Am J Transl Res 2021;13(5):5137-5146
www.ajtr.org /ISSN:1943-8141/AJTR0129489

Original Article

Efficacy comparison of high-frequency oscillatory ventilation with continuous nasal positive airway pressure in neonatal respiratory distress syndrome treatment

Jincai Lin*, Ying Shen*, Jiyuan Liu, Yinzhu Luo, Xiaoying Ma, Liyan Zhang

*Department of Neonatology, The Affiliated Fuzhou Children Hospital of Fujian Medical University, Fuzhou 350001, Fujian, China. *Equal contributors and co-first authors.*

Received January 3, 2021; Accepted February 23, 2021; Epub May 15, 2021; Published May 30, 2021

Abstract: Objectives: To compare the treatment efficacy of high-frequency oscillatory ventilation (HFOV) with nasal continuous positive airway pressure (NCPAP) in the treatment of neonatal respiratory distress syndrome (NRDS) and its effect on the expression of high-mobility group protein B1 (HMGB1). Methods: A total of 180 infants with NRDS admitted to our hospital were included and randomly assigned into the HFOV group (receiving conventional therapy and HFOV), the NCPAP group (receiving conventional therapy and NCPAP), and the conventional group (receiving conventional therapy). Qi and blood indicators, heart rate, respiratory frequency, PCO_2, and PaO_2 were observed and recorded before and after treatment, together with complications after treatment. ELISA was performed for HMGB1 Results: A distinctly lower partial pressure of carbon dioxide (PCO_2) but higher arterial partial pressure of oxygen (PaO_2) was observed in the HFOV and NCPAP groups than in the conventional group ($P < 0.05$), whereas infants in the HFOV group exhibited slight differences in these two indicators from their counterparts in the NCPAP group ($P > 0.05$). The serum HMGB1 levels in both groups were significantly higher than those in the conventional group ($P < 0.05$). Discussion: Both HFOV and NCPAP are feasible in the treatment of NRDS and may play a role in the inhibition of HMGB1.

Keywords: NRDS, HFOV, NCPAP, conventional therapy, HMGB1

Introduction

Neonatal respiratory distress syndrome (NRDS) is one of the most common medical conditions affecting premature babies [1]. It is caused by alveolar hypoplasia and the production of pulmonary surfactant [2], it is also a common phenomenon requiring care in the neonatal intensive care unit (NICU) [3]. NRDS is a respiratory distress symptom that usually occurs in preterm infants within 6 h of birth; these symptoms may aggravate and even cause respiratory failure, resulting in death [4]. The treatment options for NRDS vary from surfactant replacement therapy, ventilator therapy, and oxygen therapy to antenatal corticosteroid therapy. However, they show little benefit in the outcomes in newborns with severe NRDS [5], necessitating the development of new techniques.

A previous study investigated the early inflammatory factors related to NRDS, but these early inflammatory factors appeared early in the body and existed for a short time, which only contributed to the early diagnosis of NRDS, and there are limitations in the evaluation of the condition and prognosis of NRDS [3]. Therefore, researchers have begun to pay attention to a class of advanced inflammatory mediators represented by high mobility group protein B1 (HMGB1) that appear later in the body and exist for a long time, in order to find a possible reference index for the evaluation of the condition and prognosis of NRDS. HMGB1 is an important inflammatory mediator. It is secreted by immune cells and released into the cytoplasm and even extracellularly. It participates in and mediates the inflammatory response of various diseases such as acute lung injury, sepsis and arthritis in

adults. The severity of the disease is closely related to the prognosis [6].

High-frequency oscillatory ventilation (HFOV) is a unique mode of mechanical ventilation that works through a non-traditional gas exchange mechanism whereby ventilation is available at extremely low tidal volume and high frequency [6]. It is provided with an oscillating pump to deliver active exhalation and inhalation, oscillating around a relative pressure and a constant pressure. Its purpose is to maintain sufficient lung volume and improve oxygenation [7]. Nasal continuous positive airway pressure (NCPAP) is a strategy for noninvasively applying positive airway pressure throughout the respiratory cycle through the application of bias flow of respiratory gas to an apparatus attached to the nose. Treatment with NCPAP reduces the risk of mechanical ventilation and is effective in reducing the incidence of chronic lung diseases [8]. NCPAP has the potential to reduce mechanical ventilation-related lung injury and has become a common strategy for the early respiratory management of premature infants [9].

Considerable studies have been conducted on HFOV and NCPAP in the treatment of NRDS [10, 11], but few has focused on comparing their applications. This trial was designed to provide a reference for NRDS treatment by comparing the clinical efficacy and safety of HFOV with NCPAP and their effects on HMGB1.

Materials and methods

General data

A total of 180 infants with NRDS admitted to our hospital were enrolled and divided the HFOV group (n = 60) with HFOV based on the conventional therapy, the NCPAP group (n = 60) with NCPAP and the conventional therapy, or conventional group (n = 60) treated with the conventional therapy. Randomization was performed using a computerized randomization algorithm with sequential numbering. Of the 180 infants, patients in the HFOV group included 31 males and 29 females, aged (35.5 ± 9.6) days old with a birth weight of (1140 ± 343) g. Patients in the NCPAP group included 36 males and 24 females, aged (35.4 ± 9.5) days old with a birth weight of (1030 ± 565) g, while the conventional group consisted of 32 males and 28 females, aged 35.9 ± 9.4 days old with a birth weight of (1048 ± 315) g.

Inclusion and exclusion criteria

Inclusion criteria were as follows: confirmation of NRDS by lung ultrasound [12]; generally complete clinical data; the presence of clinical symptoms such as tachypnea, air bronchogram, and coarse lung margin. NRDS diagnostic criteria: shortness of breath (> 60 breaths/min), exhaled groaning, and three-concave signs during inhalation soon after birth. The condition progressively worsens; blood gas analysis shows a decrease in arterial blood oxygen partial pressure and an increase in carbon dioxide partial pressure. High, negative value of alkali surplus increases. X-ray manifestations that are in line with the characteristics of RDS are grade I: the brightness of the two lung fields is significantly reduced, and fine particles and net-like shadows are evenly scattered; grade II: in addition to the aggravation of grade I, there is visible Bronchial inflation signs extending to the middle and outer areas of the lung field; Grade III: the disease is aggravated, the brightness of the lung field is more reduced, and the heart and diaphragm are blurred; Grade IV: the entire lung field is white lung, and the bronchial inflation signs are more obvious, like bald leaves branches.

Exclusion criteria were as follows: extreme preterm infants; severe somatic conditions; other infectious diseases; severe congenital heart diseases; congenital malformations; infants with shock; infants with history of recurrent respiratory tract infection; infants with measles, whooping cough, or other respiratory diseases; infants with contraindication for ventilation therapies; infants who were treated with HFOV or NCPAP after the failure of conventional ventilation. Written informed consent was obtained from the subjects' guardians prior to trial entry. The trial was approved by the Medical Ethics Committee of the Affiliated Fuzhou Children's Hospital of Fujian Medical University.

Treatment

If the FiO_2 level of infants in the three groups was < 35% to maintain the oxygen saturation level required by the infants, 100-120 mg/kg of Curosurf (Chiesi Farmaceutici S.P.A., Italy, arti-

cle no.: H20181201) was used, with the first dose of 200 μmg/kg, and if necessary, the second dose was adjusted to 100 μmg/kg. The surfactant was administered according to the intubation-surfactant-extubation method (INSURE). If the FiO_2 content decreased below 30%, the infant was weaned to a humidified high-flow nasal cannula (HHFNC) (Bubble CPAP, Fisher & Paykel Healthcare Corporation Ltd.). In addition, HHFNC was discontinued when the FiO_2 content reached 21% and respiratory distress improved. NCPAP or HFOV failure was defined as apnea or pH less than 7.2 and partial CO_2 pressure greater than 60 mmHg.

Infants in the three groups were intubated by a respiratory tube, and received routine treatment such as anti-infection and supportive treatment. Infants in conventional group were given non-invasive high-frequency ventilator (Cat. No. 3090; Shanghai Meddo Medical Devices Co., Ltd, Shanghai, China) with an initial inhaled oxygen concentration ranging from 55% to 80%, peak inspiratory pressure of 20-25 cmH_2O, end-expiratory pressure of 5-8 cmH_2O, respiratory frequency of 40 times/min and inspiration time of 0.3-0.5 s. The vital signs of the infant monitored closely at all times, and the parameters were adjusted appropriately. The ventilator was evacuated when the infant's condition was stable. Infants in HFOV group received both routine therapy and HFOV provided by a non-invasive high-frequency ventilator (Cat. No. 3090; Shanghai Meddo Medical Devices Co., Ltd, Shanghai, China) with an initial inhaled oxygen concentration ranging from 25% to 100% and oscillation frequency between 9 Hz and 15 Hz. After ventilation, the amplitude and other parameters of the ventilator were adjusted. In the case of thoracic oscillation in the subjects, the ventilator was immediately stopped. Treatment with HFOV ensured an air flow rate within 11-15 L/min and PCO_2 in arterial blood within 35%-50%, while the inhaled oxygen concentration was gradually reduced.

Infants in the NCPAP group were treated with both routine therapy and NCPAP. NCPAP was started with a non-invasive high-frequency ventilator (Cat. No. 3090; Shanghai Meddo Medical Devices Co., Ltd, Shanghai, China). Initial NHFOV settings were oxygen concentration of 35%-50% and end-expiratory pressure of 4-6 cmH_2O. Then, observations followed. The oxygen concentration was lowered to 20%-34% over time and the end-expiratory pressure gradually decreased to 2-3 cmH_2O until withdrawing the ventilator.

Observation targets

The observation targets included ventilation time, oxygen exposure time, ventilator duration, and oxygen consumption time after ventilator weaning, which were recorded in the three groups. Qi and blood indicators, heart rate, respiratory frequency, PCO_2, and PaO_2 were observed and recorded before and after treatment, together with complications after treatment.

Efficacy evaluation criteria

The efficacy evaluation criteria were as follows: High efficacy: disappearance of clinical symptoms and carbon dioxide and blood oxygen saturation within the normal range. Good efficacy: improved clinical symptoms and normal carbon dioxide and blood oxygen saturation. No efficacy: no remarkable amelioration of clinical symptoms, carbon dioxide, and blood oxygen saturation. Total efficacy rate was calculated as follows: Total efficacy rate = (number of cases with high efficacy + number of cases with good efficacy)/total number of cases in each group × 100%.

Determination of HMGB1

All subjects had blood samples of 5 mL taken under a fasting state. The blood was centrifuged at 1500 r/min for 10 min and stored in a low-temperature freezer at -80°C for follow-up trials. ELISA assay was performed in accordance with the instructions of ELISA Kit for HMGB1 (BS-0664R-2; Shanghai Zhenyu Biotechnology Co., Ltd.). The kit and the samples were taken out of the freezer 30 min ahead of the assay to warm them to room temperature. The next procedure was to set a blank well (following the same steps as for the standard well and sample well, apart from no samples or enzyme-labeled reagents being added), a standard well, and a sample well. To the enzyme-labeled coated plate, 50 μL of standard sample was precisely added for the case of the standard well, whereas 40 μL of sample diluent was first added to the sample well, followed by 10 μL of the sample to be assayed. Subsequently,

the plate was sealed with microplate sealers and incubated in an incubator at 37°C for 30 min. The next step was to discard the liquid and pat the plate dry with absorbent paper, followed by the addition of washing liquid to each well; it was left to stand for 30 s, after which the washing liquid was discarded. The above steps were repeated five times. Except for in the blank well, 50 μL of enzyme-labeled reagent was placed into each well, and then the plate was sealed with microplate sealers for incubation in an incubator at 37°C for 30 min. After the liquid was discarded and the plate patted dry with absorbent paper, the washing liquid was added to each well, which was then left to stand for 30 s, followed by discarding the washing liquid. The above steps were repeated five times. Each well was first provided with 50 μL of A developer, and then 50 μL of B developer with gentle oscillation of the wells to mix the solution evenly. The plate was incubated at 37°C for 15 min before the addition of 50 μL of stop buffer to each well. Next, the optical density (OD) value at 450 nm was measured for each well within 15 min with a Fully Automated Chemiluminescence Immunoassay Analyzer (Diamond; Beijing Qinye Yongwei Technology Co., Ltd.). Finally, the HMGB1 concentration was calculated.

Statistical methods

Statistical analysis was performed using IBM SPSS Statistics 21.0 (EASYBIO, China). The intra-group enumeration data were expressed as case number/percentage [n (%)], while the chi-square test was adopted for inter-group enumeration data. The chi-squared test with continuity correction was preferred if the theoretical frequency was below 5. For measurement data, mean ± standard deviation ($\bar{x}$ ± SD) was used in this trial. Paired *t*-test was used for comparison between pre-treatment data and post-treatment data for each group. One-way ANOVA was applied for comparisons of the means of all groups. Data from two groups were compared by the LSD *t*-test, and the difference was considered statistically significant when $P < 0.05$.

Results

General data

No significant differences were found among the three groups in variables including sex, age, birth weight, place of residence, nationality, pathology, clinical symptoms, delivery mode, gestational age, parents' smoking history and alcohol abuse history ($P > 0.05$) (**Table 1**).

Comparison of clinical indicators

No marked differences were observed in oxygen exposure time, ventilation time, ventilator duration, and oxygen consumption time after ventilator weaning between the HFOV and NCPAP groups ($P > 0.05$), but these variables showed lower values in conventional group ($P < 0.05$) (**Table 2**).

Comparison of blood gas before and after treatment

Qi and blood indices did not differ markedly before treatment among the three groups ($P > 0.05$). However, HFOV and NCPAP groups had better PaO_2, $PaCO_2$, and SaO_2 than the conventional group after treatment ($P < 0.05$), although there was no significant difference between these two groups ($P > 0.05$) or in pH level after treatment among the three groups ($P > 0.05$) (**Table 3**).

Comparison of heart rate and respiration frequency before and after treatment

Remarkable differences were found in neither heart rate nor respiratory frequency among the three groups before treatment ($P > 0.05$), nor between HFOV and NCPAP groups after treatment. However, in both HFOV and NCPAP groups, these two indicators were much more favorable than those in the conventional group ($P < 0.05$) (**Figure 1**).

Comparison of PCO_2 and PaO_2 before and after treatment

PCO_2 and PaO_2 varied slightly among the three groups before treatment ($P > 0.05$). After treatment, PCO_2 in the HFOV and NCPAP groups was much lower than that in the conventional group ($P < 0.05$), while PaO_2 in the HFOV and NCPAP groups was significantly higher than that in conventional group ($P < 0.05$). There was no significant difference in PCO_2 and PaO_2 between the HFOV and NCPAP groups after treatment ($P > 0.05$) (**Figure 2**).

Comparison of clinical efficacy after treatment

In the HFOV group, high efficacy was found in 42 cases (70.00%), good efficacy in 13

Table 1. General clinical data of infants in the three groups [n (%)] ($\bar{x}$ ± SD)

Terms	HFOV group (n = 60)	NCPAP group (n = 60)	Conventional group (n = 60)	F/χ^2 value	*P* value
Sex				0.943	0.624
Male	31 (51.67)	36 (60.00)	32 (53.33)		
Female	29 (48.33)	24 (40.00)	28 (46.67)		
Age (d)	35.5 ± 9.6	35.4 ± 9.5	35.9 ± 9.4	0.047	0.955
Birth weight (g)	1140 ± 343	1030 ± 565	1048 ± 315	0.011	0.989
Place of residence				0.933	0.627
Urban	27 (45.00)	32 (53.33)	31 (51.67)		
Rural	33 (55.00)	28 (46.67)	29 (48.33)		
Nationality				2.880	0.237
Han nationality	30 (50.00)	39 (65.00)	36 (60.00)		
Minorities	30 (50.00)	21 (35.00)	24 (40.00)		
Pathology				5.704	0.681
Infectious pneumonitis	11 (18.33)	9 (15.00)	13 (21.67)		
Aspiration pneumonitis	14 (23.33)	16 (26.67)	11 (18.33)		
Wet lung	16 (26.67)	14 (23.33)	15 (25.00)		
RDS	13 (21.67)	12 (20.00)	8 (13.33)		
HIE	6 (10.00)	9 (15.00)	13 (21.67)		
Clinical symptoms				5.281	0.508
Dyspnea	18 (30.00)	15 (25.00)	21 (35.00)		
Cyanosis	22 (36.67)	19 (31.67)	13 (21.67)		
Change of mind	7 (11.67)	12 (20.00)	9 (15.00)		
Cyclical variation	13 (21.67)	14 (23.33)	17 (28.33)		
Delivery mode				0.321	0.852
Eutocia	35 (58.33)	37 (61.67)	34 (56.67)		
Cesarean section	25 (41.67)	23 (38.33)	26 (43.44)		
Gestational age (weeks)	35.1 ± 3.1	35.7 ± 3.4	35.4 ± 3.3	0.505	0.604
Parents' smoking history				0.884	0.643
Yes	26 (43.44)	21 (35.00)	24 (40.00)		
No	34 (56.67)	39 (65.00)	36 (60.00)		
Parents' alcohol abuse history				0.556	0.758
Yes	22 (36.67)	24 (40.00)	26 (43.44)		
No	38 (63.33)	36 (60.00)	34 (56.67)		

Table 2. Comparison of clinical indicators for the three groups ($\bar{x}$ ± SD)

	HFOV group (n = 60)	NCPAP group (n = 60)	Conventional group (n = 60)	*F*	*P*
Oxygen exposure time (h)	122.21 ± 2.34*	123.78 ± 2.31*	154.34 ± 2.93	3045.000	< 0.001
Ventilation time (h)	89.55 ± 1.12*	88.23 ± 1.16*	112.34 ± 2.09	4746.000	0.001
Ventilator duration (h)	73.22 ± 1.98*	74.21 ± 1.96*	85.54 ± 1.23	909.300	< 0.001
Oxygen consumption time after ventilator weaning (h)	52.33 ± 1.09*	52.21 ± 1.07*	63.93 ± 1.35	1963.000	< 0.001

Note: After treatment, *$P < 0.05$ in HFOV and NCPAP groups compared with conventional group.

(21.67%), and no efficacy in 5 (8.33%), with a total efficacy rate of 91.67%. The total efficacy rate was 90.00% in the NCPAP group, with high efficacy in 45 cases (75.00%), good efficacy in 9 (15.00%), and no efficacy in 6 (10.00%). Among infants in the conventional group, 31 experienced high efficacy (51.67%) and 13 (21.67%) good efficacy, but a total of 16

Table 3. Qi and blood indexes of the three groups before and after treatment ($\bar{x}$ ± SD)

Group	n	PaO_2 (mmHg)		$PaCO_2$ (mmHg)		SaO_2 (mmHg)		pH	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
HFOV group	60	6.03 ± 1.01	6.73 ± 1.11$^{*,\#}$	7.65 ± 0.21	7.73 ± 0.33$^{*,\#}$	7.16 ± 0.62	7.21 ± 0.63$^{*,\#}$	7.26 ± 0.62	7.30 ± 0.63$^{*,\#}$
NCPAP group	60	6.15 ± 1.21	6.84 ± 1.15$^{*,\#}$	7.55 ± 0.35	7.75 ± 0.36$^{*,\#}$	7.15 ± 0.61	7.20 ± 0.65$^{*,\#}$	7.25 ± 0.61	7.29 ± 0.65$^{*,\#}$
Conventional group	60	6.05 ± 1.18	7.73 ± 0.63*	7.59 ± 0.27	7.55 ± 0.41*	7.16 ± 0.61	7.46 ± 0.66*	7.27 ± 0.60	7.54 ± 0.60*
F		0.192	18.340	1.904	5.371	0.005	3.112	0.016	3.057
P		0.826	< 0.001	0.152	0.005	0.995	0.047	0.984	0.049

Note: $^{*}P < 0.05$ after treatment compared with that before treatment, and $^{\#}P < 0.05$ compared with that in conventional group after treatment.

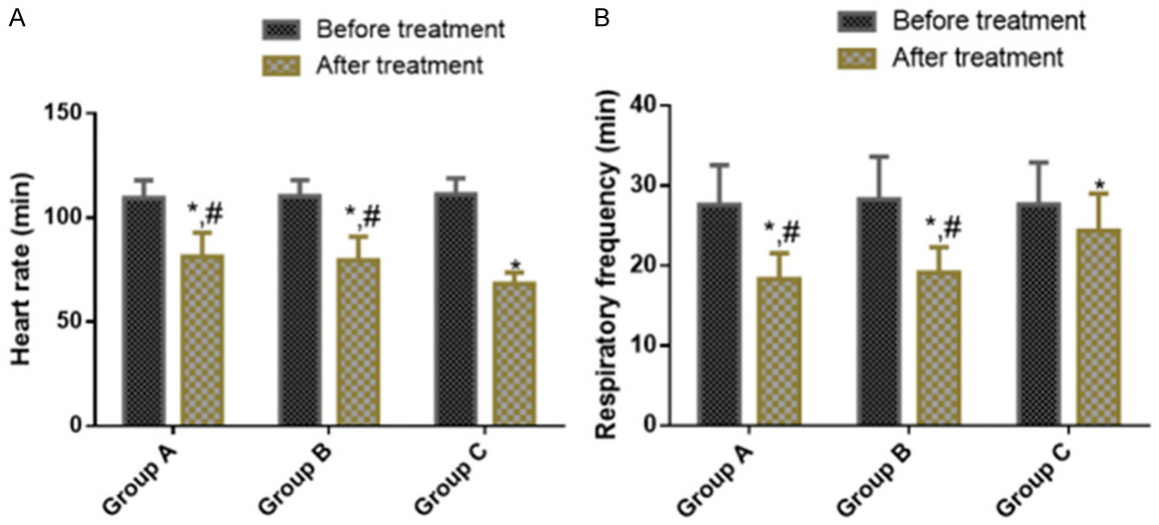

Figure 1. Comparison of Heart Rate and Respiration Frequency before and after Treatment. Remarkable differences were not found in heart rates among all groups before treatment ($P > 0.05$), or between the HFOV group and NCPAP group after treatment, although these two groups had much more favorable heart rates than the conventional group ($P < 0.05$) (A). Significant differences were not found in respiratory frequencies among all groups before treatment ($P > 0.05$), or between the HFOV group and NCPAP group after treatment, although these two groups had much more favorable respiratory frequencies than the conventional group ($P < 0.05$) (B). Note: $^{*}P < 0.05$ after treatment compared with that before treatment, and $^{\#}P < 0.05$ compared with that in conventional group after treatment.

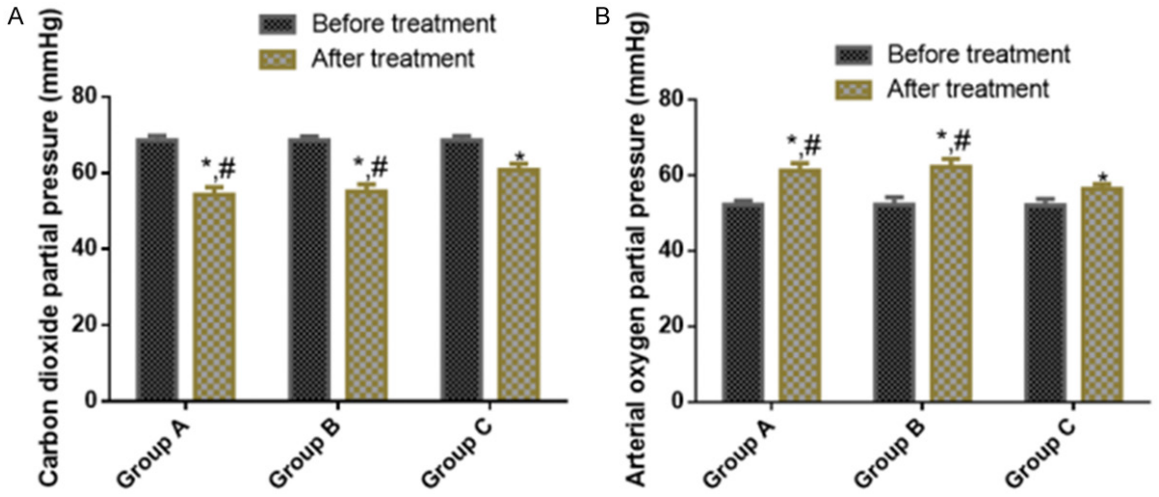

Figure 2. Comparison of PCO_2 and PaO_2 before and after Treatment. PCO_2 and PaO_2 varied slightly among the three groups before treatment ($P > 0.05$). After treatment, PCO_2 was much lower in the HFOV and NCPAP groups than that

in the conventional group ($P < 0.05$) (A), while PaO_2 was significantly higher than that in the conventional group ($P < 0.05$) (B). There was no significant difference in PCO_2 and PaO_2 between the HFOV and NCPAP groups after treatment ($P > 0.05$). Note: $^*P < 0.05$ after treatment compared with that before treatment, and $^\#P < 0.05$ compared with that in conventional group after treatment.

Table 4. Comparison of treatment efficacy among the three groups [n (%)]

Efficacy	HFOV group (n = 60)	NCPAP group (n = 60)	Conventional group (n = 60)	χ^2 value	*P* value
High efficacy	42 (70.00)	45 (75.00)	31 (51.67)	-	-
Good efficacy	13 (21.67)	9 (15.00)	13 (21.67)	-	-
No efficacy	5 (8.33)	6 (10.00)	16 (26.67)	-	-
Total efficacy rate	55 (91.67)	54 (90.00)	44 (73.33)	9.673	0.007

Table 5. Comparison of post-treatment complications among the three groups [n (%)]

Group	HFOV group (n = 60)	NCPAP group (n = 60)	Conventional group (n = 60)	χ^2 value	*P* value
P value	2 (3.33)	1 (1.67)	5 (8.33)	3.401	0.183
Intracranial hemorrhage	1 (1.67)	0 (0.00)	3 (5.00)	3.580	0.167
Ventilator-associated pneumonia	2 (3.33)	3 (5.00)	4 (6.67)	0.702	0.704
Total complications	5 (8.33)	4 (6.67)	12 (15.00)	6.146	0.046

Table 6. Comparison of HMGB1 levels among three groups after treatment ($\bar{x} \pm SD$)

Group	Number of cases	HMGB1 (pg/mL)
HFOV group	60	579.95 ± 81.26*
NCPAP group	60	571.55 ± 75.55*
Conventional group	60	785.85 ± 184.76
F		57.090
P		< 0.001

Note: After treatment, $^*P < 0.05$ in HFOV and NCPAP groups compared with conventional group.

(26.67%) lacked efficacy, making the total efficacy rate of 73.33%. As such, the HFOV and NCPAP groups had no significant differences in total efficacy rates ($P > 0.05$), although their rates were much higher than that of conventional group ($P < 0.05$) (**Table 4**).

Comparison of complications after treatment

In the HFOV group, pneumothorax occurred in 2 infants (3.33%), intracranial hemorrhage in 1 (1.67%), and ventilator-associated pneumonia in 2 (3.33%), amounting for an incidence of total complications of 8.33%. In the NCPAP group, 1 infant had pneumothorax (1.67%), 0 had intracranial hemorrhage, and 3 had ventilator-associated pneumonia (5.00%), making the incidence of total complications of 6.67%. In the conventional group, pneumothorax occurred in 5 (8.33%), intracranial hemorrhage in 3 (5.00%), and ventilator-associated pneumonia in 4 (6.67%), making the incidence of total complications of 15.00%. The incidence of total complications did not differ markedly between the HFOV and NCPAP groups ($P > 0.05$), but both of their levels were lower than that in the conventional group ($P < 0.05$) (**Table 5**).

Comparison of HMGB1 levels among three groups after treatment

The serum HMGB1 levels did not differ markedly between the HFOV group and NCPAP group ($P > 0.05$), but the serum HMGB1 levels in both groups were significantly higher than those in the conventional group ($P < 0.05$) (**Table 6**).

Discussion

Respiratory distress syndrome (RDS) is still a major disease in premature infants [13]. Pulmonary surfactant is a complex mixture of phospholipids and proteins, whose function is to reduce surface tension at the alveolar-air interface and prevent pulmonary collapse; it is formed in the physiological transition from fetus to newborn [14]. Deficiency of pulmonary

surfactant production and function, coupled with immature lung structure, is the major cause of morbidity and mortality of premature infants, especially in RDS [15, 16]. Studies have shown that NRDS treatment involves risks such as bronchopulmonary dysplasia or chronic lung disease due to mechanical ventilation (which is required to maintain neonatal vitality) [17]. In this context, there is an urgent need for alternative options for treating NRDS.

HFOV was previously thought to be a mode of lung protective ventilation with high flow rates and low tidal volumes, which contributes to the avoidance of volutrauma, such as excessive alveolar distension and high peak airway pressures, thereby facilitating lung recruitment. HFOV delivers continuous airway pressure to prevent lung collapse [18, 19]. NCPAP is a separate channel that combines a variable flow rate and is available for inhaling and exhaling gases. When a neonate inhales and exhales, gases are inhaled into the airway through the smallest pathway, and exhaled out of the smallest exhalation tube or exhaust tube, thus reducing exhalation resistance [20]. A study by Lin et al. [21] showed that compared with conventional mechanical ventilation, HFOV is a safe and reliable therapy for the treatment of RDS in premature infants, which can reduce the incidence of complications and shorten the ventilation time. Zannin et al. [22] demonstrated the effects of NCPAP in mild and severe premature infants, including improved gas exchange, stabilization of respiratory volume and end-expiratory lung volume at a lower level, and enhancing oxygenation. In both studies, it has been proven that HFOV and NCPAP are effective in treating NRDS. Regarding the trial in the present study, the findings indicated that the HFOV group and NCPAP groups were largely superior to the conventional group in terms of post-treatment factors such as clinical indicators, Qi and blood indices, heart rate, respiratory frequency, PCO_2, PaO_2, clinical efficacy, and incidence of complications, but no significant difference was found in these variables between the former two groups. This indicated the feasibility of both HFOV and NCPAP for the treatment of NRDS.

Recent studies have shown that a variety of cytokines and inflammatory mediators play critical roles in the physiological and pathological processes of NRDS [23]. As an inflammatory factor, HMGB1 is expressed in all eukaryotic cells and is involved in cell migration, growth, differentiation, and proliferation as well as the upgrading and growth of chromosomin, which is also closely related to various diseases [24]. In a study by Xue et al. [25], determination of the level of HMGB1 in the serum of infant patients may better predict the incidence and mortality of NRDS. In addition, Wang et al. [26] also found that the determined HMGB1 level was associated with the development and prognosis of NRDS. In order to obtain a deeper understanding of the possible mechanisms of action of HFOV and NCPAP in NRDS treatment, ELISA was used after treatment to determine the serum HMGB1 level in neonates in this trial. The results did not show a significant difference in HMGB1 levels between the HFOV and NCPAP groups, but these levels were distinctly lower in both groups than those in the conventional group. This proved that NRDS caused the physiological and pathological process of HMGB1 elevation at any time, while HFOV and NRDS were effective in inhibiting the HMGB1 level to treat NRDS. Thus, treatment of NRDS by inhibiting inflammatory reactions may be one of the mechanisms of HFOV and NCPAP, but the specific features of these different options remain to be determined.

This trial was performed in strict accordance with the inclusion and exclusion criteria to guarantee its rigor and reliability by eliminating significant differences among HFOV, NCPAP and conventional groups in clinical baseline data such as sex and age. Although the trial confirmed the feasibility of HFOV and NCPAP for NRDS treatment, there were certain limitations, including a lack of follow-up and a relatively small sample size. Therefore, there is a need for future studies to support the findings of this trial.

In conclusion, both HFOV and NCPAP are feasible for treating NRDS, and may work through the inhibition of HMGB1, despite some intra-treatment complications under control treatment.

Acknowledgements

This work was supported by the Fuzhou Key Clinical Specialty Construction Project (20191-

2007) and the Fuzhou Science and Technology Plan Project (2019-SZ-54) and Fuzhou Key Clinical Specialty Construction Project (201912007).

Disclosure of conflict of interest

None.

Address correspondence to: Liyan Zhang, Department of Neonatology, The Affiliated Fuzhou Children Hospital of Fujian Medical University, No. 145, Middle 817 Middle Road, Gulou District, Fuzhou 350001, Fujian, China. Tel: +86-0591-87117772; +86-13950418319; E-mail: liyanzzz319@163.com

References

[1] Hiles M, Culpan AM, Watts C, Munyombwe T and Wolstenhulme S. Neonatal respiratory distress syndrome: chest X-ray or lung ultrasound? A systematic review. Ultrasound 2017; 25: 80-91.

[2] Negi R, Pande D, Karki K, Kumar A, Khanna RS and Khanna HD. A novel approach to study oxidative stress in neonatal respiratory distress syndrome. BBA Clin 2015; 3: 65-69.

[3] Juan C, Wang Q, Mao Y, Cao Q, Li S, Qiao C, Zhang D and Zhou G. Knockdown of LncRNA MALAT1 contributes to cell apoptosis via regulating NF-kappaB/CD80 axis in neonatal respiratory distress syndrome. Int J Biochem Cell Biol 2018; 104: 138-148.

[4] Shen CL, Zhang Q, Meyer Hudson J, Cole FS and Wambach JA. Genetic factors contribute to risk for neonatal respiratory distress syndrome among moderately preterm, late preterm, and term infants. J Pediatr 2016; 172: 69-74, e62.

[5] Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B and Hubmayr RD. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med 2004; 32: 1817.

[6] Sklar MC, Fan E and Goligher EC. High-Frequency oscillatory ventilation in adults with ARDS: past, present, and future. Chest 2017; 152: 1306-1317.

[7] Facchin F and Fan E. Airway pressure release ventilation and high-frequency oscillatory ventilation: potential strategies to treat severe hypoxemia and prevent ventilator-induced lung injury. Respir Care 2015; 60: 1509-1521.

[8] Lemyre B, Laughon M, Bose C and Davis PG. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. Cochrane Database Syst Rev 2016; 12: CD005384.

[9] Lavizzari A, Colnaghi M, Ciuffini F, Veneroni C, Musumeci S, Cortinovis I and Mosca F. Heated, humidified high-flow nasal cannula vs nasal continuous positive airway pressure for respiratory distress syndrome of prematurity: a randomized clinical noninferiority trial. JAMA Pediatr 2016; [Epub ahead of print].

[10] Guo X, Sun Y, Miao J, Cui M, Wang J and Han S. No inhalation in combination with high frequency ventilation treatment in the treatment of neonatal severe respiratory failure. Pak J Med Sci 2016; 32: 1218-1223.

[11] Iacobelli S, Bonsante F, Lacoutière C, Ferdynus C, Cottenet J, Binquet C, Quantin C and Gouyon JB. Hypoproteinemia on the first day of life and adverse outcome in very preterm infants admitted to the neonatal intensive care unit. J Perinatol 2012; 32: 520.

[12] Liu J, Cao HY, Wang HW and Kong XY. The role of lung ultrasound in diagnosis of respiratory distress syndrome in newborn infants. Iran J Pediatr 2015; 25: e323.

[13] Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, Plavka R, Roehr CC, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GHA and Halliday HL. European consensus guidelines on the management of respiratory distress syndrome - 2019 update. Neonatology 2019; 115: 432-450.

[14] Somaschini M, Presi S, Ferrari M, Vergani B and Carrera P. Surfactant proteins gene variants in premature newborn infants with severe respiratory distress syndrome. J Perinatol 2018; 38: 337-344.

[15] Johansson J and Curstedt T. Synthetic surfactants with SP-B and SP-C analogues to enable worldwide treatment of neonatal respiratory distress syndrome and other lung diseases. J Intern Med 2019; 285: 165-186.

[16] Spillane NT, Zamudio S, Alvarez-Perez J, Andrews T, Nyirenda T, Alvarez M and Al-Khan A. Increased incidence of respiratory distress syndrome in neonates of mothers with abnormally invasive placentation. PLoS One 2018; 13: e0201266.

[17] Dyer J. Neonatal respiratory distress syndrome: tackling a worldwide problem. P T 2019; 44: 12-14.

[18] Guo YX, Wang ZN, Li YT, Pan L, Yang LF, Hu Y, Sun YY, Cai LM and Chen ZG. High-frequency oscillatory ventilation is an effective treatment for severe pediatric acute respiratory distress syndrome with refractory hypoxemia. Ther Clin Risk Manag 2016; 12: 1563-1571.

[19] Klapsing P, Moerer O, Wende C, Herrmann P, Quintel M, Bleckmann A and Heuer JF. High-frequency oscillatory ventilation guided by transpulmonary pressure in acute respiratory syndrome: an experimental study in pigs. Crit Care 2018; 22: 121.

[20] Courtney SE, Aghai ZH, Saslow JG, Pyon KH and Habib RH. Changes in lung volume and work of breathing: a comparison of two variable-flow nasal continuous positive airway pressure devices in very low birth weight infants. Pediatr Pulmonol 2003; 36: 248-252.
[21] Zhao J. High frequency oscillatory ventilation combined with surfactant in treatment of preterm infants with respiratory distress syndrome: report of 100 cases. Journal of Third Military Medical University 2014.
[22] Zannin E, Veneroni C, Dellaca RL, Corbetta R, Suki B, Tagliabue PE and Ventura ML. Effect of continuous positive airway pressure on breathing variability in early preterm lung disease. Pediatr Pulmonol 2018; 53: 755-761.
[23] Bhargava R, Janssen W, Altmann C, Andres-Hernando A, Okamura K, Vandivier RW, Ahuja N and Faubel S. Intratracheal IL-6 protects against lung inflammation in direct, but not indirect, causes of acute lung injury in mice. PLoS One 2013; 8: e61405.
[24] Zhao H, Zhang J and Yu J. HMGB-1 as a potential target for the treatment of diabetic retinopathy. Med Sci Monit 2015; 21: 3062-3067.
[25] Xue F, Liu C and Wang S. Influence of serum HMGB1 level on the incidence of respiratory Distress syndrome in neonates. J Biol Regul Homeost Agents 2018; 32: 1485-1489.
[26] Wang WX, Chen B, Zhang W and Zhang HR. Association between high-mobility group box 1 and neonatal respiratory distress syndrome. Zhongguo Dang Dai Er Ke Za Zhi 2017; 19: 398-401.