

## Original Article

# Comparison of the efficacy and safety of three non-invasive ventilation methods in the initial treatment of premature infants with respiratory distress syndrome

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**Abstract:** Objective: The aim of this study was to investigate the efficacy and safety of three non-invasive ventilation methods in the treatment of premature infants with respiratory distress syndrome. Methods: 240 premature infants with NRDS were selected as subjects. They were further divided into two age groups by gestational age of 32 weeks; each age group was randomly divided into three subgroups: NIPPV, NHFO and NCPAP group, with 40 infants in each group. NIPPV, NHFO and NCPAP interventions were performed in each group after the application of pulmonary surfactant (PS). PaO<sub>2</sub>, PaCO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> were measured at each time point after respiratory support. Other corresponding treatment results and complications were also compared. Results: PaO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> in all age groups were significantly increased after the application of PS and non-invasive respiratory support at different time points within the group (P<0.05), and compared with the NCPAP group, the other two groups showed significant improvement in PaO<sub>2</sub>/FiO<sub>2</sub> (P<0.05). At the gestational age less than 32 weeks, total oxygen treatment time, non-invasive ventilation time, hospital stay time and total gastrointestinal feeding time were longer in the NCPAP group than in the other two groups (P<0.05). The incidence of apnea, BPD, ROP, gas leakage, abdominal distension and reintubation, and hospitalization costs were higher in the NCPAP group than in the other two groups (P<0.05). Conclusion: Three non-invasive ventilation modes can significantly improve pulmonary oxygenation function in a short period of time, and clinical symptoms of infants can be alleviated. However, NIPPV and NHFO are more effective and safer. And, for infants with small gestational age and weak spontaneous breathing, they have more therapeutic advantages over NCPAP.

**Keywords:** Premature infants, neonatal respiratory distress syndrome, nasal continuous positive airway pressure, nasal intermittent positive pressure ventilation, nasal high-frequency oscillation ventilation

## Introduction

Neonatal respiratory distress syndrome (NRDS) is a kind of respiratory disease of neonates, which is mainly manifested by progressive aggravation of dyspnea caused by immaturity of lungs and insufficient or complete lack of pulmonary surfactant at birth [1]. It is more common in premature infants. The younger the gestational age, the lower the birth weight and the higher the morbidity, which is one of the main causes of neonatal death. Currently, the main treatment measures for this disease include: On the one hand, replacement therapy with pulmonary surfactant; On the other hand, respiratory support with ventilator to prevent alveolar atrophy and hypoxia, and more than

ever use invasive ventilators, which can significantly increase the survival rate of newborn babies. However, this method is easy to lead to a variety of serious complications [2], especially the lung injury. With the recent emergence of a variety of neonatal noninvasive ventilators, clinicians are more likely to use noninvasive ventilators. It can not only effectively improve the breathing and blood oxygen of infants, but also avoid invasive mechanical ventilation for most newborns and reduce all kinds of serious ventilator-related complications [3-5]. Therefore, it has been highly valued by many clinicians. The 2016 European consensus [6] on the prevention and treatment of neonatal respiratory distress syndrome clearly states that early use of pulmonary surfactant in combination with non-

## Three non-invasive ventilation methods in the treatment of NRDS with PS

invasive CPAP is considered to be the best treatment for neonatal respiratory distress syndrome [7].

With the rapid development of non-invasive technology, there are more and more models. Now commonly used noninvasive ventilation modes mainly include nasal continuous positive airway pressure ventilation (NCPAP), the nasal intermittent positive pressure ventilation (NIPPV), the bi-level positive airway pressure (BiPAP), humidified heated high flow nasal cannula (HHHFNC) and noninvasive high-frequency oscillatory ventilation (NHFOV) and so on [8]. However, each has advantages and disadvantages, how to choose the best mode of noninvasive ventilation for treatment of premature infants with respiratory distress syndrome has become a current research focus [9-11].

A randomized controlled trial was conducted to observe the clinical efficacy and safety of combining pulmonary surfactant (Curosurf) with NCPAP, NIPPV and NHFO respectively in the treatment of premature infant with respiratory distress syndrome, providing a selection basis for clinical doctors.

### Materials and methods

#### *Materials about the newborns*

In this study, a total of 240 premature newborns with NRDS treated in the First Affiliated Hospital of Nanchang University, from January 2016 to June 2019, were selected as research objects and analyzed. They were further divided into two age groups by gestational age of 32 weeks, which were less than 32 weeks and 32 weeks to 36+6 weeks, respectively. Each age group was randomly divided into three subgroups: NIPPV group (40 infants), NHFO group (40 infants) and NCPAP group (40 infants), NIPPV, NHFO and NCPAP interventions were performed in each group after the application of pulmonary surfactant (PS). This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. Family members of all newborns read and signed the informed consent.

Inclusion criteria: All babies were less than 37 weeks of gestational age, and newborns without congenital heart disease or genetic disorders that were diagnosed with NRDS through a

chest X-ray and by an attending physician or doctor with at least 10 years of experience.

Exclusion criteria: Newborns with other respiratory diseases or failure of important organs; newborns with congenital disabilities; surgery is needed after birth; newborns allergic to drugs adopted in this study; newborns without complete materials; newborns whose family members were reluctant to accept treatment or were uncooperative.

#### *Therapeutic scheme*

All newborns were injected with pulmonary surfactant (Curosurf) at a dose of 200 mg/kg. They were then treated with rewarming. When the temperature reached 37°C, the newborns were placed in a supine position. Airway secretions were cleaned before injection to ensure a smooth airway. Curosurf injection was injected slowly through a syringe along with and the tracheal intubation. After the vital signs, such as respiration, blood oxygen and heart rate, were stabilized, the tubes were extubated and connected with NIPPV, NCPAP and NHFO respectively for supplementary ventilation. Endotracheal aspiration was avoided without special circumstances within 6 h after administration. The newborns were observed in real time. If they still showed symptoms of respiratory distress after medication, the medication was given again 6 hours later.

#### *Adjustment of parameters of three non-invasive ventilators*

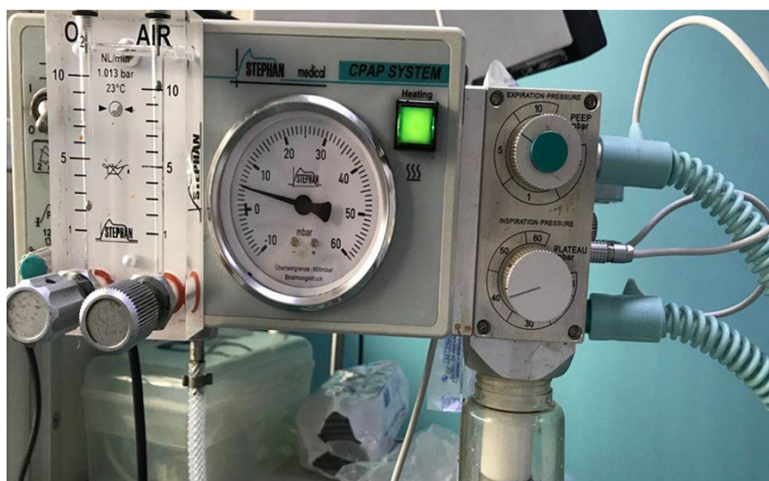
NCPAP group: NCPAP support was delivered using the CPAP SYSTEM (F.STEPHAN GmbH Medizintechnik). The initial ventilator parameters were set as follows:  $\text{FiO}_2$ : 0.30-0.50, positive end-expiratory pressure (PEEP): 4-6  $\text{cmH}_2\text{O}$ , according to percutaneous oxygen saturation ( $\text{TcSPO}_2$ ) and blood gas analysis results, the ventilator parameters of the newborns were adjusted in time to ensure that the oxygen saturation was maintained at 90-94%. The magnitude of each adjustment was as follows:  $\text{FiO}_2$ : 0.05, PEEP: 1-2  $\text{cmH}_2\text{O}$ . The indicators to stop using nCPAP were:  $\text{FiO}_2 < 0.3$ , PEEP: 4  $\text{cmH}_2\text{O}$ , the breathing of the patient was stable,  $\text{TcSPO}_2$  was over 90% and blood gas analysis was normal. See **Table 1** and **Figure 1**.

NIPPV group: NIPPV support was delivered using the COMEN NV8 ventilator. The initial

## Three non-invasive ventilation methods in the treatment of NRDS with PS

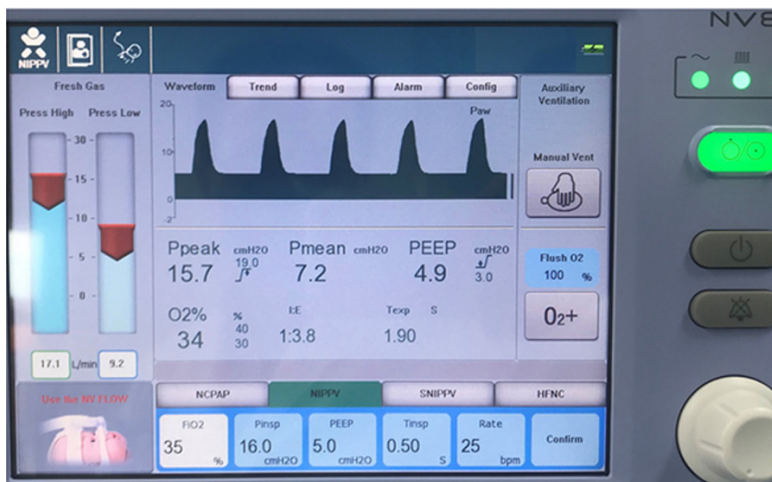
**Table 1.** Adjustment of parameters of three non-invasive ventilators

Ventilator mode	parameters	initial setting	each adjustment	Withdraw machine condition
CPAP	PEEP	4-6 cmH <sub>2</sub> O	1-2 cmH <sub>2</sub> O	4 cmH <sub>2</sub> O
	FiO <sub>2</sub>	0.3-0.5	0.05	<0.3
NIPPV	PIP	20-25 cmH <sub>2</sub> O	1-2 cmH <sub>2</sub> O	10 cmH <sub>2</sub> O
	PEEP	5-6 cmH <sub>2</sub> O	1-2 cmH <sub>2</sub> O	4 cmH <sub>2</sub> O
	FiO <sub>2</sub>	0.3-0.5	0.05	<0.3
	f	25-30	5	10
NHFO	MAP	6-12 cmH <sub>2</sub> O	1-2 cmH <sub>2</sub> O	<6 cmH <sub>2</sub> O
	Amplitude	2-3 times (MAP)	2-4 cmH <sub>2</sub> O	
	FiO <sub>2</sub>	0.3-0.5	0.05	<0.3
	f	6-12 HZ	1-2 HZ	



**Figure 1.** Ventilators used to provide CPAP.

Respiratory rate (RR) 25-30 breaths per minute; PEEP: 5-6 cmH<sub>2</sub>O; Inspiratory time 0.3 to 0.5 second; FiO<sub>2</sub>: 0.3-0.5, the ventilator parameters of the newborns were adjusted in time to ensure that the oxygen saturation was maintained at 90-94%. The indicators to stop using NIPPV were: PIP: 10 cmH<sub>2</sub>O; FiO<sub>2</sub><0.3; PEEP: 4 cmH<sub>2</sub>O; RR: 10 breaths per minute, and the breathing of the patient was stable, TcSPO<sub>2</sub> was over 90% and blood gas analysis was normal. See **Table 1** and **Figure 2**.



**Figure 2.** Ventilators used to provide NIPPV.

ventilator parameters were set as follows: Peak inspiratory pressure (PIP): 20-25 cmH<sub>2</sub>O;

NHFO group: NHFO support was delivered using the Löwenstein leoni plus ventilator. The initial ventilator parameters were set as follows: Mean airway pressure (MAP): 8 cmH<sub>2</sub>O, it can be adjusted between 6 and 12 cmH<sub>2</sub>O, and the amplitude is generally 2-3 times of the mean airway pressure, it is appropriate to have good oscillation in neck and thorax; Respiratory rate (RR): 6-12 Hz; FiO<sub>2</sub>: 0.3-0.5, the ventilator parameters of the newborns were adjusted in time to ensure that the oxygen saturation was maintained at 90-94%. The indicators to stop using NHFO were: Mean airway pressure (MAP)<6 cmH<sub>2</sub>O;



## Three non-invasive ventilation methods in the treatment of NRDS with PS



Figure 3. Ventilators used to provide NHFO.

$FiO_2 < 0.30$ , and the breathing of the patient was stable,  $TcSpO_2$  was over 90% and blood gas analysis was normal. See **Table 1** and **Figure 3**.

### Observation indexes

During the whole treatment process, changes in spontaneous respiration, percutaneous oxygen saturation and inhalation oxygen concentration of three groups of babies in two age groups were closely observed and recorded, the time before the patients received pulmonary surfactant (Curosurf) and ventilator was set at 0 hour, blood samples were collected from the radial artery for blood gas analysis at 2 hours, 12 hours, 24 hours and 48 hours after treatment with PS combined with each non-invasive ventilator to grasp the changes of  $PaO_2$  and  $PaCO_2$  and calculate P/F ( $P/F = PaO_2$  (mmHg)/ $FiO_2$ ). During the experiment, the duration of non-invasive ventilator use, total oxygen therapy duration, number of apnea cases, number of cases requiring repeated PS use, occurrence of intubation on the machine, duration of total gastrointestinal feeding, length of stay, hospitalization costs and related complications (Gas leakage, abdominal distension, neonatal necrotizing enterocolitis, intracranial hemorrhage, retinopathy of preterm infant, bronchopulmonary dysplasia) were recorded in three subgroups of babies in two age groups.

### Statistical analysis

Collected data were analyzed using SPSS20.0 statistical software. Measurement data are

represented by mean  $\pm$  standard deviation ( $\bar{x} \pm sd$ ) and were processed with one-way analysis of variance. The homogeneity of variance was tested by comparing the mean values between groups. Pairwise comparison between groups was performed by SNK-Q test (q test). Enumeration data are represented by rates (%) and were analyzed with Chisquared test or continuously corrected Chisquare test or Fisher exact probability test.  $P < 0.05$  is considered statistically significant.

## Results

### Comparison of basic data among the three groups of patients under gestational age of 32 weeks

There were no statistical differences among the three groups in gender, birth weight, gestational age, age at admission, using PS time after birth, prenatal hormone use, mode of delivery, maternal antenatal complications and Apgar scoring at birth (all  $P > 0.05$ ). See **Table 2**.

### Comparison of basic data among the three groups of patients in gestational age of 32-36+6 weeks

There were no statistical differences among the three groups in gender, birth weight, gestational age, age at admission, using PS time after birth, prenatal hormone use, mode of delivery, maternal antenatal complications and Apgar scong at birth (all  $P > 0.05$ ). See **Table 3**.

### Comparison of blood gas analysis ( $PaO_2$ , $PaCO_2$ ) and $PaO_2/FiO_2$ among the three groups of patients under gestational age of 32 weeks

$PaO_2$  in each group increased significantly with the increase of treatment time, and the comparison within the group at 0, 2, 12, 24 and 48 hours showed statistical significance (all  $P < 0.05$ ), while there was no statistically significant difference among the three groups at the same time point (all  $P > 0.05$ ).  $PaCO_2$  in each group decreased with the increase of treat-

## Three non-invasive ventilation methods in the treatment of NRDS with PS

**Table 2.** Comparison of basic data among the three groups of patients under gestational age of 32 weeks ( $\bar{x} \pm sd$ )

Characteristics	NCPAP (n=40)	NIPPV (n=40)	NHFO (n=40)	F/x <sup>2</sup>	P
Male/Female	24/16	25/15	23/17	0.21	>0.05
Weight (Kg)	1.39±0.32	1.43±0.33	1.44±0.30	1.51	>0.05
Gestational age (w)	30.31±1.58	30.82±1.60	31.02±1.88	2.12	>0.05
Admission time (h)	3.34±1.23	3.51±1.14	3.23±1.32	1.96	>0.05
Cesarean delivery	30 (75)	26 (65)	28 (70)	0.63	>0.05
Usage time of PS (h)	3.64±1.32	3.81±1.33	3.46±1.41	1.97	>0.05
Pregnancy-induced hypertension	11 (27.5)	10 (25)	13 (32.5)	0.58	>0.05
Maternal diabetes	9 (22.5)	11 (27.5)	13 (32.5)	1.00	>0.05
Premature rupture of membrane	12 (30)	14 (35)	13 (32.5)	0.23	>0.05
Antenatal steroid	18 (45)	16 (40)	17 (42.5)	0.21	>0.05
APGAR.1"	7.91±0.90	7.92±0.86	8.06±0.69	2.32	>0.05
APGAR.5"	8.06±0.65	8.13±0.57	8.14±0.74	2.19	>0.05

**Table 3.** Comparison of basic data among the three groups of patients in gestational age of 32-36+6 weeks ( $\bar{x} \pm sd$ )

Characteristics	NCPAP (n=40)	NIPPV (n=40)	NHFO (n=40)	F/x <sup>2</sup>	P
Male/Female	26/14	24/16	25/15	1.46	>0.05
Weight (Kg)	2.11±0.61	1.93±0.53	1.94±0.62	1.91	>0.05
Gestational age (w)	33.79±2.18	34.06±2.10	33.81±2.12	2.82	>0.05
Admission time (h)	3.32±1.36	3.18±1.42	3.24±1.37	1.90	>0.05
Cesarean delivery	22 (55)	20 (50)	23 (57.5)	0.47	>0.05
Usage time of PS (h)	3.51±1.43	3.34±1.51	3.43±1.42	2.01	>0.05
Pregnancy-induced hypertension	10 (25)	14 (35)	9 (22.5)	1.75	>0.05
Maternal diabetes	8 (20)	7 (17.5)	10 (25)	0.77	>0.05
Premature rupture of membrane	8 (20)	10 (25)	11 (27.5)	0.64	>0.05
Antenatal steroid	16 (40)	14 (35)	17 (42.5)	0.49	>0.05
APGAR.1"	7.67±0.81	7.84±0.75	8.01±0.78	2.12	>0.05
APGAR.5"	8.12±0.56	7.91±0.64	8.02±0.72	2.34	>0.05

ment time. However, the decrease of NCPAP group was not significant, which was less than that of the other two groups. Except for 0 hours, NHFO group and NIPPV group decreased significantly than NCPAP group at each time point, which was statistically significant (all  $P < 0.05$ ). The NHFO group was lower than the NIPPV group at the 2, 12 and 24 hours, and P/F in each group increased significantly with the increase of treatment time, which was also statistically significant (all  $P < 0.05$ ). The comparison within the group at 0, 2, 12, 24 and 48 hours showed statistical significance (all  $P < 0.05$ ), except for 0 hours. NHFO group and NIPPV group increased significantly than NCPAP group at each time point, which was statistically significant (all  $P < 0.05$ ). There was no sta-

tistically significant difference between the NHFO group and NIPPV group at the same time point (all  $P > 0.05$ ). See **Table 4**.

*Comparison of blood gas analysis ( $PaO_2$ ,  $PaCO_2$ ) and  $PaO_2/FiO_2$  among the three group of patients in gestational age of 32-36+6 weeks*

$PaO_2$  in each group increased significantly with the increase of treatment time, and the comparison within the group at 0, 2, 12, 24 and 48 hours showed statistical significance (all  $P < 0.05$ ), while there was no statistically significant difference among the three groups at the same time point (all  $P > 0.05$ ).  $PaCO_2$  in each group decreased with the increase of treatment time; the comparison between each time

## Three non-invasive ventilation methods in the treatment of NRDS with PS

**Table 4.** Comparison of Blood gas analysis (PaO<sub>2</sub>, PaCO<sub>2</sub>) and PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) among the three groups of patients under gestational age of 32 weeks ( $\bar{x}\pm sd$ )

Time	Indicators	NCPAP (n=40)	NIPPV (n=40)	NHFO (n=40)
0 hour	PaO <sub>2</sub> (mmHg)	43.6±3.4	44.4±3.2	44.7±3.6
	PaCO <sub>2</sub> (mmHg)	56.7±7.3	57.9±7.8	57.6±7.5
	P/F	107±16	108±17	110±18
2 hours	PaO <sub>2</sub> (mmHg)	57.2±6.6★	59.1±6.3★	60.3±6.0★
	PaCO <sub>2</sub> (mmHg)	55.2±5.8	45.5±4.6★,■	41.3±4.2★,■,●
	P/F	142±21★	152±22★,□	160±23★,■
12 hours	PaO <sub>2</sub> (mmHg)	63.2±5.1★	64.2±5.5★	65.3±6.1★
	PaCO <sub>2</sub> (mmHg)	54.2±3.6	40.6±3.3★,■	36.5±3.9★,■,●
	P/F	172±19★	191±21★,■	195±23★,■
24 hours	PaO <sub>2</sub> (mmHg)	71.2±7.1★	71.5±7.5★	74.3±6.9★
	PaCO <sub>2</sub> (mmHg)	53.4±3.5☆	38.6±3.7★,■	36.3±3.6★,■,●
	P/F	201±21★	238±25★,■	247±24★,■
48 hours	PaO <sub>2</sub> (mmHg)	75.1±6.2★	76.0±6.4★	78.2±6.0★
	PaCO <sub>2</sub> (mmHg)	50.5±3.8☆	36.4±3.4★,■	35.5±3.3★,■
	P/F	243±24★	254±25★,□	260±28★,■

Note: Compared with 0 hour within the group, ☆P<0.05, ★P<0.01; Compared with NCPAP group, □P<0.05, ■P<0.01; Compared with NIPPV group, ●P<0.01.

point and 0 hour point in each group was statistically significant (all P<0.05), while there was no statistically significant difference among the three groups at the same time point except for the time point of 2 h (all P>0.05). P/F in each group increased significantly with the increase of treatment time, which was also statistically significant (all P<0.05), and the comparison within the group at 0, 2, 12, 24 and 48 hours showed statistical significance (all P<0.05), except for 0 hours. NHFO group and NIPPV group increased significantly than NCPAP group at each time point, which was statistically significant (all P<0.05). There was no statistically significant difference between the NHFO group and NIPPV group at the same time point (all P>0.05), See **Table 5**.

### *Comparison of treatment of patients among the three groups of patients under gestational age of 32 weeks*

The comparison of total oxygen therapy time, non-invasive ventilator use time, total gastrointestinal feeding time, hospitalization time and hospitalization costs among the three groups showed that the CPAP group was significantly higher than NIPPV group and NHFO group (all P<0.05), however, NIPPV group and NHFO group were not statistically significant (all

P>0.05). The rate of re-intubation and the incidence of apnea were significantly higher in the CPAP group than those in the NIPPV group and the NHFO group (all P<0.05), however, NIPPV group and NHFO group were not statistically significant (all P>0.05). The incidence of PS requiring repeated use was not significantly different among the three groups (all P>0.05). See **Table 6**.

### *Comparison of treatment of patients among the three groups of patients in gestational age of 32-36+6 weeks*

The comparison of total oxygen therapy time, non-invasive ventilator use time, total gastrointestinal feeding time, hospitalization time and hospitalization costs, rate of re-intubation, the incidence of apnea and PS requiring repeated use among the three groups showed no statistically significant differences (all P>0.05). See **Table 7**.

### *Comparison of complications among the three groups of patients under gestational age of 32 weeks*

The incidence of abdominal distension, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and air leakage among the

## Three non-invasive ventilation methods in the treatment of NRDS with PS

**Table 5.** Comparison of Blood gas analysis (PaO<sub>2</sub>, PaCO<sub>2</sub>) and PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) among the three groups of patients in gestational age of 32-36+6 weeks ( $\bar{x} \pm s$ )

Time	Indicators	NCPAP (n=40)	NIPPV (n=40)	NHFO (n=40)
0 hour	PaO <sub>2</sub> (mmHg)	45.4±3.6	44.7±3.5	46.3±3.4
	PaCO <sub>2</sub> (mmHg)	54.4±6.4	53.7±6.6	54.3±6.2
	P/F	105±13	102±15	107±16
2 hours	PaO <sub>2</sub> (mmHg)	58.2±5.5★	60.1±5.3★	61.2±5.6★
	PaCO <sub>2</sub> (mmHg)	46.2±5.8★	44.5±4.3★	42.8±5.1★,■
	P/F	145±22★	158±24★,■	161±26★,■
12 hours	PaO <sub>2</sub> (mmHg)	62.2±3.6★	63.1±3.8★	65.7±3.9★
	PaCO <sub>2</sub> (mmHg)	40.2±4.6★	39.1±4.4★	38.5±4.3★
	P/F	177±22★	188±25★,■	190±26★,■
24 hours	PaO <sub>2</sub> (mmHg)	72.1±5.3★	72.6±5.8★	74.4±6.0★
	PaCO <sub>2</sub> (mmHg)	38.5±3.9★	38.4±3.3★	37.0±3.8★
	P/F	195±24★	210±26★,□	220±27★,■
48 hours	PaO <sub>2</sub> (mmHg)	74.9±5.4★	76.7±5.6★	77.0±5.0★
	PaCO <sub>2</sub> (mmHg)	38.2±3.8★	37.7±3.1★	36.4±3.9★
	P/F	240±29★	255±27★,□	263±26★,■

Note: Compared with 0 hour within the group, ★P<0.01; Compared with NCPAP group, □P<0.05, ■P<0.01.

**Table 6.** Comparison of treatment among three groups of patients under gestational age of 32 weeks

Group	NCPAP (n=40)	NIPPV (n=40)	NHFO (n=40)	F/x <sup>2</sup>	P
Total oxygen therapy time (d)	15.4±3.5	12.2±3.7★	11.7±2.9★	4.32	<0.05
Non-invasive ventilator use time (d)	5.6±0.6	4.0±0.4☆	3.8±0.8☆	3.88	<0.05
Total gastrointestinal feeding time (d)	24.3±3.3	20.1±2.9★	21.3±3.5★	4.84	<0.01
Rate of re-intubation	11 (27.5)	3 (7.5)★	2 (5)★	10.53	<0.01
PS requiring repeated use	5 (12.5)	4 (10)	4 (10)	0.26	>0.05
Incidence of apnea	17 (42.5)	3 (7.5)★	4 (10)★	19.06	<0.01
Hospitalization time (d)	34.2±8.5	29.1±9.4☆	28.4±8.9★	3.78	<0.05
Hospitalization costs (yuan)	46640±571	41720±612★	41482±576★	6.96	<0.01

Note: Compared with NCPAP group, ☆P<0.05, ★P<0.01.

**Table 7.** Comparison of treatment among three groups of patients with gestational age of 32-36+6 weeks

Group	NCPAP (n=40)	NIPPV (n=40)	NHFO (n=40)	F/x <sup>2</sup>	P
Total oxygen therapy time (d)	8.1±2.4	7.4±2.5	7.2±2.6	2.96	>0.05
Non-invasive ventilator use time (d)	4.4±0.9	4.1±0.6	4.0±1.1	2.83	>0.05
Total gastrointestinal feeding time (d)	17.0±4.3	15.1±4.9	16.3±4.5	2.23	>0.05
Rate of re-intubation	5 (12.5)	3 (7.5)	2 (5)	1.45	>0.05
PS requiring repeated use	4 (10)	2 (5)	1 (2.5)	1.92	>0.05
Incidence of apnea	7 (17.5)	3 (7.5)	3 (7.5)	2.47	>0.05
Hospitalization time (d)	21.2±5.5	19.8±6.4	19.5±5.8	2.29	>0.05
Hospitalization costs (yuan)	25860±486	25740±463	25552±474	2.63	>0.05

three groups showed that the CPAP group was significantly higher than NIPPV group and NHFO group (all P<0.05), however, NIPPV group and NHFO group were not statistically

different (all P>0.05). No statistically significant difference was found among the three groups for other complications (all P>0.05). See **Table 8**.

## Three non-invasive ventilation methods in the treatment of NRDS with PS

**Table 8.** Incidence of complications among three groups of patients under gestational age of 32 weeks

Group	NCPAP (n=40)	NIPPV (n=40)	NHFO (n=40)	F/x <sup>2</sup>	P
BPD	8 (20)	2 (5)☆	1 (2.5)☆	7.38	<0.05
ROP	10 (25)	2 (5)☆	2 (5)☆	8.93	<0.05
IVH	5 (12.5)	3 (7.5)	8 (20)	2.74	>0.05
NEC	3 (7.5)	1 (2.5)	1 (2.5)	1.47	>0.05
Gas leakage	6 (15)	1 (2.5)☆	1 (2.5)☆	5.44	<0.05
abdominal distention	17 (42.5)	4 (10)★	6 (15)★	14.05	<0.01
Nasal injury	8 (20)	10 (25)	6 (15)	1.25	>0.05

Note: Compared with NCPAP group, ☆P<0.05, ★P<0.01.

**Table 9.** Incidence of complications among three groups of patients with gestational age of 32-36+6 weeks

Group	NCPAP (n=40)	NIPPV (n=40)	NHFO (n=40)	F/x <sup>2</sup>	P
BPD	3 (7.5)	2 (5)	1 (2.5)	1.08	>0.05
ROP	4 (10)	2 (5)	2 (5)	1.03	>0.05
IVH	2 (5)	3 (7.5)	6 (15)	2.36	>0.05
NEC	2 (5)	1 (2.5)	1 (2.5)	0.68	>0.05
Gas leakage	4 (10)	1 (2.5)	1 (2.5)	2.58	>0.05
abdominal distention	9 (22.5)	2 (5)	3 (7.5)	6.11	>0.05
Nasal injury	5 (12.5)	3 (7.5)	7 (17.5)	1.83	>0.05

*Comparison of complications among the three groups of patients in gestational age of 32-36+6 weeks*

The comparison of all complications show ed no statistically significant differences among the three groups (all P>0.05). See **Table 9**.

### Discussion

Premature infants cannot produce enough lung surface active substances due to immature lung structure, which causes alveolar collapse, a marked reduction in gas exchange area, and exacerbation of the disease accompanied with apnea and the need for more vigorous breathing to overcome alveolar collapse. Over the past 40 years, endotracheal intubation or invasive mechanical ventilation has been widely used in the treatment of neonatal respiratory distress syndrome, especially in very premature infants with respiratory distress syndrome [12]. Before the promotion of exogenous pulmonary surfactant and prenatal steroid hormones, it may be a major measure to reduce the death rate of infants with neonatal respiratory distress syndrome. However, in animal models of respiratory distress syndrome, even short-term invasive ventilation was found to be

associated with lung inflammation and lung injury, and reduced effect of endogenous lung surfactant and inhibition of the growth and development of alveoli. Lung injury caused by mechanical ventilation of spring wave gas volume (volume injury), overpressure across the lung (barometric injury), shear injury caused by uneven and repeated airway dilatation (atelectasis injury), and massive release of biochemical substances caused by mechanical stress in the body to promote the inflammatory response of the lung (biological injury) are the characteristics of ventilators related lung injury [12-14]. Ventilator-associated lung injury is believed to be a major cause of neonatal chronic lung disease or BPD [7, 15, 16]. The leading cause of lung injury is the endotracheal tube [17, 18], which increases the risk of airway injury, lung and systemic infection. Therefore, we should try our best to avoid the use of invasive ventilation with endotracheal intubation to reduce the incidence of ventilator-related complications. Recently, with the continuous development of medical technology and the emergence of noninvasive interface for newborn babies, noninvasive ventilation has gradually become a suitable technique for the treatment of neonatal respiratory distress syndrome, and has



## Three non-invasive ventilation methods in the treatment of NRDS with PS

achieved promising curative effects, which has been increasingly applied in clinical practice.

The results of this study showed that  $\text{PaO}_2$  was significantly increased and  $\text{PaCO}_2$  was decreased in three groups of babies of two ages at 2 h, 12 h, 24 h and 48 h after the application of lung surfactant combined with non-invasive respiratory support. However, compared with the NIPPV group and the NHFO group, the NCPAP group had a tendency of carbon dioxide retention in the younger age group (<32 weeks), but it was still within the allowable range of hypercapnia, among which the NHFO group showed the most significant decrease in carbon dioxide. The reasons may be as follows: Relatively young babies have incomplete respiratory center development, weak spontaneous breathing and poor respiratory muscle development. At the same time, airtight mouth and nose should be used to avoid air leakage to ensure the pressure of CPAP during the NCPAP mode of assisted ventilation. Moreover, the air intake in this mode is continuous, and the pressure generated does not change alternately from high to low. This will affect the spontaneous breathing of babies to different degrees, which may easily lead to apnea in babies and increase the risk of  $\text{CO}_2$  retention. While NIPPV, on the other hand, increases the preset frequency of intermittent positive airway pressure based on nasal continuous positive airway pressure ventilation (NCPAP). As a result, the pressure in the pharynx of babies presents intermittent alternation, and this alternation of pressure causes intermittent expansion effect in the pharynx and larynx, thus achieving the purpose of stimulating respiratory movement and reducing the occurrence of apnea in babies, at the same time, the intermittent increase of pressure has a higher average airway pressure than that of NCPAP, which leads to the reexpansion of collapsed alveoli, the improvement of hypoxemia, the increase of tidal volume and minute ventilation, and the excretion of carbon dioxide. NHFO superimposes the function of pressure oscillation on the basis of noninvasive continuous positive airway pressure, without synchrony with the infant's breath, aiding to enhance  $\text{CO}_2$  elimination and alveolar recruitment [19, 20], and inhalation and exhalation are both active processes, which have been shown to improve the activity of the glottis and maintain glottis opening dur-

ing inhalation. Hadj-ahmed et al [21] published the results of an animal experiment in 2015, which showed that when compared with other non-invasive ventilation modes, NHFO did not show the contraction myoelectric activity of glottis in the inspiratory phase. It keeps the glottis open. This mechanism has the potential to reduce the incidence of apnea in preterm infants, and at the same time,  $\text{CO}_2$  is better discharged by flushing the dead space of the upper respiratory tract and active exhalation function.

$\text{PaO}_2/\text{FiO}_2$  is a good indicator of body oxygenation. The results of this study suggested that P/F increased significantly with the extension of time in three groups of babies of different ages, and the differences at each time point within the group were statistically significant (all  $P < 0.05$ ). Among the three groups of different age groups, NHFO group and NIPPV group improved significantly compared with NCPAP group, and the difference was statistically significant (all  $P < 0.05$ ). The reason may be that NIPPV has a relatively high average airway pressure than NCPAP, which can better expand the collapsed alveoli, increase minute ventilation, improve hypoxemia and lung oxygenation in the course of ventilation [22]. And NHFO, as described above, improves glottic activity and can keep the glottis open during the inhalation phase, because noninvasive ventilation does not deliver air directly to the lungs through a trachea tube or tracheotomy as invasive ventilation does. Instead, the noninvasive ventilation delivers air to the patient's nasal cavity through a nasal plug or nasal mask, and the gas must pass through the glottis to reach the lung, so whether the glottis is open or not in the inspiratory stage has a significant impact on the effect of non-invasive ventilation. NHFO ventilation mode enables the glottis to remain open during the inspiratory stage, so as to better absorb the airflow to maintain blood oxygen.

Comparison of clinical treatment and complications in three groups of babies of different ages: The comparison results of non-invasive ventilator ventilation time and total oxygen therapy time among the three groups of patients under gestational age of 32 weeks showed that the NCPAP group was significantly higher than the NIPPV group and the NHFO group, and the differences were statistically

significant (all  $P < 0.05$ ). However, there was no difference between the NIPPV group and the NHFO group. The incidence of apnea and invasive ventilation requiring tracheal intubation in the NCPAP group was significantly higher than that in the NIPPV group and the NHFO group, and the differences were statistically significant (all  $P < 0.05$ ), which is consistent with the research results of Zhu XW et al [23-25]. However, there was no difference between the NIPPV group and the NHFO group. The total oxygen therapy time, non-invasive ventilator ventilation time, hospital stay and total gastrointestinal feeding time of the three groups of babies in gestational age of 32-36+6 weeks showed that the NCPAP group was slightly higher than that of the NIPPV group and the NHFO group, and the rate of apnea and invasive ventilation requiring tracheal intubation in the NCPAP group was also slightly higher than that of the NIPPV group and the NHFO group, but the comparison was not statistically significant (all  $P > 0.05$ ). This may be related to the fact that although the NCPAP ventilation model can provide continuous positive airway pressure ventilation for infants, it has a poor effect on premature infants with poor development of respiratory centers and weak spontaneous breathing, because it is prone to be associated with apnea, which is consistent with the research results of Rittayamai et al [26]. The incidence of bronchopulmonary dysplasia and retinopathy of prematurity at gestational age of less than 32 weeks indicated that the NCPAP group was significantly higher than that of NHFO group and NIPPV group, and the differences were statistically significant (all  $P < 0.05$ ). The occurrence of neonatal bronchopulmonary dysplasia and retinopathy of prematurity is closely related to the use of oxygen. The NCPAP group increased significantly, which may be related to the longer total oxygen use time. The occurrence of air leakage was significantly higher in the NCPAP group than in the NIPPV group and NHFO group at gestational age of less than 32 weeks, which was statistically significant (all  $P < 0.05$ ). The incidence of air leakage was also higher in the NCPAP group at gestational age of 32-36+6 weeks than the other two groups, but there was no statistical significance (all  $P > 0.05$ ). It may be associated with the continuous airflow given by NCPAP. Babies with small gestational age have weak spontaneous breathing; these babies do not expel air well, thus it is easier to facilitate the occurrence of air leakage. In the age group with gestational age less

than 32 weeks, the total gastrointestinal feeding time of the NCPAP group was later than that of the NHFO group and the NIPPV group. It may be associated with a significant increase in abdominal distension in the NCPAP group, which resulted in a longer period of intravenous nutritional support in the NCPAP group. Therefore, compared with NIPPV and NHFO, NCPAP increased the hospitalization days and hospitalization costs of patients. However, in gestational age of 32-36+6 weeks, the incidence of air leakage and abdominal distension in the NCPAP group was also higher than that in the other two groups, but there was no statistical significance. This may be associated with enhanced spontaneous breathing and more mature respiratory muscle development in relatively older neonates, which can achieve relatively good exhalation through self-breathing and reduce the occurrence of air leakage and abdominal distension.

In conclusion, all the three noninvasive ventilation modes (NIPPV, NHFO, NCPAP) can improve the oxygenation function of neonatal lungs in a short time. However, NIPPV and NHFO are new noninvasive ventilation modes in the treatment of neonatal respiratory distress syndrome, as compared with classical NCPAP non-invasive ventilation mode. The results showed that they could not only rapidly improve the lung oxygenation function of babies, shorten the time of oxygen therapy and non-invasive ventilator assisted ventilation, but also significantly reduce the incidence of apnea, abdominal distension, carbon dioxide retention and gas leakage. At the same time, complications such as BPD and ROP were also relatively few, the duration of total gastrointestinal feeding was shortened, and the incidence of re-invasive ventilator ventilation was reduced. In addition, compared with NCPAP, NIPPV and NHFO have stronger advantages and better efficacy and safety in infants with small gestational age and weak spontaneous respiration.

### Disclosure of conflict of interest

None.

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## Three non-invasive ventilation methods in the treatment of NRDS with PS

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