

Bi-level Nasal Positive Airway Pressure (BiPAP) versus Nasal Continuous Positive Airway Pressure (CPAP) for Preterm Infants with Birth Weight Less Than 1500 g and Respiratory Distress Syndrome Following INSURE Treatment: A Two-center Randomized Controlled Trial*

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Summary: The present study aimed to examine the effectiveness of bi-level positive airway pressure (BiPAP) versus continuous positive airway pressure (CPAP) in preterm infants with birth weight less than 1500 g and respiratory distress syndrome (RDS) following intubation-surfactant-extubation (INSURE) treatment. A two-center randomized control trial was performed. The primary outcome was the reintubation rate of infants within 72 h of age after INSURE. Secondary outcomes included bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP) and incidences of adverse events. Lung function at one year of corrected age was also compared between the two groups. There were 140 cases in the CPAP group and 144 in the BiPAP group. After INSURE, the reintubation rates of infants within 72 h of age were 15% and 11.1% in the CPAP group and the BiPAP group, respectively ($P>0.05$). Neonates in the BiPAP group was on positive airway pressure (PAP) therapy three days less than in the CPAP group (12.6 d and 15.3 d, respectively, $P<0.05$), and on oxygen six days less than in the CPAP group (20.6 d and 26.9 d, respectively, $P<0.05$). Other outcomes such as BPD, NEC, ROP and feeding intolerance were not significantly different between the two groups ($P>0.05$). There was no difference in lung function at one year of age between the two groups ($P>0.05$). In conclusion, after INSURE, the reintubation rate of infants within 72 h of age was comparable between the BiPAP group and the CPAP group. BiPAP was superior to CPAP in terms of shorter durations (days) on PAP support and oxygen supplementation. There were no differences in the incidences of BPD and ROP, and lung function at one year of age between the two ventilation methods.

Key words: noninvasive ventilator; neonate; bronchopulmonary dysplasia; continuous positive airway pressure

With the advances in neonatal care, the survival rate of infants with birth weight less than 1500 g has dramatically increased. Despite antenatal steroid therapy and surfactant replacement therapy, bronchopulmonary dysplasia (BPD) remains a major cause of mortality and morbidity in extremely low birth weight infants. The National Institute of Child Health and Human Development Neonatal Research Network reported that the incidence of BPD was up to 40% in infants with birth weight less than 1000 g^[1].

Ventilator-induced lung injury includes alveolar structural damage, pulmonary edema, inflammation and

fibrosis, which are the histological features of BPD^[2]. The intubation-surfactant-extubation (INSURE) method may decrease the need for mechanical ventilation (MV), and thus reduce the incidence of BPD in infants with respiratory distress syndrome (RDS)^[3]. Dani *et al* demonstrated that treatment of preterm infants with RDS using the INSURE method reduced the need for MV and the incidence of BPD^[4,5]. However, continuous positive airway pressure (CPAP) only rescues 80% of babies with birth weight less than 1250 g from MV^[6]. CPAP fails in the remaining 20% of babies who need reintubation. Other non-invasive respiratory support options, such as non-invasive intermittent positive pressure ventilation (NIPPV) and bi-level positive airway pressure (BiPAP), may be more effective than CPAP in preventing the need for MV following INSURE treatment.

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Several randomized clinical trials (RCTs) have proven that NIPPV decreases the frequency of apnea related to prematurity, and facilitates primary respiratory support and respiratory support post-extubation as compared to CPAP^[7-9]. However, serious side effects including gastric perforation have been reported, and clinicians remain uncertain about the role of NIPPV in the management of neonates^[10].

BiPAP is another option of non-invasive respiratory support that provides two alternating levels of background pressure leading to changes in the infant's functional residual capacity (FRC). Possible benefits include tiny actual breaths delivered from the small change in pressure and reflex "triggering" of spontaneous breaths via stimulation. The slightly higher pressures used may also help to prevent atelectasis, compared to CPAP^[11]. Our research team conducted a retrospective study to compare the effectiveness of BiPAP and CPAP, and found that BiPAP reduced the need for intubation within the first 72 h of age in preterm infants less than 32 weeks, as compared to CPAP^[12]. As there is no published study comparing BiPAP with CPAP in preterm infants with birth weight less than 1500 g and RDS following INSURE treatment, this study aimed to examine the effectiveness of BiPAP *versus* CPAP in preterm infants with birth weight less than 1500 g and RDS following INSURE treatment.

1 MATERIALES AND METHODS

1.1 Inclusion and Exclusion Criteria

This randomized control trial (ChiCTR-ICR-15005879) was conducted in two level-3 neonatal intensive care units (NICU) between January 2015 and December 2018. The study protocol was approved by the Ethics Committee of Huazhong University of Science and Technology. Informed consent was obtained from a parent or guardian prior to enrollment.

Infants with birth weight less than 1500 g, born in Tongji Hospital and Xiangyang Central Hospital, who suffered from RDS following INSURE treatment, were considered eligible for inclusion in this study. The RDS diagnosis was based on increased work of breathing within four hours of life. RDS was confirmed by typical radiological pattern with decreased lung expansion, reticulogranular pattern and air bronchograms^[12]. Infants with lethal congenital anomalies and upper airway tract abnormalities were excluded.

1.2 Allocation and Grouping

All enrolled infants received caffeine (loading dose 20 mg/kg within 24 h of age, followed by 10 mg/kg per day until corrected age at 34 weeks). The infants were allocated to either BiPAP or CPAP group using a table of random numbers concealed in opaque envelopes. Blinding was not possible due to the nature of the intervention.

At the two study centers, positive airway pressure was started in the NICU, which is located adjacent to the delivery room. INSURE treatment was completed within six h of age.

1.3 Study Intervention

Before INSURE procedure, all neonates were in CPAP, with the initial pressure of 5 cmH₂O. After INSURE procedure, in the BiPAP arm, the respiratory rate was set at 30 breaths per min with an inspiratory time of 1 s. The pressures in the BiPAP arm were 9/5 cmH₂O. In the CPAP arm, the pressure of CPAP was 6 cmH₂O. Criteria for extubation included saturation maintained at 90%–95% in FiO₂≤0.25, with no increased respiratory distress and apnea. Criteria for reintubation included apnea (>3 episodes per h) or FiO₂>0.4 to maintain SpO₂>88% or respiratory acidosis (pH<7.25 and PCO₂>60). The infant flow system (Viasys Healthcare Inc. USA) was used in this study^[12].

1.4 Data Collection

Maternal history, neonatal perinatal factors, the reintubation rate of infants within 72 h of age after INSURE, and the mortality rate were collected from the medical records. The incidence of moderate and severe BPD, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), patent ductus arteriosus (PDA), periventricular leukomalacia (PVL), feeding intolerance, length of stay in hospital, duration of positive pressure, and oxygen supplementation were obtained. Lung function at one year of corrected age was compared between the two groups.

1.5 Sample Size Calculation

This study included independent cases and controls, with one control per case. Prior data indicated that the probability of exposure among controls was 0.8. If the true probability of exposure among cases was 0.92, 130 cases and 130 controls were needed to be able to reject the null hypothesis that the exposure rates for cases and controls were equal, with probability (power) 0.8. The type I error probability associated with this test of this null hypothesis was 0.05. An uncorrected chi-squared statistic was used to evaluate this null hypothesis.

1.6 Statistical Analysis

Continuous variables were compared using the Student's *t*-test, while categorical variables were compared using the Fisher's test. Differences in the primary and other categorical outcomes were estimated along with 95% confidence intervals. A *P* value <0.05 was considered statistically significant.

2 RESULTS

2.1 Baseline Characteristics and Perinatal Factors of the Two Groups

A total of 886 neonates were born with birth

weight less than 1500 g during the study period (January 2015 to December 2018) in the two centers. Among them, 181 neonates were intubated in the delivery room, 112 neonates needed oxygen by nasal prong only, and 593 neonates received non-invasive positive airway pressure (PAP) ventilation soon after birth. Among the infants who received non-invasive PAP ventilation soon after birth, 45 neonates were intubated and received MV, 216 remained on CPAP and did not need surfactant, and 332 neonates received INSURE procedure. After INSURE, 48 neonates remained intubated, and the remaining 284 neonates were enrolled in this study.

Informed consent was obtained from the parent/guardian of the 284 neonates, of which 140 neonates were randomly assigned to the CPAP group and 144 to the BiPAP group (fig. 1). Baseline characteristics and perinatal factors of the two groups were similar (table 1).

2.2 Primary Outcome

After INSURE, the reintubation rates of infants within 72 h of age were 15% and 11.1% in the CPAP group and BiPAP group, respectively ($P>0.05$). The mortality rates showed no significant differences between the two groups (11.4% in the CPAP group and 12.5% in the BiPAP group, $P>0.05$).

2.3 Secondary Outcomes

Averagely, neonates in the BiPAP group were on PAP three days less than in the CPAP group (12.6 d and 15.3 d, respectively, $P<0.05$), and on oxygen six days less than in the CPAP group (20.6 d and 26.9 d, respectively, $P<0.01$). Other outcomes such as moderate and severe BPD, NEC, ROP, PDA, PVL, feeding intolerance, and length of stay in hospital were not significantly different between the two groups ($P>0.05$) (table 2).

For the follow-up study, there were 67 and 60 infants in the BiPAP group and CPAP group,

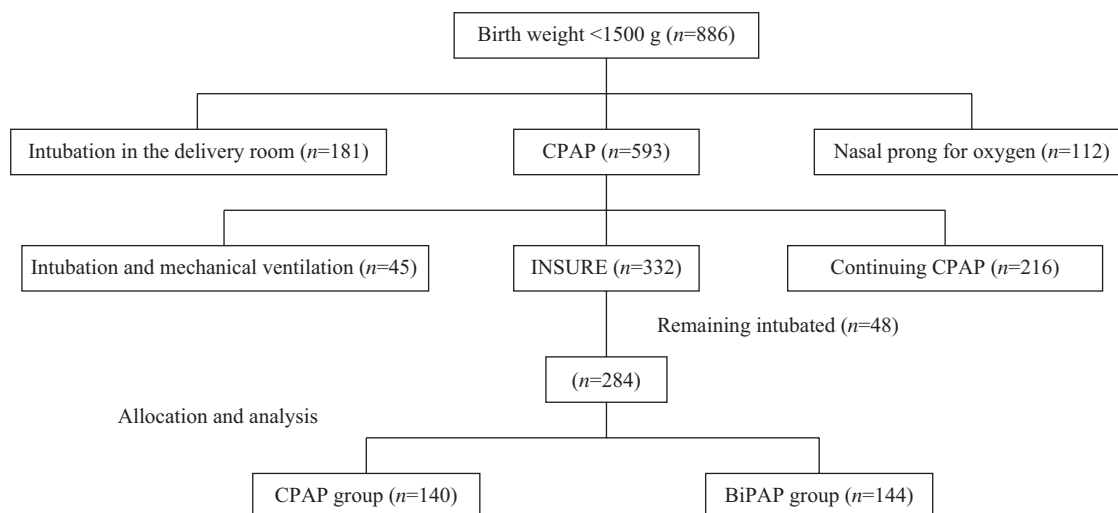


Fig. 1 Flow chart of the participants

BiPAP, bi-level nasal positive airway pressure; CPAP, continuous positive airway pressure; INSURE, intubation-surfactant-extubation

Table 1 Baseline characteristics and perinatal factors of the two groups

Parameters	CPAP (n=140)	BiPAP (n=144)	P values (univariate analysis)
Gestational age (weeks), mean (SD)	29.6 (2.0)	30.1 (1.8)	0.06
Birth weight (g), mean (SD)	1264 (152)	1251 (158)	0.49
Male, n (%)	74 (53)	84 (58)	0.58
Cesarean section, n (%)	78 (56)	84 (58)	0.71
Singletons, n (%)	104 (74)	114 (79)	0.15
<i>In vitro</i> fertilization, n (%)	26 (19)	20 (14)	0.33
Apgar score at 5 min, mean (SD)	8 (1)	8 (1)	0.1
Antenatal steroid, n (%)	107 (76.4)	97 (67.4)	0.11
Pregnancy-induced hypertension, n (%)	34 (24.3)	45 (31.3)	0.23
PPROM, n (%)	40 (28.6)	44 (30.6)	0.79
Chorioamnionitis, n (%)	16 (11.4)	16 (11.1)	0.93
IUGR, n (%)	42 (30.0)	48 (33.3)	0.61
Time to implement INSURE after birth (h), mean (SD)	6.3 (4.9)	6.7 (5.2)	0.91

PPROM, prolonged premature rupture of the membrane; IUGR, intrauterine growth retardation; INSURE, intubation-surfactant-extubation

respectively. No difference in lung function was noted at one year of age between the two groups ($P>0.05$) (table 3).

3 DISCUSSION

Although invasive MV has led to improvement in neonatal survival in the last 40 years, the prolonged use of this technique may predispose infants to many possible complications, including BPD^[13, 14]. The European Consensus Guidelines on the Management of Respiratory Distress Syndrome recommend noninvasive ventilation as the best respiratory support for preterm infants with RDS^[15]. Several studies have compared the effectiveness of different types of noninvasive PAP support including nasal high frequency oscillatory ventilation (NHFOV),

NIPPV, CPAP and humidified high flow nasal prong (HHFNP)^[16-19], but the results were inconsistent. For example, Chen *et al* showed that NHFOV is superior to CPAP in terms of reintubation rate^[16]; while Klotz did a randomized controlled cross-over trial in 26 preterm infants, and found no difference in failure of noninvasive respiratory support ($P=0.051$) between the two ventilatory support methods. Ding found that NIPPV had higher rate of successful extubation and removal from noninvasive ventilation compared with CPAP^[18]. However, serious side effects including gastric perforation were reported when using NIPPV for management of neonates^[10].

Since research on the comparison of BiPAP and CPAP is limited, our team conducted a retrospective study to compare the effectiveness of BiPAP and CPAP, and found that BiPAP reduced the need for intubation

Table 2 Secondary outcomes of survivors in the two groups

Secondary outcomes	CPAP (n=140)	BiPAP (n=144)	P values (univariate analysis)
Days on PAP, mean (SD)	15.3 (10.7)	12.6 (9.0)	0.03*
Days on oxygen supplement, mean (SD)	26.9 (17.9)	20.6 (13.4)	0.002**
Length of stay (days), mean (SD)	40.2 (17.1)	36.5 (13.8)	0.06
Time to total enteral feeding (days), mean (SD)	19.6 (10.4)	17.2 (8.8)	0.06
Moderate and severe BPD, n (%)	11 (8.9)	8 (6.3)	0.25
PDA, n (%)	18 (14.5)	16 (12.7)	0.38
Grade 3/4 IVH and/or PVL, n (%)	22 (17.1)	23 (18.3)	0.54
ROP, n (%)	11 (8.9)	8 (6.3)	0.30
NEC stage 2 or higher, n (%)	4 (3.2)	10 (7.9)	0.08

BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; IVH, intraventricular hemorrhage. * $P<0.05$, ** $P<0.01$

Table 3 Comparison of lung function at one year of age between the two groups

Parameters	BiPAP group (n=67)	CPAP group (n=60)	P values
MV (L/min)	2.94±0.33	2.67±0.30	0.58
VT (mL)	89.63±24.72	88.27±11.11	0.48
VT/kg (mL/kg)	8.40±0.81	8.70±0.92	0.82
RR (times/min)	36.36±7.73	30.77±3.18	0.54
T_I (s)	0.69±0.12	0.79±0.08	0.53
T_E (s)	1.10±0.23	1.21±0.15	0.70
T_I/T_E	0.64±0.06	0.66±0.04	0.86
T_{PTEF} (s)	0.17±0.03	0.24±0.04	0.25
T_{PTEF}/T_E (%)	15.57±1.63	19.70±2.55	0.24
V_{PTEF} (mL)	17.6±4.79	20.20±1.47	0.63
V_{PEF}/V_E (%)	19.63±0.98	23.26±1.47	0.11
Mean inspiratory flow (mL/s)	128±21.57	114±15.62	0.63
Mean expiratory flow (mL/s)	80±5.86	73.67±6.89	0.52
PEF (mL/s)	137.67±21.67	121.33±24.84	0.65
TEF ₇₅ (mL/s)	136.67±21.17	120.00±24.00	0.63
TEF ₅₀ (mL/s)	109.33±14.34	98.33±14.34	0.62
TEF ₂₅ (mL/s)	72.00±4.51	64.67±3.18	0.25
TEF _{50}/TIF₅₀ (%)}	70.17±4.19	74.23±6.43	0.62

Data are given as mean ± standard deviation (SD). MV, minute ventilation volume; VT, tidal volume; RR, respiratory rate; T_I , inspiratory time; T_E , expiratory time; P_{TEF} : peak tidal expiratory flow; T_{PTEF} : time to peak tidal expiratory flow; T_{PTEF}/T_E : the ratio of time to peak tidal expiratory flow over total expiratory time; V_{PTEF} : expiratory volume at peak tidal expiratory flow; V_{PEF}/V_E : the ratio of volume to peak expiratory flow to total expiratory volume; PEF: peak expiratory flow; TEF₇₅: tidal expiratory flow at the remaining 75% tidal volume; TEF₅₀: tidal expiratory flow at the remaining 50% tidal volume; TEF₂₅: tidal expiratory flow at the remaining 25% tidal volume; TEF_{50}/TIF₅₀: the ratio of tidal expiratory flow to tidal inspiratory flow at the remaining 50% tidal volume}

within the first 72 h of age in preterm infants less than 32 weeks of age, as compared to CPAP^[12]. Herein, we conducted a prospective study to compare BiPAP with CPAP in preterm infants with birth weight less than 1500 g and RDS following INSURE treatment. This study found that the reintubation rate of infants within 72 h of age after INSURE was not significantly different between the BiPAP group and the CPAP group. The discrepancy in the two studies is probably due to different population enrolled and different pressure setting. In the current study, the population was more premature; the initial pressure setting in the CPAP group was higher (6 cmH₂O) than in the BiPAP group. Brien *et al* compared the effectiveness of BiPAP and CPAP, and found no difference in maintaining successful extubation at seven days; however, their study was underpowered as the trial was stopped early^[6]. Our results are consistent with theirs.

A significantly shorter duration (days) on PAP support and oxygen supplementation was found in this study, although no differences were noted in the incidence of moderate and severe BPD and ROP. These results are consistent with Lista *et al*'s study, which showed that preterm infants with RDS receiving BiPAP needed fewer days of respiratory support and supplemental oxygen than those receiving CPAP^[11].

Nevertheless, there are some limitations in our study. First, this study included a relatively mature group of preterm infants (gestational age 30 weeks) with low antenatal steroid (70%). Therefore, it is difficult to expand these results to other populations with higher antenatal steroid treatment. Second, the CPAP and BiPAP used in this study were from Viasys Healthcare Inc, USA. It is unclear whether the results can apply to other forms of CPAP. Third, numerous patients failed in follow-up at one year of age, which could induce potential bias. Finally, INSURE technique was exclusively applied in all the included patients, thus we are not sure whether the results are suitable for neonates with less invasive surfactant administration (LISA).

In conclusion, this study demonstrated no significant difference between the BiPAP group and the CPAP group in terms of reintubation rate within 72 h of age after INSURE procedure. Significantly shorter durations (days) of PAP support and oxygen supplementation were found in the BiPAP group than in the CPAP group.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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