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The clinical effects of two non-invasive ventilation modes on premature infants with respiratory distress syndrome

A randomized controlled trial

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Abstract

Background: To compare the safety and effectiveness of nasal noninvasive high- frequency oscillatory ventilation (NHFOV) and duo positive airway pressure (DuoPAP) applications in preterm babies with respiratory distress syndrome (RDS).

Methods: This was a randomized controlled trial. Forty-three premature infants with RDS treated in the neonatal intensive care unit of Huaibei Maternal and Child Health Hospital from January 2020 to November 2021 were selected as the research participants. They were randomly divided into the NHFOV group (n = 22) and DuoPAP group (n = 21). General conditions, including the arterial oxygen partial pressure (PaO_2), carbon dioxide partial pressure ($PaCO_2$), oxygenation index (OI), the incidence of apnea at 72 hours, duration of noninvasive respiratory support, maternal high-risk factors, total oxygen consumption time, total gastrointestinal feeding time, and the frequency of intraventricular hemorrhage (IVH), neonatal necrotizing enterocolitis (NEC), and bronchopulmonary dysplasia (BPD) and apnea were compared between the NHFOV group and DuoPAP group at 12 and 24 hours after noninvasive respiratory support.

Results: There was no noteworthy difference between the 2 groups with respect to PaO_2, $PaCO_2$, OI, IVH, and NEC and BPD at different nodes (all $P > .05$).

Conclusion: The endpoints of PaO_2, $PaCO_2$ and OI and complications of IVH, NEC, BPD and Apnea, and did not reveal any statistical differences between NHFOV and DuoPAP during the respiratory support in preterm babies with RDS.

Abbreviations: BPD = bronchopulmonary dysplasia, CPAP = continuous positive airway pressure, DuoPAP = duo positive airway pressure, FiO_2 = fraction of inspiration O_2, IVH = intraventricular hemorrhage, MAP = mean airway pressure, NEC = neonatal necrotizing enterocolitis, NHFOV = nasal noninvasive high- frequency oscillatory ventilation, NIV = noninvasive ventilation, OI = oxygenation index, $PaCO_2$ = carbon dioxide partial pressure, PaO_2 = arterial oxygen partial pressure, PVL = periventricular leukomalacia, RDS = respiratory distress syndrome.

keywords: duo positive airway pressure, nasal high frequency ventilation, neonatal, noninvasive respiratory support mode, respiratory distress syndrome

1. Introduction

Respiratory distress syndrome (RDS) is a common condition in infants born prematurely. RDS is a prevalent severe health issue that affects preterm infants. RDS is distinguished by its rapid onset and rapid progression, it can be fatal if not appropriately managed. RDS is a leading cause of newborn death.[1–3] Most of infants affected by RDS require respiratory support. Mechanical ventilation is a critical medical intervention in the case of RDS, but it may result in many complications such as pressure injury, pulmonary air leak, ventilator-related infection, and so on,[4–6] and all of which compromise premature infants long-term lung quality. In order to lower the rate of bronchopulmonary dysplasia, invasive mechanical ventilation has been substituted by noninvasive ventilation (NIV) in the treatment of RDS in premature newborns.[7,8] NIV is the administration of respiratory assistance without the use of direct tracheal intubation. NIV, when performed correctly, can significantly reduce the requirement for conventional endotracheal intubation and mechanical ventilation.[7,8]

NIV is typically used with smaller, "simpler," but increasingly advanced "noninvasive" ventilators capable of providing a variety of respiratory support modes. Both noninvasive nasal high frequency ventilation (NHFV) and duo positive airway pressure

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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(DuoPAP) (DuoPAP, also named as bi-level positive airway pressure) are the most used NIV modalities, and they significantly decrease CO_2 retention in preterm babies with RDS and improved blood gas analyzer markers without increasing the prevalence of adverse effects.[9,10] NHFV is a novel noninvasive modality that combines nasal continuous positive airway pressure (CPAP) with high-frequency oscillatory ventilation.[11] This model exhibits a good performance in improve oxygenation and promotes continuous glottal opening.[11] For this reason, NHFV is also known as supraglottic CPAP.[12] The glottal opening can significantly improve the efficiency of airflow, thereby ensuring the safety and effectiveness of NIV.[11,12] DuoPAP ventilation produces 2 levels of CPAP, with frequency and duration controlled by the physician. Therefore, DuoPAP should theoretically be superior to CPAP in terms of alveolar expansion, functional residual capacity, and improvement in respiratory function.[13] However, there are few reports comparing the clinical effects of NHFV and DuoPAP for treating RDS for infants.

This study aimed to compare the clinical outcomes of NHFV to DuoPAP in preterm infants with RDS.

2. Subjects and Methods

2.1. Subjects

This protocol has been registered on National Medical Research Registration Platform of China (No. MR-34-21-010666). The present study was approved by the Medical Ethics Committee of Huaibei Maternal and Child Health Hospital (No. FYL2020004). All parents of the recruited infants voluntarily signed the informed consent form. Premature infants from the neonatal intensive care unit of Huaibei Maternity and Child Health Care Hospital were recruited between January 2020 and November 2022. The follow-up of each participating infant ended when the infant was discharged.

The following were the eligibility criteria: baby was premature (born before 36 weeks of pregnancy); premature infants with RDS requiring respiratory support; and received 1 dose of surfactant, and or exposure to antenatal corticosteroids. The diagnostic criteria for RDS were as follows[14]: presents with breathing problems at birth that progressively worsen, flaring nostrils, rapid breathing, grunting sounds when breathing, and chest retractions and cyanosis; RDS based on chest X-ray, with grade I and II RDS classified as mild, and grades III and IV RDS classified as severe; and patients had an arterial oxygen partial pressure/fraction of inspiration O_2 (PaO_2/FiO_2) ratio of < 300 (PaO_2 < 60 mm Hg). The exclusion criteria were as follows: premature infants with infections (6 hours to 3 days, white blood cells ≥ $30\chi10^9$; C-reactive protein ≥ 3mg/L within 6 hours, or C-reactive protein ≥ 5mg/L within 6–12 hours), anemia (neonatal venous blood ≤ 130g/L within 2 weeks), and dyspnea caused by pulmonary hemorrhage; congenital malformations including patent ductus arteriosus (Ductus arteriosus was still not closed 72 hours after birth by bedside ultrasound examination, and the left-to-right shunt flow was more than 50%); heart failure. If the newborn had unsmooth crying and the heart rate was lower than 100 beats/minute, initial resuscitation management was given, and T-Piece positive pressure ventilation.

A total of 43 premature infants with RDS were recruited (Fig. 1). Before grouping, the infants received NIV in the neonatal intensive care unit without caffeine given. A "random number table randomization" was used to sample these infants and they were divided into NHFV group (n = 22) and DuoPAP group (n = 21), and the assessment results were blinded to the assessor.

2.2. Procedures

No endotracheal intubation was proceeded prior to NIV. Surfactant (Poractant Alfa injection) was given by opening the airway with a laryngoscope, injecting a thin tube into the trachea. After about 1 minute, the hose was pulled out and the whole process of noninvasive ventilation was continuous during this procedure. The observation group was treated with an NHFV ventilator (SLEbaby 5000; SLE LIMITED, South Croydon Surrey, UK). The NHFV parameters were as follows: FiO_2, 0.30 to 0.40; frequency, 6 to 12 Hz; and mean airway pressure (MAP), initially set to 8 cm H_2O and adjusted between 6 and 12 cm H_2O.[15] The change in lung volume was quantified by a change in rib cage volume between the 8th and 9th ribs; its magnitude was 2 to 3 times that of MAP. The specific judgment was based on the oscillation of the cervical and thoracic spine. Indications for ventilator weaning were as follows: when MAP < 6 cm H_2O, FiO_2 < 0.30, and blood oxygen saturation > 90%, nasal cannula oxygen therapy can be used instead of ventilator. The initial parameters with the subsequent adjustments were as follows for the control group treated using a DuoPAP (ACUTRONIC Medical Systems AG, Hirzel, Zurich, Switzerland): FiO_2, 0.30 to 0.40; PEEP, 5 cm H_2O; PIP, 12 to 15 cm H_2O; inspiratory time, 0.5 seconds; and RR, 30 to 40 breaths/minute. The step changes in FiO_2, PIP, and PEEP were 0.05, 2 cm H_2O, and 1 to 2 cm H_2O, respectively. The indications for ventilator weaning were as follows: FiO_2 < 0.3; PEEP ≤ 3 cm H_2O; PIP ≤ 5 cm H_2O without presentations of dyspnea; blood oxygen saturation > 90%; and no abnormalities on blood gas analysis.

NIV was provided when the patient was transferred to the neonatal ward (within 12 hours after birth) and was given continuously for 24 hours, after which it was given sporadically and the time was gradually reduced, depending on the patient's reaction. NIV was continued if the patient improved within the first 4 hours, and clinical assessments were performed every 2 hours until the patient was free of RDS.

2.3. Observation indicators

Basic data and primary and secondary endpoints were collected for both groups by reviewing medical records. The basic data collected included gender, birth weight, gestational age. The primary endpoints were PaO_2, carbon dioxide partial pressure ($PaCO_2$) and oxygenation index (OI) 12 and 24 hours after the start of NIV. The incidences of intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and apnea during the first 72 hours were the secondary endpoints. In addition, the treatment effects including duration of NIV, duration of nasal cannula oxygen therapy, length of hospital stay, time to full feeding and maternal high-risk factors related to the parturients, the use rates of antenatal corticosteroid and surfactant and delivery mode were compared between groups.

3. Statistical method

All statistical analyses were conducted using SPSS 22.0 (IBM, Armonk, NY). Measurement data obeying a normal distribution were expressed as mean ± standard deviation. The intergroup comparison of the measurement data was made using a *t* test. Count data were expressed as constituent ratios and compared between the 2 groups using a X^2 test. A $P < .05$ indicates a significant difference.

4. Results

noninvasive support successfully treated all studied cases. No failed individuals were recorded. The mean gestational age of the 22 infants recruited in the NHFV group was 32.82 ± 1.87 weeks. Their mean bodyweight was 2088.86 ± 583.37 g. 21 infants in the DuoPAP group had a mean gestational age of 32.57 ± 2.69 weeks and a mean bodyweight of 2125.24 ± 781.74 g. There was no significant difference in the

statistical comparison of the above information between the 2 groups (Table 1, all $P > .05$).

There were no significant differences in the PaO_2, $PaCO_2$ and OI values at different time points between the 2 groups for the primary endpoints ($P > .05$; Table 2). The secondary endpoints of IVH, NEC, and BPD, apnea at 72 hours, as well as the total incidence of complications, showed no significant differences between the 2 groups ($P > .05$; Table 3). In terms of NIV treatment effects, the durations of NIV, the nasal cannula oxygen treatment, length of hospital stay, and time to full enteral feeding, there were no significant differences between the 2 groups ($P > .05$; Table 4).

There was no significant difference between the 2 groups in terms of risk factors related to delivery, the use rates of antenatal corticosteroids and surfactant or mode of delivery ($P > .05$; Table 5).

5. Discussion

NIV is an important life-saving measure for RDS in infants.[7–10] NHFV has excellent outcomes in treating premature infants with

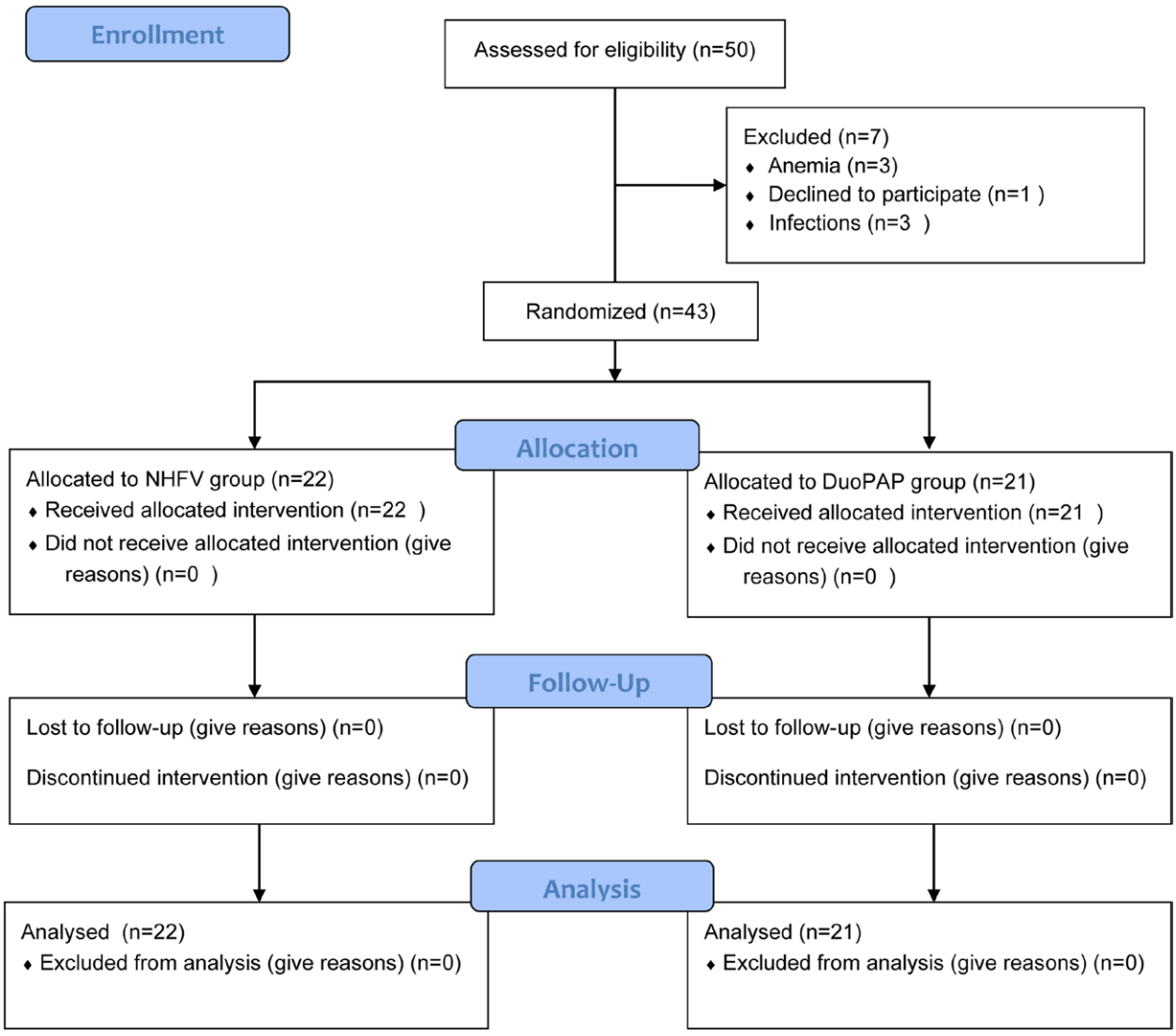

Figure 1. Flow Diagram of infants with RDS included in this study. RDS = respiratory distress syndrome.

Table 1

Comparison of treatment effects between the 2 groups (mean ± SD).

	NHFV (n = 22)	DuoPAP (n = 21)	*t*	*P*
Gestational age (w)	32.82 ± 1.87	32.57 ± 2.69	0.04	.75
Bodyweight (g)	2088.86 ± 583.37	2125.24 ± 781.48	0.17	.86

DuoPAP = duo positive airway pressure, SD = standard deviation.

Table 2

Comparison of the primary endpoints at 12 and 24 hours after starting noninvasive ventilation in both groups (mean ± SD).

	NHFV (n = 22)	DuoPAP (n = 21)	*t*	*P*
PaO_2/mm Hg*				
Up to 12 h on a ventilator	85.23 ± 35.80	77.88 ± 32.16	0.71	.48
Up to 24 h on a ventilator	84.95 ± 29.98	87.53 ± 26.36	0.30	.77
$PaCO_2$/mm Hg**				
Up to 12 h on a ventilator	41.86 ± 12.16	46.38 ± 13.66	1.16	.26
Up to 24 h on a ventilator	38.05 ± 9.80	39.00 ± 9.51	0.37	.75
OI value***				
Up to 12 h on a ventilator	299.73 ± 126.33	273.33 ± 115.86	0.71	.48
Up to 24 h on a ventilator	319.27 ± 126.27	336.33 ± 116.65	0.46	.65

DuoPAP = duo positive airway pressure, OI = oxygenation index, PaCO2 = carbon dioxide partial pressure, PaO2 = arterial oxygen partial pressure, SD = standard deviation.

* PaO_2 = automatically measured the partial pressure of oxygen in arterial blood;

** $PaCO_2$ = automatically measured the partial pressure of carbon dioxide in arterial blood;

*** oxygenation index = automatically measured as the mean airway pressure (Paw) $FIO_2 \times 100/PaO_2$, where FIO_2 is the percent of inspired oxygen that the patient is receiving.

Table 3

Comparison of the secondary endpoints between the 2 groups (n [%]).

	NHFV	DuoPAP	$\chi 2$	*P*
IVH	0	1 (1.81)		
PVL	8 (36.36)	8 (38.10)		
NEC ≥ II stage	0	0		
BPD	2 (9.10)	4 (19.05)		
Apnea	0	0		
Overall incidence (%)	10 (45.48)	13 (31.90)	1.17	.28

PVL is divided into 4 grades. After admission, the bedside cranial ultrasonography showed PVL of the included infants were in the range of 1 to 2 grades. Dynamic follow-up showed no aggravation and had no effect on the prognosis of the infants.

BPD = bronchopulmonary dysplasia, DuoPAP = duo positive airway pressure, IVH = intraventricular hemorrhage, NEC = neonatal necrotizing enterocolitis, PVL = periventricular leukomalacia.

Table 4

Comparison of treatment effects between the 2 groups (mean ± SD).

	NHFV (n = 22)	DuoPAP (n = 21)	*t*	*P*
Duration of noninvasive ventilation (h)	64.45 ± 31.91	102.81 ± 101.06	1.66	.11
Duration of nasal cannula oxygen therapy (h)	123.64 ± 59.11	175.24 ± 172.12	1.30	.21
Length of hospital stay (d)	18.64 ± 10.23	23.19 ± 13.87	1.22	.25
Time to full feeding (h)	12.50 ± 7.71	16.33 ± 9.93	1.41	.18

DuoPAP = duo positive airway pressure, SD = standard deviation.

Table 5

Analysis of prenatal risk factors in both groups (n [%]).

	NHFV (n = 22)	DuoPAP (n = 21)	$\chi 2$	*P*
High-risk factors associated with the parturients*	13 (59.10)	15 (71.43)	0.72	.40
Antenatal corticosteroids use	12 (54.55)	9 (42.86)	0.59	.44
Surfactant use	14 (63.64)	16 (76.19)	0.80	.37
Delivery mode (caesarean section or not)	9 (40.91)	9 (42.86)	0.02	.90

DuoPAP = duo positive airway pressure.

* High-risk factors: gestational diabetes, gestational hypertension, placental abruption and premature rupture of membranes > 18 hours.

respiratory failure.[9] Our study confirmed a similar clinical value of the NHFV to the DuoPAP in premature infants with RDS. We compared $PaCO_2$, FiO_2, and OI values and the incidence of complications between premature infants with RDS receiving NHFV or DuoPAP. No significant differences existed between NHFV and DuoPAP in the ability to improve oxygenation. The 2 modalities also had similar efficacy in reducing CO_2. These results find that NHFV is not superior to DuoPAP, which agrees with the results in previous report by Mukerji et al[16]

NHFV has a low reintubation rate without increasing the rate of complications.[17] DuoPAP diminishes the need for invasive mechanical ventilation and complications in the treatment of neonatal respiratory distress syndrome.[18,19] No differences are found in rates of invasive mechanical ventilation 72 hours and 7 days postrandomization or BPD in a report that compares the effectiveness of NHFV and DuoPAP.[16] Another report finds that the incidence of BPD, IVH ≥ grade 3, PVL, NEC ≥ II stage, abdominal distension, and nasal trauma were similar between the NHFV and DuoPAP groups.[9] The most important markers for monitoring the course of the adaptation period are arterial blood gases, respiratory rate, the patient's subjective sense of dyspnea, and the patient's degree of alertness. If the NIV fails,

it should be withdrawn as quickly as feasible and the patient intubated.[1,5,7] In our study, the comparison of complications of NEC ≥ II stage, BPD and apnea within 72 hours did not reveal any statistical differences between NHFV and DuoPAP groups during the respiratory support in preterm babies with RDS. Both modalities prevented the need for endotracheal intubation in our small scaled study. In addition, our study found no difference in the incidence of IVH, PVL between the 2 groups. These results are consistent with previous reports.[9,16]

Our study indicated that there were no significant differences between NHFV and DuoPAP groups in the durations of NIV and nasal cannula oxygen treatment, length of hospital stay and time to full enteral feeding, which are similar to previous reports.[9,16] There was no significant difference between the 2 groups in terms of delivery risk factors, prenatal corticosteroid and surfactant use, or mode of delivery as well, which needs further validation due to few related reports.

There are some limitations to our study that should be mentioned. First, the sample size is limited, which needs further validation of multi-center studies with large sample. Second, there is no subgroup analysis such as gestation age.

6. Conclusion

Both NHFV and DuoPAP effectively reduced CO_2 retention in premature infants with RDS and improved blood gas analysis indicators without increasing the incidence of adverse reactions. Both modalities can be considered safe and effective modes of ventilation, but randomized controlled trials with larger sample sizes should be used to further validate our findings.

Author contributions

Conceptualization: Hui Wang.
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Supervision: Hui Wang.
Validation: Yinlong Zhang.
Writing – original draft: Hui Wang.
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References

[1] Chiumello D, Brochard L, Marini JJ, et al. Respiratory support in patients with acute respiratory distress syndrome: an expert opinion. Crit Care. 2017;21:240–5.
[2] Niemarkt HJ, Hutten MC, Kramer BW. Surfactant for respiratory distress syndrome: new ideas on a familiar drug with in-novative applications. Neonatology. 2017;111:408–14.
[3] Englert JA, Crouser ED. Steroids and β-agonists in acute respiratory distress syndrome: timing is everything. Crit Care Med. 2017;45:914–5.
[4] Walter JM, Corbridge TC, Singer BD. Invasive mechanical ventilation. South Med J. 2018;111:746–53.
[5] Wang H, Shi LP, Ma XL, et al. Application of noninvasive high-frequency oscillatory ventilation for respiratory support in extremely low birth weight infants. Chin J Pediatr. 2017;55:177–81.
[6] Hua J, Qian C, Luo Z, et al. Invasive mechanical ventilation in COVID-19 patient management: the experience with 469 patients in Wuhan. Crit Care. 2020;24:348.
[7] Behnke J, Lemyre B, Czernik C, et al. Non-invasive ventilation in neonatology. Dtsch Arztebl Int. 2019;116:177–83.
[8] Tobin MJ. Principles and Practice of Mechanical Ventilation. New York, PA, USA: The McGraw-Hill Companies, Inc; 2006:426.
[9] Chen W, Chen Z, Lai S, et al. Noninvasive high-frequency oscillatory ventilation versus bi-level positive pressure ventilation in premature infants with respiratory failure: a retrospective study. Pak J Med Sci. 2022;38:1353–9.
[10] Pan R, Chen GY, Wang J, et al. Bi-level Nasal Positive Airway Pressure (BiPAP) versus Nasal Continuous Positive Airway Pressure (CPAP) for preterm infants with birth weight < 1500 g and respiratory distress syndrome following INSURE treatment: a two-center randomized controlled trial. Curr Med Sci. 2021;41:542–7.
[11] Wu J, Zhai J, Liu X, et al. Clinical application of noninvasive high-frequency oscillatory ventilation plus heated humidified high-flow nasal cannula therapy. Chin J Pediatr Emerg Med. 2021;28:165–70.
[12] Null DM, Alvord J, Leavitt W, et al. High-frequency nasal ventilation for 21 d maintains gas exchange with lower respiratory pressures and promotes alveolarization in preterm lambs. Pediatr Res. 2014;75:507–16.
[13] Malakian A, Aramesh MR, Agahin M, et al. Non-invasive duo positive airway pressure ventilation versus nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome: a randomized controlled trial. BMC Pediatr. 2021;21:301.
[14] Shao XM, Ye HM, Qiu XS. Practical Neonatology. 4th ed. Beijing: People's Medical Publishing House; 2011:395–8.
[15] Teng QL, Liu ZY, He XC. Efficacy analysis of noninvasive high-frequency oscillatory ventilation in 42 very low birth weight infants with respiratory distress syndrome. Anhui Med Pharm J. 2022;26:172–5.
[16] Mukerji A, Sarmiento K, Lee B, et al. Non-invasive high-frequency ventilation versus bi-phasic continuous positive airway pressure (BP-CPAP) following CPAP failure in infants <1250 g: a pilot randomized controlled trial. J Perinatol. 2017;37:49–53.
[17] Li Y, Wei Q, Zhao D, et al. Non-invasive high-frequency oscillatory ventilation in preterm infants after extubation: a randomized, controlled trial. J Int Med Res. 2021;49:300060520984915.
[18] Zhou B, Zhai JF, Jiang HX, et al. Usefulness of DuoPAP in the treatment of very low birth weight preterm infants with neonatal respiratory distress syndrome. Eur Rev Med Pharmacol Sci. 2015;19:573–7.
[19] Solevåg AL, Cheung PY, Schmölzer GM. Bi-level noninvasive ventilation in neonatal respiratory distress syndrome. a systematic review and meta-analysis. Neonatology. 2021;118:264–73.