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Original Article

Early Nasal Intermittent Positive Pressure Ventilation (NIPPV) versus Nasal Continuous Positive Airway Pressure (NCPAP) for Respiratory Distress Syndrome (RDS) in Infants of 28-36 weeks gestational age: a Randomized Controlled Trial

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ABSTRACT

Background: Early nasal continuous positive airway pressure (NCPAP) has emerged as a primary modality of respiratory support for preterm infants with respiratory distress syndrome (RDS). However, 30%-40% of these newborns need subsequent mechanical ventilation. Nasal intermittent positive pressure ventilation (NIPPV) is a promising alternative to NCPAP, especially in post-extubation settings, apnea of prematurity, or NCPAP failure as the primary mode of respiratory support in RDS. Application of these two methods in neonates with RDS needs further studies.

Methods: This open-label randomized clinical trial (RCT) was stratified by gestational age (i.e., 28-32 and 33-36 weeks). The sample included 78 infants divided into the two groups of 37 NIPPV and 41 CPAP. We compared the effect of ventilator delivered asynchronous NIPPV with NCPAP in reducing the need for invasive ventilation within 48 h of non-invasive support in infants of 28-36 weeks with RDS [onset of distress within ≤ 6 h of life with a fraction of inspired oxygen (FiO2) ≥ 0.25 compatible with chest radiograph]. The FiO2 > 0.3 and/or Downes score ≥ 4 were the indications for surfactant therapy administered by endotracheal tube. The infants were extubated and returned to their initial assigned mode of support within 60 min. The primary outcome was considered as failure of the allocated mode within 48 h.

Results: According to our findings, the two groups showed no significant difference in terms of failure rates with 5 (13.5%) and 6 (15%) failed NIPPV and NCPAP cases (P=0.8). There was a trend toward less surfactant therapy in NIPPV [12 (32.4%) vs. 22 (53.7%), P=0.06], and lower Downes score in the first 12 h. The hazard ratio (HR; adjusted for gestation, surfactant therapy, and birth weight) for failure in NIPPV was similar to that of NCPAP (HR=1.03) at 95% confidence interval. No difference in air leaks or abdominal distension was noted between the two groups.

Conclusion: Early NIPPV may not have a benefit, compared to NCPAP as a primary mode of respiratory support for infants with RDS.

Keywords: Asynchronous, Nasal continuous positive airway pressure, Nasal intermittent positive pressure ventilation, Non-invasive ventilation, Respiratory distress syndrome

Introduction

Non-invasive ventilation (NIV) is a term applied to a variety of devices capable of supporting ventilation without using endotracheal tube. This phenomenon is receiving increasing attention due to reducing the damage that often occurs with mechanical ventilation. Short-term application of NIV in neonates is not a new concept in the neonatal respiratory care

community. In fact, manual resuscitators affixed with oronasal masks and positive end-expiratory pressure (PEEP) valves are commonly used to assist the infants with insufficient respiratory efforts and respiratory failure (1).

The long-term use of automated NIV in neonates was first reported in 1952 by Donald and Lord in a paper entitled "Automated Respiration: Studies in Atelectasis Neonatorum," (2) about two decades prior to the initial description of neonatal CPAP by Gregory et al. in 1971.

Application of NIV for preterm neonates has become established as an effective bridge between invasive ventilation and unsupported breathing. CPAP has been shown to reduce extubation failure and the rate of chronic lung disease (CLD), as well as treating respiratory distress syndrome (RDS) and apnea of prematurity (AOP) (3-6). Some infants managed with early CPAP develop respiratory failure as the result of ongoing lung disease (7), AOP (8), or progressive atelectasis (9).

Efforts to reduce these failure rates prompted the use of NIPPV as it may provide sufficient support to avoid endotracheal intubation in some infants. Utilizing NIPPV is well established in many adults (10-14) and pediatric conditions (15). It can be used in a synchronized (SNIPPV) or non-synchronized manner to supplement the breathing efforts of infants (16).

Kiciman et al. (17) found reduced thoracoabdominal motion asynchrony during SNIPPV, in comparison with NCPAP. Aghai et al. (18) revealed that SNIPPV diminishes the act of breathing in preterm infants. Moreover, these authors stated that SNIPPV increased tidal volume and minute volume, compared to NCPAP (18). Trials have found that NIPPV is more effective than NCPAP in decreasing the rate of extubation failure without adverse gastrointestinal compli-cations in preterm neonates (19, 20)..

Initiation of MV in the first days of a preterm neonate life is the leading cause of broncho-pulmonary dysplasia (BPD) and ventilator-associated morbidities (20, 21). Two randomized controlled trials (RCTs) have revealed that early NIPPV reduced the need for endotracheal intubation within the first 72 h of life more than NCPAP.

This prospective RCT using standardized protocols for intubation and surfactant therapy aimed to evaluate NIPPV usage instead of NCPAP in preterm neonates. In addition, we assessed the need for intubation within the first 48 h of life after random assignment of the subjects into the early NIPPV and NCPAP groups.

Methods

This single-center, open-label RCT with stratified block randomization was conducted at level III Neonatal Intensive Care Unit (NICU) in multispecialty Kasturba Hospital, Manipal, India during October 2011-December 2012. Preterm neonates of 28-36 weeks admitted to the NICU with respiratory distress were included in the study. The inclusion criteria entailed being preterm neonate (< 37 weeks) and Downes score ≥ 3. Neonates with congenital cyanotic heart disease, major congenital malformations, and air leak syndromes were excluded.

The enrolled infants received NIV as the primary respiratory support within the first four hours of life and did not require invasive respiratory management. The neonates with severe respiratory distress received the INSURE (Intubation-Surfactant administration-Extubation) followed by the NIV.

Preterm infants were randomly allocated to either NCPAP or NIPPV groups using block randomization. The participants were stratified based on gestational age as the strata of 28-32 and 33-36 weeks, each of which included two intervention groups. Allocation concealment was done by the sequentially numbered sealed envelope. Group A received the NCPAP, while Group B received the NIPPV.

Blocks of four with six A and B combinations, including ABAB, BABA, AABB, BBAA, BAAB, ABBA were made. Twenty such blocks were made by a person other than the investigators and were numbered as 1-20. When a new neonate was admitted to the unit, a person other than the researchers randomly picked one of the blocks made. If the selected combination was ABAB, the subject was first put on the NCPAP and then on the NIPPV and so on.

Downes score for respiratory distress (which encompasses respiratory rate, retractions, grunting, air entry, and oxygen use) was assessed every four hour for the first 24 h post-randomization. The demographic data of the infant, such as date of birth, admission, gestational age, birth weight, gender, Apgar score, antenatal steroid administration, mode of delivery, and basic vitals on admission were recorded.

The used ventilator was Drager Babylog 8000 plus for the NIPPV and NCPAP. Moreover, the utilized interface was the Drager Baby Flow Neo Nasal Masks of small, medium, and large size with

a head cap. An orogastric tube was inserted and kept open to decompress the stomach and allow feeding. Cap with appropriate size was used after measuring the head circumference ensuring to cover the ears.

The initial settings applied for the NIPPV were positive inspiratory pressure (PIP) of 11-18 cmH_2O depending on adequate chest rise and synchrony with breaths delivered with positive end-expiratory pressure (PEEP) of 3-5 cmH_2O, inspiratory time of 0.36-0.4 sec, and respiratory rate of 18-30 bpm. The NCPAP settings entailed the PEEP of 3-5 cm H_2O, flow rate set at 5-6 L/min, and a fraction of inspired oxygen (FiO_2) of 21%, which gradually raised based on the target saturation for both interventions similarly.

Monitoring and recording of the target oxygen saturation were maintained in the range of 92%-95%. The parameters like PEEP and FiO_2 were increased if the distress increased (Downes score augmented) or the oxygen saturation dropped below the range. In addition, the FiO_2 was elevated in increments of 2-4%. The ventilator parameters, namely PIP, PEEP, FiO_2, respiratory rate, flow rate, inspiratory time, and measured mean airway pressure (MAP) were recorded every four hour for the first 48 h.

Maintenance of the circuit and nasal interface was performed routinely. Care of the airway included cleaning nostrils with saline drops and suction to ensure patency. The gas that reached the newborn was maintained at about 37°C and 100% humidity. Pulse oximeter saturation, heart rate, respiratory rate, and blood pressure were monitored continuously by Philips IntelliVue Patient Monitor MP20 monitor (Netherlands). An Orogastric tube of 5FG or 6FG was inserted to decompress the stomach and allow feeding.

The abdominal girth was measured every four hour for the first 48 h when the infant was on the NIV. Furthermore, the time required to reach full feed, as well as the rate and volume of given food were monitored and recorded daily. The oxygen requirement was monitored continuously showing that respiratory support and NICU were not needed in neither days. All the preterm neonates of ≤ 34 weeks gestational age requiring mechanical ventilation or affected with AOP received methylxanthines.

In addition, a neurosonography screening was completed for intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) in the first and 4th weeks of life for all the infants under 34 weeks of gestation. Moreover, screening for retinopathy of prematurity (ROP) was carried out

according to the standard guidelines. The NCPAP was discontinued in case the settings were PEEP of 4 cm H_2O and FiO_2 of 21% with a flow rate of ≤ 6 cm H_2O. In NIPPV, the settings would be PIP ≤ 14 cmH_2O, PEEP ≤ 4 cmH_2O with the rate of ≤ 22 bpm, in addition to FiO_2 of 21%.

It should be mentioned that we switched from NIPPV to NCPAP when the feed intolerance (i.e., persistent gastric aspirates > 50% of the previous feed) occurred with abdominal distension of > 2cm from baseline or worsening of the Downes score. On the other hand, the criteria to change from was that the neonate could not maintain the $SpO_2 > 85\%$ with PEEP of 6 cmH_2O and a FiO_2 of 40%. Furthermore, when the ABG revealed hypercapnia with $PaCO_2 ≥ 55mmHg$, the infant had bradycardia, or presented repeated apneic episodes not responding to stimulation, the switch from NCPAP to NIPPV was performed.

The primary outcome was 'failure' of non-invasive respiratory support necessitating intubation and mechanical ventilation within 48 h of non-invasive ventilator support. The criteria for 'failure' was considered the same for the two groups. Failure was defined as $PaCO_2 > 65$ mmHg, pH < 7.2, or three apnea episodes in one hour or more than one requiring intermittent positive pressure ventilation (IPPV), or $FiO_2 > 40\%$ to maintain $SpO_2 ≥ 88\%$. The secondary outcomes included the duration of respiratory support, duration of NICU stay, days to reach full feed, as well as complications, such as ROP, PVL, IVH, necrotizing enterocolitis (NEC), and feed intolerance.

The data retrieved from our unit during 2008-2010 showed that 40% of the preterm neonates who started on early NCPAP for RDS required invasive ventilation within 48 h. The sample size for this study was calculated based on the formula for a proportion with the power of 80% and α = 5% (23). A total of 82 participants as 41 in each group needed to be enrolled.

All the data were statistically analysed using the SPSS software version 16. The continuous measures were compared between the groups by student t-test, in addition to Man Whitney U and Chi-square tests for the non-parametric continuous variables. Kaplan-Meier survival analysis was carried out for both interventions. Moreover, the hazards ratio was analyzed using Cox Proportional method.

The study protocol was approved by the Institutional Ethics Committee (IEC) and was also registered under the Clinical Trial Registry of India (CTRI) with the registration code of

CTRI/2012/12/003241. Informed consents were taken from the parents of the infants who fulfilled the inclusion criteria following explaining the study. There was no source of funding for this study.

Results

A total of 78 neonates were included in the intervention during the study period. The distribution of infants in the strata was as shown in the CONSORT flowchart (Figure 1). There were 46 neonates of 28-32 weeks gestational age with 23 in each intervention group and a total of 32 in the 33-36 weeks gestational age group with 18 and 14 neonates in the NCPAP and NIPPV interventions, respectively.

The demographic characteristics and received supportive treatment were analyzed between the groups showing that the distribution was similar in either of the interventions. Out of the 78 subjects enrolled in the study 41 received NCPAP and 37 received NIPPV. Six neonates failed in the NCPAP intervention, whereas five failed in the NIPPV intervention group. Statistical analysis demonstrated no significance with P-value > 0.05.

The overall duration of NIV and days in NICU were similar in both test groups and indicated no statistically significant difference. The days to reach full feed was also analysed and the two groups were found to be significantly different, which states that the neonates in NIPPV group required fewer days (Table 2). The Downes score was recorded every four hour post-intervention for the first 24 h and the statistical evaluation
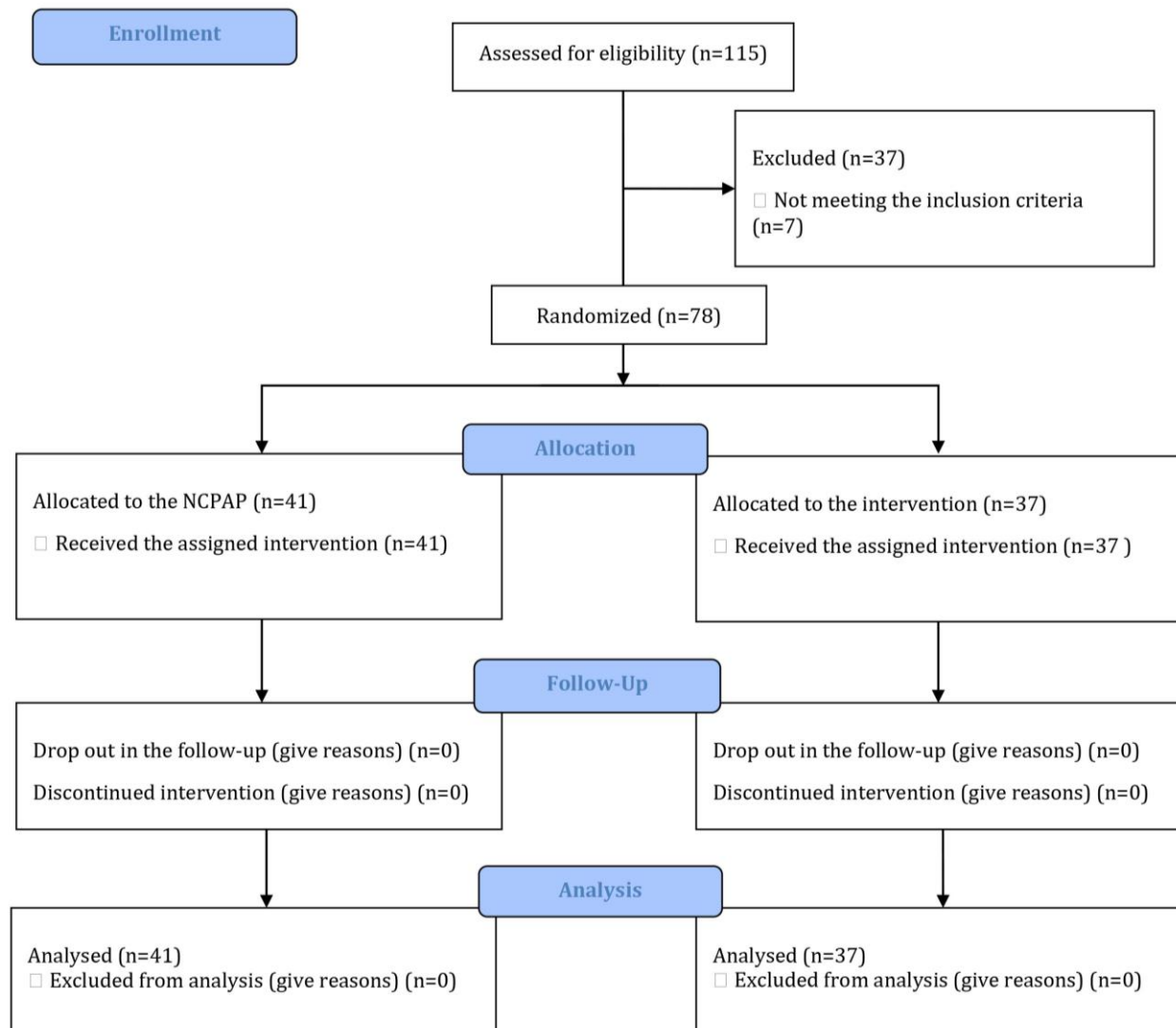

Figure 1. CONSORT flow diagram of the study

Table 1. Demographic characteristics and supportive treatment of neonates

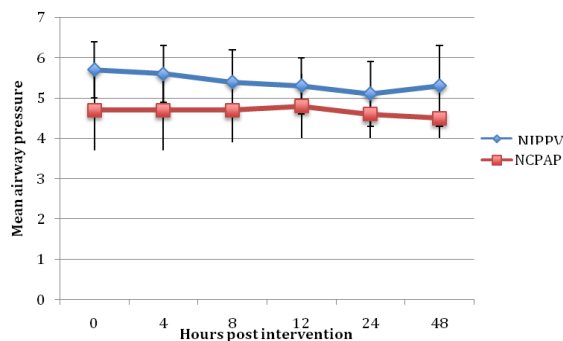| Characteristics		NIPPV(n=37)	NCPAP(n=41)	P-value
Gestation in weeks from birth (mean±S.D)		31.8±2.5	31.7±2.3	0.8
Weight (g) (mean±SD)		1400±433.1	1440±429.2	0.7
Gender (Male) (%)		22 (59.5%)	24 (58.5%)	0.9
	NVD	6 (16.2)	8 (19.5)	
Mode of delivery (%)	LSCS	30 (81.1)	31 (75.6)	0.8
	AVD	1 (2.7)	2 (4.9)	
	1 min	7(2-9)	7(5-10)	0.6
Apgar	5 min	9(2-9)	9(4-9)	0.7
Hematocrit (mean±SD)		48.2±5.5	46.9±7.6	0.3
Complete antenatal steroid (%)		24 (65)	23 (56.1)	0.1
Caffeine or aminophylline therapy (%)		13 (35.1)	20 (48.8)	0.2
Surfactant therapy (%)		12 (32.4)	22 (53.7)	0.06
Culture positive sepsis (%)		3 (7.3)	1 (2.7)	0.3

*NVD: normal vaginal delivery, LSCS: lower section caesarean section, AVD: assisted vaginal delivery

Table 2. Primary and respiratory outcomes of the neonates in the NCPAP and NIPPV groups

Outcome		NCPAP (n=41)	NIPPV (n=37)	P value
Failure (%)		6 (14.6)	5 (13.5)	0.574
Downes score (baseline)	h	3 (0-7)	3 (0-6)	0.3
	04	1.9 (1.4)	2.4 (1.5)	0.09
Post intervention Downes score at	08	1.2 (1.1)	1.9 (1.5)	0.02
different time points (in h)	12	0.9 (1)	1.5 (1.5)	0.02
	24	1 (1.8)	1.2 (1.5)	0.4
	04	6 (16.2)	12 (29.3)	0.1
Proportion of the infants with Downes	08	5 (13.5)	8 (19.5)	0.4
score ≥ 4	12	5 (13.5)	7 (17.1)	0.7
	24	15 (40.5)	11 (27)	0.2
Duration of the NIV (h) Median Interquartile range		37 (16, 72)	28 (16, 45)	0.431
Days in NICU (days) Median Interquartile range		23 (13.5, 37)	29 (14.5, 40.5)	0.889
Full feed Median Interquartile range		8 (5, 11)	4.5 (4, 9.75)	<0.001

showed no significant difference between the groups (Table 2).

Moreover, the MAP was recorded every four hour for the first 48 h. The line graph (Figure 2) plotted with the means indicated that the NIPPV group neonates received higher MAP than the NCPAP group (P < 0.01). The latter result clearly states that on the NIPPV, the delivered MAP is higher due to the two levels of pressures delivered. However, we need to further hypothesize the physiological effects of greater MAP delivered during NIPPV.

The delivered FiO_2 was also recorded and analysed every four hours for the first 48 h of the intervention (Figure 3). It was revealed that the oxygen requirement was not significantly

* P < 0.01 for the delivered MAP at each time point
Figure 2. Delivered mean airway pressure in the NIPPV versus NCPAP*
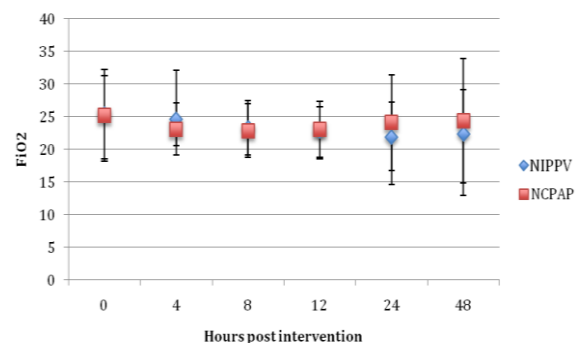
*P-value not significant at any time point
Figure 3. Fraction of inspired oxygen to maintain target saturations in NIPPV versus NCPAP (Mean±SD)*

Table 3. Complications of the NIV

Complication	NCPAP (n=41)	NIPPV(n=37)	P-value
Feed Intolerance (%)	4/39 (10.3%)	6/35 (17.1%)	0.502
NEC (%)*	1/41 (5.7%)	2/35 (2.4%)	0.592
Dilated Bowel(%)	5/36 (13.9%)	4/29 (13.8%)	1
Air Leak(%)	2/40 (5%)	2/36 (5.6%)	1
ROP (%)*	8/32 (25%)	4/23 (17.4%)	0.742
PVL (%)	0 (0%)	1/24 (4.2%)	1
IVH (%)	1/36 (2.8%)	0/24 (0%)	1

*NEC: necrotizing enterocolitis, ROP: retinopathy of prematurity, PVL: periventricular leuckomalacia , IVH: intraventricular hemorrhage
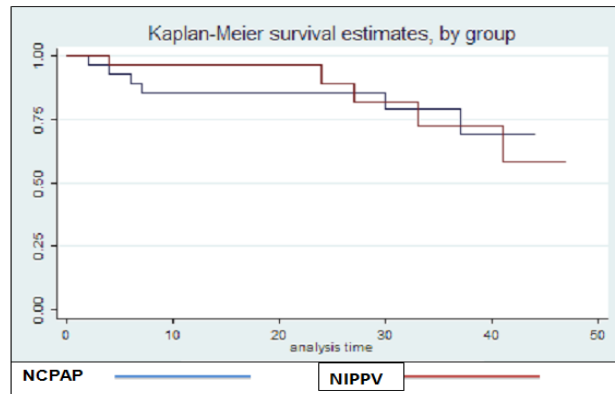

Figure 4. Kaplan–Meier survival analysis estimates for failure of either the NIPPV or NCPAP in the first 48 h after start of the intervention (P-value=0.9)

Table 4. Adjusted hazards ratio for failure of the NIPPV as compared to the NCPAP in the study population*

Variable	Hazard ratio (95% CI)	P-value
Intervention (NIPPV)	1.03 (0.3, 3.6)	0.9
Surfactant therapy	0.3 (0.1, 1.2)	0.09
Gestational age	1 (0.7, 1.5)	0.9
Birth weight	1 (0.9, 1.1)	0.7

* By Cox proportional hazards method

different between the groups. Among the 78 neonates, eight (10.2%) were diagnosed with AOP, six of which being in the NCPAP group and two in the NIPPV group. All the eight infants tolerated the NIV support well.

The complications associated with preterm birth were closely monitored. It was observed that the complications between the two modes of NIV were not different significantly (Table 3). There was an isolated case of IVH grade I in the NCPAP group of the lower gestation strata. Furthermore, 12 neonates had ROP out of which six were diagnosed with stage I and six with stage II. Three of these cases had zone 2 affected and nine had zone 3 affected. The NEC was found in three neonates and two succumbed with stage III and stage IV. One neonate was diagnosed to have stage II NEC and survived.

Kaplan–Meier survival analysis for the failure of NIPPV or NCPAP in the first 48 h post-intervention was performed (P=0.9; Figure 4). The hazards ratio (Table 4) for failure of NIV was studied with respect to the intervention, surfactant therapy, birth

weight, and gestational age by Cox proportional method. The P-value was not found as significant for any of the mentioned factors. Therefore, we could infer that the criteria used for surfactant therapy may be an important confounding factor that needs further investigations.

Apart from the outcomes and complications, the range of parameters used during the NIV were recorded and analysed. The mean of PIP used in the NIPPV ranged from 12-16 cmH_2O with the lowest PIP of 10 cmH_2O and highest PIP of 20 cmH_2O. The mean respiratory rate used in the NIPPV had a range of 21-28 breaths/min with the lowest and highest rates as 12 and 45 breaths/min, respectively.

Discussion

The currently common method for supporting the neonates with respiratory distress is the NCPAP. Nearly half of all the neonates who are supported with the CPAP will still develop respiratory failure that requires potentially injurious endotracheal intubation and invasive ventilation. Consequently,

the aim of any neonatal clinician is to minimize invasive ventilation whenever possible to avoid the multiple complications arising due to this form of therapy (22).

The NIPPV is a form of respiratory assistance that provides greater respiratory support than the CPAP and may prevent intubation in a larger fraction of neonates who would otherwise fail CPAP. In this study, we compared the NCPAP with NIPPV as a primary mode of ventilation. It was shown that the NIPPV for preterm neonates might have the same benefits as the NCPAP. There was no statistically significant difference between the groups in terms of need for intubation. In 2009, an RCT performed by Sai Kishore et al. (23) concluded that the NIPPV was more beneficial than the NCPAP in infants of 28-30 weeks as a primary mode of ventilation.

Another study by Jucille Meneses et al. demonstrated that the early NIPPV did not decrease the need for mechanical ventilation in the first 72 h of life, compared to the NCPAP (27). In our study, we observed that the duration of the NIPPV support in hours was shorter than the NCPAP; however, this was not statistically significant. The days to reach full feed was also evaluated and no significant difference was found between the two interventions. We could learn that there was no difference between the two groups in the pace to reach full feed.

The previous studies have mentioned that a higher MAP was used in the NIPPV. A Cochrane review completed by Davis PG et al. (24) concluded that the MAP generated during the NIPPV may be higher than that of the NCPAP. Therefore, the differences regarding the outcomes may result from the higher MAP in the NIPPV group.

We found in our study that MAP was significantly high in the NIPPV group of the 28-32 weeks strata. No previous study has mentioned the range of PIP and respiratory rate used in the NIPPV. In the current study, we realized that the applied PIP had a range of 10-20 cmH$_2$O. The respiratory rate used in the NIPPV ranged from 12 to 45 breaths/min. It is postulated that the NIPPV due to high MAP and superior support reduces the work of breathing (WOB) and provides more stabilization to the neonate.

In a Cochrane review by Lymre et al. (25) concerning comparison of the SNIPPV and NCPAP, the data reported a decrease in the WOB during inspiration, elastic work of breathing, and resistive work of breathing even at lower delivered pressure. Another study by Aghai et al. (26) found that when compared to NCPAP,

adding ventilator-delivered PIP during the SNIPPV reduces WOB in premature infants.

The complications associated with NIV are of great concern. We observed that the incidence of complications was similar in both groups. Garland et al. (27) reported gastrointestinal perforation due to NIPPV. Meneses et al. (28) found no gastrointestinal complications in their study. These authors also stated that the incidence of necrotizing enterocolitis, as well as the time to full feed were the same in both groups. Although in the present study there were a few isolated cases of NEC, air leak, feed intolerance, and ROP, the two groups were not significantly different.

In our study, we concluded that the NIPPV as a primary mode of NIV in preterm neonates is at par with the NCPAP when the need for invasive ventilation was compared during the first 48 h. In addition, it may reduce the need for surfactant replacement therapy.

Conclusion

According to the findings of this study, early NIPPV may not be superior to the NCPAP as a primary mode of respiratory support for infants with RDS; however, it was shown to have the same benefits. The NIPPV may diminish the need for surfactant replacement therapy in this group of neonates.

Limitations

The current study was underpowered and the long-term outcomes are not reported in this trial. The leak during the delivery of the NIV was not measured and the NIPPV settings were lower than the reported trials.

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Conflicts of interests

The authors of this study declared no conflicts of interest.

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