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Original Article

Comparative study on the efficacy of continuous nasal positive airway pressure and bilevel positive airway pressure in the treatment of newborn respiratory distress syndrome

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Abstract: In this study, patients with newborn respiratory distress syndrome (NRDS) were selected as the subjects and randomly divided into a NCPAP Group and a BiPAP group. The NCPAP group was given Nasal Continuous Positive Airway Pressure (NCPAP), and the BiPAP group was treated with Bilevel Positive Airway Pressure (BiPAP). After 7 d of treatment, the efficacy of treatment was evaluated. Results showed that the combination of BiPAP and Gu Er Su in treating NRDS can shorten their length of ventilator application and stay, improve blood gas level and lung function, and reduce inflammatory factor levels.

Keywords: NCPAP, CPAP, Gu Er Su, newborn respiratory distress syndrome, clinical efficacy

Introduction

Newborn respiratory distress syndrome (NRDS), also known as hyaline membrane disease (HMD), is often reported in premature babies, who soon after birth show progressive and aggravated respiratory distress, which if not effectively treated upon onset, will evolve into respiratory failure. The younger the gestational age, the higher the risk of NRDS [1, 2]. According to clinical studies [3, 4], NRDS involves complicated causes and manifests as deficiency of pulmonary surfactant (PS) pathologically and physiologically, leading to alveolus pulmonis shrinkage. Within 6 to 12 h, the disease will aggravate and become serious, causing three depression signs upon inspiration, with groaning, etc. Some patients will have characteristic manifestations seen under X ray. Most NRDS cases require invasive or non-invasive assisted ventilation support [5]. In recent years, with the continuous development of medical technologies, a large number of patients are directly treated by non-invasive ventilation to reduce complications arising from invasive ventilation [6, 7]. As can be found in previous studies [8, 9], nasal continuous positive airway pressure (NCPAP) is capable of reducing the mortality of premature babies and the dependence on invasive ventilation in NRDS patients. At present, NCPAP is widely used in neonates and infants with respiratory failure and dyspnea, which can prevent any possible adverse consequences caused by the use of pure oxygen in neonates. However, its clinical application involves complicated operation systems, high requirements on nurses, and fixation of patients' head during treatment, which increase the difficulty of nursing [10].

Bilevel positive airway pressure (BiPAP) is a new non-invasive ventilation method developed from time cycled-controlled mechanical ventilation, under which two different CPAP levels exchange in cycle at the preset breathing time, and the ventilator switches between two levels of positive airway pressure [11, 12]. Clinically applied, BiPAP can maintain high air flow and stable support pressure. It is suitable for chronic obstructive pulmonary diseases in acute

exacerbation, cardiac pulmonary edema (CPE), acute attack of asthma and perioperative population [13]. Gu Er Su is a natural extract which can alternatively compensate for the insufficient cardiac PS in NRDS patients [14]. Therefore, with NRDS patients as the study subject, this study compared the efficacy of NCPAP and BiPAP combined with Gu Er Su in NRDS treatment.

Materials and methods

Clinical materials

A total of 150 NRDS patients delivered in our hospital from May 2017 to August 2019 were included and randomized into the NCPAP group (n=98) and BiPAP group (n=52).

Inclusion and exclusion criteria

Inclusion criteria: patients were diagnosed based on clinical manifestations and chest X-ray according to the NRDS diagnosis criteria in *Practical Neonatology*, treated by Bovine Lung Phospholipid Injection (Gu Er Su) with indications, and complied with the indications for NCPAP/BiPAP with stable vital signs.

Exclusion criteria: some patients were rejected as their guardians declined the application of Gu Er Su or they were preventively treated with PS, if they had concurrent diseases such as congenital deformity, congenital diaphragmatic hernia, complex congenital heart disease or white lung according to X-ray examination before treatment, or concurrent diseases in the blood system, autoimmune system or other organic disorders. Signed informed consent was obtained from their guardians. The study was approved by the ethics committee of the Qingdao Municipal Hospital.

Treatment methods

Patients were warmed during recovery from oxidosis after delivery and for reinforcement of resistance against infection, and were given nutritional support. Lying flat on the back, patients had their mouth and nose cleaned. Both groups were treated by Bovine Lung Phospholipid Injection (Gu Er Su) (Chiesi Farmaceutici S.p.A., GYZ No.: H20030599) by inhalation at a dose of 200 mg/(kg·d) for 3 to 5 min each time, which could be repeated 2 to 3 times based on the patients' conditions [15, 16].

NCPAP group: patients in this group were treated by NCPAP with the CAPA-B ventilator for infants (produced by Stephan, a company in Germany). Parameters were set in consideration of the patients' conditions, including FiO_2 between 30.0%-40.0%, positive end expiratory pressure (PEEP) between 5-7 cm H_2O, and flowrate between 6-8 L/min, which were adjusted according to the assay results. During treatment, patients' oxygen saturation of the blood was consolidated, and reduced to 21% when it ranged from 93 to 95% or increased to 60.06% when it ranged from 85% to 88% by downward or upward regulation of FiO_2 by 5%. Criteria for ventilator removal: when FiO_2 dropped to 21%, other parameters reduced to or maintained at the primary parameters, and the children' conditions were stable for a continuous 24 h without abnormality in blood gas, then the ventilator was removed. Efficacy was evaluated after 7 d of treatment.

Observation indices

(1) Time of therapy and medical expense. Both groups completed the 7 d treatment. During the treatment, ventilator application, oxygen therapy, assisted respiration, length of stay, and medical expenses of NCPAP and BiPAP groups were recorded. (2) Blood gas level. Five ml of venous blood was drawn from the two groups before and 7 d after treatment, centrifuged, and assayed for PH, $PaCO_2$ and PaO_2 levels by a blood gas analyzer (48 h dynamic monitoring) [17, 18]. (3) Inflammatory factor levels. Five ml of venous blood was drawn from the two groups before and 7d after treatment. After centrifugation, TNF-α and IL-10 levels were assayed by ELISA method, and serum ferritin (SF) level was assayed by immunofluorescence [17]; (4) Lung function level. Tidal volume per body weight in kg, respiratory rate (RR), TPEE/tE and VPEF/NE with a pulmonary function test apparatus before and 3 d after treatment [19]; (5) Safety and prognosis. The 2 groups were observed for nasal injury, air leak, abdominal distension, intracranial hemorrhage, pneumorrhagia, bron-

Table 1. Comparison between the 2 groups for clinical materials

Clinical Materials		BiPAP Group (n=52)	NCPAP Group (n=98)	x^2	*P*
Gender (n)	Male	31 (59.62)	54 (55.10)	1.294	0.059
	Female	21 (40.38)	44 (44.90)		
Gestational age (week)		30.98±3.16	31.03±3.19	0.194	0.537
Weight (g)		2314.69±25.93	2328.70±26.84	0.394	0.771
1 min Apgar score (score)		8.00±1.12	9.00±1.01	0.668	0.066
5 min Apgar score (score)		8.14±1.15	9.03±1.03	1.103	0.682
Mode of delivery	C-sect	23 (44.23)	44 (44.90)	0.593	0.341
	Vaginal delivery	29 (55.77)	54 (55.10)		
Use of hormones before delivery	Yes	45 (86.54)	73 (74.49)	1.285	0.698
	No	7 (13.46)	25 (25.51)		
Chest X-ray classification	I-II	15 (28.85)	24 (24.49)	0.748	0.553
	III-IV	37 (71.15)	74 (75.51)		

Table 2. Comparison between the 2 groups for time of therapy, length of stay and medical expenses (d, $\bar{x} \pm s$)

Group	N	Time of Mechanical Ventilation	Time of Assisted Respiration	Length of Stay	Oxygen Uptake (h)	Medical Expense (RMB 10,000)
BiPAP group	52	3.58±0.77	3.27±0.69	23.51±4.69	24.69±4.61	2.59±0.43
NCPAP group	98	6.82±1.05	7.45±0.98	25.17±6.81	36.91±5.74	2.60±0.45
T	/	6.382	7.817	1.771	6.336	5.327
P	/	0.000	0.000	0.325	0.000	0.698

chopulmonary dysplasia (BPD), ventilation failure and mortality during treatment.

Statistical analysis

Statistical analysis was performed with SPSS 18.0. In case of nominal data expressed as [n (%)], comparison studies were carried out through X^2 test. In case of numerical data it was expressed as $\bar{x} \pm s$, comparison studies were carried out through *t* test. For all statistical comparisons, significance was defined as P<0.05.

Results

Comparison of the clinical materials between the 2 groups

All patients were thoroughly examined and diagnosed. No statistical difference was found between the 2 groups in terms of gender, gestational age, weight, 1 min Apgar score, 5 min Apgar score, mode of delivery, use of hormones before delivery, chest X-ray, and classification (*P*>0.05, **Table 1**).

BiPAP shortens time of therapy and medical expenses compared with NCPAP

The length of stay and medical expense of the BiPAP group and the NCPAP group were (23.51±4.69, 25.17±6.81) days, RMB (2.59±0.43, 2.60±0.45) (Unit: RMB 10,000 Yuan), respectively; between which, no statistical difference was observed (P>0.05). For length of mechanical ventilation, assisted respiration and oxygen uptake, the reported data were (3.58±0.77) d, (3.27±0.69) d and (4.69±4.61) h in the BiPAP group; (6.82±1.05) d, (7.45±0.98) d and (36.91±5.74) h in the NCPAP group (P<0.05, **Table 2**).

BiPAP improves blood gas level compared with NCPAP

Before and 7 d after being intervened with noninvasive ventilation combined with Gu Er Su, the 2 groups had no statistical difference in blood gas levels (P>0.05), and PH level (7.35±1.21, 7.34±1.20) (P>0.05). Seven days after treatment, the $PaCO_2$ and PaO_2 levels reached 56.81±3.59 cm H_2O and 69.73±3.08

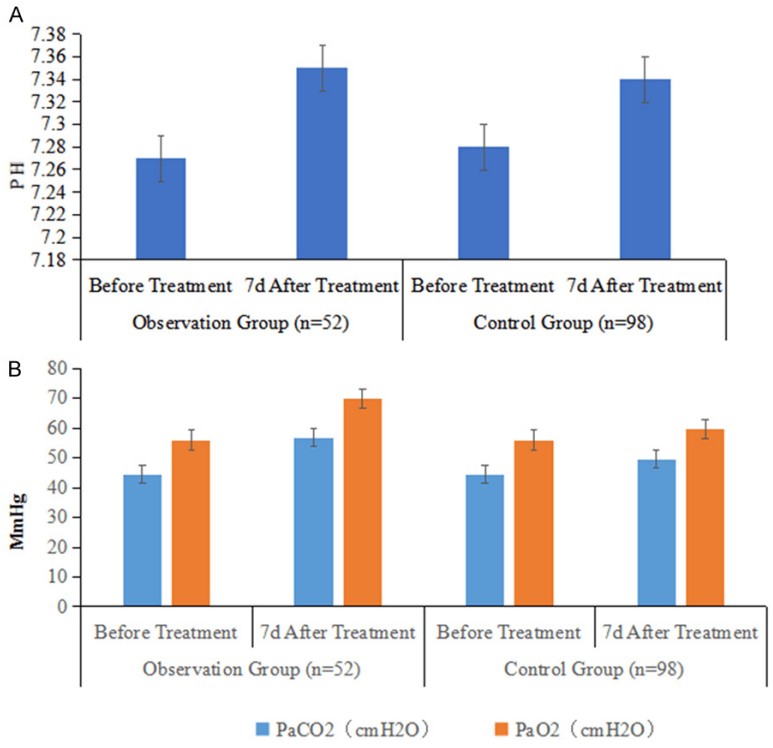

Figure 1. Comparison between the 2 groups for blood gas levels. Note: A: PH values before and after treatment in both groups. B: $PaCO_2$ and PaO_2 levels before and after treatment in both groups. Before treatment, the 2 groups had no statistical difference in $PaCO_2$, PaO_2, and PH levels (P>0.05). After treatment, $PaCO_2$, PaO_2 and PH levels had intragroup and intergroup significance, P<0.05.

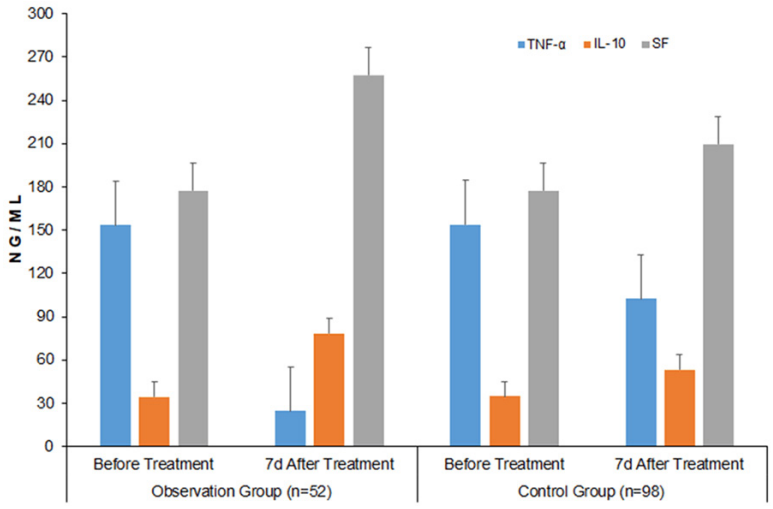

Figure 2. Comparison between the 2 groups for inflammatory factors. Before treatment, no statistical difference was observed between the two groups (P>0.05). After treatment, TNF-α and IL-10 levels were reduced and the SF level was increased in both groups, among which the difference was more significant in the BiPAP group (P<0.05).

cm H_2O in the BiPAP group; 49.48±3.41 cm H_2O and 59.63±2.85 cm H_2O in the NCPAP group, which had intragroup and intergroup significance (P<0.05, **Figure 1**).

BiPAP reduces inflammatory factor levels compared with NCPAP

No statistical difference was observed between the 2 groups in terms of inflammatory factors before intervention with noninvasive ventilation combined with Gu Er Su (P>0.05). Seven days after treatment, both groups achieved a reduction in the levels of TNF-α and IL-10, and an increase in SF level (P<0.05), which were more significant in the BiPAP group (P<0.05, **Figure 2**).

BiPAP improves lung functions compared with NCPAP

Before intervention, the 2 groups demonstrated no statistical difference in lung function (P>0.05). Seven days after noninvasive ventilation combined with Gu Er Su, in the BiPAP group, the VT/kg level was (6.32±0.45) mL/kg, RR was (46.72±3.05) times/min, which were lower than the NCPAP group which were (6.73±0.68) mL/kg, and (50.43±3.42) times/min (P<0.05); but its TPEE/tE [(29.44±3.41)%] and VPEF/NE [(32.61±3.06)%], were higher than the NCPAP group which were (26.71±3.38)% and (26.71±3.38)% (P<0.05, **Table 3**).

BiPAP yields better safety and prognosis compared with NCPAP

During treatment, the 2 groups had no statistical difference in terms of hemorrhoid frequency, intracranial hemorrhage, pneumorrhagia, BPD, ventilation failure and

Table 3. Comparison between the 2 groups for lung function level ($\bar{x} \pm s$)

Group		VT/kg (mL/kg)	RR (time/min)	TPEE/tE (%)	VPEF/NE (%)
BiPAP group (n=52)	Before treatment	6.89±0.73	55.45±3.69	25.34±3.23	27.49±2.95
	3 d after treatment	6.32±0.45[a,b]	46.72±3.05[a,b]	29.44±3.41[a,b]	32.61±3.06[a,b]
NCPAP group (n=98)	Before treatment	6.90±0.75	55.46±3.71	25.35±3.25	27.51±2.98
	3 d after treatment	6.73±0.68[b]	50.43±3.42[b]	26.71±3.38[b]	30.12±3.01[b]

[a]*P*<0.05 as compared with the NCPAP group, and [b]*P*<0.05 as compared with conditions before treatment.

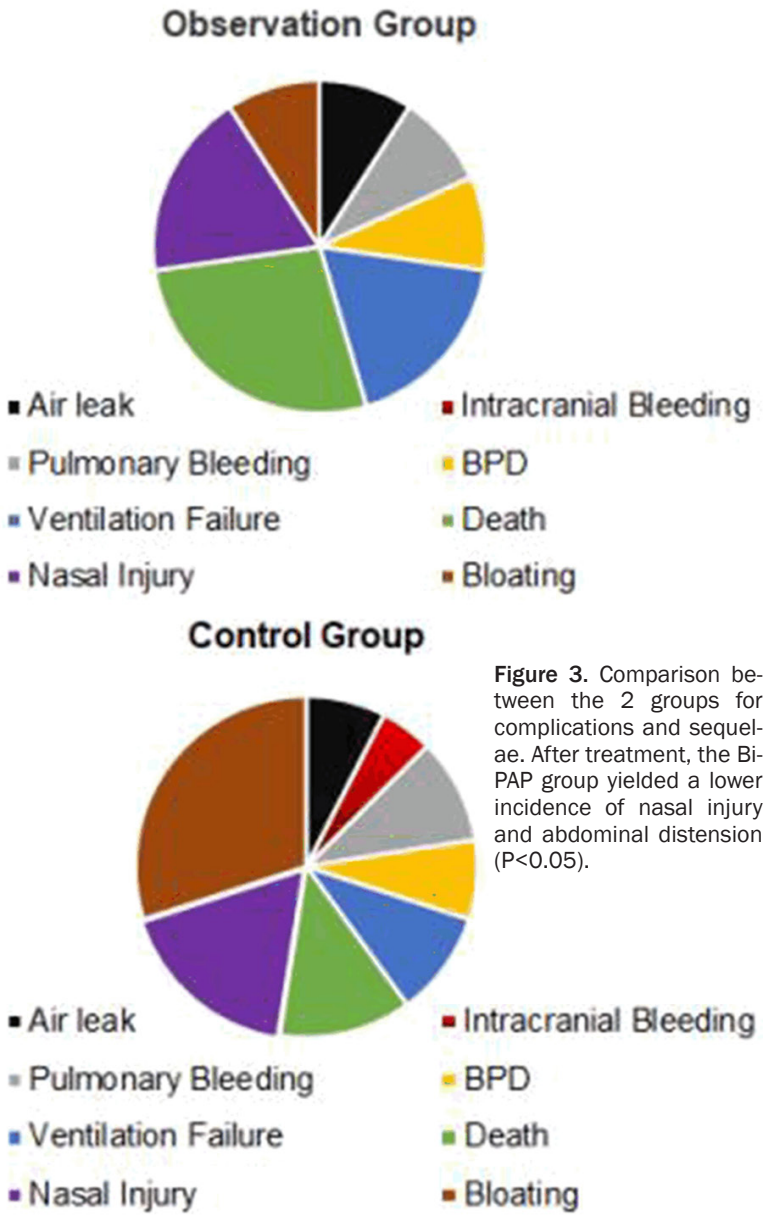

Figure 3. Comparison between the 2 groups for complications and sequelae. After treatment, the BiPAP group yielded a lower incidence of nasal injury and abdominal distension (P<0.05).

mortality (P>0.05). After treatment, the BiPAP group yielded a lower incidence of nasal injury and abdominal distension (P<0.05, **Figure 3**).

Discussion

NRDS is a disease caused by reduced secretion of PS and hypodevelopment of lung tissues. It mainly develops in premature babies, occuring 6 h after delivery in most of the cases, and can worsen in 2 d, and leads to progressive respiratory failure in serious cases [20]. It can improve 2-4 d in case the case of the baby surviving. So far, clinical treatment of NRDS is capable of improving the symptoms, increasing the survival, and avoiding continuous deterioration as much as possible. PS is a quite complicated mixture of a variety of phospholipids and specific proteins, etc. It can regulate alveolar tension, improve the neonate's gas exchange function and lung compliance, prevent the shrinkage of alveolus pulmonis and raise the oxygen saturation of blood. Previous studies have demonstrated that [21]: the secretion of PS requires 22-24 weeks, but may be insufficient, however, in some patients whose alveolar cells are hypodeveloped. As an exogenous PS extracted from the surface of alveolus pulmonis on pigs' lungs, Gu Er Su contains lecithin, hydrophobic proteins, etc., which can reach the lungs after inhalation to reduce the incidence of bucking, improve symptoms and extend the development of the

conditions [22]. Pharmacological results show that [23] to fully leverage the efficacy of Gu Er Su, it needs to be combined with mechanical ventilation to facilitate the distribution and absorption of the drug in alveolus pulmonis of NRDS patients.

NCPAP is a commonly adopted noninvasive ventilation mode in NRDS patients to stop alveolus pulmonis from collapse at the end of respiration, enhance gas exchange, and improve ventilation and gas exchange function [24]. In the meantime, the mode supports exchange of function during treatment to ensure the accurate implementation of cardio-pulmonary resuscitation, reduce the incidence of oxygen poisoning, alleviating or remedying patients' hyoxemia. It is high-quality, highly-efficient, noninvasive and safe as a stable temperature and humidity inhaled gas [25]. However, the clinical application of NCPAP has high requirements on nurses who are have solid expertise, and it may increase the nursing workload. In recent years, BiPAP is applied in the treatment of newborn respiratory distress syndrome in combination with Gu Er Su and ventilators, achieving ideal effects. In this study, the 2 groups had no statistical difference in length of stay and medical expense ($P>0.05$), but the BiPAP group reported shorter length of mechanical ventilation, assisted respiration and oxygen uptake than the NCPAP group ($P<0.05$), indicating that the combination of BiPAP and Gu Er Su can shorten the time of NRDS therapy and benefit the patients in recovery. BiPAP is defined as a noninvasive ventilation therapy providing respiratory support at 2 pressure levels. The airway pressure can be set according to the patients' conditions, and change between the upper and lower limits to achieve stable exhalation and inspiratory time. In the meantime, during BiPAP treatment, the pressure level and duration are configurable as needed to enjoy the advantages of pressure supported ventilation (PSV) and PEEP. According to previous studies, the application of BiPAP in NRDS patients can dilate collapsed and closed alveolus pulmonis, increase functional residual capacity, improve lung compliance, reduce the work of breathing and allow the patients autonomously respiration at different levels. Also from previous studies, it is learned that [26], BiPAP can intermittently provide upper limit pressure to raise the AWP. This process helps to ameliorate patients' oxygenation and carbon dioxide exhaustion. In this study, the 2 groups demonstrated no statistical difference in terms of PH 7 d after treatment ($P>0.05$), but the BiPAP group's $PaCO_2$ and PaO_2 levels exceeded the NCPAP group's ($P<0.05$), indicating that BiPAP is capable of improving the blood gas level and slowing down disease progression in NRDS patients.

TNF-α is cell factor produced by macrophages. Expressing at a lower levels in healthy human bodies, TNF-α can directly kill tumor cells but has little obvious effect on normal cells [27]. Clinically, TNF includes TNF-α and TNF-β, both capable of inhibiting Gegenbaur cells, stimulating the cell factors of osteoclasts, and dilating blood vessels. IL-10 is an immunomodulatory factor directly participating in the growth and differentiation of cells, inflammatory and immunological reactions of organs. Clinical studies have proved that [28] IL-10 plays a key role in the inhibition of tumors, infection and organs, and in diseases of the blood system as well as the cardiovascular system. Foreign scholars have found in their studies that IL-10 has multiple biological roles, including immunoregulation and disease regulation. Generally, it maintains a dynamic balance in a healthy body, but may rise as a result of relative low immunity levels in patients and other various factors, and play various key roles in the development and progression of diseases. SF is a compound of ferroprotein and Fe3+. Its expression directly reflects if the body is iron-deficient or iron-overloaded. Clinical studies have revealed that ferroprotein is an important storage of iron in human bodies. It directly participates in the regulation of the immunologic system, and reflects the body's nutritional status. Meanwhile, patients with reduced serum ferroprotein level are assumed to be iron-deficient. In NRDS patients with compromised respiratory functions, continuous stress will lead to elevated TNF-α and IL-10 levels, and reduced SF level, which is a sign of anemia. Therefore, in this study, BiPAP and NCPAP were combined with Gu Er Su for treatment, and the results indicated that 7 d after treatment, the BiPAP group achieved a reduction in TNF-α, IL-10, VT/kg, RR, and a rise in SF, TPEE/tE and VPEF/NE ($P<0.05$) compared to the NCPAP

group, indicating that both NPPVs, when combined with Gu Er Su, can achieve better efficacy in NRDS treatment. However, the BiPAP group is more effective as it can control the conditions from development, improve patients' lung function level and yield better prognosis.

Regardless of BiPAP's better effects in NRDS patients, some scholars found in their studies that this method is associated with a rising incidence of pulmonary pneumothorax and pulmonary emphysema, affecting patients' tolerance to treatment. Referring to some foreign scholars' studies, with the continuous development of medical technologies, the newly designed rhinobyons can give rise to the Coanda effect by reducing the expiratory resistance patients have and reduce the incidence of pneumothorax and CO_2 retention. In this study, the BiPAP group and NCPAP group had no statistical difference in hemorrhoid frequency, intracranial hemorrhage, pneumorrhagia, BPD, ventilation failure and mortality during treatment ($P>0.05$); after treatment, the BiPAP group reported a lower incidence of nose injury, and abdominal distension as compared with the NCPAP group ($P<0.05$), indicating that the BiPAP combined with Gu Er Su is more safe and helpful to increase the treatment tolerance in NRDS patients. In order to raise NRDS patients' treatment beneficial effects, stomach tubes are inserted in general cases to ensure their sufficient nutrition and avoid or reduce the incidence of abdominal distension or feeding intolerance, in order to promote recovery. At the same time, vital sign monitoring is enhanced during treatment and the ventilator is removed as early as possible according to the individual's specific criteria.

In conclusion, the combination of BiPAP and Gu Er Su in treating NRDS patients can shorten their length of ventilator application and hospital stay, improve blood gas levels and lung function, and reduce inflammatory factor levels. Based on this good treatment sequelae and low incidence of complications, the combination will be further applied.

Disclosure of conflict of interest

None.

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