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Title: Effects of infant flow Bi-NCPAP on apnea of prematurity**Running head:** Bi-NCPAP on apnea

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Abstract

Background: Infant flow biphasic nasal continuous positive airway pressure (Bi-NCPAP) and regular NCPAP (Re-NCPAP) are equally useful with respect to the rate of successful weaning from mechanical ventilation. However, it remains unclear whether Bi-NCPAP or Re-NCPAP is more effective for reducing apnea of prematurity (AOP).

Methods: A multicenter randomized controlled study was conducted in a population consisting of 66 infants assigned to receive Bi-NCPAP and 66 assigned to receive Re-NCPAP for respiratory support after extubation. Primary outcome was the number of AOP events during the 48-hour observation period after successful extubation, defined as no reintubation and no adverse events associated with the use of NCPAP during the observation period. The secondary outcome was successful extubation. Reintubation was at the discretion of the attending physician.

Results: Baseline characteristics were similar between the two groups. The number of AOP events during the 48-hour observation period was significantly lower in infants with Bi-NCPAP than those with Re-NCPAP (5.2 ± 6.5 vs. 10.3 ± 10.9 per infant, respectively, $P = 0.002$). The rate of successful extubation tended to be greater in those with Bi-NCPAP than with Re-NCPAP (92.4% [61/66] vs. 80.3% [53/66], respectively, $P = 0.074$). Adverse events occurred in only one of 132 infants; erosive dermatitis developed on the nose after application of Re-NCPAP. The risk of reintubation did not differ significantly between the two groups (7.6% [5/66] for Bi-NCPAP vs. 18.2% [12/66] for Re-NCPAP, $P = 0.117$).

Conclusions: Bi-NCPAP was superior to Re-NCPAP for reduction of AOP following extubation.

Key words: apnea, bronchopulmonary dysplasia, low birth weight, methylxanthine, tracheal intubation

Introduction

Premature infants often require tracheal intubation and mechanical ventilation. However, long-term use of invasive mechanical ventilation with tracheal intubation is associated with increased risk of bronchopulmonary dysplasia (BPD)¹. Therefore, early use of nasal continuous positive airway pressure (NCPAP) after short-term invasive respiratory support is recommended². A previous study in premature baboons³ suggested that the early use of NCPAP may mitigate the decreased brain growth and cerebral neuropathologies observed in preterm infants requiring ventilation. In human trials of caffeine for apnea of prematurity (AOP)^{4,5}, one-week reduction of mechanical ventilation with tracheal intubation was associated with reduced risk of BPD,⁴ and caffeine for AOP improved the rate of survival without neurodevelopmental disability at 18 – 21 months⁵.

However, AOP occurs frequently during respiratory support with regular NCPAP (Re-NCPAP), resulting in unsuccessful extubation. In contrast to Re-NCPAP, biphasic NCPAP (Bi-NCPAP) cycles between upper and lower (baseline) level pressures as determined by the four parameters, i.e., lower CPAP level, upper CPAP level, time at upper level, and rate (cycles/min at upper level). As the use of nasal intermittent positive airway pressure was suggested to be more effective than NCPAP in reduction of AOP⁶ and respiratory failure leading to reintubation⁷⁻¹⁰, cyclic changes in airway pressure may contribute to the reduction of AOP and respiratory failure after extubation.

A recent study by O'Brien et al.¹¹ unexpectedly exhibited no advantage of Bi-NCPAP over Re-NCPAP with regard to the rate of successful weaning from mechanical ventilation. However, it remains to be determined which of these treatment modalities, Re-NCPAP or Bi-NCPAP, is more effective for reduction of AOP in infants during weaning from invasive mechanical ventilation. The present prospective randomized study was conducted at five neonatal intensive care units (NICU) to determine whether Re-NCPAP or Bi-NCPAP is more effective for reduction of AOP in infants after extubation.

Materials and Methods

This study was conducted between December 1, 2011, and April 30, 2013, after approval of the protocols (Table 1) by the institutional review boards of the five hospitals participating in this study (Kagoshima City Hospital, Kimitsu Chuo Hospital, Funabashi Central Hospital, Gifu Prefectural General Medical Center, and Fukuda Hospital).

Participants and study protocols (Table 1)

Parents of eligible infants were approached for participation in this trial and written informed consent was obtained prior to extubation and automatic assignment via the website of the registration center (Mythos Co. Ltd., Tokyo, Japan) to one of two treatment modalities (Re-NCPAP or Bi-NCPAP) for respiratory support after extubation. All participants met all three conditions listed in Table 1.

After randomization and extubation, infants were treated with Bi-NCPAP or Re-NCPAP using the apparatuses shown in Table 1. Clinical conditions, especially focusing on AOP and adverse events associated with use of the two modalities, were monitored over the 48-hour observation period after application of the treatment. Methylxanthine, but not doxapram hydrochloride hydrate¹², could be used during the 48-hour observation period. The definition of AOP and apparatuses used for the detection of AOP were shown in Table 1.

The primary outcome was the number of AOP in infants with successful extubation (Table 1), which was defined as no reintubation and no adverse events associated with the use of Bi-NCPAP/Re-NCPAP during the 48-hour observation period. This was based on the assumption that the risk of reintubation and adverse events did not differ between the two groups. No predefined criteria for reintubation were set because of concern regarding delayed reintubation. Thus, reintubation was performed at the discretion of the attending physician in each case. The secondary outcome was successful extubation.

Statistical analysis

Sample size was determined by power analysis using Sample-Power (1.0; SPSS, Inc., Chicago, IL) based on the following two assumptions: (1) approximately 10% of participants do not complete the 48-hour observation period requiring reintubation irrespective of treatment modality, and (2) in comparison with Re-NCAP, Bi-NCPAP can reduce AOP by > 20%. Data are presented as medians with range or means \pm standard deviation. Statistical analyses were performed using the JMP10[®] statistical software package (SAS, Cary, NC). ANOVA and Tukey–Kramer HSD (honestly significant difference) tests were used to compare means. The Wilcoxon/Kruskal–Wallis method was used to compare medians. The Kaplan–Meier method was used to compare chronological changes in the fraction of infants with continued NCPAP and no AOP. Fisher’s exact probability test was used to compare categorical variables. In all analyses, $P < 0.05$ was considered to be statistically significant.

Results

A total of 135 infants were originally included in this study, with 67 and 68 infants assigned to the Bi-NCPAP group and the Re-NCPAP group, respectively. However, three infants (one with Bi-NCPAP and two with Re-NCPAP) were excluded from the analyses because their treatments were not based on the protocols (Fig. 1). Thus, both groups consisted of 66 infants.

Baseline characteristics were similar between the two groups (Table 2). Of these 132 participants, 61 infants with Bi-NCPAP and 53 infants with Re-NCPAP completed the 48-hour observation period without reintubation and adverse events, experiencing successful extubation (Fig. 1), and were therefore judged as suitable for inclusion in analysis of the primary outcome.

Primary outcome

Methylxanthine was used in all 114 infants with successful extubation. The total numbers of AOP events during the 48-hour observation period were 317 in the 61 infants with Bi-NCPAP and 548 in the 53 infants with Re-NCPAP. The mean number of AOP was significantly lower among infants with Bi-NCPAP than among those with Re-NCPAP (5.2 ± 6.5 vs. 10.3 ± 10.9 per infant, respectively, $P = 0.002$) (Fig. 2).

The number of infants with no AOP events at all during the 48-hour observation period did not differ significantly between the two groups (30% [18/61] for Bi-NCPAP and 17% [9/53] for Re-NCPAP, $P = 0.129$). However, the number of infants with ≥ 15 AOP events was significantly lower for the Bi-NCPAP group than the Re-NCPAP group (8.2% [5/61] vs. 30% [16/53], respectively, $P = 0.003$) (Fig. 2). The Kaplan–Meier analysis of chronological changes in fraction of infants that had never experienced AOP indicated a significant difference in risk of AOP between the two groups ($P = 0.025$) (Fig. 3).

Secondary outcome

Sixty-one of 66 infants (92%) with Bi-NCPAP and 53 of 66 infants (80%) with Re-NCPAP completed the 48-hour observation period without occurrence of reintubation and adverse events (Fig. 1). Thus, the number of infants with successful extubation tended to be greater in the Bi-NCPAP group than the Re-NCPAP group ($P = 0.074$).

Among the 18 infants without successful extubation, only one experienced an adverse event; in this case, erosive dermatitis developed on the nose 23 hours after application of Re-NCPAP using Infant Flow™ NCPAP Driver (Fig. 1). The remaining 17 were reintubated during the 48-hour observation period; the risk of reintubation did not differ significantly between the two groups (7.6% [5/66] for Bi-NCPAP vs. 18.2% [12/66] for Re-NCPAP, $P = 0.117$).

Discussion

The present study clearly demonstrated that Bi-NCPAP was more effective than Re-NCPAP with respect to reduction of AOP in assistance of weaning from mechanical ventilation.

As AOP is a major reason for unsuccessful NCPAP in many trials irrespective of the method used to assist in weaning from mechanical ventilation^{6–10, 14, 15}, it may be important to analyze the effects of specific treatment modalities on AOP. To our knowledge, there have been no previous controlled randomized studies comparing AOP in infants treated with Bi-NCPAP and Re-NCPAP. In this study, the number of AOP events was significantly lower among infants with Bi-NCPAP than among those with Re-NCPAP (5.2 ± 6.5 vs. 10.3 ± 10.9 times per infant for 48 hours after extubation, respectively), and Kaplan–Meier analysis revealed a significant difference in the risk of AOP between the two groups ($P = 0.025$). These results suggested that the risk of AOP was reduced by approximately 50% with use of Bi-NCPAP.

Theoretically, with use of Bi-NCPAP, functional residual capacity is recruited by the upper CPAP level and maintained with the lower baseline CPAP level, thus decreasing the workload of breathing. In addition, exogenous cyclic changes in airway pressure appeared to stimulate respiration in many studies⁶⁻¹⁰; the use of nasal intermittent positive airway pressure was associated with fewer AOP events compared with Re-NCPAP⁶ as well as successful extubation⁷⁻¹⁰, although conflicting results were also reported in some studies^{15, 16}. These two mechanisms may have been associated with the reduced risk of AOP in infants treated with Bi-NCPAP observed in this study.

In this study, the criteria for reintubation were not predefined due to concerns regarding delayed reintubation, and the decision for reintubation was made at the discretion of the attending physician. Although this was a major drawback in assessment of the secondary outcome of successful extubation, the number of infants with successful intubation tended to be greater for Bi-NCPAP than for Re-NCPAP in this study (92.4% [61/66] vs. 80.3% [53/66], respectively, $P = 0.074$), which was partly consistent with the results of a previous study by O'Brien *et al.*¹¹ in which the rate of successful extubation defined as no reintubation for 7 days after extubation was also not significantly different between Bi-NCPAP and Re-NCPAP groups (67% [45/67] vs. 58% [40/69], respectively, $P = 0.292$). However, they¹¹ stated that they were not able to recruit a predetermined sample size to demonstrate a significant difference and concluded that the effectiveness and safety of Bi-NCPAP compared to Re-NCPAP should be confirmed in a large multicenter trial as their results were limited by inadequate sample size.

There was a considerable difference between the study of O'Brien *et al.*¹¹ and our study in absolute successful extubation rates even after taking into account the difference in definition of successful extubation. The present study was comparable to the study of O'Brien *et al.*¹¹ with regard to GW at delivery (approximately 27 weeks for both studies) and cohort size (132 infants in this study vs. 136 infants in the previous study), but not age at enrollment (14 days of age in this study vs. approximately 3 days of age in the previous study). Thus, our study population had more advanced age than that in the study by O'Brien *et al.*¹¹. This may explain the considerable difference in absolute successful extubation rate between the two studies.

In conclusion, this randomized controlled study strongly suggested that the use of Bi-NCPAP was superior to that of Re-NCPAP with respect to number of AOP events during assistance of weaning from mechanical ventilation. This was further supported by the finding that the rate of successful extubation tended to be higher in the Bi-NCPAP than the Re-NCPAP group. No adverse events were reported in the 66 infants with Bi-NCPAP. Further studies in larger populations may indicate a significant advantage of Bi-NCPAP over Re-NCPAP with regard to successful weaning from mechanical ventilation.

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Disclosure

The authors declare no conflict of interest.

Author contribution

All authors (CI, SI, YO, EK, TT, YY, YM, TK, and HM) participated in the design of the study, and all authors except HM collected data on each participant in this study. CI performed the statistical analysis and drafted the manuscript. IS and HM coordinated the study and helped to draft the manuscript. All authors have read and approved the final manuscript.

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Figure legends

Fig. 1. Flow diagram of study participants

*, Three infants were excluded from the analyses because treatments were not based on the protocols: one in the Bi-NCPAP group was given doxapram hydrochloride hydrate for AOP and two in the Re-NCPAP group underwent a switch of modality from Re-NCPAP to Bi-NCPAP 22 and 43 hours after extubation without any reason being given, respectively. Five of 66 infants with Bi-NCPAP and 12 of 66 infants with Re-NCPAP required reintubation during the 48-hour observation period. Only one of 132 infants with Bi-NCPAP/Re-NCPAP experienced an adverse event, i.e., erosive dermatitis in the nose 23 hours after initiation of the treatment hampered continued application of Re-NCPAP in this case.

Fig. 2. Numbers of AOP events in 61 infants with Bi-NCPAP and 53 infants with Re-NCPAP

The numbers of AOP events in each infant in the 48-hour observation period are indicated. The mean number of AOP events was significantly lower for the Bi-NCPAP group than the Re-NCPAP group (5.2 ± 6.5 vs. 10.3 ± 10.9 per infant, respectively, $P = 0.002$). The number of infants with no AOP events at all did not differ significantly between the two groups (30% [18/61] vs. 17% [9/53], respectively, $P = 0.129$). However, the number of infants with ≥ 15 AOP events was significantly lower for the Bi-NCPAP group than the Re-NCPAP group (8.2% [5/61] vs. 30% [16/53], respectively, $P = 0.003$).

Fig. 3. Chronological changes in fraction of infants that had never exhibited AOP during the 48-hour observation period

The cohorts were similar to those in Fig. 2. Kaplan–Meier analysis indicated that the two groups were significantly different with regard to the risk of AOP ($P = 0.025$), suggesting that infants were significantly less likely to exhibit AOP with Bi-NCPAP than with Re-NCPAP.

Fig. 1.

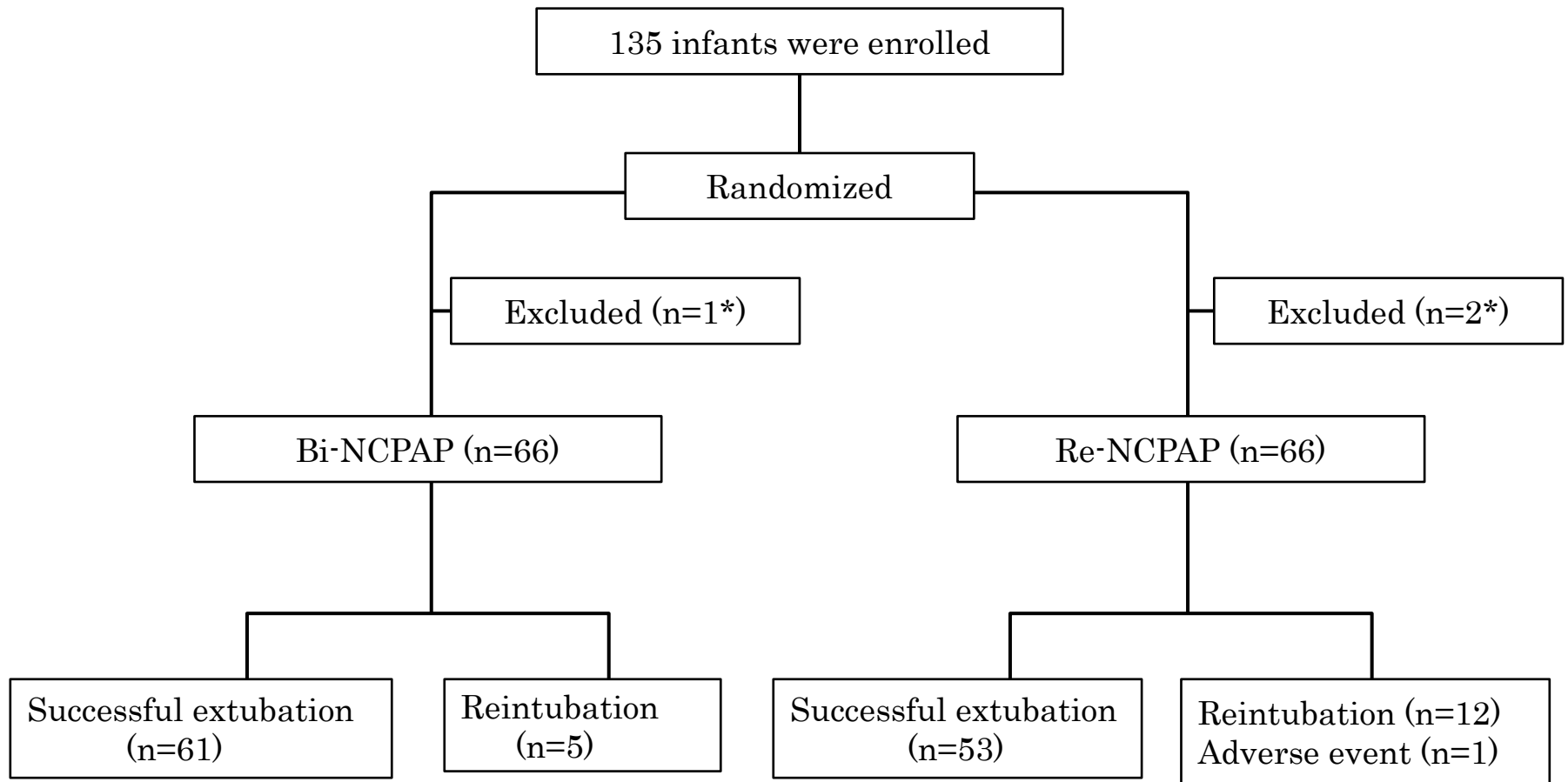


Fig. 2.

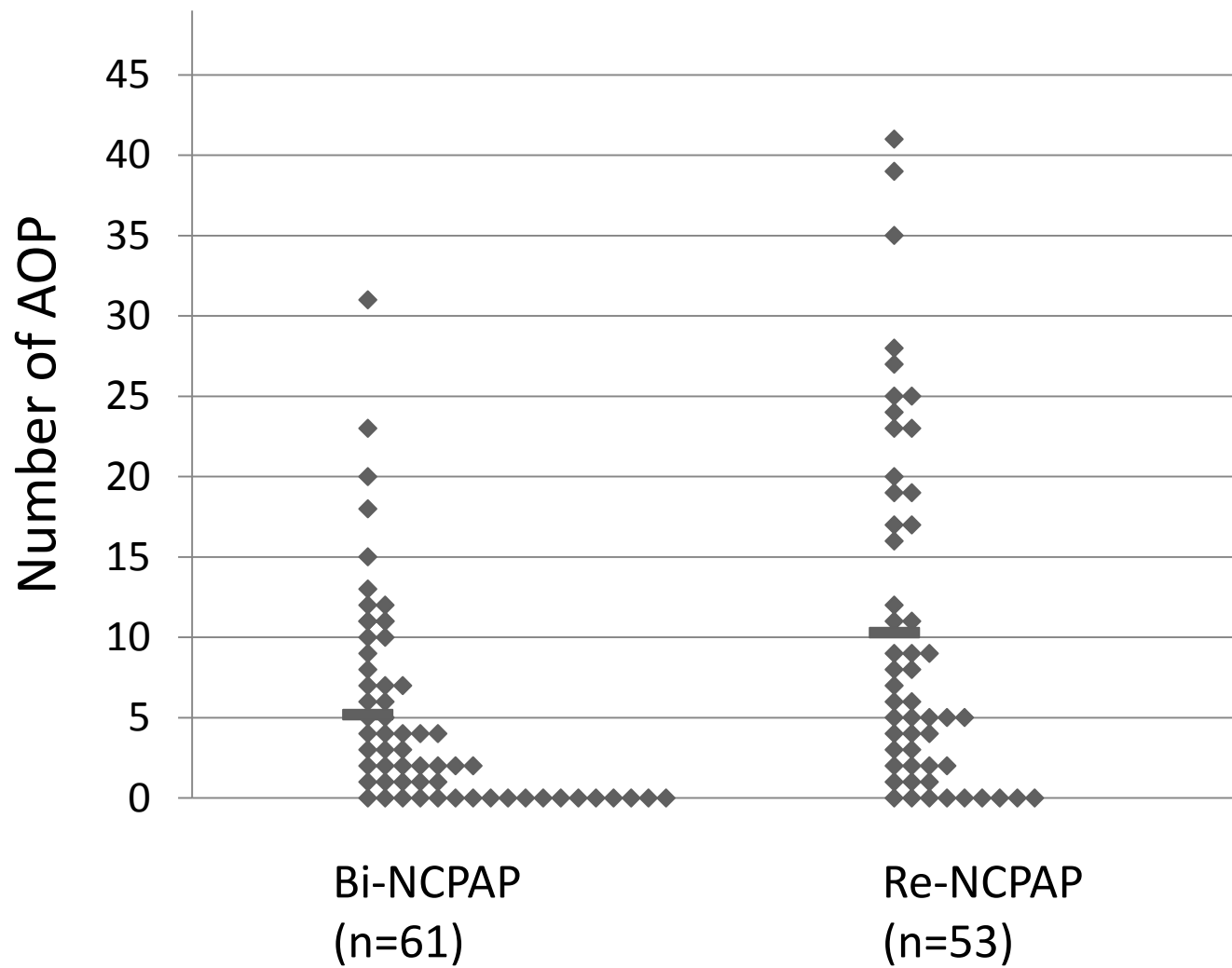


Fig. 3.

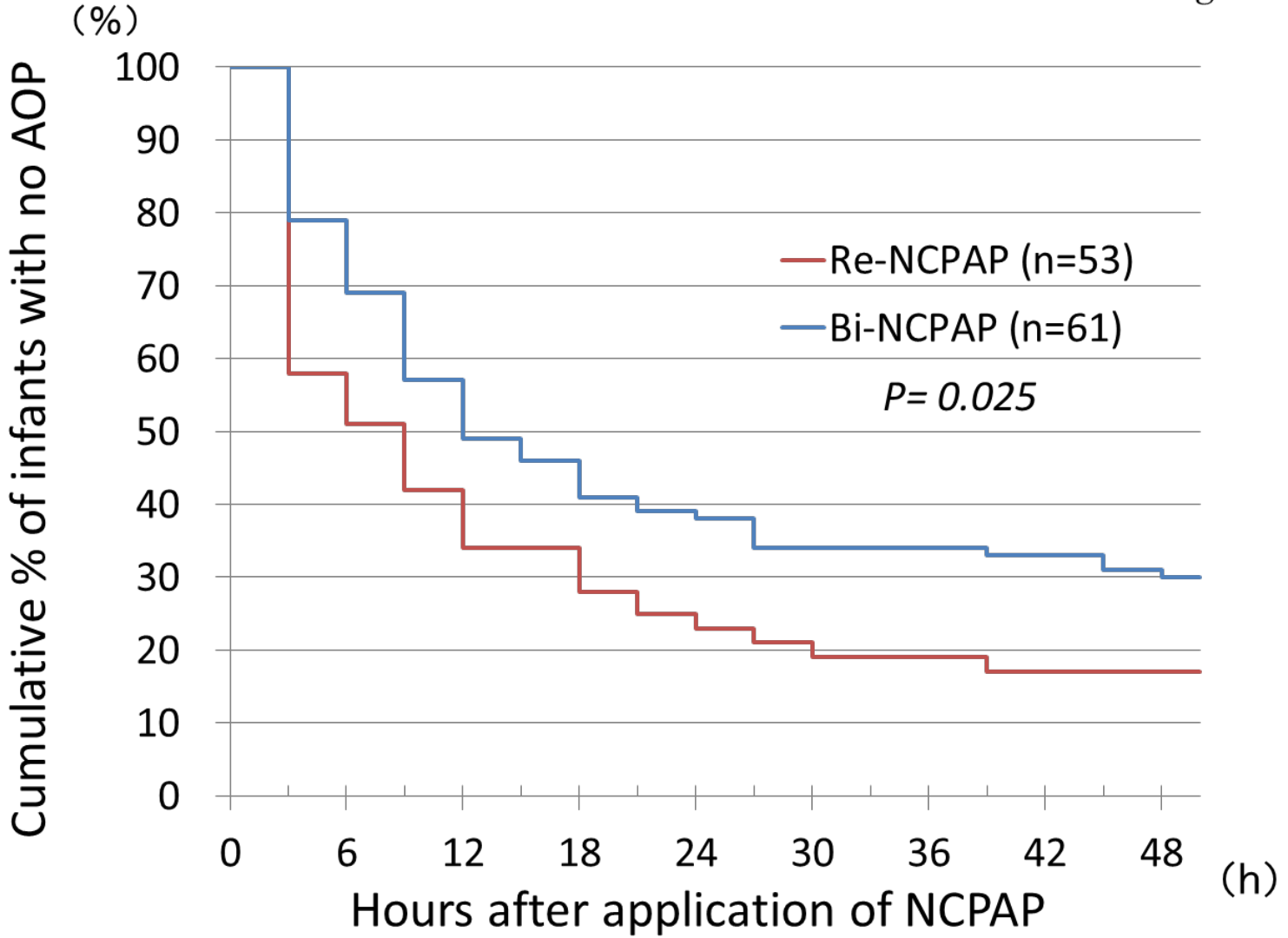


Table 1. Protocols for this study

I. Candidates were required to fulfill all of the following three conditions:

- 1) Corrected gestational age ≥ 26 weeks, but born at gestational week < 30 .
- 2) Without any of the following complications: IVH (Grade $\geq III^{12}$), PVL, PDA requiring treatment, severe asphyxia at birth with 5-min Apgar score < 4 , septicemia, neuromuscular disease, chromosomal aberration, and major congenital malformations.
- 3) Being intubated without history of unsuccessful extubation and stable respiration meeting both of the following conditions:
 - PIP of 14 – 16 cmH₂O or MAP of 7 – 8 cmH₂O.
 - FiO₂ ≤ 0.35 with SpO₂ $\geq 85\%$.

II. Written informed consent from parents before extubation.

III. Registration and randomization at the Center (Mythos Co. Ltd., Tokyo, Japan).

IV. Extubation and application of Bi-NCPAP or Re-NCPAP with the following settings:

- Bi-NCPAP using Flow[®] SIPAP[™] (CareFusion Corp., San Diego, CA) with PEEP of 5.0 ± 1.0 cmH₂O, PIP of 8.0 ± 1.0 cmH₂O, time at upper level of 1.0 s, and rate of 30 bpm.
- Re-NCPAP using uniphasic mode of Infant Flow[®] SIPAP[™] (CareFusion Corp.) or Infant Flow[™] NCPAP Driver (CareFusion Corp.) with PEEP of 5.0 ± 1.0 cmH₂O. V. Treatments during 48-hour observation period after application of Bi- or Re-NCPAP.

- 1) Methylxanthine, but not doxapram hydrochloride hydrate¹³ (Dopram[™]; Kissei Co. Ltd., Nagano, Japan) can be used.
- 2) Detection of AOP using Dash 3000/4000/5000[™] (GE Healthcare Co. Ltd., Waukesha, WI), IntelliVue MP 40/50[™] (Philips, Eindhoven, The Netherlands), Infinity[™] Delta (Dräger Co. Ltd., Lübeck, Germany), or Life Scope VL940R[™] (Nihon Kohden Co. Ltd., Tokyo, Japan).

VI. Definition of AOP in this study.

- Apnea lasting ≥ 20 s.
- Apnea lasting < 20 s with bradycardia < 100 bpm or SpO₂ $< 85\%$.

VII. Definition of successful extubation.

- No reintubation and no adverse events associated with the use of Bi-NCPAP/Re-NCPAP during the 48-hour observation period.
- Reintubation can be performed at the discretion of the attending physician.

VIII. Primary and secondary outcomes.

- The primary outcome was the number of AOP events in infants with successful extubation.
- The secondary outcome was successful extubation.

AOP, apnea of prematurity; IVH, intraventricular hemorrhage; MAP, mean airway pressure; PDA, patent ductus arteriosus; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; PVL, periventricular leukomalacia.

Table 2. Baseline characteristics of the two groups

	Bi-NCPAP (n=66)	Re-NCPAP (n=66)	P-value
Maternal age (year)	31.0 (29.0-36.0)	31.0 (27.3-36.0)	0.791
Maternal hypertension	13 (19.7%)	8 (12.3%)	0.232
Clinical CAM			
Present	3 (4.5%)	6 (9.1%)	0.296
Absent	63 (95.5%)	60 (90.9%)	
Histological CAM			
Present	20 (30.3%)	29 (43.9%)	0.035
Absent	44 (66.7%)	29 (43.9%)	
Unknown	2 (3.0%)	8(12.1%)	
Antenatal steroid	37 (56.1%)	29 (43.9%)	0.163
Gestational week			
At birth	27.6 (26.2-28.7)	27.3 (25.7-28.1)	0.169
At enrollment*	30.0 (29.0-31.3)	30.0 (28.6-31.3)	0.310
Days after birth	13.5 (5.0-37.5)	15.5 (5.0-31.8)	0.764
Body weight (g)			
At birth	930 (765-1058)	928 (759-1076)	0.834
At enrollment	1042 (921-1215)	1014 (849-1294)	0.915
Male infant	38 (57.6%)	39 (59.1%)	0.860
Respiratory status before extubation			
Ventilation mode			
SIMV	64 (97.0%)	65 (98.5%)	0.556
HFO	2 (3.0%)	1 (1.5%)	
Ventilator setting			
FiO2	0.21 (0.21-0.21)	0.21 (0.21-0.23)	0.321
PIP	15.0 (13.0-16.0)	15.0 (14.0-16.0)	0.586

CAM, chorioamnionitis; HFO, high frequency oscillation; IMV, intermittent mandatory ventilation; PIP, peak inspiratory pressure; SIMV, synchronized intermittent mandatory ventilation.

*, corrected gestational week