gestational age, for infants born before 32-week gestational age. Thus, we only assessed the incidence of BPD in patients born between 22- and 31-week gestational age.

STATISTICAL ANALYSIS

We compared the demographic and clinical characteristics of the NCPAP/NIPPV and HFNC groups. Continuous variables are expressed as medians and interquartile ranges, or means and standard deviations, and categorical variables are expressed as percentages (%). Statistical differences between the two groups were analyzed using the Mann-Whitney U test for continuous variables, while categorical variables were compared using Fisher's exact test or the chi-square test.

The patient characteristics included sex, gestational weeks at birth, birth weight, length of initial intubation, and preexisting chronic comorbidities. We identified chronic diseases such as chromosomal abnormalities and congenital heart diseases using the Pediatric Complex Chronic Conditions Classification System [14]. We excluded neonatal diseases, such as preterm infants and low-birth-weight babies, as preexisting comorbidities.

Hospital volume was defined as the average annual number of patients per institution during the study period. We categorized eligible patients into tertiles (low-, medium-, and high-volume)

We conducted propensity score overlap weighting analyses. We performed multivariate logistic regression analysis to estimate the propensity scores for receiving NCPAP/NIPPV. The dependent variables included sex, gestational age at birth, birth weight, duration of initial intubation, preexisting comorbidities, and hospital volume. A generalized estimation equation was fitted to the regression model to adjust for in-hospital clustering. The C-statistic was used to discriminate between the models. Each patient was weighted by the predicted probability of receiving the opposite treatment. The absolute standard mean differences were calculated to assess the balance of covariates between the two groups and a difference of >10% indicated imbalance. The details of the overlap weighting analysis methods are described elsewhere [15]. Then, a logistic regression model was used for the two weighted groups to calculate the risk ratios with delta-method standard errors of the NCPAP/NIPPV group compared to the HFNC group [16].

Subgroup analyses were also conducted to reveal potential differences that could be attributed to prematurity of the patients. In the first subgroup we included patients born between 22–31 gestational weeks, that is, extremely preterm infants born before 28 gestational weeks and very preterm infants between 28–31 gestational weeks. In the second subgroup, we only included patients born between 32–36 gestational weeks, that is, moderately preterm infants born between 32–33 gestational weeks and late preterm infants between 34–36 gestational weeks. We performed the same overlap weighting analyses as in the main analysis. In our study, BPD was diagnosed only in patients born between 22–31 gestational weeks; therefore, the incidence of BPD was analyzed only in this group.

Statistical analyses were performed using the Stata software (version 17.0; StataCorp LP, College Station, TX, USA). For all tests, the threshold for significance was set at $p < 0.05$.

Written informed consent was not required owing to the anonymity of the patients in the database. This study was approved by the Institutional Review Board of the University of Tokyo (approval number: 3501-(5) [May 19th, 2021]).

RESULTS

During the study period, 376,684 preterm infants were identified from the Diagnosis Procedure Combination database. After applying the exclusion criteria, we identified 1,203 preterm infants eligible for our study, including 525 (43.6%) in the NCPAP/NIPPV group and 678 (56.4%) in the HFNC group (**Supplemental Fig. 1**). All patients who received HFNC were hospitalized after 2015. The baseline characteristics of eligible preterm infants in the two groups are shown in **Table 1**. The patient characteristics were originally well balanced (**Table 1**), except for the length of initial intubation and categories of hospital volume. The C-statistic for the propensity score was 0.69. After overlap weight analysis, all characteristics were well balanced between the NCPAP/NIPPV and HFNC groups.

Table 2 shows the results of the main overlap weighting analysis among all enrolled preterm patients. The proportion of the composite outcome of in-hospital death and reintubation within 7 days of the initial extubation was significantly lower in the NCPAP/NIPPV group than in the HFNC group (risk ratio [RR], 0.62; 95% confidence interval [CI], 0.47–0.83; $p = 0.001$). The difference in length of stay was not significant between

Table 1 Demographic and clinical characteristics of the preterm patients undergoing nasal continuous positive airway pressure (NCPAP)/nasal intermittent positive pressure ventilation (NIPPV) or high-flow nasal cannula (HFNC)

	All patients		ASD (%)	Overlap-weighted patients		ASD (%)
	NCPAP/NIPPV (N = 525)	HFNC (N = 678)		NCPAP/NIPPV (N = 602)	HFNC (N = 602)	
Sex (male), %	58.3	58.6	0.5	58.3	58.3	0.0
Gestational week at delivery (weeks), median (interquartile range)	30 (27–32)	30 (27–33)	5.1	30 (27–32)	30 (27–33)	0.0
Birth weight (gram), median (interquartile range)	1279 (892–1750)	1316 (876–1844)	5.8	1307 (920–1802)	1316 (876–1844)	0.0
Length of initial intubation (days), mean (standard deviation)	22.5 (38.3)	28.9 (40.1)	16.3	25.7 (47.2)	25.7 (30.8)	0.0
Having any comorbidities [a], %						
No	90.5	86.6	12.2	10.8	10.8	0.0
Yes	9.5	13.4	–	89.2	89.2	
Hospital volume [b], %						
Low	33.5	9.7	60.4	17.2	17.2	0.0
Middle	39.2	38.8	0.9	43.4	43.4	0.0
High	27.2	51.5	51.2	39.4	39.4	0.0

Abbreviations: NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; HFNC, high-flow nasal cannula; ASD, absolute standard difference.
[a] We defined preexisting comorbidities apart from neonatal diseases using the Pediatric Complex Chronic Conditions Classification System.
[b] We divided the study patients into three hospital volume groups according to the average number of patients per institution in each year.

Table 2 Propensity score-overlap weighted effects of nasal continuous positive airway pressure (NCPAP)/nasal intermittent positive pressure ventilation (NIPPV) compared to high-flow nasal cannula (HFNC) among preterm infants born between 22 and 36 gestational weeks (N = 1203)

	Risk ratio	95% confidence interval	p
Composite outcome of in-hospital death and reintubation within 7 days after extubation	0.62	0.47, 0.83	0.001
In-hospital death	0.24	0.06, 0.91	0.035
Reintubation within 7 days after extubation	0.64	0.48, 0.86	0.003
	Risk difference	95% confidence interval	p
Length of hospital stay (days)	−0.37	−9.7, 9.0	0.94
Duration of any respiratory support [a] (days)	−8.6	−16.5, −0.7	0.033

Abbreviations: NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; HFNC, high-flow nasal cannula.
[a] Respiratory support included supplemental oxygen and mechanical ventilation.
Risk ratios and differences are for the NCPAP/NIPPV group with reference to the HFNC group.

the NCPAP/NIPPV and HFNC groups (difference, −0.37 days; 95% CI, −9.71 to 8.97; p = 0.94). On the contrary, the difference in duration of any respiratory support was significant (difference, −8.6 days; 95% CI, −16.5 to 0.7; p = 0.03).

Among 792 patients born between 22–31 gestational weeks, there was also significant difference in the composite outcome of in-hospital death and reintubation within 7 days of the initial extubation between the NCPAP and HFNC groups (RR, 0.68; 95% CI, 0.50–0.93; p = 0.011) (**Table 3**). We observed significant differences between the two groups in the duration of any respiratory support (difference, −10.2 days; 95% CI, −20.0 to −0.39 days; p = 0.04). The NCPAP/NIPPV group had a significantly

Table 3 Propensity score-overlap weighted effects of nasal continuous positive airway pressure (NCPAP)/nasal intermittent positive pressure ventilation (NIPPV) compared to high-flow nasal cannula (HFNC) among preterm infants born between 22 and 31 gestational weeks (N = 792)

	Risk ratio	95% confidence interval	p
Composite outcome of in-hospital death and reintubation within 7 days after extubation	0.68	0.50, 0.93	0.011
In-hospital death	0.19	0.03, 1.2	0.067
Reintubation within 7 days after extubation	0.71	0.51, 0.97	0.032
Bronchopulmonary dysplasia	0.67	0.46, 0.96	0.031
	Risk difference	95% confidence interval	p
Length of hospital stay (days)	1.8	−9.4, 13.0	0.31
Duration of any respiratory support [a)] (days)	−10.2	−20.0, −0.39	0.04

Abbreviations: NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; HFNC, high-flow nasal cannula.
[a)] Respiratory support refers to supplemental oxygen and/or mechanical ventilation.
Risk ratios and differences are for the NCPAP/NIPPV group with reference to the HFNC group.

Table 4 Propensity score-overlap weighted effects of nasal continuous positive airway pressure (NCPAP)/nasal intermittent positive pressure ventilation (NIPPV) group compared to nasal cannula (HFNC) among preterm infants born between 32 and 36 gestational weeks (N = 411)

	Risk ratio	95% confidence interval	p
Composite outcome of in-hospital death and reintubation within 7days after extubation	0.60	0.25, 1.43	0.22
In-hospital death	0.34	0.04, 2.9	0.33
Reintubation within 7days after extubation	0.63	0.26, 1.52	0.28
	Risk difference	95% confidence interval	p
Length of hospital stay (days)	0.94	−12.4, 14.3	0.14
Duration of any respiratory support [a)] (days)	−1.9	−13.6, 9.7	0.74

Abbreviations: NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; HFNC, high-flow nasal cannula.
[a)] Respiratory support included supplemental oxygen and mechanical ventilation.
Risk ratios and differences are for the NCPAP/NIPPV group with reference to the HFNC group.

lower incident rate of BPD (RR, 0.67; 95% CI, 0.46–0.96; p = 0.031). These results in patients born between 22–31 gestational weeks are consistent with the results of our main analysis.

On the contrary, among 411 patients born between 32–36 gestational weeks, there was no significant difference in the composite outcome of in-hospital death and reintubation (RR, 0.60; 95% CI, 0.25–1.43; p = 0.22) (**Table 4**). No differences in secondary outcomes were observed among patients born between 32–36 gestational weeks. Significant differences in all outcomes were observed in preterm infants born between 32–36 gestational weeks.

DISCUSSION

In our main analysis, preterm infants who underwent NCPAP/NIPPV for post-extubation support were likely to have a lower composite outcome of in-hospital death and reintubation and a shorter duration of respiratory support. In the subgroup analysis of infants born between 22–31 gestational weeks, NCPAP/NIPPV was significantly superior to HFNC in terms of reducing death and/or reintubation and shortening the duration of respiratory support. In addition, a lower incidence of BPD was observed in the NCPAP/NIPPV group. In contrast, among infants born between 32–36 gestational weeks, NCPAP/NIPPV was compatible with HFNC in all outcomes. The analysis showed no significant difference in length of hospital stay between the NCPAP/NIPPV and HFNC groups.

Our main results were consistent with those of a previous randomized controlled trial that revealed the inferiority of HFNC as a post-extubation respiratory support

for avoiding reintubation, especially among preterm infants born between 22–31 gestational weeks [5]. Our study has some strengths that support the findings of previous studies. First, we used a large dataset that included patients with comorbidities. Second, we considered the length of the initial intubation, which may be related to the severity of initial respiratory distress. Third, in clinical settings, clinicians often change the respiratory support modes of NCPAP devices based on the patient's condition. Thus, our study design was more realistic than those of studies that only compared NCPAP and HFNC.

To date, direct comparisons between NCPAP/NIPPV and HFNC have been scarce in terms of the incidence of BPD and the duration of respiratory support. In the current study, we showed that patients receiving HFNC had a significantly higher incidence of BPD and significantly longer duration of respiratory support. Our study showed that the effects of NCPAP/NIPPV or HFNC differed depending on the gestational weeks. However, there is insufficient previous physiological or clinical research to support our findings. It is imperative to undertake other larger-scale studies to compare NCPAP/NIPPV to HFNC, especially in extremely preterm infants and very preterm infants. Additionally, it is essential to uncover potential divergent psychological effects on premature lungs between NCPAP/NIPPV and HFNC.

The superiority of NCPAP/NIPPV for post-extubation support in our study may have resulted from the various respiratory support modes of the NCPAP devices, including NCPAP mode and NIPPV mode. Previous meta-analyses have shown that NIPPV was more effective than NCPAP in avoiding reintubation, whereas HFNC was equivalent to NCPAP [1, 7]. In these previous studies, NCPAP and HFNC were equivalent, whereas NIPPV was superior to NCPAP or HFNC as post-extubation support. Our current study compared the combination of NCPAP, which was shown to be compatible with HFNC, and NIPPV, which was considered superior to HFNC, with HFNC. Therefore, NCPAP/NIPPV may be more effective for providing post-extubation support. The superiority of NCPAP/NIPPV was also observed in a previous randomized controlled study [5].

In our sub-analyses, no significant differences in any outcome were observed between NCPAP/NIPPV and HFNC among patients born between 32–36 gestational weeks. In this population who are not at high risk of severe respiratory distress, HFNC therapy may be an alternative to post-extubation respiratory support. However, to the best of our knowledge, there has not been enough physiological evidence to elucidate the variations in the effects of HFNC therapy among patients of varying degrees of prematurity. Thus, further studies are needed.

LIMITATIONS

Our study had some limitations. First, our database did not contain laboratory data, vital signs, or prenatal information. We adjusted the severity of respiratory distress according to patient characteristics at admission and the duration of initial intubation; however, these adjustments may have been insufficient. Second, we did not adjust for the use of respiratory-stimulating medicines, such as caffeine citrate and aminophylline. Third, we did not evaluate the mechanical devices of each therapy and ventilation mode, such as FiO2 for NCPAP/NIPPV and HFNC and flow rate for HFNC. Fourth, we did not distinguish between the patients who needed noninvasive positive airway pressure management for weaning and those who needed it for treating extubation failure. Last, we did not include the incidences of treatment-related complications (such as nose trauma and pneumothorax) in the outcomes, owing to a lack of an exact date of onset for these complications in our database. Therefore, treatment-related complications could be outcomes and confounding factors for device choice.

CONCLUSIONS

In our large observational study, preterm infants receiving NCPAP/NIPPV for post-extubation support had a lower risk of in-hospital death, reintubation, and BPD than those receiving HFNC. NCPAP/NIPPV may provide superior respiratory support in preterm infants, especially those born between 22–31 gestational weeks.

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest in relation the work presented in the manuscript.

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