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ORIGINAL ARTICLE

Nasal intermittent positive pressure ventilation after surfactant treatment for respiratory distress syndrome in preterm infants <30 weeks' gestation: a randomized, controlled trial

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Objective: To compare the effect of early extubation to nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) on the need for mechanical ventilation via endotracheal tube (MVET) at 7 days of age in preterm infants <30 weeks' gestation requiring intubation and surfactant for respiratory distress syndrome (RDS) within 60 min of delivery.

Study Design: Multicenter, randomized, controlled trial. A total of 57 infants were randomized within 120 min of birth to NCPAP (BW 1099 g and GA 27.8 weeks) and 53 infants to NIPPV (BW 1052 g, and GA 27.8 weeks). Infants were stabilized on NCPAP at birth and were given poractant alfa combined with MVET within 60 min of age. When stabilized on MVET, they were extubated within the next hours or days to NCPAP or NIPPV.

Result: A total of 40% of infants needed MVET at 7 days of age in the NCPAP group compared with 17% in the NIPPV group (OR: 3.6; 95% CI: 1.5, 8.7). Days on MVET were 12 ± 11 days in NCPAP group compared with 7.5 ± 12 days in the NIPPV group (median 1 vs 7 days; $P = 0.006$). Clinical bronchopulmonary dysplasia (BPD) was 39% in the NCPAP group compared to 21% in the NIPPV group (OR: 2.4; 95% CI: 1.02, 5.6). Physiological BPD was 46% in the NCPAP group compared with 11% in the NIPPV group (OR: 6.6, 95% CI: 2.4, 17.8; $P = 0.001$). There were no differences in any other outcomes between the two groups.

Conclusion: NIPPV compared with NCPAP reduced the need for MVET in the first week, duration of MVET, and clinical as well as physiological BPD in preterm infants receiving early surfactant for RDS.
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Introduction

Respiratory distress syndrome (RDS) is the most common respiratory morbidity in preterm infants. Surfactant therapy and mechanical ventilation have become the standard of care in preterm infants with RDS. Bronchopulmonary dysplasia (BPD) continues to remain a major morbidity among preterm very low birth weight infants despite the increasing use of antenatal steroids, surfactant therapy and significant advances in mechanical ventilation.[1–3] BPD is associated with both short- and long-term morbidities in very low birth weight infants. Factors associated with BPD include prolonged intubation, mechanical ventilation, barotrauma, volutrauma or oxygen-induced lung inflammation.[4] Early surfactant administration followed by extubation to nasal continuous positive airway pressure (NCPAP) or NCPAP alone without surfactant therapy have been shown to decrease the incidence of BPD in very low birth weight infants in observational studies.[5,6] Findings of a multicenter randomized controlled trial[7] investigating whether early versus late treatment with surfactant reduced the requirement of mechanical ventilation in very preterm infants primarily supported by NCPAP found that early surfactant treatment improved oxygenation 6 h after randomization and reduced the need for mechanical ventilation via endotracheal tube (MVET) before discharge from 68 to 25%. In addition, early surfactant administration followed by extubation to NCPAP in infants <30 weeks gestational age significantly decreased the need for MVET to 0% by 7 days of age compared with 43% in the mechanical ventilation group.[8] However, several studies have shown that a significant number of infants treated with NCPAP alone or following extubation from MVET fail NCPAP and require reintubation.[9–15] Furthermore, two recent large trials[11,15]

evaluating the effects of early NCPAP did not show a decrease in BPD. The most common reasons for extubation failure are recurrent apnea, bradycardia or desaturations, and or development of respiratory acidosis.[16]

Nasal intermittent positive pressure ventilation (NIPPV) is a non-invasive mode of ventilation that augments the infant's spontaneous breath efforts by providing a back up rate.[17] Synchronized as well as non-synchronized NIPPV have been shown to be effective in preterm infants requiring respiratory support by reducing the incidence of apnea of prematurity and atelectasis, improving ventilation-perfusion matching and decreasing extubation failures.[18–22] Retrospective[23,24] as well as prospective, randomized, controlled studies[21,25] found that the incidence of BPD was also reduced in infants managed by NIPPV. Use of NIPPV as a primary mode of respiratory support during the initial management RDS has been shown to decrease the need for mechanical ventilation as compared with NCPAP.[21,26,27]

We hypothesized that early extubation to NIPPV in preterm infants <30 weeks gestation with RDS given surfactant shortly after birth will be associated with a decreased need for MVET at 7 days of age, a shorter duration of MVET, and it also might decrease the incidence of BPD.

Methods

Study objectives

The primary objective of this multicenter, randomized, controlled clinical trial was to compare the impact of early extubation to NIPPV versus NCPAP soon after surfactant (Poractant alfa, Chiesi Farmaceutici SpA) administration on the need for MVET at 7 days of age in preterm infants between $26^{0/7}$ weeks and $29^{6/7}$ weeks' gestation intubated for respiratory distress soon after delivery. Study was conducted between October 2006 and November 2008. Preterm infants <600 g birth weight, postnatal age >120 min, infants not requiring intubation and surfactant within 60 min of birth, out born infants, infants with Apgar score of 0 at 1 min of age and infants with major congenital anomalies were excluded. Prespecified secondary outcomes included the number of surfactant doses, days on synchronized, intermittent mandatory ventilation (SIMV), days on NIPPV, days on CPAP and supplemental oxygen, mortality, pneumothorax, pulmonary hemorrhage, patent ductus arteriosus, intraventricular hemorrhage (>grade II), periventricular leukomalacia, necrotizing enterocolitis (⩾stage II), spontaneous intestinal perforation, retinopathy of prematurity (>stage II), use of postnatal steroids for prevention or treatment of BPD, infants alive with supplemental oxygen at 36 weeks PMA (clinical BPD), physiological BPD, growth (weight at 36 weeks and/or discharge), and length of hospital stay. Physiological BPD was defined as any infant requiring >30% oxygen to maintain saturation by pulse oximeter (SpO_2) between 90 and 96% or on positive pressure support or, in case of infants requiring <30% oxygen, the need for any supplemental oxygen to maintain SpO_2 >90% after room air challenge for 30 min at 36 ± 1 week PMA or at discharge.[28]

Data were collected on case report forms developed for the trial. Entry criteria, exclusion criteria, ventilatory management for SIMV, NCPAP and NIPPV, and criteria for extubation and reintubation were made available on a website that was active during this trial (http://www.nippv.us). Staff education on SIMV, NCPAP and NIPPV management was performed at each of the participating centers. All centers that enrolled patients in this study had prior experience with the use of NCPAP and NIPPV. All women who presented at gestational ages between $26^{0/7}$ to $29^{6/7}$ weeks inclusive were screened for eligibility. Infants were not randomized until the first dose of surfactant had been administered after birth. Randomization was stratified according to center and gestational age ($26^{0/7}$ to $27^{6/7}$ weeks and $28^{0/7}$ or $29^{6/7}$ weeks), and was performed by an independent statistician, who prepared sequentially numbered, sealed, opaque envelopes. Institutional Review Board (IRB) approval was obtained from all participating sites. Trial was registered with http://www.ClinicalTrials.gov (NCT00486850). Written informed consent was obtained from parents or legal guardians before any infant was enrolled in this study.

Study intervention

All infants: initial stabilization. Preterm infants were stabilized on NCPAP using T-piece resuscitator (Neo-Puff^R) in the delivery room and were given poractant alfa at 200 mg kg^{-1} dose within 60 min of age at the discretion of the local clinical care team (Figure 1). Infants intubated either in the delivery room or soon after admission to newborn intensive care unit were eligible for inclusion in the study. Infants who received surfactant were initially stabilized on SIMV mode. Peak inspiratory pressure (PIP) was adjusted to deliver exhaled tidal volume of 4–7 ml kg^{-1}, positive end expiratory pressure (PEEP) was set between 5–7 cm H_2O, pressure support of 30–50% of delta pressure, inspiratory time of 0.35–0.45 s with a flow termination sensitivity set at 10% of peak flow and the rate was adjusted to keep PCO_2 in the target range but not to exceed 40 bpm during SIMV. Oxygenation was monitored using a pulse oximeter, and supplemental oxygen was weaned rapidly to maintain oxygen saturation between 84 and 92%. Ventilator settings were adjusted to maintain pH between 7.25 and 7.45, and PCO_2 between 40 and 60 mm Hg. Caffeine citrate was started as soon as possible or before extubation. Although clinicians were allowed to extubate infants from higher ventilator settings, infants who remained stable on minimal ventilator settings (mean airway pressure <6 cm H_2O and $FiO_2 \leqslant 0.3$) for 12 h were given a mandatory trial of extubation in both groups.

NCPAP group. Infants meeting the extubation criteria were extubated to nasal CPAP of 5 cm H_2O and remained on NCPAP for

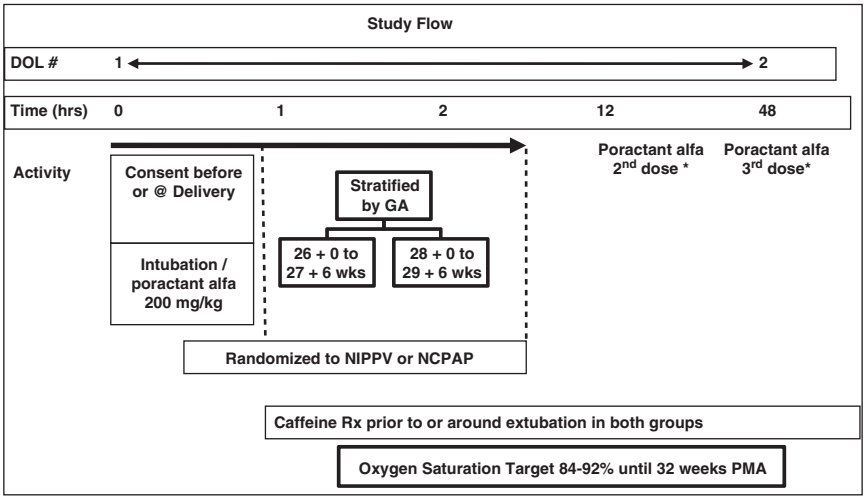

Figure 1 NIPPV vs NCPAP study design. GA, gestational age; NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; PMA, postmenstrual age.

at least 72 h or for as long as there was a need for supplemental oxygen during the first week of life. NCPAP level was increased to a maximum of 8 cm H_2O to optimize lung recruitment. NCPAP was provided using short binasal prongs and bubble CPAP, SiPAP with no back up rate or conventional ventilator CPAP.

NIPPV group. Infants randomized to NIPPV were extubated within 120 min of birth to NIPPV if they required less than 60% supplemental oxygen and or stable on minimal ventilatory settings for 12 h without significant respiratory acidosis. Nasal or nasopharyngeal prongs were used to deliver NIPPV. The prong size was based on the weight of the infants. None of the subjects received synchronized NIPPV (sNIPPV), as there was no device capable of delivering sNIPPV available in USA. NIPPV was generated using conventional mechanical ventilator (Avea ventilator, Viasys Health Care, CareFusion, Yorba Linda, CA, USA) or SiPAP device with a back up rate (CareFusion). During NIPPV, PIP was started at 10–15 cms H_2O above PEEP, PEEP was set at 5 cms H_20, inspiratory time of 0.5 s and back up or mandatory rate was set between 30 to 40 bpm. The FiO_2 was adjusted to maintain oxygen saturation in the target range. Attempts were made to maintain infants on NIPPV for a minimum period of 24 h after extubation. NIPPV was discontinued when the infants were weaned to PEEP of 5 cm H_2O with back up rate <10 bpm and FiO_2 <0.3 for 6–12 h, and <4 apneic episodes per hour requiring stimulation or <2 episodes requiring bag mask ventilation. Infants may be weaned to nasal cannula from NCPAP if they met the above criteria. Nasal cannula flow was restricted to a maximum of 2 LPM, in order to avoid inadvertent CPAP due to high flow. Nasal interfaces used to deliver NCPAP or NIPPV included nasal prongs (Agyle prongs, Sherwood Medical, St Louis, MO, USA; Inca prongs, Ackrad Laboratories, Cranford, NJ, USA; Neotech Products, Chatsworth, CA, USA) or nasopharyngeal prongs (Neotech Products). Preterm infants managed on INtubation, SURfactant and Extubation (INSURE) approach are typically extubated to NCPAP. As extubation to NCPAP results in failures requiring reintubation, our study design specifically evaluated the effects of post-INSURE extubation to NCPAP versus NIPPV.

Treatment failures (both groups). Infants were reintubated if they met one or more of the following criteria: >4 episodes of apnea per hour requiring stimulation or >2 episodes per hour requiring bag/mask ventilation; $FiO_2>0.60$ to maintain SpO_2 between 84–92%; pH <7.25 and $PCO_2>65$ torr on two consecutive blood gases, drawn 2 h apart. Infants failing NCPAP or NIPPV requiring reintubation could be rescued with high frequency oscillatory or jet ventilation. Following reintubation, infants remained intubated for at least 24 h before extubation was attempted in both groups. Infants who required supplemental oxygen >30% could be briefly intubated for surfactant administration and immediately extubated to assigned treatment in both groups. Up to two additional doses of poractant alfa at 100 mg kg^{-1} every 12 h during the first 48 h of age were allowed. Intubation for surfactant administration was not considered as extubation failure in either group. Data on reintubation and repeat doses of poractant alfa were collected in both groups. Caffeine was continued in patients who required reintubation.

Statistics

The need for MVET at 7 days of age in preterm infants <30 weeks gestational age has been reported to range between 43[8] and 63%.[7]

On the basis of data collected from our own center (LAC + USC Medical Center) and from published data in very low birth weight infants, a sample size of 50 infants in each group was needed to demonstrate a 50% reduction in the need for MVET at 7 days of age (power of 0.8 and an α-error of 0.05). An additional 10 patients (10%) were recruited to allow for any dropouts. An analysis of the primary endpoint was based on intention to treat analysis of all randomized, eligible subjects. Statistical analyses were performed using Student's *t* test for continuous normally distributed variables and with the Wilcoxon rank sum test for non-parametric variables. Comparison of proportions and analysis of categorical variables was performed using 2-tailed Fisher's exact test and logistic regression analysis. A *P*-value of <0.05 was considered statistically significant. Odds ratios with 95% CI and χ^2 tests were used to compare proportions between the two groups for the main dichotomous outcomes and multivariate logistic regression to control for potentially confounding effects of center, gender, BW, GA, antenatal steroid use and multiple births was done.

Interim analysis was performed by an independent statistician after 50 patients were enrolled and results were submitted to the Data Safety Monitoring Board (DSMB) members. They monitored for mortality and other adverse events, and made a recommendation about continuation of the study. The DSMB would not disclose any findings to avoid any biases except to issuing a continue or discontinue statement. If there was a statistically significant difference in the primary endpoint at a *P*-value <0.02 or statistically higher incidence in mortality within one of the treatment groups, DSMB was advised by the statistician for consideration of stopping the study.

Results

Figure 2 (consort diagram for the study) shows the number of preterm neonates who were assessed for eligibility, the number of eligible neonates, and the number of subjects who were randomly assigned to NCPAP or NIPPV. A total of 110 neonates were enrolled and the baseline characteristics of the study population randomized to NIPPV ($n = 53$) and NCPAP ($n = 57$) are shown in Table 1. There were no statistically significant differences in neonatal or maternal characteristics between the two groups. A total of 45%of the infants assigned to NIPPV and 44% in the NCPAP group were in the lower gestational age strata ($26^{0/7}$ to $27^{6/7}$ weeks). Baseline FiO_2 (0.30 ± 0.11 vs 0.30 ± 0.12) or MAP (8 ± 2 vs 8 ± 1 cm H_20) in the NIPPV vs NCPAP groups, respectively, were similar between the groups at randomization. Figure 3 depicts the results on the primary and secondary outcomes. The primary outcome of infants not requiring MVET at 7 days of age was 17% (9/53) in the NIPPV group and 42% (24/57) in the NCPAP group (OR: 3.6, 95% CI: 1.5, 8.7; $P = 0.005$). Of the confounding variables analyzed, only BW and GA were significantly related to the primary outcome. As these were comparable in the two groups, adjusting for them had very little effect on the group comparison. The odds ratios in fact increased from 3.6 to more than 4 following adjustment by either BW or GA. BPD at 36 weeks was 21% (11/53) in the NIPPV group and 39% (22/57) in the NCPAP group (OR: 2.4, 95% CI: 1.02, 5.6; $P = 0.040$). Physiological BPD was 11% (6/53) in the NIPPV group and 46% (26/57) in the NCPAP group (OR: 6.6, 95% CI: 2.4, 17.8; $P = 0.001$). Respiratory specific outcomes are shown in Table 2. There were no differences in time of first dose of surfactant, need for additional doses or in pneumothorax. More infants were extubated by 2 h of age in the NIPPV group ($P = 0.006$). Number of infants extubated by 12 h of age were similar between the groups

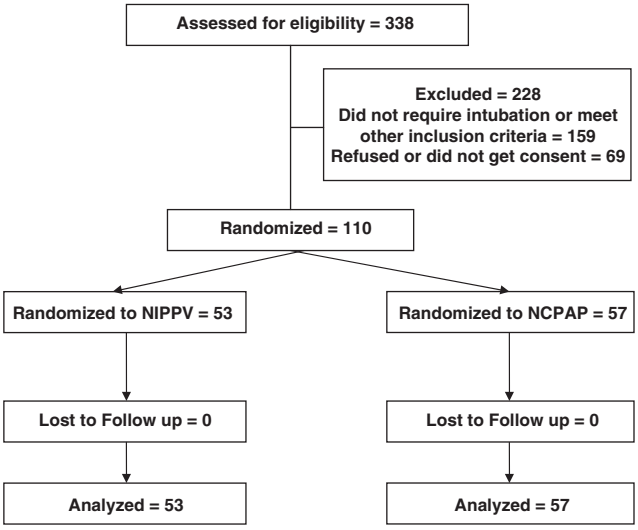

Figure 2 Number of infants screened and randomized to the treatment groups.

Table 1 Demographics of the study population

	NIPPV (n = *53*)	*NCPAP* (n = *57*)	P
Birth weight, mean ± s.d., g	1052 ± 223	1099 ± 201	0.88
Gestational age, mean ± s.d., weeks	27.8 ± 0.9	27.8 ± 0.9	0.61
$26^{0/7}-27^{6/7}$ Weeks, *n* (%)	24 (45)	25 (44)	0.88
$28^{0/7}-29^{6/7}$ Weeks, *n* (%)	29 (55)	32 (56)	0.88
Small for gestational age, *n* (%)	4 (7.5)	1 (1.8)	0.15
Clinical chorioamnionitis, *n* (%)	13 (25)	13 (23)	0.83
PT-PROM, *n* (%)	21 (40)	21 (37)	0.764
Antenatal steroids, *n* (%)	36 (68)	38 (67)	0.89
C-section, *n*, (%)	37 (70)	45 (79)	0.27
Apgar at 1′-median	6	6	0.85
Apgar at 5′-median	8	8	0.35
Male gender, *n* (%)	31 (58)	33 (58)	0.95

Abbreviations: NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; PT-PROM, preterm-prolonged rupture of membranes.

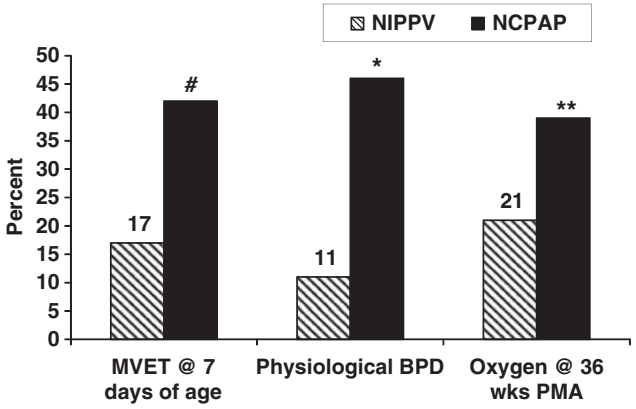

Figure 3 Primary and secondary outcomes. †Logistic regression to control for potentially confounding effects of GA, gender, center, antenatal steroid use and multiple births was done; #$P = 0.005$, *$P = 0.001$, **$P = 0.04$, MVET, mechanical ventilation via endotracheal tube; BPD, bronchopulmonary dysplasia; PMA, postmenstrual age.

Table 2 Respiratory specific outcomes

	NIPPV (n = *53*)	*NCPAP* (n = *57*)	P
Age at first dose of surfactant, min	28 ± 14	27 ± 14	0.698
Surfactant ⩾ 2 doses, *n* (%)	9 (17)	12 (21)	0.59
Pneumothorax, *n* (%)	1 (1.9)	2 (3.5)	0.60
Extubated by 2 h of age, *n* (%)	9 (17)	1 (2)	0.006
Extubated by 12 h of age, *n* (%)	30 (57)	24 (42)	0.129
Primary extubation by 7 days of age, *n* (%)	49 (92)	43 (60)	0.016
Failed extubation by 7 days of age, *n* (%)	4 (8)	14 (25)	0.004
Failed extubation at any time before discharge, *n* (%)	12 (23)	33 (58)	0.0001
On MVET at 7 days of age	9 (17)	24 (42)	0.005
MVET, days, (median)	7.5 ± 12 (1)	12 ± 11 (7)	0.006
Days on NCPAP	5 ± 5	10 ± 9	0.0008
Days on nasal cannula	25 ± 16	28 ± 16	0.30
Days on oxygen	29 ± 24	38 ± 25	0.05

Abbreviations: MVET, mechanical ventilation via endotracheal tube, NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation.
Data are mean ± s.d., except where indicated.

(30/53 and 24/57); however, significantly more infants were extubated by 7 days of age in the NIPPV group (49/53 vs 43/57; $P = 0.016$). Primary or first successful extubation occurred more frequently in the NIPPV group when compared with the NCPAP group (92 vs 60%; $P = 0.016$). Percent of infants failing first or subsequent extubations was significantly less in the NIPPV group (23 vs 58%; $P = 0.0001$). There were no differences in the days on NCPAP or on nasal cannula, but there was a trend towards less days on supplemental oxygen in the group assigned to NIPPV (29 vs 38 days; $P = 0.05$). Total days on MVET was 7.5 ± 12 days in the NIPPV group and 12 ± 11 days in the NCPAP group (median 1 vs 7 days, respectively; $P = 0.006$). Conventional ventilators were used in eight patients to deliver NIPPV or NCPAP in the NIPPV group and in seven patients in the NCPAP group.

Table 3 Clinical outcomes in the study population

	NIPPV (n = *53*)	*NCPAP* (n = *57*)	P
PDA, *n* (%)	27 (51)	32 (56)	0.59
PDA–ligation, *n* (%)	3 (5.7)	3 (5.3)	0.93
NEC, *n* (%)	2 (3.8)	4 (7)	0.68
SIP, *n* (%)	0 (0)	3 (5.3)	0.224
IVH > grade II, *n* (%)	2 (3.8)	0 (0)	0.23
ROP > stage II, *n* (%)	1 (1.9)	1 (1.8)	0.99
Weight at discharge, mean ± s.d., g	2636 ± 570	2680 ± 642	0.65
Deaths, *n* (%)	1 (1.9)	1 (1.8)	0.96
LOS, mean ± s.d., days	70 ± 21	71 ± 28	0.512
Gastric perforations, *n*	0	0	—

Abbreviations: IVH, intraventricular hemorrhage; LOS, length of stay; NCPAP, nasal continuous positive airway pressure; NEC, necrotizing enterocolitis; NIPPV, nasal intermittent positive pressure ventilation; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; SIP, spontaneous intestinal perforation.

Overall clinical outcomes are shown in Table 3. There were no differences in patent ductus arteriosus, patent ductus arteriosus requiring ligation, postnatal steroid use, necrotizing enterocolitis ⩾ stage II, spontaneous intestinal perforation, intraventricular hemorrhage > grade II, periventricular leukomalacia or retinopathy of prematurity > stage II. One infant died in each group. No increase in the incidence of feeding intolerance was noted in either group. Total length of stay (70 ± 21 vs 71 ± 28 days) was also similar between NIPPV and NCPAP group. Time to reach full feeds was not different between the two groups.

Discussion

Early extubation of surfactant treated preterm infants to NIPPV significantly decreased the need for MVET at 7 days of age and the duration of MVET. This approach also resulted in significant reductions in BPD at 36 weeks and physiological BPD in these infants who are at highest risk for adverse pulmonary outcomes. Our results are consistent with two other studies of early use of NIPPV vs NCPAP for the initial/primary treatment of RDS.[21,25] Previous studies using NCPAP as a primary mode of respiratory support or following extubation reported failures requiring intubation or reintubation.[9–16,29] These investigators used different types of nasal interfaces, such as single versus binasal prongs and different CPAP generators like bubble CPAP, infant flow drivers and conventional mechanical ventilators. CPAP failure rates by 3 to 7 days ranged from 19.7 to 80% in these studies. Most common reasons for failures were recurrent episodes of apnea, bradycardia and desaturations or the development of respiratory acidosis.

Four randomized controlled trials using NIPPV have shown significant decrease in extubation failures as compared with NCPAP.[18–20,22] Exact mechanisms by which NIPPV improves efficacy are not known. NIPPV technique has been shown to improve lung recruitment due to higher mean airway pressure, decreased work of breathing,[30] improved thoracoabdominal motion asynchrony, decreased flow resistance through the nasal prongs, and may improve lung mechanics.[31] Addition of PIP above PEEP during NIPPV breaths may also increase flow delivery through the upper airway. Moretti *et al*.[22] demonstrated that during sNIPPV using flow triggering delivered more tidal and minute volumes when compared with NCPAP.

Only one study by Bhandari *et al*.[25] evaluated the role of sNIPPV post surfactant therapy for RDS in 41 preterm infants. They demonstrated that the use of sNIPPV after surfactant treatment significantly decreased BPD (10 vs 33%, $P = 0.04$) when compared to infants managed on IMV. They found no difference in the total duration of MVET or sNIPPV. In our study, we compared NIPPV with NCPAP post surfactant therapy and showed that NIPPV use resulted in significant decrease in the duration of MVET and a reduction in BPD. Recently, Meneses *et al*.[32] reported results from a large group of preterm infants (26 to $33^{6/7}$ weeks' GA) randomized to early NIPPV or NCPAP. More infants who were treated with surfactant remained extubated in the NIPPV group when compared with NCPAP in this study (10.9 vs 27.1%; RR 0.40 (95% CI 0.18, 0.86)). NIPPV and early surfactant therapy may have a synergistic effect in decreasing BPD secondary to minimizing MVET during the transitional period, during which time preterm infant's lung may be more susceptible to volutrauma or oxygen-related lung inflammation.

The most serious complication reported with the use of NIPPV in neonates has been gastric perforation.[33] However, none of the studies in the past 16 years reported any association with necrotizing enterocolitis or gastric or other intestinal perforations and NIPPV use.[18–22,25,32]

Initiation and/or maintenance of mechanical ventilation via the endotracheal tube during the first week of life may activate the alveolar macrophages, leading to the release of pro-inflammatory cytokines. Exposure to oxygen in high concentrations via the endotracheal tube also potentiates the inflammatory cascade. Furthermore, ventilator-associated pneumonia may contribute to the ongoing inflammation in the lung, eventually leading to BPD. Three studies[21,24,25] suggest that early extubation to NIPPV may be an important modifier of BPD, even if the total duration of mechanical ventilation is not different. In a large retrospective study, Bhandari *et al*.[24] reported that use of sNIPPV was associated with decreased BPD, BPD/death, neurodevelopmental impairment and neurodevelopmental impairment/death when compared with infants managed on NCPAP. Our finding from this prospective study is consistent with these studies, in terms of decreasing BPD. Furthermore, due to significant decrease in apnea, bradycardia or desaturations during NIPPV, it is possible that cumulative exposure to supplemental oxygen might have been less. During NIPPV, hypopharyngeal concentration of oxygen is also lower due to mixing with room air during spontaneous breathing, which may also indirectly decrease the exposure to high oxygen concentration. In our study, patients in both groups were treated with caffeine. Caffeine treatment has been shown to have an independent effect in decreasing BPD.[34] Combination of decrease in oxygen exposure and barotrauma/volutrauma from MVET might have augmented the beneficial effects of caffeine in decreasing BPD. It is also possible that higher mean airway pressure delivered at the nasal interface during NIPPV may have resulted in maintaining optimal lung expansion than during NCPAP. However, this is unlikely, as NCPAP level was increased in patients with low lung volumes. Interestingly, physiological BPD was higher than clinical BPD at 36 weeks PMA in our study. This may have been due to the fact that oxygen reduction test was done at 36 ± 1 week PMA and a common practice of using low flow nasal cannula on room air to decrease spontaneous desaturation episodes. Use of low flow nasal cannula with room air precluded inclusion of babies for the diagnosis of clinical BPD at 36 weeks PMA. Our findings also suggest that the use of physiological BPD may better reflect the extent of lung injury in preterm infants, who may not be receiving any supplemental oxygen at 36 weeks PMA.

Studies comparing NIPPV vs NCPAP and sNIPPV vs IMV or SIMV have all shown a significant reduction in extubation failures and a decrease in BPD with NIPPV. Even brief periods of MVET may contribute to lung injury, and further studies are needed to evaluate the efficacy of NIPPV as a primary mode with or without surfactant administration in the youngest infants at highest risk for adverse pulmonary outcomes. Antenatal steroid use was relatively low in our population due to the fact that study centers received high risk pregnancies with limited or no prenatal care. However, even in the recently published study from USA, full course of antenatal steroid use was only around 70%.[15] Low antenatal steroid use, coupled with including only infants who required intubation and surfactant therapy for RDS, might have contributed to the higher incidence of BPD in our study population. Long-term neurodevelopmental outcomes as well as upper airway development following prolonged periods of nasal ventilation need to be evaluated. Limitations of our study include: assignments to NIPPV or NCAP could not be blinded; in an attempt to minimize any bias, minimum extubation criteria were kept the same in both the groups; only infants who required mechanical ventilation and surfactant treatment before randomization were included; low flow nasal cannula was not considered as a form of pressure support; episodes of apnea, bradycardia or desaturations were not quantified between the two groups. We also excluded infants <26 weeks or birth weight <600 grams.

Conclusions

In this prospective, randomized, controlled trial, we have demonstrated that NIPPV use results in less need for MVET at 7 days of age, less days on MVET, and may provide significant pulmonary benefits of decreasing clinical or physiological BPD when compared with NCPAP.

Conflict of interest

The authors declare no conflict of interest.

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