A comparison of the effect of bi-level positive airway pressure and synchronized intermittent mandatory ventilation in preterm infants with respiratory distress syndrome

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Abstract

Background: Bi-level positive airway pressure (BiPAP) and synchronized intermittent mandatory ventilation (SIMV) can be used to achieve peak inspiratory pressure and positive end-expiratory pressure to avoid alveolar collapse and improve oxygenation in preterm infants during the treatment of respiratory distress syndrome (RDS), and there is an urgent demand for evaluating the effects and prognoses of these two ventilation modes. Methods: We conducted a retrospective study on preterm infants ([?] 32 weeks and < 2500 g) from March 2015 to March 2020 with BiPAP (n = 63) and SIMV (n = 63). The primary outcomes were successful treatment and weaning within 72 hours, the demand for a second pulmonary surfactant supply and the need for a second respiratory support. The secondary outcome was the incidence of complications. Results: There were no significant differences (P>0.05) in the primary outcomes or the incidence of complications (pneumonia, apnoea, respiratory failure, air leak syndrome, persistence of patent ductus arteriosus, neonatal sepsis, necrotizing enterocolitis, retinopathy of prematurity, and intraventricular haemorrhage). There were significant differences (P<0.05) in the incidence of pulmonary haemorrhage, bronchopulmonary dysplasia and IVH ([?] grade II). Conclusion: Although both BiPAP and SIMV achieved good early treatment outcomes of RDS in preterm infants, BiPAP support is recommended for reducing the incidence of pulmonary haemorrhage, bronchopulmonary dysplasia and IVH ([?] grade II) if infants are tolerant. Attempts should be made to prevent these complications from happening with the use of SIMV support if infants are intolerant.

Key Words

Respiratory Distress Syndrome; Preterm infants; Bi-level positive airway pressure; Synchronized intermittent mandatory ventilation

Introduction

Respiratory distress syndrome (RDS) remains a significant disease among preterm infants, especially for infants with a gestational age of no more than 32 weeks. Although the lung compliance of premature infants with RDS can be improved after alveolar surfactant replacement therapy[1], most infants need ventilation support to maintain positive end-expiratory pressure (PEEP) and peak inspiratory pressure (PIP) in order to avoid alveolar collapse and improve oxygenation. An inappropriate mode of ventilation support leads to a higher incidence rate of bronchopulmonary dysplasia (BPD) and chronic lung diseases[2]. The pathophysiology of RDS results in the lungs being difficult to open and easy to collapse. Therefore, applying PIP and PEEP via either non-invasive support (bi-level positive airway pressure, BiPAP) or invasive support (synchronized intermittent mandatory ventilation, SIMV) is effective for recruiting the lungs and maintaining the functional residual capacity (FRC) and minute ventilation volume (MVV)[3,4]. Compared to the traditional non-invasive support method of continuous positive airway pressure (CPAP), BiPAP reduces the need for intubation within the first 72 hours of age[5] and shortens the length of stay in the hospital[6]. Because of the difficulty in

maintaining ventilation capacity (VC), carbon dioxide retention and sputum blockage in the airway easily occur. Compared to BiPAP, SIMV decreases carbon dioxide retention due to the establishment of artificial airways via intubation. However, it leads to a longer length of stay in the hospital and a higher incidence rate of BPD in extremely preterm infants[7].

As an increasing number of neonatologists are choosing non-invasive support (BiPAP) rather than invasive support (SIMV)[8], there is an urgent demand for effective evaluations of treatments related to these two ventilation modes. We made an effort to determine the differences in treatment effects and prognoses between these two ventilation modes by performing retrospective analyses on premature infants with a gestational age of less than or equal to 32 weeks over the past 5 years.

Methods

Subjects

We performed a retrospective study on preterm infants with a gestational age of less than or equal to 32 weeks who were admitted to our neonatal intensive care unit (NICU) from March 2015 to March 2020 and who were treated with BiPAP or SIMV without tranquilizers in Fujian Province Maternal and Child Health Hospital within 6 hours after birth. All preterm infants were diagnosed with RDS by chest X-ray and clinical characteristics within 6 hours after birth. The surfactants were administered at a dose of 100-200 mg/kg (Curosurf, Chiesi, Parma, Italy) immediately one or more times. The chest X-ray results of preterm infants with RDS were categorized as grades 1 to 4 according to the degree of disease. The exclusion criteria were preterm infants with the following conditions: infants who had respiratory tract malformations, diaphragmatic hernia, congenital oesophageal atresia, tracheoesophageal fistula, chromosomal disease or inherited metabolic diseases; and infants who did not survive eventually or were discharged automatically within 72 hours after birth. A total of 224 preterm infants ([?] 32 weeks and $<$ 2500 g) were previously included in the study. However, for various reasons, 98 infants were eventually excluded (15 of respiratory tract malformations, 18 of diaphragmatic Hernia, 12 of esophageal fistula, 11 of chromosomal or inherited metabolic diseases, and 42 of not survival or discharged automatically $<$ 72 h).

Ventilator parameters

A total of 126 preterm infants were divided into two groups: a BiPAP group and a SIMV group. BiPAP support was delivered using the infant-driver device (Infant Flow System, CareFusion Corp, Palm Springs, California, USA). To maintain an oxygen saturation (SaO_2) of 89-93%, the initial ventilator parameters were as follows: positive end-expiratory pressure and peak inspiratory pressure of 3-6 and 6-8 cmH_2O, a fraction of inspired oxygen (FiO_2) of 0.21-0.60, an inspiratory time (Ti) of 0.30-0.50 seconds and a respiratory rate (RR) of 20-40 movements per minute (mpm). Weaning was started with a progressive reduction of the respiratory rate to 20 mpm with a set fraction of inspired oxygen ([?] 0.25) and SaO_2 of 89-93%, followed by a reduction in the positive end-expiratory pressure down to 3 cmH_2O and a reduction in the peak inspiratory pressure down to 6 cmH_2O. SIMV support was delivered using the intubation ventilator device (SLE5000 System, SLE Corp, South Croydon Surrey CR2 6PL, UK). To maintain an SaO_2 of 89-93%, the initial ventilator parameters were PEEP and PIP values of 3-7 and 16-25 cmH_2O, an FiO_2 of 0.25-1.00, a Ti of 0.30-0.50 s and an RR of 30-45 mpm. Weaning from SIMV was performed when patients tolerated a reduction in RR to 30 mpm with a progressive reduction of the set FiO_2 [?] 0.40 and SaO_2 of 89-93%, followed by a reduction in the positive end-expiratory pressure down to 3 cmH_2O and a reduction in the peak inspiratory pressure down to 15 cmH_2O. Successful treatments were defined as follows: a. the symptoms of dyspnoea in infants were significantly improved; b. the results of chest X-ray re-examination indicated an improvement in lung transparency or returned to normal within 24 hours; c. compared to the initial results of the arterial partial pressure of oxygen (PaO_2)/FiO_2, the final results were higher and more than 250 at 72 hours after birth; d. blood gas analysis indicated no carbon dioxide retention, hypoxemia, or acid-base balance disorders; e. after respiratory support for 72 hours, the ventilator parameters were decreased, or infants were weaned with the saturation maintained at 89-93%. However, during the entire treatment, when there was a progressive increase in breathing rates and an occurrence of complications (e.g., severe pulmonary haemorrhage, severe

pneumonia, severe sepsis, and repeated apnoea), and when the current ventilator parameters were unable to maintain a saturation of 89-93%, we adjusted to a ventilation mode of high frequency oscillatory ventilation (HFOV).

The perinatal characteristics of the infants were recorded: gestational age (GA) and birth weight (BW), small for gestational age (SGA), sex, amniotic fluid traits, mode of delivery, multiple pregnancies, grade of chest X-ray, occurrence of premature rupture of membranes and severe asphyxia, use of dexamethasone (DXM) before delivery, arterial partial pressure of carbon dioxide (PCO_2) and SaO_2 in the beginning, and main maternal pregnancy diseases, including placental abruption, gestational diabetes mellitus (GDM), intrauterine infection (IAI), and hypertension during pregnancy. Intrauterine infection was defined as cervical or palace cavity secretions tested positive, mother fever (axillary temperature [?] 37.3-degree Celsius) or increased in C-reactive protein and white blood cell count ([?] $1.5*10^9$/L) during pregnancy. Other time variables were recorded for each infant, including the hours of oxygen use and the days of stay in the hospital. Preterm infants were monitored by using oxygen saturation monitoring (BeneVision N12 Neo, Mindray Corp, Guangdong Province, China). The following ventilator parameters were recorded for each infant: FiO_2, RR, PEEP, PIP, and Ti. The primary outcomes were successful treatment and weaning within 72 hours, the demand for a second pulmonary surfactant (PS) supply and the need for a second respiratory support. The secondary outcome was the incidence of complications: pneumonia, apnoea, respiratory failure, air leak syndrome, pulmonary haemorrhage, BPD, persistence of patent ductus arteriosus (PDA), neonatal sepsis, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and intraventricular haemorrhage (IVH).

Statistical analysis

The statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp, Armonk, NY, USA). The clinical characteristics of the infants are expressed as the mean ± SD (standard deviation). In analyses of continuous data, if fit to a normal distribution, the variables were analysed by t-tests; if not, they were analysed by the Wilcoxon test. Chi-square tests or Fisher's exact tests were used in the analyses of categorical variables as appropriate. Results with $P<0.05$ were considered statistically significant.

All patients were contacted by telephone to obtain verbal informed consent.

Results

In the BiPAP group, the mean gestational age was 29.5 ± 1.3 weeks, and the mean birth weight was 1357.3 ± 263.8 g. In the SIMV group, the mean gestational age was 29.1 ± 2.0 weeks, and the mean birth weight was 1299 ± 337.3 g. The perinatal characteristics of the infants ([?] 32 weeks and < 2500 g) in the two groups are reported in Table 1, and there were no significant differences ($P>0.05$) for all variables. The initial PCO_2 values in the SIMV group and the BiPAP group were not different ($P=0.124$), and after 72 hours of ventilation support, the final PCO_2 values were similar (44.76 +- 8 vs 43.38 +- 8) ($P=0.224$). As shown in Table 2, we found that the hours of oxygen use and the number of days of stay in the hospital in the SIMV group were longer than those in the BiPAP group. There was much more oxidative damage in the preterm infants from the SIMV group during the treatment of RDS, which resulted in detriments to the functions of some important organs, such as the eyes and lungs.

The primary outcome characteristics are shown in Table 3. There were no significant differences ($P>0.05$) in the primary outcomes, including successful treatment and weaning within 72 hours, the demand for a second pulmonary surfactant (PS) supply and the need for a second ventilation support in either group. Although the rates of successful treatment of RDS in the two groups were approximately equal, the number of infants weaned within 72 hours in the BiPAP group was higher than that in the SIMV group (5 vs 1), and the number of infants who demanded a second PS supply (3 vs 9) and further respiratory support (23 vs 29) were lower than those in the SIMV group. The secondary outcome characteristics are also shown in Table 3. No significant differences ($P>0.05$) in the incidence of complications were observed: pneumonia, apnoea, respiratory failure, air leak syndrome, persistence of PDA, neonatal sepsis, NEC, ROP or IVH. Through further analysis of the incidence of ROP, the morbidity of ROP ([?] stage II) in the SIMV group was higher than that in the BiPAP group (80.0% vs 50.0%). Moreover, through further analysis of the incidence of IVH,

the morbidity of IVH ([?] grade II) in the SIMV group was higher than that in the BiPAP group (26.1% vs 5.6%).The incidences of pulmonary haemorrhage and BPD were lower in preterm infants in the BiPAP group than in the SIMV group (P<0.05). No infants in the BiPAP group had pulmonary haemorrhage.

Discussion

Previous studies have reported the effects of some modes of ventilation in the treatment of RDS in prematurity, such as BiPAP vs nasal synchronized intermittent positive pressure ventilation (NSIPPV)[9]; nasal bi-level PAP (N-BiPAP) vs sigh-PAP (n-SiPAP) [10]; and nasal intermittent positive pressure ventilation (NIPPV) vs nasal continuous positive airway pressure (NCPAP)[11]. This is the first report to compare normal-frequency-assisted ventilation for preterm infants ([?] 32 weeks and < 2500 g) followed by RDS between invasive ventilation with SIMV and non-invasive ventilation with BiPAP. Although SIMV can reduce the mean arterial pressure, improve oxygenation, coordinate spontaneous breathing with ventilators, and exercise the function of respiratory muscles, it requires intubation, and the long-term establishment of artificial airways increases the incidence rate of ventilator-associated pneumonia (VAP)[12]. The intubation procedure in SIMV support is extremely distressing, causing an increase in the pro-inflammatory cytokines implicated in pain responses[13]. In contrast, the avoidance of airway intubation in BiPAP support is associated with a reduction in the incidence of chronic lung disease among preterm infants with respiratory distress syndrome[3].

European consensus guidelines on the management of RDS in 2019[1] mentioned that if intubated, babies can often be extubated to CPAP (BiPAP), HFNC or NIPPV immediately following surfactant, and judgement needs to be made if an individual baby will tolerate this. However, if infants are intolerant, invasive ventilation is requisite. The successful treatment rate of RDS was highly supported by either BiPAP or SIMV (60.3% vs 54.0%) within 72 hours after birth in our study (Table 3). Not only were the hours of oxygen use and the number of days of stay in the hospital longer, but the incidence of BPD was also higher in the SIMV group than in the BiPAP group (Tables 2 and 3). Long-term oxidative stress is more likely to damage lung tissues and cause BPD[14]. Exposure to high concentrations of oxygen resulted in significant damage to the developing lung. It has been demonstrated that even a period of two hours under invasive mechanical ventilation associated with higher oxygen levels may lead to lung inflammation[15]. Therefore, during the treatments of RDS, the lower oxygen concentrations (30–60%) were used to protect the developing lung, and we maintained the SaO_2 around 89-93%. Oxidative stress can result in ROP because of the susceptibility of the phospholipid-rich retina to reactive oxygen species that can be generated in high or low oxygen[16]. Only less than a quarter of infants had ROP in both groups (22.2% of BiPAP vs 23.8% of SIMV), and the incidence was not significantly different in our retrospective analysis (Table 3). Although we could not confirm whether BiPAP or SIMV had a relationship with ROP, more instances of ROP ([?] stage II) occurred in preterm infants in the SIMV group. Further prospective clinical research needs to be done in preterm infants with RDS. In extremely low-birth-weight infants, Munro et al.[17] found that cerebral blood flow (CBF) was autoregulated above (and pressure-passive below) a breakpoint that averages approximately 30 mmHg, and lower CBF was related to IVH[18]. With different ventilation approaches, the median CBF in the SIMV group was 14.44 (2.70–32.10) and that in the CPAP group was 31.69 (13.59–34.93) for preterm infants[19]. A network meta-analysis[20]found that SIMV (OR=8.22, 95%, CI: 1.25-29.44, P<0.05) schemes seemed to have increased the risk of IVH in preterm infants with RDS. We also found that the morbidity of IVH ([?] grade II) in the SIMV group was higher than that in the BiPAP group. An article[21] mentioned that the complication rate of pulmonary haemorrhage was 2.5% with mechanical ventilation. If the pressure associated with ventilation is too high, the incidence of pulmonary haemorrhage can be significantly increased. In our study, we found that the required initial levels of PIP in the SIMV group were significantly higher than those in the BiPAP group (19.1 +- 1.8 vs 6.8 +- 0.5, P<0.05), which might be one of the reasons for an increased risk of pulmonary haemorrhage. After receiving haemostatic drugs and assisted ventilation with HFOV, all preterm infants with pulmonary haemorrhage in the SIMV group survived and were eventually successfully weaned.

The triggering of BiPAP is initiated by the patient's spontaneous breathing using a pressure or flow rate trigger mechanism, and good man-machine cooperation can provide adequate ventilation support and reduce

the work of breathing. The mode of BiPAP support might be an advantage to spontaneously breathing patients and reduced early extubation failure in very preterm neonates with RDS within seven days from extubation[22]. It is a way of using a single airway with low resistance to reduce the length of stay in the NICU[23] and weaning as soon as possible. We found that 7.9% of preterm infants were successfully weaned in the BiPAP group, and only 1.6% of preterm infants were successfully weaned in the SIMV group within 72 hours (Table 2). No establishment of an artificial airway in BiPAP support avoids the harms associated with normal feeding and swallowing and retains the functions of heating, humidification and filtering in the upper airway. In accordance with SIMV, BiPAP provides a constant PEEP and PIP to infants assisted with ventilation each time, which can ensure that the airway pressure is constant at the pre-set level and avoid volume injuries. In our study, the incidence rates of air leakage syndrome were at a low level, only 4.8% in the BiPAP group and 1.6% in the SIMV group (Table 2). Because of the insufficient peak inspiratory pressure of BiPAP, it is difficult for infants with severe RDS to release carbon dioxide while the airway resistance is high, and the alveolar compliance is probably poor. SIMV provides a relatively higher peak inspiratory pressure during ventilation, and the establishment of an artificial airway can also ensure the patency of the main trachea, which is more beneficial to the release of carbon dioxide. In our retrospective study, we found that the clearance of carbon dioxide in the BiPAP group was not worse than that in the SIMV group after 72 hours of respiratory support (P>0.05). An article reported[24] that infants with RDS in the BiPAP group had better clearance of carbon dioxide and lower FiO2 requirements than other types of NIV, such as CPAP.

The comparison between BiPAP and SIMV in RDS was the first to involve preterm infants ([?] 32 weeks and < 2500 g) with similar characteristics over a period of five years. By combining the results of this study, the advantages and disadvantages of the two different ventilation supports were elaborated, which might be useful for helping neonatologists choose appropriate ventilation support during the treatment of RDS in preterm infants ([?] 32 weeks and < 2500 g). We retrospectively enumerated the complications that were likely to result from SIMV support compared with BiPAP support during the treatment of RDS (e.g., BPD, pulmonary haemorrhage, IVH [?] grade II), which might help to prevent these complications from occurring in the future.

Because of the strictly selected inclusion criteria for preterm infants, only 126 of them were included in the study. Further prospective research should be done to confirm these results. Additionally, the long-term follow-up and comparison of outcomes of infants in the SIMV and BiPAP groups throughout childhood is necessary, and we will track these data continuously. Because multiple confounding factors existed, we were unable to analyse the relationship between ventilator-associated pneumonia and two different ventilation supports in the treatment of RDS. Therefore, it is necessary to carry out further prospective studies.

Conclusion

Both BiPAP and SIMV achieved good early treatment of RDS in preterm infants. Although the incidence of some complications, including pneumonia, apnoea, respiratory failure, air leak syndrome, the persistence of PDA, neonatal sepsis, NEC, ROP and IVH caused by the two ventilation supports were not significantly different, there was a higher incidence rate of complications, including BPD, pulmonary haemorrhage, and IVH [?] grade II, in the SIMV group. To reduce the occurrence of these complications, BiPAP support is recommended if infants are tolerant. We retrospectively enumerated the complications that were likely to result from SIMV support during the treatment of RDS and aimed to prevent these complications from happening with the use of SIMV support if infants are intolerant in the future.

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Conflict of Interests:

The authors declare that they have no conflict of interest.

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