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Original Research

Bi-PAP is not superior to NCPAP in the premature twins with respiratory distress syndrome: a prospective cohort study

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Abstract

Background: Recently, non-invasive ventilation has been widely used due to the reduction of adverse effects of endotracheal intubation. Nevertheless nearly no researches have compared the efficacy of non-invasive respiratory support between preterm twins. The objective of this study was to determine if there is a decreased non-invasive ventilation (NIV) failure from bi-level positive airway pressure (Bi-PAP) vs nasal continuous positive airway pressure (NCPAP) in preterm twins as initial ventilation. **Methods**: This prospective cohort study enrolled 100 pairs preterm twins who were admitted to the NICU at Yunnan Qujing Maternity and Child Health Care Hospital from 2017.10 to 2020.09 for respiratory distress syndrome. One of the twin was randomly assigned to Bi-PAP, meanwhile another to NCPAP. The primary outcome was the incidence of NIV failure. Secondary outcomes was the occurrence rate of side-effects of NIV. **Results**: A total of 100 pairs preterm twins were included in statistical analysis. No distinct differences were found in NIV failure between groups (NCPAP vs Bi-PAP, 5% vs 2%, $p = 0.248$). We did not find any statistical difference in secondary outcome between Bi-PAP and NCPAP. **Conclusions**: In this prospective cohort study, among preterm twins with RDS, NCPAP was noninferior to Bi-PAP with respect to the reduction of the need for invasive mechanical ventilation (IMV).

Keywords: respiratory distress syndrome; bi-level positive airway pressure; nasal continuous positive airway pressure; preterm twins

1. Introduction

Respiratory distress syndrome (RDS) is the leading cause of death among preterm in NICU, with extensive alveolar collapse and decreased pulmonary compliance due to pulmonary surfactant (PS) deficiency [1,2]. The death rate of preterm infants greatly reduced due to the introduction of mechanical ventilation. However it was followed by a series of acute complications and chronic complications such as air leak syndrome, abdomen distends, subglottic stenosis, bradycardia, infection, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and intraventricular hemorrhage (IVH) [3–5]. In the treatment of RDS, non-invasive ventilation (NIV) was recommended by European Consensus Guidelines and American Academy of Pediatrics [6,7]. Continuous positive airway pressure (CPAP) is the most widely used non-invasive respiratory supports. CPAP is a ventilation technique that provides a constant positive pressure for the inhalation and exhalation phases of preterm infants with spontaneous breathing, which can increase functional residual capacity (FRC) and oxygen partial pressure (PaO_2) and improve lung compliance [8,9]. Bi-level positive airway pressure (Bi-PAP) provides two levels of continuous positive airway pressures. Bi-PAP is a flow-triggered pressure support ventilation mode with the inspiratory phase providing a high pressure level (equivalent to pressure support (PSV)) and the expiratory phase providing a low pressure level (equivalent to PEEP) [10]. Theoretically, Bi-PAP should have an improvement in tidal volume and reduction in work of breathing compared to NCPAP [11]. However, Some literatures have compared the two non-invasive ventilation mode, showing a discrepancy results whether in preventing extubation failure or initial respiratory support [12–19]. As we all know, outcomes can be affected by pregnancy-related diseases and some latent undiscovered maternal factors. To avoid these element, we conducted this study in preterm twins. Surprisingly, little research has been done on the comparison between preterm twins. There is thus a clear need for us to design a prospective trials to test whether Bi-PAP is superior to NCPAP as initial ventilation in preterm infants <37 weeks.

2. Materials and methods

We conducted a prospective cohort study of 100 pairs preterm twins who were admitted to the NICU at Yun-

nan Qujing Maternity and Child Health Care Hospital from 2017.10 to 2020.09 for respiratory distress syndrome requiring respiratory support. Each of the twins involved were randomly assigned to the NCPAP group or the Bi-PAP group in a 1:1 ratio. In other words, one of a pair was randomly distributed to Bi -PAP, meanwhile another to NCPAP. The study was approved by the local ethics committees and registered at www.chictr.org.cn Number: ChiCTR2100045680 (registration date, 23 April 2021). All parents of the newborns signed the written informed consent form before participation in the study.

Patients meeting the following criteria were included in the study: (1) gestational age(GA) $<$37 weeks, (2) preterm twins with RDS requiring noninvasive respiratory support, (3) parental consent obtained.

Exclusion criteria included: intubation for any reason; congenital abnormality of the airway, esophagus or lungs, congenital heart disease, pneumorrhagia, inherited disease, intraventricular hemorrhages or sepsis.

2.1 Diagnoses of RDS

Clinical manifestations and chest X-ray findings are the main basis for diagnosis of RDS. The main clinical manifestations of RDS are nasal flaring, respiratory distress, tachypnea, and cyanosis and grunting showing up within the first 24 h of life. Grain shadow, air bronchogram or white lung were the typical X-ray picture of RDS [20].

2.2 Noninvasive ventilation strategies

Noninvasive respiratory support criteria were defined as follows [21]: (1) Early prophylactic use in the delivery room for the extremely premature infants (gestational age 25–28 weeks) with spontaneous breathing; (2) Preterm infants who are at high risk for RDS (gestational weeks $<$30 weeks) and do not require intubation for stabilization; (3) when fraction of inspired oxygen (FiO_2) $>$0.30 by mask, nasal catheter, or hood for oxygen, arterial oxygen tension (PaO_2) $<$50 mmHg or transcutaneous oxygen saturation ($TcSO_2$) $<$0.90; (4) apnea of prematurity.

Continuous positive airway pressure system provides for NCPAP (CareFusion, Stephan, Fabian). Infants on NCPAP received positive end expiratory pressure (PEEP) of 6 cm H2O initially, which was adjusted between 6 and 8 cm H2O according to the condition of infant's respiratory. FiO_2 was adjusted between 0.21–0.40, until a SpO_2 of 90–95% was maintained. When the pressure is less than 4–5 cm H2O, evacuation of NCPAP can be considered when there is no apnea, bradycardia, no increase in respiratory work, and no decrease in $TcSO_2$ [21].

Bi-PAP was provided by Infant Flow-driver device (CareFusion, Fabian). Infants on Bi-PAP received higher CPAP level (Phigh) of 8 cm H2O initially, which was adjusted to between 8–9 cm H2O. Lower CPAP level (Plow) was 5 cm H2O initially and adjusted to be between 4–6 cm H2O. T High (Time upper level): 0.6–0.7 s, rate: 30–40 breaths/min. FiO_2 was adjusted between 0.21–0.40, until a SpO_2 of 90–95% was maintained. It's the time for weaning from Bi-PAP when the parameters were reduced to Phigh 6 cm H2O, Plow 4 cm H2O, pressure conversion frequency 15 times /min, FiO_2 $<$0.30, and no clinical manifestations of RDS.

Criteria for intubation or NIV failure: There was no improvement or persistent aggravation after the use of noninvasive respiratory support (shortness of breath, groaning, three depressions and cyanosis without relief), accompanied by the following conditions: (1) PaO_2 $<$50 mmHg (FiO_2 requirement $>$0.60). (2) Hypercarbia and acidosis (pCO_2 $>$65 mmHg and pH $<$7.20;). (3) Apnea as $\geq$4 episodes per hour or the need for mask ventilation $\geq$2 times per hour [21].

2.3 Surfactant administration

Surfactant (Curosurf; 200 mg/kg) treatment was conducted by the INSURE (intubation, surfactant, extubation) technique in the case of FiO_2 $>$0.30 (gestational age $<$26 weeks) or FiO_2 $>$0.4 (gestational age $>$26 weeks) to maintain SpO_2 of 90–94%. 100 mg/kg of Surfactant were given for an additional doses, at least 12 h after previous conduction, three doses at most [22].

2.4 Caffeine treatment

Caffeine (Caffeine Citrate Injection) was recommended for RDS to avoid apnea. 20 mg/kg was for an initial dose, 5–10 mg/kg was for a maintenance dose [22].

2.5 Outcome

The primary outcome was the incidence of NIV failure or the need for intubation and IMV, the time of the follow-up was 4 weeks after discharge.

Secondary outcomes included the length of hospital day, intraventricular hemorrhage (IVH) $\geq$grade 3, predischarge mortality, retinopathy of prematurity (ROP) $>$stage II, bronchopulmonary dysplasia (BPD) (O_2 dependency at 28 days) [23], pneumothorax , and necrotizing enterocolitis (NEC) $\geq$stage II; abdomen distends (defined as $>$10% increase in abdominal girth); Neurological function score (TIMP test was conducted after weaning from NIV) [24]; the need for PS and caffeine treatment; IVH was classified according to Papile *et al.* [25]. NEC was classified as described in Bell staging [26].

2.6 Statistical analysis

Student's *t* test was used to determine the statistical significance of differences between groups if the continuous data were normally distributed and described by the means and standard deviations (SDs).The nonparametric H test was used for abnormal distribution. The categorical variable were described as rates and percentages by means of Fisher's exact test or chi-square analysis. *p* values were judged significant if they were less than 0.05. All statistical

Table 1. Perinatal characteristics of preterm infants.

Parameter	Bi-PAP (n = 100)	NCPAP (n = 100)	*p*
GA	33 (31–34)	33 (31–34)	1
BW	1700 (1450–2000)	1677 (1440–1900)	0.580
Gender (Male)	59	50	0.201
1 Apgar score	8 (7–8)	8 (7–8)	0.939
5 Apgar score	8 (8–8)	8 (8–8)	0.828
10 Apgar score	8 (8–8)	8 (8–8)	0.378
SNAPPE II	0 (0–12)	0 (0–12)	0.820
Caesarean birth	66	66	1
Premature rupture of membranes	51	51	1
Antenatal corticosteroids	51	51	1
Diabetes	3	3	1
Cholestasis of pregnancy	1	1	1
Pernicious placenta previa (PPP)	3	3	1

NCPAP, nasal continuous positive airway pressure; Bi-PAP, Bi-level positive airway pressure; GA, gestational age week; BW, birth weight; *p*, *p*-value of Bi-PAP vs NCPAP.

data analyses were accomplished with the use of SPSS statistical software (version 22.0, IBM Corp., Armonk, NY, USA).

3. Results

256 patients admitted to NICU at Yunnan Qujing Maternity and Child Health Care Hospital, parents of 234 infants were consented. 16 infants were transferred to another site and 8 patients discharge within 24 hours after admission. 10 infants (3.9%) were excluded from this study. Of the 10 excluded neonates, 2 neonates were diagnosed with congenital malformation. 8 neonates were excluded for congenital heart disease; Thus, a total of 200 preterm infants were enrolled in final (Fig. 1). Of the 200 study-eligible infants (91 females, 109 males),the average gestational age was 33-week (range 27–36 weeks) and a birth weight ranging from 670 g to 2900 g. General clinical characteristics of newborn babies are summarized in Table 1. Baseline characteristic were similar between the two studied groups.

Primary and secondary outcomes are shown in Table 2.The difference was not statistically significant in NIV failure between NCPAP and Bi-PAP (NCPAP vs Bi-PAP, 5% vs 2%, $p = 0.248$). Secondary outcomes did not differ significantly between the NCPAP and Bi-PAP groups. No differences were noted in the incidence of NEC (1% vs 0%), ROP (15% vs 13%), BPD (31% vs 29%), PS treatment (67% vs 70%), IVH $\geq$1 (15% vs 14%), caffeine treatment (43% vs 47%), nosocomial infection (10% vs 9%), abdomen distends (29% vs 22%), Neurological function score (52.17 ± 6.794 vs 52.27 ± 5.673, $p = 0.918$). There were two infant deaths in NCPAP and Bi-PAP respectively. The 4 preterm infants had NIV failure with subsequent intubation and death due to the infection. No pneumothorax occurred in the two groups.

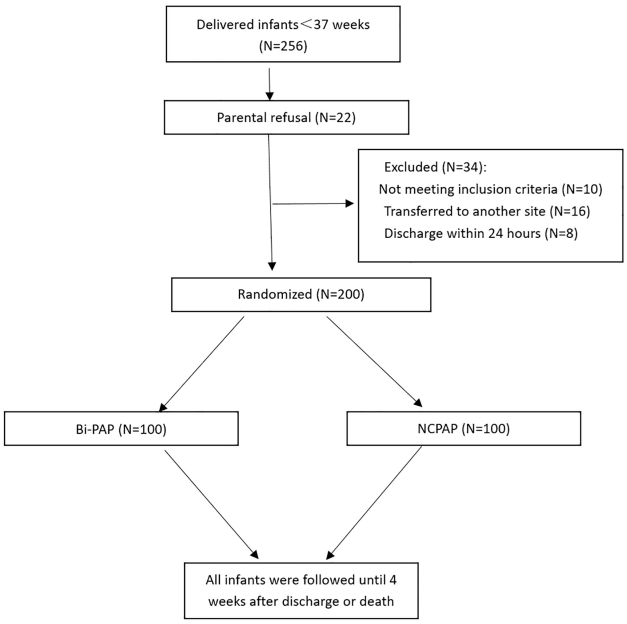

Fig. 1. Flow chart of infants' recruitment.

4. Discussion

This trial was conducted to compare the efficacy and safety of Bi-PAP to NCPAP as initial support in preterm twins with respiratory distress syndrome. In order to avoid the interaction of maternal pregnancy-related diseases and the influence of disease severity on the outcome, preterm twins was involved in our study. No literature data was reported about the different efficiency of Bi-PAP and NCPAP in preterm twins with RDS. This study shows that NCPAP and Bi-PAP are not significantly different with respect to the rate of NIV failure, rates of complications, in-hospital mortality, neurological function score, and length of hospital stay. These findings suggest that Bi-PAP is not superior to NCPAP as an initial management of respiratory distress in these premature twins.

Table 2. Primary and secondary outcomes.

Parameters	Bi-PAP (n = 100)	NCPAP (n = 100)	*p*
IMV	2	5	0.248
NEC	0	1	0.368
ROP	13	15	0.976
PNX	0	0	1
BPD	29	31	0.585
PS treatment	70	67	0.648
Caffeine treatment	47	43	0.570
Nosocomial infection	9	10	0.809
IVH	14	15	0.934
death	2	2	1
Abdomen distends	22	29	0.256
HS	23 (16–38.75)	24.5 (16.25–40.75)	0.715
expenses	35578.56 (23962.0–63765.88)	35355.78 (22945.57–65262.19)	0.854
Neurological function score	52.27 $\pm$ 5.673	52.17 $\pm$ 6.794	0.918

Bi-PAP, Bi-level positive airway pressure; NCPAP, nasal continuous positive airway pressure; NEC, necrotizing enterocolitis; IMV, invasive mechanical ventilation; ROP, retinopathy of prematurity; PNX, pneumothorax; BPD,bronchopulmonary dysplasia; PS, pulmonary surfactant; IVH, intraventricular hemorrhage; HS, hospital stay; *p*, *p*-value of Bi-PAP vs NCPAP.

Consistent with our study, Mi-Ji Lee *et al*. [17] also found that there was no statistically significant difference in treatment failure, clinical effectiveness and safety compared with NCPAP in infants of RDS (n = 93, GA 30–35 weeks). Over 80% of premature babies in our study were also born between 30 and 35 weeks of gestation. We speculate that Bi-PAP might have no advantage on older gestational age groups. However, a randomized trail (RCT) involved 540 infants with GA <30 weeks demonstrated that the rate of extubation failure within 48h have no difference between Bi-PAP and NCPAP (57/270 vs 55/270, $p = 0.97$ at equivalent MAP (<6 cm H2O) [18]. A population study conducted by Anne Lee Solevåg [27] showed that Bi-PAP successfully treated the patients who had failed NCPAP ventilation and reduced morbidity such as ROP (OR 0.57, $p < 0.05$), and IVH (OR 0.37, $p < 0.001$) compared to invasive mechanical ventilation which means that Bi-PAP is effective than NCPAP and avoid invasive mechanical ventilation. There are a few studies explore the gas change as follows. A retrospective observational study, focused on 78 full term neonates, get the conclusion that Bi-PAP could improve CO_2 removal and reduces FiO_2 requirement with respect to NCPAP as initial ventilation [28]. The findings were also proved by Gao X *et al*. [29]. Moreover, Bi-PAP was also proved to improve gas exchange in preterm infants after weaning from mechanical ventilation (n = 20, GA 24–31 weeks) [30]. Although these studies have shown that Bi-PAP can effectively reduce the partial pressure of carbon dioxide and increase the partial pressure of oxygen and oxygen saturation within 24 hours, but we think just only in the early stage of gas exchange, whether it can be sustained in the later stage has not been explored. The different mean airway pressures (MAP) between the two ventilations can influence a lot. Contrary to the studies above, Lampland *et al*. [31] set same MAP and compared the two ventilation in a randomized crossover study, providing that Bi-PAP does not improve CO_2 removal nor oxygenation. The limitation of this study is the small sample size. It is a pity our study did not explore the gas exchange. A multicenter retrospective study focused on 191 very low birth-weight infants, showing that NIV failure was greater in group NCPAP (22/66) than in group Bi-PAP/N-SIPPV (11/63, 11/62) ($p < 0.05$), but there was no significant correlation in secondary outcomes between these groups [32]. However Karel O'Brien *et al*. [27] conducted a RCT similarly focused oninfants $\leq$1250 g, finding the rate of reintubation in the first 7 days following extubation was not significantly different between the two groups (45/67 vs 40/69, $p = 0.27$). Therefore it is not conclusive about the effectiveness of Bi-PAP in very low birth-weight infants. The study of Kong Ling- Kai *et al*. [33] found that early use of Bi-PAP can significantly reduce the rate of mechanical ventilation at 48 h and 72 h in comparison to NCPAP but cannot shorten the duration of respiratory support, oxygen demand, hospital stay, and the incidence of BPD. In 2015, Zhi-Hui Rong *et al*. [16] performed a retrospective cohort study of bi-level CPAP vs standard nasal CPAP in babies <32 weeks. The results of this cohort study is in agreement with previous observations, showing that Bi-PAP is better than NCPAP for RDS, with a significant reduction in the need for IMV within the first 72 h of birth. Studies of Lista *et al*. [12] have shown that compared with NCPAP, Bi-PAP can significantly shorten respiratory support, length of stay and dependence of oxygen in premature infants (GA 28–34 weeks) with moderate RDS, but did not reduce the rate of MV, decrease the rate of death and the incidence of adverse clinical outcomes such as BPD. Lista's study did not reveal the observation time of reintubation, our study fol-

lowed the rate of IMV of the patients 4 weeks after they discharge showingthe same findings. The different time-points of evaluation may contribute to the discrepancy between previous studies and our results. Similar to the above literature, we did not find any statistical difference in secondary outcomes, especially in the rate of BPD.

This study innovatively uses preterm twins to balance many potential mother-related influences and included a neurodevelopmental assessment. As we all know, the outcomes are closely related to many factors, such as the severity of RDS, the birth weight of the child, gestational age, and whether there are other secondary diseases, especially infections. The choice of ventilation mode is based on comprehensive consideration of all factors. The limitations of the study are: (1) the different MAP of the two ventilation (2) we did not discuss the gas blood. (3) In clinical practice, PEEP was adjusted according to the condition of patients, therefore, we cannot promise that the PEEP are the same all the time between the two NIV strategies. (4) Over 80% of premature babies in our study, the gestational age is between 30 and 35 weeks. This was a relatively mature group of preterm infants, Maybe, Bi-PAP have a bigger influence on younger infants. Only 3% patients were born before 28 weeks, so it is hard for us to perform a subgroup analysis due to the small sample size.

5. Conclusions

This trial provides evidence that there is no clinically significant difference in NIV failure rates between Bi-PAP and NCPAP when used in preterm twins born before 36 weeks. Further investigations are needed to explore the safety and efficiency of Bi-PAP.

Abbreviations

BPD, Bronchopulmonary dysplasia; Bi-PAP, Bi-level positive airway pressure; FRC, Functional residual capacity; IMV, Invasive mechanical ventilation; IVH, Intraventricular hemorrhage; PS, Pulmonary surfactant; PEEP, Positive end-expiratory pressure; PaO_2, Oxygen partial pressure; ROP, Retinopathy of prematurity; RDS, Respiratory distress syndrome; MAP, Mean airway pressures; NEC, Necrotizing enterocolitis; NIV, Non-invasive ventilation; NICU, Neonatal intensive care unit; NCPAP, Nasal continuous positive airway pressure.

Author contributions

XD conceptualized, designed the study and collected the data. HC was a major contributor in analyzing the data and writing the manuscript. CZ collected data and reviewed the manuscript. HY completed the ethics registration and clinical trial registration. YS conceptualized and designed the study, accomplished the article-extracting and data analysis, critically reviewed the manuscript for important intellectual content. FL conceptualized and designed the study, accomplished the article-extracting and data analysis, critically reviewed the manuscript for important intellectual content. CL conceptualized and designed the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

We have got the ethics approval at Medical Theory Committee of Qujing Maternal and Child Health Hospital, Yunnan Province and the reference number is QJFYLL2018-KY001. Consent was obtained by the parents of involved preterm infants.

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Conflict of interest

The authors declare no conflict of interest.

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