Original article

Noninvasive ventilation in preterm neonates - Nasal continuous positive airway pressure *VS* Nasal intermittent positive pressure ventilation – A randomised controlled trial

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Abstract

Background: Noninvasive ventilation (NIV) has been used in preterm neonates in the past few decades, with the main objective of reducing the exposure to invasive ventilation. It proves to be safe and effective but the best option is yet to be determined. **Objective**: To determine, if nasal intermittent positive pressure ventilation (NIPPV) decreases the need for mechanical ventilation in the first 48 h when given as a respiratory support post-extubation in preterm neonates compared to nasal continuous positive airway pressure (NCPAP). It is a randomised controlled trial. **Method:** Preterm neonates (gestational age 28-36 weeks) with respiratory distress requiring invasive ventilation were randomly assigned to receive NIPPV or NCPAP as postextubation respiratory support. The primary outcome was the need for mechanical ventilation within the first 48 hours of life. **Results:** A total of 32 neonates in postextubation NIV group after stratification to gestational age of 28-32 weeks and 33-36 weeks. The need for invasive mechanical ventilation in the first 48 h was not different in both NIPPV (11.1%) and NCPAP (7.1%). The complications associated with these modes were also compared and analysed. There was no difference noted. **Conclusions:** NIPPV did not decrease the need for mechanical ventilation compared to NCPAP, overall, in the first 48 hours of support. It could be considered as safe and beneficial compared to NCPAP. However, further studies have to assess the potential benefits and complications associated with NIPPV in preterm neonates.

Keywords: Preterm neonates, Nasal continuous positive airway pressure, Nasal intermittent positive airway pressure.

Introduction

Noninvasive ventilation (NIV), a term applied to a variety of devices capable of supporting the ventilation without the use of an endotracheal tube, is receiving increasing attention as a means for reducing the damage often incurred with the mechanical ventilation. There is a renewed interest in the nasal continuous positive airway pressure ventilation (NCPAP) and other types of NIV namely, nasal intermittent positive pressure ventilation (NIPPV) to support the neonates with respiratory diseases.

The application of NIV to preterm neonates has been an effective bridge between the ventilation and unsupported breathing. CPAP has been shown to reduce the extubation failure, treat respiratory

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How to cite this article: Skariah AT, Lewis L, Sasi A. Noninvasive ventilation in preterm neonates - Nasal continuous positive airway pressure *vs* Nasal intermittent positive pressure ventilation. Ind J Resp Care 2013; 2:206-12.

distress syndrome, apnoea of prematurity[1] and reduce the rates of chronic lung disease (CLD).[2,3,4] Some infants managed with early CPAP develop respiratory failure due to ongoing lung disease,[4] apnoea of prematurity[5] or progressive atelectasis.[6] Efforts to reduce these failure rates prompted the use of NIPPV as it may provide sufficient support to avoid endotracheal intubation in some infants. The use of NIPPV is well established in many adult[7-11] and paediatric conditions.[4,12] It can be used in a synchronised (SNIPPV) or nonsynchronised manner to supplement the infants' own breathing efforts.[13]

Methods

This was a prospective, stratified, randomised controlled study. Preterm neonates (28-36 weeks) admitted to the Neonatal Intensive Care Unit, Kasturba Hospital, Manipal from May, 2011-February, 2012 with respiratory distress (Downe's score ≥ 3) requiring invasive respiratory support for > 2 h were included in the study. The preterm neonates with congenital cyanotic heart disease, major congenital malformations and air leak syndromes were excluded.

The infant demographic data such as date of birth, admission, gestational age, birth weight, gender, APGAR score, antenatal steroid administration, mode of delivery and vital signs were recorded at the time of admission. These neonates receiving invasive mechanical ventilation were extubated when they were on minimal ventilator settings (PIP 12-14 cm H_2O, FIO_2< 30% and PEEP 4-5 cm H_2O and rate of 25-30 bpm). After extubation, the neonates were randomly allocated to either NCPAP or NIPPV by using block randomisation. They were stratified based on the gestational age (28-32 weeks and 33-36 weeks). In each stratum, there were two groups (interventions): Group A (NCPAP) and Group B (NIPPV). When a new neonate was admitted to the unit, a person other than the investigator randomly assigned the neonate to any of the two interventions based on age and block randomisation. Downe's score for respiratory distress was assessed for every four hours for the first 24 h after randomisation.

The ventilator *viz*., Drager Babylog 8000 plus was used for NIPPV and NCPAP. The interface named Drager Baby Flow Neo Nasal Masks of small, medium and large size with head cap was used. Orogastric tube was inserted and kept open to decompress the stomach and closed while feeding. An appropriate sized cap was used after measuring the head circumference, ensuring to cover the ears.

The initial settings used for NIPPV were PIP of 11-18 cm H_2O depending on adequate chest rise and synchrony with breaths delivered with PEEP of 3-5 cm H_2O, inspiratory time of 0.36-0.4 s, respiratory rate of 18-30 bpm.

The NCPAP settings were PEEP of 3-5 cm H_2O. The flow rate was set at 5-6 L/min and fraction of inspired oxygen (FiO_2) of 21% and gradually increased if SpO_2 fell below 88% for both interventions similarly. Oxygen saturation was maintained in the range 88-92%.

The parameters such as PEEP and FiO_2 were increased if the distress increased (Downe's score increased) or the oxygen saturation dropped below the range. FiO_2 was increased in increments of 2-4%. The ventilator parameters such as PIP, PEEP, FiO_2, respiratory rate, flow rate and inspiratory time were recorded for every four hours for the first 48 h. The mean airway pressure was also recorded.

The maintenance of the circuit and the nasal interface was done on routine basis. Care of the airway was taken by cleaning nostrils with saline drops and suction to ensure patency. Condensed water from the inspiratory and expiratory circuit was removed for preventing resistance which may increase the work of breathing. The gas that reached the baby was maintained at about 37°C and at 100 % humidity. Oxygen saturation recorded by pulse oximeter, heart rate, respiratory rate and blood pressure were monitored continuously by the Philips Intelli Vue MP20 patient monitor. An orogastric tube of 5 F or 6 F was inserted to decompress the stomach and closed only to allow feeding. The abdominal girth was measured for every four hours for the first 48 h when the baby was on noninvasive ventilation and

the time required to reach full feed, the rate and volume of feeds given were monitored and recorded daily.

There was a continuous monitoring of the requirement of oxygen, number of days requiring respiratory support and number of days in NICU. All preterm neonates ≤ 34 weeks gestational age requiring mechanical ventilation or with apnoea of prematurity received methylxanthines. A neurosonogram screening for intraventricular haemorrhage and periventricular leukomalacia was performed in the first week and 4th week of age for all babies below 34 weeks of gestation. Screening for the retinopathy of prematurity (ROP) was performed as per the standard guidelines.

When the settings were PEEP of 4 cm H_2O and FiO_2 of 21% with a flow rate of ≤ 6 L/min, NCPAP was discontinued. In NIPPV, the thresholds for discontinuation were PIP of ≤ 14 cm H_2O, PEEP of ≤ 4 cm H_2O with a rate of ≤ 22 bpm and FiO_2 of 21%. NIPPV was changed to NCPAP if there was feed intolerance (persistent gastric aspirates more than 50% of previous feed) with abdominal distension (more than 2cm from baseline) or worsening of Downe's score. Likewise, NCPAP was changed to NIPPV if the baby was not maintaining SpO_2 above 85% with PEEP of 6 cm H_2O and a FiO_2 of 40%, if the ABG revealed hypercarbia with $PaCO_2$ of ≥ 55 mm Hg, or if the baby had bradycardia or apnoeic episodes unresponsive to stimulation.

Primary and secondary outcome measures

The primary outcome was a '*failure*' of noninvasive respiratory support necessitating intubation and mechanical ventilation within 48 hours of initiation of noninvasive ventilator support. The criteria for 'failure' were the same for the two groups and it was met by at least one of the following: $PaCO_2$ > 60 mm Hg with pH < 7.2 or apnoea (> 20 s or < 20 s with cyanosis or bradycardia; HR < 100/min) occurring more than three episodes in one hour.

The secondary outcomes observed were duration of respiratory support, duration of NICU stay, days to reach the full feed and complications such as retinopathy of prematurity, periventricular leukomalacia, intraventricular haemorrhage, necrotising enterocolitis and feed intolerance.

The study protocol was approved by the institutional ethics committee. Informed consent was taken from the parents of the newborns who fulfilled the inclusion criteria. SPSS version 16.0 was used for statistical analysis. Continuous measures between the groups were compared using student's t-test while nonparametric continuous outcomes were compared using Mann Whitney U test and Chi-square test.

Results

A total of 32 neonates were randomised after stratifying according to their gestational age. There were 21 neonates with 9 and 12 neonates in NCPAP and NIPPV intervention in the lower gestational age (28-32 weeks) respectively. In the higher gestational age strata (33-36 weeks), there were a total of 11 neonates with 5 and 6 in NCPAP and NIPPV intervention respectively *(Figure 1)*. *Table 1* shows the baseline characteristics of the neonates in the study. The supportive treatment for the neonates was also recorded and described in *Table 2*.

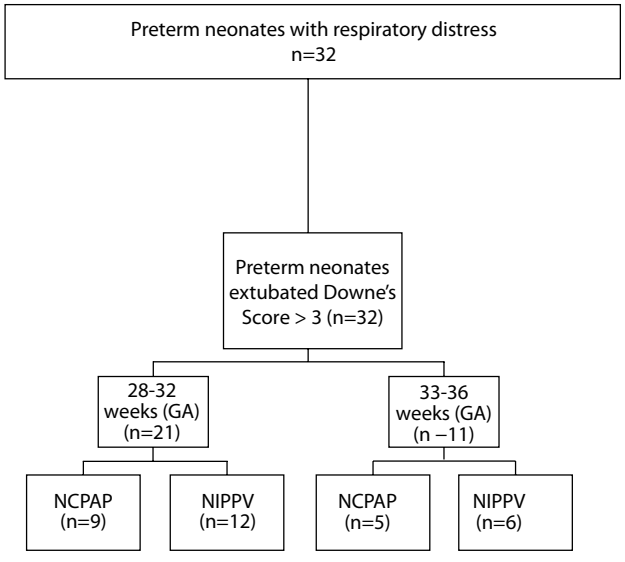

Figure 1: Flowchart of the participants , GA - gestational age NCPAP - nasal continuous positive airway pressure ventilation, NIPPV - nasal intermittent positive pressure ventilation

Table 1: Baseline characteristics of the neonates

Baseline characteristics	Postextubation NIV			
	28-32 weeks		33-36 weeks	
	NCPAP (n = 9)	NIPPV (n = 12)	NCPAP (n = 5)	NIPPV (n = 6)
Birth Weight (g) (mean ± S.D)	1160 ± 282.63	1200 ± 249.26	1773 ± 122.45	1770 ± 549.23
Gender M:F (n)	5:4	9:3	1:4	4:2
Mean gestation in weeks (mean ± SD)	30.66 ± 1.80	29.83 ± 1.40	33.60 ± 0.89	33.83 ± 0.75
Mode of delivery NVD*	1	4	1	1
LSCS*	7	8	4	4
AVD*	1	Nil	Nil	1
PCV (mean ± S.D)	45.35 ± 9.57	48.06 ± 5.76	40.16 ± 10.1	47.21 ± 6.53
Antenatal steroid (%)	6/8[#] (75)	7/12 (58.3)	1/4 [#] (25)	2/6 (33.3)

*NVD – Normal Vaginal Delivery, LSCS – Lower Segment Caesarean Section, AVD – Assisted Vaginal Delivery, PCV – Packed Cell Volume

[#]Information about the antenatal steroid treatment provided to the mother at the referring centre was not available in one neonate.

Table 2: Supportive treatment of the neonates

Therapy	Postextubation NIV			
	28-32 weeks		33-36 weeks	
	NCPAP (n=9)	NIPPV (n=12)	NCPAP (n=5)	NIPPV (n=6)
Methylxanthines				
Caffeine n (%)	4 (44.4)	5 (41.7)	1 (20)	2 (33.3)
Aminophylline n (%)	4 (44.4)	6 (50)	1 (20)	1 (16.7)
Surfactant therapy				
Surfactant n (%)	8 (88.9)	11 (91.7)	4 (80)	4 (66.7)
Other				
Antibiotics n (%)	5 (55.6)	9 (75.3)	4 (80)	3 (50)
TPN n (%)*	8 (88.9)	10 (83.3)	5(100)	3 (50)

*TPN- Total parenteral nutrition

The primary outcome did not differ significantly in both NIPPV and the NCPAP groups. NCPAP was administered to 14 neonates out of whom one failed NIV in the lower gestation age group and there was no failure in the other strata. When NIPPV was administered to 18 neonates, one neonate in each stratum failed (no statistical significance, p value > 0.05). The overall duration of NIV and days in NICU were similar in both the intervention groups and showed no statistical significance.

No significant differences were noted in both the treatment groups for other secondary respiratory outcomes *(Table 3)*. All other clinical outcomes (complications) were similar in both the treatment groups *(Table 4)*. There was an isolated case of intraventricular haemorrhage in the lower gestation strata NCPAP group.

Ventilator parameters were recorded for every four hours for the first 48 hours. The mean airway pressure and fraction of inspired oxygen (FiO_2) were common in both the interventions. The mean

Table 3: Complications of NCPAP and NIPPV

Complications	28-32 weeks		p value	33-36 weeks		p value
	NCPAP (n=9)	NIPPV (n=12)		NCPAP (n=5)	NIPPV (n=6)	
Feed intolerance (%)	2/8# (25)	Nil	0.08	Nil	Nil	-
NEC (%)*	1/9 (11.1)	Nil	0.257	Nil	Nil	-
Dilated bowel (%)	1/9 (11.1)	Nil	0.830	4/5 (80)	1/5# (20)	0.058
Air leak (%)	Nil	Nil	-	1/5 (20)	Nil	0.251
ROP (%)*	2/8# (25)	3/10# (30)	0.814	Nil	1/6 (16.7)	0.453

*NEC- Necrotising enterocolitis, ROP- Retinopathy of prematurity

#The total number is less compared to the enrolled number of subjects in this group due to failed outcome.

of maximum FiO_2 used was compared and it showed a higher oxygen requirement in the NIPPV group in both strata. A line graph plotted comparing the two groups is as below in *Figure 2*.

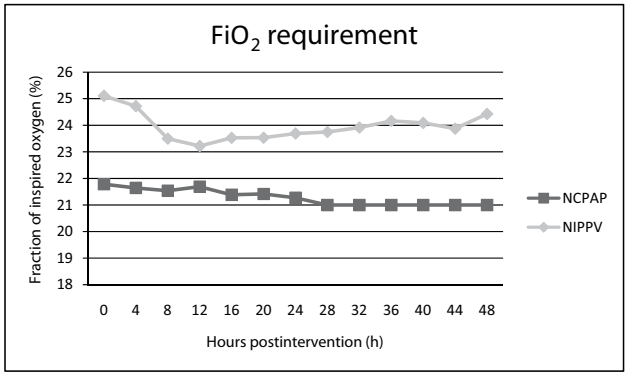

Figure 2: Line graph comparing FiO_2 used in NCPAP and NIPPV

Mean airway pressure (MAP) was recorded for every four hours for the first 48 h for each neonate in the study. A line graph plotted with the means of MAP for every four hours in two groups is as shown in *Figure 3*. The graph depicts that the MAP in NIPPV was higher than NCPAP although the statistically significant difference could not be demonstrated.

Apart from the outcomes and complications *(Table 3)*, the range of parameters used during NIV were also recorded and analysed. The PIP used in NIPPV ranged from the lowest PIP of 10 cm H_2O to the highest PIP of 20 cm H_2O. The respiratory rate used in NIPPV ranged from 18 to 23 breaths/min.

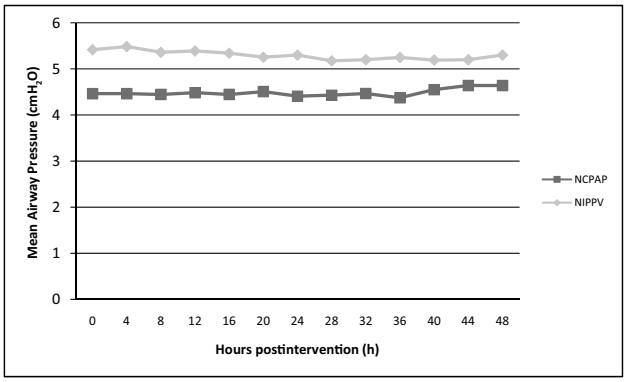

Figure 3: Line graph of MAP in NIPPV and NCPAP

Discussion

The current trend for treating neonates with respiratory distress is nasal continuous positive airway pressure (CPAP). However, nearly half of these neonates will still develop respiratory failure requiring endotracheal intubation. This can be difficult, traumatic and fraught with complications. Invasive ventilation also is more complicated in neonates. Thus, it would be prudent to minimise the need for invasive ventilation to reduce complications of treatment.[14]

NIPPV provides greater respiratory support than CPAP and may prevent intubation in a larger fraction of neonates who would otherwise fail CPAP. In this study, NCPAP was compared with NIPPV as a respiratory support postextubation. It showed that NIPPV was as good as NCPAP for preterm neonates. There was no statistical significance when

the need for intubation was analysed. In a RCT done by Sai Kishore *et al*[15], they found that NIPPV was more beneficial (with a statistical significance) than NCPAP in 28-30 weeks as a primary mode of ventilation. In the study by Jucille Meneses *et al*[16], the authors concluded that early NIPPV did not decrease the need for mechanical ventilation when compared to NCPAP, overall, in the first 72 h of life.

In the present study, the duration in hours of the NIPPV support is lesser than NCPAP except for 28-32 weeks strata group but this is not statistically significant. The time to reach full feeds is not significant and it is different in both the interventions.

Previous studies have mentioned that a higher MAP was used in NIPPV. A Cochrane review done by Davis PG *et al*[17] concluded that the mean airway pressure (MAP) generated during NIPPV may be higher than nasal CPAP and therefore the differences in outcomes may be due to a higher MAP in the NIPPV group.

No previous study has mentioned the range of PIP and respiratory rate being used in the NIPPV. The range of PIP used 10 – 20 cmH_2O with a median PIP of 13 cm H_2O. The range of the respiratory rate seen in the NIPPV was 12 – 45 breaths/min with a median of 24 breaths/min.

It is postulated that NIPPV due to high MAP and superior support reduces the work of breathing (WOB) and provides more stabilisation to the neonate. In a Cochrane review by Lymre *et al*[18] on the NIPPV compared to NCPAP, the data reported a decrease in the work of breathing during inspiration, elastic work of breathing and resistive work of breathing even at the lower delivered pressure. Another study by Zubair H Aghai *et al*[19] found that when compared to NCPAP, the addition of ventilator-delivered PIP during SNIPPV decreased the WOB in premature infants.

The complications associated with NIV are of great concern. In this study, the incidence of complications is similar in both the groups. Garland *et al*[20] reported gastrointestinal perforation due to NIPPV. Jucille Meneses *et al*[21] had found no gastrointestinal complications in his study. He also stated that the incidence of necrotising enterocolitis (NEC) as well as the time to full feeds was the same in both groups. In our study there are a few isolated cases of NEC, air leak, feed intolerance and retinopathy of prematurity (ROP) but they are not related to any particular group.

Conclusion

This study suggests that NIPPV is as safe as NCPAP for supporting preterm neonates. The duration of NIV support, the number of days in NICU, days to reach full feeds and complications are similar in both the groups. MAP is significantly higher in NIPPV than the NCPAP group in 28-32 weeks strata. NIPPV is as beneficial and safe as NCPAP but more subjects need to be enrolled to concrete the hypothesis.

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