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High-frequency oscillatory ventilation versus synchronized intermittent mandatory ventilation plus pressure support in preterm infants with severe respiratory distress syndrome

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Abstract

Background: Mechanical ventilation and surfactants are the standard treatment of preterm respiratory distress syndrome (RDS). The effects of the primary ventilation model on bronchopulmonary dysplasia (BPD) and long-term neurodevelopment outcomes are controversial. The purpose of this study was to compare the efficacy and safety of high-frequency oscillatory ventilation (HFOV) and synchronized intermittent mandatory ventilation plus pressure support ventilation (SIMV-PSV) in preterm infants with severe RDS.

Methods: A total of 366 eligible preterm infants were randomly assigned to treatment with HFOV (n = 184) or SIMV-PSV (n = 182). Surfactant was applied if PaO_2/FIO_2 < 200 after 2 hours of ventilation. Primary outcomes were mortality or incidence of BPD. Secondary outcomes were duration of ventilation and hospitalization, surfactant requirements, pneumothorax, retinopathy of prematurity (ROP) ≥ stage 2, and neurodevelopment at 18 months of corrected age.

Results: Survival and complete outcome data were available for 288 infants at 18 months of corrected age. Incidence of death or BPD was significantly higher in the SIMV-PSV group (p = 0.001). The duration of mechanical ventilation and hospitalization was shorter and the incidence of surfactant requirement and ROP was lower in the HFOV group (p < 0.05). Moderate or severe neurological disability was less frequent in the HFOV group than in the SIMV-PSV group at 18 months (p <

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0.05). The combination of HFOV and surfactant dramatically reduced negative outcomes in preterm infants with severe RDS.

Conclusion: Initial ventilation with HFOV in preterm infants with severe RDS reduces the incidence of death and BPD and improves long-term neurodevelopment outcomes.

Key words: high-frequency oscillatory ventilation, respiratory distress syndrome, preterm infants, neurodevelopment

Clinical Trial Registration Number: NCT01496508

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Background

With the progress of medical technology and the development of neonatal intensive care units (NICU) in China, the survival of preterm infants has greatly improved [1]. Respiratory distress syndrome (RDS) is common in preterm infants born at less than 32 weeks of gestational age [2-4], and surfactants and mechanical ventilation have been the standard treatment [5]. However, despite advances in neonatal respiratory care, a considerable number of preterm infants develop chronic lung disease, termed bronchopulmonary dysplasia (BPD) [5-8], that is associated with neonatal death, prolonged neonatal intensive care stay, and impaired neurodevelopment [9]. BPD has a multifactorial pathogenesis and invasive mechanical ventilation is one of its most important causative factors.

High-frequency oscillatory ventilation (HFOV) was developed as a new ventilation technique in the late 1970s. Animal studies showed that HFOV produced less lung injury and improved pulmonary outcomes compared to conventional mechanical ventilation (CV) [10]. HFOV was expected to result in less BPD and mortality when used as a primary model of ventilation compared to CV in the treatment of RDS [8]. However, there is disagreement regarding the advantage of HFOV over CV in the treatment of RDS in preterm infants with respect to the prevention of death, BPD, intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL) over the short term [6, 8, 11-13]. Even though a recent meta-analysis of individual patient data

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indicated that HFOV was as effective as CV in preterm infants [6], the limited reports on the long-term effects of HFOV and CV on the neurodevelopment of preterm infants with RDS are in disagreement [11, 12]. These conflicting results are probably due to heterogeneity in study design, patient characteristics, and outcome definition. Thus the safety and long-term neurodevelopmental outcomes of HFOV for preterm infants with severe RDS remain uncertain. Our hypothesis was that early use of HFOV with a lung volume recruitment strategy can provide a clinically important benefit in terms of mortality, incidence of BPD, and moderate to severe neurological disability at 18 months for infants with severe RDS born before 32 weeks compared to CV methods using synchronized intermittent mandatory ventilation plus pressure support ventilation (SIMV-PSV).

Methods

Patient Population

Preterm infants eligible for the study were infants admitted to the NICU with gestational ages < 32 weeks and birth weights < 1500 g and who developed RDS requiring mechanical ventilation less than 24 hours after birth, presented with a ratio of partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FIO_2) less than 200 (determined when patients were in positive expiratory end pressure with nasopharyngeal continuous positive airway pressure or conventional mechanical ventilation), and had radiographic evidence of severe RDS. In the two NICU wards, preterm infants with spontaneous breathing and respiratory distress were put on

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nasopharyngeal continuous positive airway pressure (nCPAP). If the infants had clinical symptoms of worsening respiratory distress or hypoxemia, or if they had recurrent apnea and bradycardia episodes, they were intubated and positive pressure ventilation was provided through a T-piece (Neopuff, Fisher & Paykel Healthcare, Auckland, New Zealand). Infants in such cases had not been breathing spontaneously or nCPAP had failed. The PaO_2:FiO_2 ratio was determined at the time of randomization and throughout the study when the infants were either on nCPAP with a pressure of 6 cm H_2O and FIO_2 of more than 0.5 or were intubated with synchronized intermittent mandatory ventilation (SIMV) with peak inspiratory pressure (PIP) set at 20, positive expiratory end pressure (PEEP) at 5 cm H_2O, and FIO_2 at 0.4. Infants with genetic metabolic diseases, congenital abnormalities, pneumothorax, or grade III–IV intracranial hemorrhage before randomization were excluded from the study as were some infants where parental consent could not be obtained. Switching from SIMV to HFOV and vice-versa was not allowed in instances of treatment failure, and crossover was not an option. However, HFOV-treated neonates were allowed to continue on SIMV until final extubation at a point when HFOV was considered not suitable (for example, reintubation for apneas without evidence of pulmonary disease or established severe BPD). In this case, the neonates remained in the HFOV group during statistical analysis.

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A total of 1461 preterm infants weighing less than 1500 g were admitted to the NICU during the study period, of which 950 had RDS and 366 met the criteria for entry into the study. One hundred eighty-four preterm infants were randomly assigned to receive SIMV-PSV and 182 to receive HFOV within 24 h after being admitted to the NICU according to randomization by number. Two infants in the SIMV-PSV group and one infant in the HFOV group with late-diagnosed congenital heart disease were subsequently excluded. Seven infants dropped out during treatment by parental request (Fig. 1). This prospective study was performed from June 2007 to December 2009 in Zhengzhou Children's Hospital of Henan Province and Nanjing Children's Hospital of Jiangsu Province, China. The ventilation strategies were performed identically at both study sites. This study was approved by the Life Science Ethics Committee of Zhengzhou University and the local Research Ethics Committee at the participating centers in accordance with the Helsinki Declaration. Written informed consent was obtained from both parents when an infant was admitted to the NICU.

Randomization

Eligible patients were assigned to the SIMV-PSV group or the HFOV group based on a computer-generated randomization plan. Randomization was stratified per center according to gender and gestational age (< 28 weeks or ≥ 28 weeks). The allocation ratio was 1:1 using variable block sizes. Randomization to the SIMV-PSV or HFOV group was carried out by random number allocation sequence upon securing the order

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of admission to the NICU and within 30 minutes after written informed consent was obtained.

Ventilation strategies

An SLE5000 infant ventilator was used as the high-frequency ventilator and a Servo-i-Maquet was used as the conventional mechanical ventilator. Ventilation strategies for both groups aimed to emphasize lung recruitment and avoid atelectasis. The optimal lung inflation was determined as expansion to 8 to 9.5 ribs for most of the infants and 7 to 8 ribs for infants with air leakage (emphysema or pneumothorax without drainage) [14]. Oxygenation was used as an indirect marker for ideal lung volume. Following intubation (the inner diameter of endotracheal tubes was 2.5 mm to 3.0 mm, and cuffed endotracheal tubes were not used with the infants enrolled in this study), HFOV was initiated at a continuous distending pressure (CDPst) of 6 to 8 cm H_2O. CDP was increased in steps of 1 to 2 cm H_2O until oxygenation no longer improved or FIO_2 was less than or equal to 0.25 (opening pressure, CDPo). Next, the CDP was decreased in steps of 1 to 2 cm H_2O until oxygenation deteriorated indicating alveolar/saccular collapse (closing pressure, CDPc). The lung was then once again opened (CDPo) and the pressure was set at 2 cm H_2O above the CDPc (this was the optimal CDP, CDPopt).

The time interval between pressure steps depended on the change in oxygenation. If

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oxygenation did not change following a pressure step or if it stabilized after FIO_2 adjustment, the clinician waited at least 2 min before taking the next pressure step. The pressure amplitude was set in such a way that chest oscillations were visible with a frequency of 10 Hz. The inspiration time was set at the default values in the SLE5000 infant ventilator. The pressure, amplitude, and frequency were kept constant during the recruitment procedure [15]. If an infant received surfactant, the CDPc, CDPo, and CDPopt were once more determined by the same procedure as described above but with a minimum time interval between pressure steps of 5 min. The procedure started with decremental pressure steps unless the FIO_2 increased to greater than 0.25 after surfactant treatment in which case CDP was increased in search of the new CDPo. If the CDP could be reduced to 8 cm H_2O without compromising oxygenation, the closing procedure was stopped and the corresponding CDP was designated as the CDPopt [15].

During lung volume recruitment for HFOV, the expired tidal volume, DCO_2, pressure amplitude (ΔP), and mean airway pressure (MAP) were measured dynamically with the SLE5000 ventilator. DCO_2 is the Gas Transport Coefficient and is analogous to MV (minute ventilation) during CV. MV is calculated as TV (tidal volume) $\times$ frequency, but in HFOV the value for DCO_2 is calculated by $(TV)^2 \times$ frequency. The compliance of the lung and the efficacy of lung volume recruitment were evaluated from the change in tidal volume (2–2.5 mL/kg will give normal PCO_2), DCO_2 (values

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around 80/kg will result in normocarbia), and oxygenation. This open lung approach is feasible in the majority of preterm infants with RDS and does not lead to hemodynamic instability. Extubation was considered when CDPst was ≤ 7 cm H_2O and the pressure amplitude of oscillation reached 10 to 15 cm H_2O.

SIMV-PSV was delivered by time-cycled, pressure-supported, pressure-limited, flow-triggered ventilators starting with an exhaled tidal volume of 4 to 6 mL/kg (the preferred target range was 5 to 6 mL/kg), PIP as needed to achieve adequate chest expansion (typically 14 to 20 cm H_2O), and PEEP of 4 to 6 cm H_2O. Our aim was to maintain lower tidal volumes (less than 6 mL/kg) by using lower PIP and optimal PEEP to maximize lung volume recruitment. Inspiratory times were 0.25 to 0.40 s, respiratory rates were ≤ 60/min (typically 30–40/min plus pressure support), the level of pressure support was started at 50% of the PIP and thereafter maintained at or decreased gradually below this level to a minimum of 30% as tolerated, and FIO_2 was set as required to maintain target oxygen levels. Flow trigger sensitivity was set at the maximum level. The weaning process was initiated when the following parameters were achieved: PIP < 14 cm H_2O, PEEP < 4 cm H_2O, and FIO_2 < 0.3. Extubation was considered when the patient's condition was stable for 12 h to 24 h and adequate oxygenation could be maintained with an FIO_2 < 0.3 and a respiratory rate < 25/min.

All infants were extubated from HFOV or SIMV-PSV onto nCPAP (Infant Flow,