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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,

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Electro Medical Equipment), then weaned onto a nasal cannula, and then finally allowed to breathe room air. Successful extubation was defined for both groups as lasting longer than 72 h without clinical deterioration requiring re-intubation. No infant needed to be ventilated again within the next 72 h following extubation.

Surfactant treatment

If PaO_2/FIO_2 in the two groups was less than 200 after 2 hours of ventilation, the patients were given rescue surfactant therapy (Curosurf, 200 mg/kg). A subsequent dose (100 mg/kg) was administered 12 hours after the first dose if PaO_2/FIO_2 remained less than 200 [16]. Surfactant was administered by means of in-line catheters (Pacific Hospital Supply Co.), and suctioning was performed 6 h after surfactant administration (except for those patients who required suction sooner) by means of an in-line suction catheter (Neonatal Closed Tracheal Suction System, Pacific Hospital Supply Co.). Ventilation continued during the administration of surfactant and suctioning. Treatment with surfactant required permission from the parents because surfactant is expensive and needed to be paid for by the parents. Without permission, the infants were given rescue treatment instead of surfactant.

Medical Treatment

All infants in whom patent ductus arteriosus subsequently developed were treated with oral ibuprofen (indomethacin and ibuprofen are not given intravenously in China)

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or by surgical ligation without prophylactic ibuprofen. We followed established protocols for the use of diuretics and for the use of bronchodilators for the treatment of chronic lung disease without the use of steroids. Bronchodilator therapy was allowed, but not required, for infants more than 14 days of age who were ventilated with FIO_2 greater than 0.4. Diuretics were used sparingly if there were clinical/radiographic features of pulmonary edema in an infant with evolving or established BPD[17].

Data collection

All patient vital signs, including blood pressure, heart rate, oxygen saturation, ventilator settings, and arterial blood gases, were monitored both before and during mechanical ventilation, and PaO_2/FIO_2 was calculated. Primary outcomes were mortality or incidence of BPD [18] as determined by an oxygen reduction test at 36 weeks of post-menstrual age (PMA) and further graded by severity using criteria adapted from the National Institute of Child Health and Human Development. Mild BPD was defined as the need for supplemental oxygen for $\geq$ 28 days. Moderate BPD was defined as the need for supplemental oxygen at PMA of 36 weeks without positive pressure support. Severe BPD was defined as the need for positive pressure support.

Secondary outcomes were the total number of days on mechanical ventilation, duration of hospital stay, surfactant requirement, and the occurrence of retinopathy of prematurity (ROP) stage 2 or higher, pulmonary hemorrhage, patent ductus arteriosus,

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necrotizing enterocolitis, or pneumothorax. Long-term outcomes were moderate or severe disabilities at 18 months of corrected age, including severe hearing loss, blindness, cerebral palsy, or a mental developmental index (MDI) < 70 as determined by the Bayley Scales of Infant Development, Second Edition. Follow-up was performed in the Department of Child Healthcare of the two hospitals. Doctors were blind as to group allocation during follow-up until 18 months of corrected age.

Statistical analyses

The minimum sample size of 172 in each group was estimated based on an expected negative outcome in the SIMV-PSV group of 25%, a two-sided 0.05 significance level, an 80% chance of detecting a relative 30% decrease in frequency, and an estimated 15% loss to follow-up. Analyses were performed according to the intention-to-treat principle, and all who could be evaluated were included.

All analyses were performed using SPSS 17.0 (SPSS Chicago, IL USA). Quantitative data are expressed as mean ± standard deviation (SD). Entry data and outcome differences were compared by *t*-test and Fisher's exact tests. Comparison of MAP, PaO_2/FIO_2, and $PaCO_2$ between continuous variables was by one-way analysis of variance (ANOVA) with two-sided *p* values. Subgroup interaction analyses were performed on the basis of gender, gestational age, birth weight, single or multiple birth, antenatal steroid or postnatal surfactant treatment, and intubation time for

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mechanical ventilation. All subgroup statistical analyses were evaluated by the Breslow-Day test for interaction. The kappa test was used to examine whether the results were consistent between the two centers. The level of statistical significance was set at $p < 0.05$.

Results

Respiratory Parameters

Respiratory analyses were performed on the 179 infants in the SIMV-PSV group and the 177 infants in the HFOV group. There were no differences in baseline characteristics between the groups (Table 1). MAP, PaO_2/FIO_2, and $PaCO_2$ were not significantly different between the SIMV-PSV and HFOV groups before randomization. The changes in these parameters during the first 48 hours are shown in Figure 2, and a significant difference was observed at 4 h after ventilation ($p < 0.05$). The $PaCO_2$ reduction occurred more quickly in the case of HFOV compared to SIMV-PSV.

Outcomes

Seventeen preterm infants died during treatment: 13 in the SIMV-PSV group (13/179 = 7.3%) (5 from pulmonary hemorrhage, 3 from renal failure, 2 from stage III necrotizing enterocolitis, 2 from sepsis, and 1 who did not respond to SIMV-PSV and surfactant), and 4 in the HFOV group (4/177 = 2.3%, $p = 0.04$) (2 from pulmonary

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hemorrhage, 1 from renal failure, and 1 from sepsis). A total of 41 preterm infants were diagnosed with BPD at 36 weeks of PMA, 28 in the SIMV-PSV group (28/166 = 16.9%) and 13 in the HFOV group (13/173 = 7.5%, p = 0.02). A total of 58 preterm infants died or were diagnosed with BPD: 41 in the SIMV-PSV group (41/179 = 22.9%) and 17 in the HFOV group (13/177 = 9.6%) (p = 0.001) (Table 2). In the Zhengzhou center, the number of infants suffering from BPD in the SIMV-PSV group was 16/92 and in the HFOV group it was 6/93. The number of deaths in the SIMV-PSV group was 7/99 and in the HFOV group it was 2/99. In the Nanjing center, the number of infants suffering from BPD in the SIMV-PSV group was 12/74 and in the HFOV group it was 7/82. The number of deaths in the SIMV-PSV group was 6/80 and in the HFOV group it was 2/84. The results were consistent between the two centers (p >0.4, Kappa test).

Subgroup analyses for primary outcomes were stratified according to sex, gestational age, birth weight, antenatal steroid or surfactant use, intubation time, and multiple births. There were no differences in basic characteristics between the SIMV-PSV and HFOV groups except that the rate of surfactant use was lower in the HFOV group (p = 0.001) (Table 3). The significant improved outcome with HFOV was noticed in the infants less than 28 weeks gestation by X^2 test (p = 0.019). However, the subgroup statistical analyses evaluated by the Breslow-Day test for interaction did not show significant differences for the effects of gestational age, as well as sex, birth weight, antenatal steroid use, surfactant treatment, intubation time, or multiple births on BPD or death between the SIMV-PSV and HFOV groups (Table 4). The incidence of death

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or BPD in the SIMV-PSV group without surfactant treatment was 33% and the incidence of death or BPD in the SIMV-PSV with surfactant or HFOV without surfactant groups was about 15% and was similar in the two groups. The incidence of death or BPD in the HFOV with surfactant group was 4% and this was 88% less than in the SIMV-PSV without surfactant group (Table 4).

The duration of mechanical ventilation and hospital stay length for survivors was shorter in the HFOV group than in the SIMV-PSV group ($p = 0.0007$ and $p = 0.04$, respectively). Surfactant was required in 45% of the HFOV group and in 62% of the SIMV-PSV group ($p = 0.002$). ROP (≥ stage 2) was twice as frequent in the SIMV-PSV group compared to the HFOV group ($p = 0.04$). The rate of pulmonary hemorrhage was 15% in the SIMV-PSV group and 8% in the HFOV group ($p = 0.045$). There was no difference in the occurrence of patent ductus arteriosus, necrotizing enterocolitis, or pneumothorax between the two groups (Table 5).

Long-term neurodevelopmental outcomes at 18 months of corrected age were available for 143 patients in the SIMV-PSV group and 145 patients in the HFOV group (288/356 = 81%). Seventeen patients (13 in the SIMV-PSV group and 4 in the HFOV group) died in the hospital and 51 patients (23 in the SIMV-PSV group and 28 in the HFOV group) were lost to follow-up (the clinical characteristics were no different between the two groups). The incidence of severe hearing loss and visual impairment was similar between the SIMV-PSV and the HFOV groups. Of the 288 infants, 19 developed cerebral palsy (6.6%), including 14 in the SIMV-PSV group and

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5 in the HFOV group ($p = 0.03$). The incidence of MDI < 70 was significantly higher in the SIMV-PSV group compared to the HFOV group ($p = 0.03$) (Table 6).

Discussion

The debate on whether HFOV or CV the best ventilation strategy to support premature infants with RDS has gone on for more than 20 years[6]. A Cochrane review that evaluated 17 studies of 3,652 infants failed to obtain conclusive evidence as to which mechanical ventilation support is more effective; moreover, no Chinese population study was included in that review [19]. These conflicting reports about ventilation support are probably due to heterogeneity in study design, patient characteristics, and outcome definition. Furthermore, the long-term neurodevelopmental outcomes of employing different kinds of ventilation initially for preterm infants with severe RDS are still uncertain[11, 12, 20].

Our prospective and randomized investigation of initial use of HFOV or CV (using SIMV-PSV) on preterm Chinese infants with severe RDS showed that infants receiving HFOV, as compared with those receiving SIMV-PSV, had a significantly reduced incidence of death or BPD; that the duration of mechanical ventilation and hospitalization they required were shorter; and that they had less neurological disability at 18 months of age. The use of HFOV based on the optimal lung volume strategy has been shown to improve survival without an increase in the incidence of

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chronic lung disease [21]. As demonstrated in animal models, HFOV improved lung function and mechanics and reduced inflammatory mediator levels[8]. Animals receiving HFOV with an optimal lung volume strategy showed early and sustained improvement in pulmonary mechanics and gas exchange [22]. Early and exclusive use of HFOV combined with an optimal lung volume strategy had a beneficial effect during the acute phase of lung injury[23] and may be associated with a better neuromotor outcome [12].

RDS occurs in about 50% of preterm infants born at less than 30 weeks of gestational age, and mechanical ventilation and surfactant therapy have become the standard of care in such cases. However, BPD and severe brain injury remain the major causes of morbidity in preterm infants. There is growing evidence that the strategy used during mechanical ventilation may influence the pulmonary outcome in preterm infants with RDS. HFOV is believed to cause less injury to the immature lung compared to other mechanical ventilation techniques, and several reports have shown that HFOV improves pulmonary outcomes in preterm infants with RDS to a greater extent than CV [8, 13]. Other studies, however, did not show a clear benefit on respiratory outcome from using HFOV [11].

The effects of HFOV on the brain are also controversial. Some studies suggest an increased risk of both IVH and PVL [16], but other randomized controlled trials of

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HFOV studies report no difference [11, 21] or report reduced rates of cerebral palsy [12]. IVH and PVL are major risk factors for poor neurodevelopmental outcomes in extremely premature infants [24]. In this study, the incidence of cerebral palsy or MDI <70 was higher in the SIMV-PSV group compared with the HFOV group (Table 6). This is not likely to be related to the relatively high gestational age in the SIMV-PSV group because the mean gestational age between the two groups was not different (Table 1). Furthermore, both IVH and PVL are maturation-dependent events with potential for the subsequent occurrence of cognitive, behavioral, or attention deficits as well as cerebral palsy [25, 26]. The relatively high gestational age should result in relatively low incidences of cerebral palsy or MDI <70. In our study, we found no differences in the occurrence of IVH or PVL between the groups, but the incidence of cerebral palsy was three times higher in the SIMV-PSV group. This indicates that either the predictive value of IVH or PVL, or both, is limited or that the neonatal brain has a significant degree of plasticity.

Previous studies on long-term neurological outcomes among preterm infants report conflicting results [11, 12, 20]. In our case we found a lower incidence of moderate or severe disability in the HFOV group compared to the SIMV-PSV group, in contrast to previous reports, thus indicating that HFOV is relatively safe and effective in treating preterm infants with severe RDS. The discrepancy between our current results and

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those of previous studies is probably attributable to variations in the study's entrance criteria or is related to differences in the study populations.

Exogenous surfactant is the undisputed first-line treatment of choice for RDS in preterm infants in developed countries. However, the high cost of surfactant and basic neonatal supportive care remains a barrier to the implementation of surfactant replacement therapy in low-income countries [27]. Exogenous surfactant is expensive and is not used prophylactically for every preterm infant, especially in small towns and rural areas. A recent retrospective investigation of neonatal respiratory failure in China showed that about 50% of all infants with RDS were treated with surfactant, which was similar to what our study found [28]. The introduction of surfactant replacement treatment significantly reduced mortality in infants with RDS [29]. Therefore, prophylactic surfactant treatment in extremely preterm infants has been recommended, along with protocols on the timing of administration, the surfactant preparation, and the dosage regimen [30].

Despite the effectiveness of surfactant treatment in cases of RDS, BPD remains an important adverse outcome in preterm infants, and its incidence has been directly related to the duration of invasive ventilation via an endotracheal tube [31]. For this reason, pressure support ventilation and volume guarantee (VG) are two new neonatal positive-pressure ventilation techniques that have been developed to avoid

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overdistension and atelectasis [32]. This non-invasive ventilation strategy combines nCPAP with a method of selective surfactant administration and has shown results similar to prophylactic surfactant treatment [33]. However, an early prediction of nCPAP failure in preterm infants with early surfactant rescue treatment is important to reduce BPD [34]. nCPAP has redefined the care of premature neonates but does not sufficiently off-load the burden of high work of breathing, nor is nCPAP capable of providing effective alveolar ventilation for neonates whose condition worsens. As such, approximately 50–67% of very low birth weight premature neonates supported initially with nCPAP develop severe respiratory failure that requires intubation and invasive ventilation. Approximately 25–38% of all premature infants regardless of birth weight fail nCPAP following surfactant administration and require re-intubation and invasive ventilation [35].

Studies have demonstrated that HFOV, when combined with an optimum volume strategy, reduced the need for supplemental surfactant [16, 23] without negatively influencing the outcome [4]. In our study, the need for early surfactant rescue was significantly less in the HFOV group compared to the SIMV-PSV group. Moreover, the incidence of BPD and mortality was lowest in the combined HFOV–surfactant rescue group. These results show that outcomes can be significantly improved if exogenous surfactant is used selectively during HFOV in preterm infants with RDS.

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Some limitations in our study must be mentioned. First, the number of patients lost to follow-up was quite high. This was probably related to a lack of health insurance, the high cost of hospitalization, the fact that some parents were unable to afford the cost of medical treatment, or the poor prognosis of the most severe cases. The migration of some families from rural to urban areas might be another reason cases were lost to follow-up. Second, surfactant was not used for all patients in this study due to its high cost. The decision of whether or not to administer surfactant was determined in consultation between doctors and parents and was based on family income. This is a significant problem, especially for patients from rural areas. Third, there were more males than females in this study, and a similar trend has been reported in other studies based on Chinese populations [28, 36]. This imbalance in sex ratio is reportedly related to China's one-child policy, illegal prenatal screening, and sex-selective abortion in rural areas [37]. The gender effect on the morbidity and mortality of premature infants has been reported previously [38]. Finally, some infants born at 31 to 32 weeks of gestation who were relatively mature were also included in this study, although nowadays they would be less likely to be ventilated. However, the number of such patients was very small and probably did not affect our results. Despite these limitations, our study indicates that initial HFOV is safe and effective in reducing mortality, the incidence of BPD, and neurodevelopmental disabilities at 18 months of age in a Chinese population of preterm infants with severe RDS.

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List of abbreviations

BPD: bronchopulmonary dysplasia; CDP: continuous distending pressure; CDPc: closing continuous distending pressure; CDPo: opening continuous distending pressure; CDPopt: optimal continuous distending pressure; CV: conventional mechanical ventilation; FIO_2: fraction of inspiration oxygen; HFOV: high-frequency oscillatory ventilation; IVH: intraventricular hemorrhage; MAP: mean airway pressure; MDI: mental developmental index; nCPAP: nasopharyngeal continuous positive airway pressure; NEC: necrotizing enterocolitis; NICU: neonatal intensive care units; PaO_2: partial arterial oxygen pressure; PEEP: positive expiratory end pressure; PIP: peak inspiratory pressure; PMA: postmenstrual age; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; SIMV: synchronized intermittent mandatory ventilation.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HS, RC, WK, HX, CZ, and YZ collected data. HS, RC, and CZ were responsible for the study concept, design, data analysis, and interpretation. HS, XW, and CZ drafted and revised the text. All the authors have given final approval to the manuscript.

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Figure legends

Figure 1: Study flow. The schematic flowchart describes the recruitment, randomization, and follow-up evaluation of patients. The term 'dropped out' refers to parents who requested that the patient be withdrawn from the study, and the term 'lost to follow-up' means that contact with the family was lost during the follow-up period.

Figure 2: Respiratory parameters. The dynamic changes of MAP, PaO_2/FIO_2, and $PaCO_2$ between the HFOV and SIMV-PSV groups before and 48 h after randomization. * $p < 0.05$.

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Table 1. Baseline characteristics

	SIMV-PSV (n = 179)	HFOV (n = 177)	*p*-value
Male/Female	116/63	112/65	0.83
Gestational age (wk)	29.5 ± 2.3	29.3 ± 2.5	0.43
Birth weight (g)	1117 ± 241	1129 ± 199	0.61
Apgar Score at 5 min	7.5 ± 1.2	7.7 ± 1.1	0.10
The timing of intubation (h)	5.3 ± 4.8	5.7 ± 5.0	0.44
The timing of randomization (h)	5.9 ± 5.1	5.8 ± 4.9	0.85
Number of nCPAP determining P/F ratio	23 (13)	19 (11)	0.62
Number of CV determining P/F ratio	156 (87)	158 (89)	0.62
Number of infants <1000g	50 (28)	53 (30)	0.73
Prenatal steroid use（%）	131 (73)	136 (77)	0.46
Maternal chorioamnionitis（%）	14 (8)	12 (7)	0.84
Maternal diabetes （%）	4 (2)	5(3)	0.75
Maternal hypertension（%）	50 (28)	53 (30)	0.73
Preeclampsia（%）	9 (5)	10 (6)	0.82
Premature rupture of membranes（%）	55 (31)	51 (29)	0.73
Twins and triplets（%）	48 (27)	50 (28)	0.81
Fetal distress（%）	41 (23)	38 (21)	0.80
Intrauterine growth retardation（%）	11 (6)	9 (5)	0.82
Sepsis（%）	36 (20)	34 (19)	0.89

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Table 2. Primary outcomes

	SIMV-PSV (n = 179)	HFOV (n = 177)	Relative Risk (95% CI) *	*p*-value
Death or BPD (%)	41/179 (22.9)	17/177 (9.6)	0.42 (0.25–0.71)	**0.001**
Death (%)	13/179 (7.3)	4/177 (2.3)	0.31 (0.10–0.94)	**0.04**
BPD at 36 weeks (%)	28/166 (16.9)	13/173 (7.5)	0.45 (0.24–0.83)	**0.01**
Severe BPD (%)	10/166 (5.4)	3/173 (1.7)	0.29 (0.08–1.03)	**0.049**

* CI = confidence interval

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Table 3. Subgroups according to baseline characteristics

Groups	SIMV-PSV	HFOV	total	χ^2	*p*-value
Sex					
Male (%)	116 (65)	112 (63)	228 (64)	0.090	0.764
Female (%)	63 (35)	65 (37)	128 (36)		
Gestational age					
<28 weeks (%)	53 (30)	56 (32)	109 (31)	2.049	0.359
28–30 weeks (%)	110 (61)	112 (63)	222 (62)		
30–32 weeks (%)	16 (9)	9 (5)	25 (7)		
Birth weight					
<1000 g (%)	50 (28)	53 (30)	103 (29)	0.175	0.676
1000–1500 g (%)	129 (72)	124 (70)	253 (71)		
Antenatal steroid					
Yes (%)	131 (73)	136 (77)	267 (75)	0.633	0.426
No (%)	48 (27)	41 (23)	89 (25)		
Surfactant					
Yes (%)	110 (61)	79 (45)	189 (53)	10.110	**0.001**
No (%)	69 (39)	98 (55)	167 (47)		
Intubation time					
<4h (%)	88 (49)	89 (50)	177 (50)	0.045	0.833
>4h (%)	91 (51)	88 (50)	179 (50)		
Multiple birth					
Single (%)	131(73)	127 (72)	258 (72)	0.092	0.762
Twin (%)	48 (27)	50 (28)	98 (28)		

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Table 4. Subgroup analyses for primary outcomes

	Death or BPD (n = 58)				Death (n = 17)				BPD (n = 41)			
	SIMV-PSV	HFOV	Relative Risk (95% CI)	*p*-value for interaction	**SIMV-PSV**	HFOV	Relative Risk (95% CI)	*p*-value for interaction	**SIMV-PSV**	HFOV	Relative Risk (95% CI)	*p*-value for interaction
Sex				0.84				0.79				0.71
Male (%)	28/116 (24)	11/112 (10)	0.41[0.21-0.78]		9/116 (8)	3/112(3)	0.35[0.10-1.24]		19/107 (18)	8/109 (7)	0.41[0.19-0.90]	
Female (%)	13/63 (21)	6/65 (9)	0.45[0.18-1.10]		4/63 (6)	1/65 (2)	0.24[0.03-2.11]		9/59 (15)	5/64 (8)	0.51[0.18-1.44]	
Gestational age				0.72				0.06				0.53
<28 weeks (%)	21/53 (40)	10/56 (18)	0.45[0.24-0.87]		9/53 (17)	2/55 (4)	0.21[0.05-0.95]		12/44 (27)	8/54 (15)	0.54[0.24-1.21]	
28–30 weeks (%)	19/110 (16)	6/112 (4)	0.31[0.13-0.75]		4/110 (4)	1/112(1)	0.25[0.03-2.16]		15/106 (14)	5/111 (5)	0.26[0.12-0.85]	
30–32 weeks (%)	2/16 (13)	1/9 (11)	0.89[0.09-8.50]		0/16 (0)	1/9 (1)			1/16 (6)	0/8 (0)		
Birth weight				0.83				0.56				0.47
<1000 g (%)	18/50 (43)	9/53 (17)	0.47[0.23-0.95]		8/50 (16)	2/53 (4)	0.24[0.05-1.06]		10/42 (24)	7/51 (14)	0.58[0.24-1.38]	
1000–1500 g (%)	23/129 (18)	8/124 (6)	0.36[0.17-0.78]		5/129 (4)	2/124(2)	0.42[0.08-2.11]		18/122 (15)	6/122 (5)	0.33[0.14-0.81]	
Antenatal steroid				0.47				0.15				0.90
Yes (%)	23/131 (18)	8/136 (6)	0.34[0.16-0.72]		8/131 (6)	1/136(1)	0.12[0.02-0.95]		15/123 (12)	7/135 (5)	0.43[0.18-1.01]	
No (%)	18/48 (38)	9/41 (22)	0.59[0.30-1.16]		5/48 (10)	3/41 (7)	0.70[0.18-2.76]		13/43 (30)	6/38 (16)	0.52[0.22-1.24]	
Surfactant				0.50				0.86				0.48
Yes (%)	18/110 (16)	3/79 (4)	0.23[0.07-0.76]		6/110 (5)	1/79 (1)	0.23[0.03-1.89]		12/104 (12)	2/78 (3)	0.22[0.05-0.96]	
No (%)	23/69 (33)	14/98 (14)	0.43[0.24-0.77]		7/69 (10)	3/98 (3)	0.30[0.08-1.13]		16/62 (26)	11/95(12)	0.45[0.22-0.90]	
Intubation time				0.61				0.43				0.91
<4h (%)	32/88 (36)	13/89 (15)	0.40[0.23-0.71]		9/88 (10)	2/89 (2)	0.22[0.05-0.99]		23/79 (29)	11/87(13)	0.43[0.23-0.83]	
>4h (%)	9/91 (10)	4/88 (5)	0.46[0.15-1.44]		4/91 (4)	2/88 (2)	0.52[0.10-2.75]		5/87 (6)	2/86 (2)	0.41[0.08-2.03]	
Multiple birth				0.48				0.36				0.99
Single (%)	27/131 (21)	9/127 (8)	0.34[0.17-0.70]		7/131 (5)	1/127(1)	0.15[0.02-1.18]		20/124 (16)	9/126 (7)	0.44[0.21-0.94]	
Twin (%)	14/48 (29)	8/50 (18)	0.55[0.25-1.19]		6/48 (13)	3/50 (6)	0.48[0.13-1.81]		8/42 (19)	4/47 (9)	0.45[0.15-1.38]	

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Table 5. Secondary outcomes

	SIMV-PSV (n = 179)	HFOV (n = 177)	*p*-value
Mechanical ventilation (days)	5.7 ± 5.0	4.0 ± 4.0	**<0.001**
Hospital stay for survivors (days)	31.6 ± 21.7	27.0 ± 20.2	**0.04**
Intracranial hemorrhage grade III–IV	27/179 (15)	30/177 (17)	0.67
Periventricular leukomalacia	16/179 (9)	10/177 (6)	0.31
Surfactant requirement (%)	110/179 (62)	79/177 (45)	**0.002**
Surfactant requirement > 1 dose	40/179 (22)	18/177 (10)	**0.002**
Timing of surfactant > 1 dose	13.9 ± 2.7	19.3 ± 2.5	**<0.001**
ROP (≥stage 2) (%)	19/179 (11)	8/177 (5)	**0.04**
Pulmonary hemorrhage (%)	27/179 (15)	14/177 (8)	**0.045**
Patent ductus arteriosus (%)	45/179 (25)	41/177 (23)	0.71
Necrotizing enterocolitis (%)	16 / 179 (9)	13 /177 (7)	0.7
Pneumothorax (%)	21/179 (12)	10/177 (6)	0.06

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Table 6. Neurodevelopmental outcomes at 18 months of corrected age

	SIMV-PSV (n = 143)	HFOV (n = 145)	*p*-value
Cerebral palsy (%)	14/143 (10)	5/145 (3)	**0.03**
MDI <70 (%)	45/143 (31)	29/145 (20)	**0.03**
Visual impairment (%)	4/143 (3)	2/145 (1)	0.45
Severe hearing loss (%)	4/143 (3)	3/145 (2)	0.72

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Fig.1

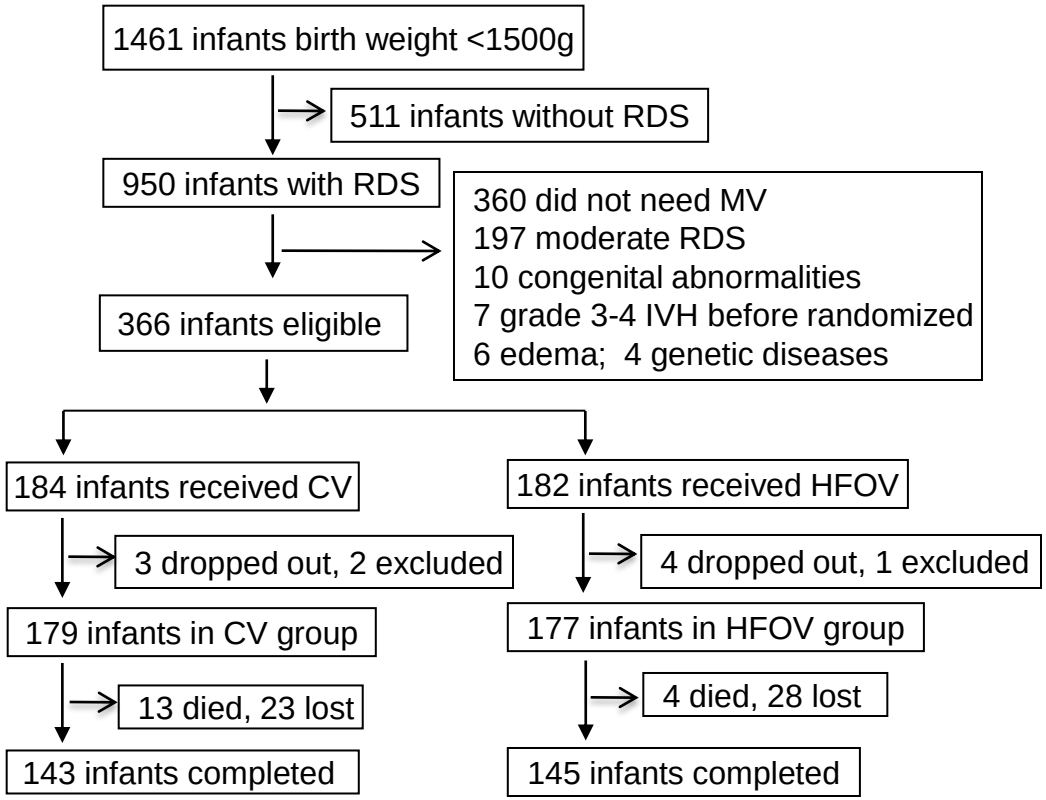

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Fig.2