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Original Research Article

Nasal CPAP vs Bi-level Nasal CPAP in preterms with RDS: a randomized control study

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ABSTRACT

Background: Ventilator induced lung injury prevention may begin from birth, and respiratory support without endotracheal intubation is an attractive option in preterm baby with Respiratory distress syndrome (RDS). The objective of the study was to evaluate the clinical course and respiratory outcomes in preterm infants with moderate RDS assigned from birth to Nasal Continuous Positive Airway Pressure (NCPAP) or Bi-level Nasal Continuous Positive Airway Pressure (Bi-level NCPAP).
Methods: 60 infants of 28-34 weeks GA (<35 wks GA), affected by moderate RDS, were considered eligible and were randomized to NCPAP (CPAP level=6cm H2O, Group A n=30) or to Bi-level NCPAP (lower CPAP level=4.5 cmH2O; higher CPAP level=8 cmH2O, Group B n=30), provided with the variable flow devices (Infant Flow CPAP vs Infant Flow SiPAP™, Viasys Healthcare, Yorba Linda, CA).
Results: Length of ventilation, oxygen dependency, need for intubation and occurrence of air leaks were considered as outcomes. Infants showed similar characteristics at birth (Group A versus Group B: GA 30.4±2 wks versus 30.3±2wks, BW 1433±545g versus 1415±560g. Group A underwent longer respiratory support (6,2±2 days versus 3,8±1 days, p=0.025), longer O2 dependency (13,8±8 days versus 6,5±4 days, p=0.027) and was discharged later (GA at discharge 36,7±2,5 weeks versus 35,6±1,2 weeks, p=0.02). All infants survived. No BPD or neurological disorders occurred.
Conclusions: Bi-level NCPAP was associated with better respiratory outcomes versus NCPAP, and allowed earlier discharge, inducing the same changes in the cytokine levels. In our population, it was well tolerated and safe.

Keywords: Bi-level nasal continuous positive airway pressure, Nasal continuous positive airway pressure, Neonate, Respiratory distress syndrome, Respiratory outcome, Ventilation

INTRODUCTION

Despite antenatal steroid treatment, mechanical ventilation and surfactant replacement therapy, bronchopulmonary dysplasia (BPD) still remains a major cause of mortality and morbidity in very preterm infants. Ventilator induced lung injury prevention may begin from birth, and respiratory support without endotracheal intubation is an attractive option.

Nasal continuous positive airway pressure (NCPAP) reduces the risk of re-intubation and, when used in the acute phase of RDS in infants born at 25-28 weeks GA, it reduced both the length of oxygen dependency and length of ventilation while it did not reduce the rate of death or BPD; the use of high levels of PEEP was associated to a higher incidence of pneumothorax.[1-3]

Moreover, the early use of continuous positive airway pressure (CPAP) showed to be of advantage in reducing

the need of mechanical ventilation (RR 0.55; 95% CI 0.32-0.96).[4]

Bi-level NCPAP is a non-invasive respiratory support which is much more similar to a CPAP than to ventilation: actually, it provides two alternating levels of CPAP in order to switch the functional residual capacity (FRC) of the neonate between two different levels. The theoretical benefits of the Bi-level NCPAP are that the FRC switching may recruit unstable alveoli (or prevent their collapse) with the generation of a tidal volume (Vt) by the delta pressure between two levels of CPAP, and off-load some of the respiratory work. "Bi-level NCPAP" is a term that, in our opinion, well fits the definition because it provides a phasic increase in pressure.

Migliori et al demonstrated that N-BiPAP, as compared to N-CPAP, improved gas exchange in the same cohort of preterm infants with repeated cycles of the two supports.[5]

As far as we know there have been no published reports comparing NCPAP and Bi-level NCPAP with variable flow system in the treatment of the acute phase of moderate RDS, in terms of safety and efficacy.

We hypothesized that an early application of Bi-level NCPAP in preterm infants with RDS may induce a different inflammatory response when compared with NCPAP and may have a different effect on length of ventilation, oxygen dependency, need for intubation and occurrence of air leaks.

METHODS

This study was performed in a tertiary level NICU from June 2016 to December 2016 in RNT Medical College, Udaipur, Rajasthan, India. Infants of 28-34 weeks' gestational age, inborn, affected by moderate RDS, were considered eligible. Infants with lethal congenital anomalies or requiring muscle relaxant, severe intraventricular hemorrhages (intraventricular hemorrhage (IVH) >grade II), chorioamnionitis, sepsis (positive blood culture) or suspected infection (e.g., prolonged rupture of membranes, mother fever) were excluded. Written informed parental consent was obtained in the delivery room, during the prenatal interview, or in the first hour of life (Figure 1).

Moderate RDS was diagnosed within the first hour of life on radiological and clinical criteria (a/A PO_2 ratio range for the definition of moderate RDS was 0.30.35; before randomization, within the first hour of life, each patient underwent chest X-ray).

After delivery all neonates underwent the same management, following our NICU protocol: initial stabilization was provided in the delivery room by sustained inflations using a pressure level of 20-25 cmH_2O for 10-15" seconds (by a flow controlled, pressure limited mechanical device specifically designed for neonatal resuscitation-Neopuff, Fisher and Paykel Healthcare, Auckland, New Zealand) Then we reduced it to a pressure level of 5 cmH_2O and with the minimal fractional inspired oxygen concentration (FiO_2), to maintain an oxygen saturation (SpO_2) of 85% up to 93% (or up to 95% in larger infants).[6] Subsequent FiO2 adjustment and weaning and (SpO_2) monitoring followed our NICU protocols.

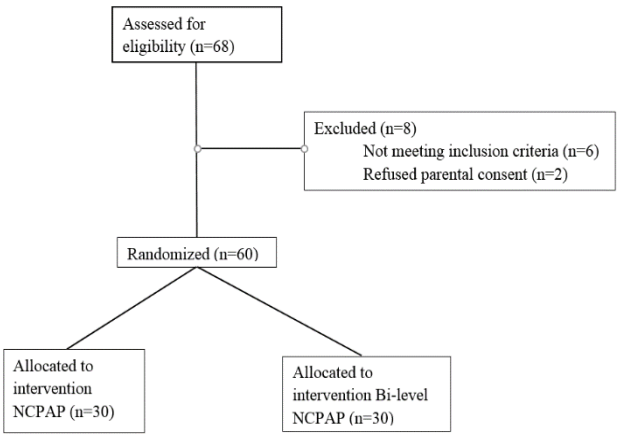

Figure 1: Consort flow diagram of the trial.

Endotracheal bovine natural surfactant (Survanta®, 100 mg/Kg) was administered with the INSURE method (Intubation-Sufactant administration- Extubation) if the preset criteria of the NICU protocols were met.

All infants enrolled in the study were sequentially numbered after birth and were randomized at one hour of life NCPAP group (Group A) or Bi-level NCPAP group (Group B) (Infant Flow versus Infant Flow SiPAP™, Viasys™) using a table of random numbers and using a stratified randomization for gestational age (GA 28-31 wks; GA 32-34 wks).

The four parameters to be adjusted during the use of the Bi-level NCPAP are:

- Lower CPAP level (indicated on the SiPAP™ device as "Pres low")
- Upper CPAP level (indicated on the SiPAP™ device as "Pres high")
- Time high (T_{high}) = the time of maintenance of upper CPAP level (indicated on the SiPAP™ device as "Ti") 4) pressure exchange rate, (indicated on the SiPAP™ device as "Rate"). Infant Flow® SiPAP™ provides variable flow Bi-level NCPAP.

Short bi-nasal prongs were used in both groups and the used prongs size was the largest one that fit the infant's nares without blanching the surrounding tissue. In Group A, we set a CPAP level of 6 cmH_2O. Weaning occurred following NICU protocols with the progressive reduction of the set CPAP level.

In Group B, we set a lower CPAP level of 4.5 cmH_2O and an upper CPAP level of 8 cmH_2O, T_{high} set at 0.5-0.7 sec with a pressure exchange rate of 30 times/minute at beginning. Weaning occurred following NICU protocols with progressive reduction of the set pressure exchange rate (minimum 15 pressure exchanges/min) and, subsequently, with the reduction of the upper CPAP level (minimum upper CPAP level 6 cm H_2O).

In both groups, during respiratory support or in spontaneous breathing, we set a minimal fractional inspired oxygen concentration (FiO_2) to maintain oxygen saturation in the suggested limits.[6] Intubation criteria were: arterial pH <7.20, paO_2 <50 mmHg with FiO_2 >0.50 and paCO2 >65 mmHg, or >4 episodes of apnea in one hour or >2 episodes of apnea in one hour requiring repeated stimulation or bag-and-mask ventilation despite adequate prongs fixing and CPAP delivery. Mechanical ventilation was stopped when FiO_2 was <0.40, MAP was <6 cm H_2O, and paO_2 and $paCO_2$ were >50 and <65 mmHg, respectively. The extubation of mechanically ventilated infants was mandatory within 2 hours after they reached extubation criteria. Similar blood gas goals were achieved to wean from respiratory support in both groups, as in our NICU protocols. CPAP was discontinued when neonates with adequate spontaneous respiratory effort had FiO_2 <0.30, PEEP ≤4 cm H_2O, paO_2 >50 mmHg, and $paCO_2$ <65 mmHg. Heart rate, systemic blood pressure, oxygen saturation was continuously monitored while arterial blood gas tension measurements were performed from an indwelling catheter or by capillary puncture. The following data were also recorded: length of ventilation meant as total duration of respiratory support, surfactant treatment (n° of doses needed), incidence of air leaks (n° of cases of pneumothorax) and oxygen dependency on day 28 and/or at 36 wks of post conceptional age and survival. The research protocols have been approved by the Institutional Ethics Committee. Normally distributed data were compared with use of the unpaired Student's t-test and non-parametric outcomes with use of the X^2 test. Data within each group were compared by ANOVA test. Statistical significance was considered at $p<0.05$.

RESULTS

Table 1: Characteristics of infants in group A (NCPAP) and group B (Bi-level NCPAP) at the time of randomization (values expressed as means ±SD).

	Group A (n=30)	Group B (n=30)
Birth weight (g)	1433 ± 545	1415 ± 560
GA (wks)	30.4 ± 2	30.3 ± 2
Cord pH	7.34 ± 0.05	7.28 ± 0.12
N° infants treated with antenatal steroids (%)	8 (26.6)	4 (13.3)

P value is not significant

68 infants were considered eligible, 8 were excluded for chorioamnionitis, suspected sepsis or refused parental consent. Forty infants were studied and randomized at one hour of life to group A (NCPAP) (n=30) and to group B (Bi-level NCPAP) (n=30) (Table 1).

Table 2 shows clinical characteristics of the infants; we did not observe significant differences between the two groups. The respiratory and ventilatory status of each group at the time of the randomization was similar.

Table 2: Respiratory and clinical outcomes in group A and group B.

	Group A (n=30)	Group B (n=30)	P value
Length of respiratory support (days) (mean±SD)	6.5±2	3.9±1	0.023
O_2 dependency (days) (mean±SD)	14.2±7	6.6±3	0.028
GA at discharge (wks) (mean±SD)	36.7±2.5	35.6±1.2	0.02

No steroids were given in the first week of life. FiO2 administered at the time of the randomization did not differ between the two groups.

Respiratory outcomes are shown in Table 2: respiratory support and O2 dependency lasted significantly longer in group A; no differences were noted in incidence of re-intubation (5/30 versus 4/30), INSURE practice (7/30 versus 7/30), total number of mean surfactant doses (1 versus 1), pneumothorax (3/30 versus 1/30) in group A versus group B respectively. No bronchopulmonary dysplasia (BPD = O_2 dependency at 28 days), chronic lung disease (CLD = O_2 dependency at 36 wks), necrotizing enterocolitis (NEC) or deaths occurred in the two groups. There were not significant differences in the incidence of mortality rate, retinopathy of the prematurity (ROP), BPD and CLD between the two groups.

DISCUSSION

There is evidence that some non-invasive respiratory supports reduce the rate of re-intubation of very premature infants. There is some not conclusive evidence that non-invasive respiratory supports may be useful in the treatment of apnea. There is limited evidence that these supports may be used as primary approach to moderate RDS in its acute phase; an international European randomized controlled trial that will give useful indication about the optimal respiratory strategy to adopt in high risk premature infants is still ongoing.[7-11]

Our choice of settings was empirical, since the effects of different settings during Bi-level NCPAP on the success of this respiratory support have not been investigated yet and most studies do not mention the applied parameters (in particular T_{high}).

There is no evidence that a longer T_{high} may optimize lung recruitment but it is obviously referred to continuous flow systems.

Nevertheless, in the Bi-level NCPAP group we set the Thigh at 0.5-0.7 sec, the minimal time considered effective to allow the newborn to complete at least one inspiration at upper CPAP level. We set the pressure exchange rate at 30/minute to increase minute ventilation, with a reduced risk of lung de-recruitment.

Since we investigated the differences between two different variable flow system supports, we compared a mean airway pressure level of 6 cm H2O (in group A = NCPAP) to a mean airway pressure level of 6 cm H2O (in group B = Bi-level NCPAP): this choice seemed to make the two groups comparable.

The different duration of ventilatory support between these modalities is an important clinical result, since it implies the achievement of a precocious clinical stability for premature infants.

We speculate that respiratory support and O2 dependency lasted significantly more in NCPAP group probably because of a less stable lung recruitment: Bi-level NCPAP might be more efficacious in stabilizing the airways, in reaching and maintaining the optimal FRC allowing spontaneous breathing on two different levels of CPAP. The significatively precocious time of discharge in the Bi-level NCPAP group may be attributed to a more rapid achievement of stable clinical condition in these babies.

Limitations of this study include the small number of patients and the lack of blindness of the NICU staff, so our results will need further wider studies to be confirmed. From our clinical preliminary observations, we hypothesize that a T_{high} of 1 second would better support the infant breathing and this is now under study in a new cohort of infants.

CONCLUSION

In conclusion, this new ventilatory strategy seems to be efficacious when used in preterm infants in the acute phase of moderate RDS. However, further investigations are necessary to establish the best strategy and appropriate ventilator parameters that ensure both safety and efficiency.

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