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Original Article

Comparison of therapeutic effects of budesonide and ambroxol combined with bovine pulmonary surfactant on neonatal respiratory distress syndrome

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Abstract: Objective: To explore the role of budesonide (BUD)/ambroxol (AMB) with bovine pulmonary surfactant (PS) on neonatal respiratory distress syndrome (NRDS). Methods: Altogether 90 cases of children with NRDS treated in our hospital from September 2019 to May 2020 were collected. Among them, 45 cases were treated with BUD combined with PS as the control group (CG), and the other 45 cases were treated with AMB combined with PS as the observation group (OG). The curative effect, arterial blood gas index (PaO_2, $PaCO_2$, PaO_2/FiO_2), treatment time (CPAP usage time, oxygen time, length of stay), symptom recovery time (pulmonary rales disappearance time, cough disappearance time, antipyretic disappearance time), complications and death, repeated medication, inflammatory index (TNF-α, IL-6, IL-10), oxidative stress index (GSH-Px, SOD, MDA) were observed and compared. Results: The total effective rate of the OG was higher than that of the CG. Arterial blood gas index, inflammatory index and oxidative stress index were better in the OG. CPAP usage time, oxygen time, length of stay, pulmonary rales disappearance time, cough disappearance time and antipyretic disappearance time were shorter in the OG. Complications, deaths and repeated medication were lower in the OG. Conclusion: AMB with PS is superior to BUD with PS in NRDS, which is useful for clinical treatment.

Keywords: Neonatal respiratory distress syndrome, budesonide, ambroxol, bovine pulmonary surfactant

Introduction

Neonatal respiratory distress syndrome (NRDS) causes premature infant death and morbidity, and belongs to common respiratory diseases. Its pathogenesis is related to pulmonary surfactant (PS) abnormalities [1, 2]. PS abnormalities include PS deficiency or immature structure, which can lead to the formation of transparent membrane analogs on trachea and is also the origin of hyaline membrane disease, the alias for NRDS [3]. PS can maintain a stable micro-environment and prevent the fluid in pulmonary capillaries from transferring to pulmonary interstitium or accumulating in the alveoli. Currently, PS has become an effective and well-tolerated treatment for NRDS [4, 5]. According to data, NRDS occurs in about 1% of newborns. Premature infants with gestational age less than 28 weeks are more than 50% more likely to suffer from NRDS, and the mortality rate of NRDS in developed countries can reach as high as 60% [6]. At present, the existence of PS combination therapy for NRDS has gradually shown its unique advantages in safety, survival rate and oxygenation improvement, such as PS combined with nasal continuous positive airway pressure [7]. Therefore, it is still of great significance to continue exploring PS combination therapy for reducing the mortality of NRDS in children.

The pathological process of NRDS also involves excessive activation of inflammatory cytokines, and its underlying trigger mechanism is also related to hypoxemia and hypercapnia [8, 9]. Budesonide (BUD) belongs to the glucocorticoid family, has anti-inflammatory activity, and can be applied to gastrointestinal diseases and respiratory diseases including NRDS [10-12].

BUD and PS are often used in combination to treat NRDS. According to reports by Ke et al. [13], the drug effect of BUD combined with PS in aerosol form was significantly better than that of BUD combined with PS in solution, and the improvement degree of arterial blood gas index of BUD combined with PS in aerosol form was the greatest. There were also reports revealing that the combination of BUD and PS was helpful to reduce the risk of chronic lung diseases [14]. Ambroxol (AMB) is a pleiotropic respiratory disease treatment drug, which integrates anti-inflammatory, antioxidant, immune regulation and other functions [15]. In the study by Zhang et al. [16], AMB was helpful to prevent NRDS and neonatal death, and it was the best intervention method compared with placebo, betamethasone and dexamethasone. It has also been reported that AMB can mediate SP secretion and is beneficial to relieve pulmonary inflammatory state [17].

At present, there are few comparative studies on the therapeutic effects of BUD combined with PS and AMB combined with PS. The novelty of this study is to fill in the gaps in this field, hoping to provide new insights for the treatment of NRDS.

Data and methods

General information

Altogether 90 cases of children with NRDS treated in our hospital from September 2019 to May 2020 were collected, in which 45 cases were treated with BUD combined with PS as the control group (CG), containing 28 boys and 17 girls, with an average gestational age of (29.75±1.38) weeks. Another 45 cases were treated with AMB combined with PS as the observation group (OG), containing 25 boys and 20 girls, with an average gestational age of (30.24±1.40) weeks. This study was approved by the Ethics Committee, and all guardians of the children have signed informed consent forms. Inclusion criteria: the diagnosis conformed to European NRDS diagnostic criteria [18]; the children were not aged more than 37 weeks; respiratory distress symptoms occurred within 12 hours after birth, including cyanosis, moaning, inspiratory three concave signs, shortness of breath, and even respiratory failure; the respiratory sound of auscultation for both lungs was relatively low; chest X-ray examination showed bronchial hyperemia or ground-glass opacity in both lungs. Exclusion criteria: children with congenital heart disease or malformation; children with severe infection or severe pneumonia; children with immune system defects; children who inhaled amniotic fluid or meconium; children complicated with heart failure, cardiogenic shock, pulmonary hypertension, and pulmonary hemorrhage; death occurred within 24 hours of admission; children in shock. The inclusion criteria were applicable to both groups of children.

Treatment method

Routine treatment: all children received routine care and PS (Shuanghe Modern Medical Technology Co., Ltd, Beijing, China, H20052128) and continuous positive pressure ventilation (CPAP) treatment after birth. PS administration method: during administration, the drug was injected into the lungs through a tracheal cannula, and the insertion depth was appropriate to just reach the lower opening of the tracheal cannula. The medicine was divided into 4 parts (supine position→right supine position→left supine position→semi-supine position), with 10-15 s injection each time, and the air bag pressure assisted ventilation was carried out for about 1 min at the administration intervals. Sputum aspiration was not permitted within 6h of medication. The administration was usually applied only once, and sometimes it could be applied 2 times according to the condition. The interval time was 12 hours or more, the repeated dose was the same as the first. CPAP treatment method: the parameters were set according to the condition and blood gas analysis, and the machine was gradually removed when the patient's condition improved, clinical symptoms disappeared, and blood gas index was stable.

Treatment scheme of CG: in addition to the conventional PS treatment, 0.25 mg/kg pulmicort respules (BUD suspension for inhalation) (AstraZeneca Pharmaceutical Co., Ltd., Wuxi, China, H20030410) was administered in the same way as PS. Ventilator parameters were adjusted according to children's condition and blood gas analysis was conducted during administration.

Treatment plan of the OG: in addition to the conventional PS treatment, 30 mg/(kg·d) AMB injection (Pharmaceutical Research Institute

Co., Ltd., Tianjin, China, H20041473) was given, and 1 mL (7.5 mg) AMB hydrochloride injection was added to 10 ml of 0.09% sodium chloride solution with intravenous drip by infusion pump twice a day for 5 days.

Efficacy evaluation

The curative effect was evaluated by observing the symptoms and vital signs 12 hours after treatment. A child with stable breathing, no moaning, cyanosis and other symptoms, acid-base balance, electrolyte balance, normal blood gas index, and clear double lung texture was regarded as markedly effective. A child with relatively stable breathing, no symptoms such as moaning and cyanosis, improved blood gas index and abnormal chest X-ray was considered effective. Respiratory, moaning, cyanosis and other symptoms of children have not improved or even become more serious, were regarded as ineffective. The total effective rate = markedly effective cases + effective cases/ total cases.

Observation index

Arterial blood of children before and after treatment was collected, and arterial blood gas indexes such as partial pressure of blood oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), and PaO_2/FiO_2 were recorded at T0 (before medication), T1 (6 hours after medication) and T2 (12 hours after medication), and were measured by Cobas b123 automatic blood gas, electrolyte and biochemical analyzer (Queensland Biotechnology Development Co., Ltd., Shanghai, China). CAPA usage time, oxygen time, length of stay and other treatment times, pulmonary rales disappearance time, cough disappearance time, antipyretic disappearance time and other symptom recovery times were recorded and compared. The incidence rate of complications, mortality rate and repeated medication rate of pneumonia, leukomalacia, retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH) were observed and recorded. A sample of 3 ml of fasting venous blood was collected, centrifugated at 1500× g and at 4°C for 10 min to obtain the serum. Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10) and other inflammation-related indexes were determined by ELISA [19] according to the kit instructions (Shanghai Guang Rui Biological Technology Co., Ltd., Shanghai, China, QTE10208, QTE10-457, QTE11652). Oxidative stress indexes such as glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), malondialdehyde (MDA) and other oxidative stress indexes were determined in strict accordance with kit instructions (Shanghai Guang Rui Biological Technology Co., Ltd., Shanghai, China, human Elisa kit 212, human Elisa kit 416, human Elisa kit 1084).

Statistical analysis

GraphPad Prism 6 (GraphPad Software, San Diego, USA) was applied to analyze the data and illustrate the pictures. The counting data was expressed by the number/percentage (n/%), the measurement data was expressed by mean ± SEM. Chi square test, independent sample t-test and paired t-test were applied to compare the counting data, measurement data, and for intra-group comparison before and after treatment. When the theoretical frequency in chi-square test was less than 5, the continuity correction chi-square test was applied. Repeated measurement analysis of variance was used for multiple-time point comparisons. When $P<0.05$, the difference was statistically significant.

Results

Baseline data

There were no evident differences in gender, delivery mode, average gestational age, birth weight, neonatal score (Apgar score) [20], onset time, alveolar arterial oxygen partial pressure ratio ($a/A\ PO_2$), family type, residence and Chest X-ray grade between the OG and CG ($P>0.05$). See **Table 1**.

The curative effect of BUD combined with PS was better

The total effective rate of the OG was evidently higher than that of the CG (90.91% VS 75.56%) ($P<0.05$). See **Table 2**.

The arterial blood gas index of BUD combined with PS was better

There was no evident difference in PaO_2, $PaCO_2$, PaO_2/FiO_2 between the two groups ($P>0.05$). The PaO_2 and PaO_2/FiO_2 at T1 of the two groups of children were significantly increased, while $PaCO_2$ was decreased.

Table 1. Baseline data [n (%), mean ± SD]

Factor	n	Control group (n=45)	Observation group (n=45)	χ^2/t	P
Gender				0.413	0.520
Male	53	28 (62.22)	25 (55.56)		
Female	37	17 (37.78)	20 (44.44)		
Mode of delivery				0.180	0.671
Cesarean delivery	50	24 (53.33)	26 (57.78)		
Spontaneous delivery	40	21 (46.67)	19 (42.22)		
Gestational age (weeks)				0.179	0.673
<30	42	22 (48.89)	20 (44.44)		
≥30	48	23 (51.11)	25 (55.56)		
Mean gestational age (weeks)	90	29.75±1.38	30.24±1.40	1.672	0.098
Birth weight (g)	90	1503.10±195.82	1520.44±198.23	0.417	0.677
Apgar score (points)	90	6.81±0.74	6.63±0.69	1.193	0.236
Time of onset (h)	90	3.05±0.56	3.23±0.61	1.458	0.148
a/A PO_2	90	1.45±0.13	1.48±0.12	1.138	0.258
Family type				0.598	0.278
Single parent family	18	8 (17.78)	10 (22.22)		
Normal family	72	37 (82.22)	35 (77.78)		
Residence				0.729	0.393
Rural	38	17 (37.78)	21 (46.67)		
Urban	52	28 (62.22)	24 (53.33)		
Chest X-ray grade				2.761	0.251
Grade I	22	14 (31.11)	8 (17.78)		
Grade II	36	18 (40.00)	18 (40.00)		
Grade III	32	13 (28.89)	19 (42.22)		

PaO_2 and PaO_2/FiO_2 in the OG were higher than those in CG, and $PaCO_2$ was lower than those in the CG (P<0.05). The PaO_2 and $PaCO_2$ of the two groups of children at T2 decreased, while PaO_2/FiO_2 increased. The PaO_2 and PaO_2/FiO_2 of the OG were significantly higher than those of the CG, and $PaCO_2$ was evidently lower than that of the CG (P<0.05). See **Figure 1**.

The treatment time of BUD combined with PS was shorter

CAPA usage time, oxygen time and length of stay in the OG were evidently shorter than those in the CG (P<0.05). See **Figure 2**.

The recovery time of symptoms of BUD combined with PS was shorter

The pulmonary rales disappearance time, cough and fever disappearance time in the OG were evidently shorter than that in the CG (P<0.05). See **Figure 3**.

The complications, mortality and repeated medication rate of BUD combined with PS were lower

The incidence of pneumonia, leukomalacia, ROP, IVH and other complications, the mortality rate, and the repeated medication rate in the OG were evidently lower (P<0.05). (See **Table 3**).

Inflammation response of BUD combined with PS was evidently inhibited

Before treatment, there was no evident difference in TNF-α, IL-6, IL-10 and other inflammatory indexes between the OG and CG (P>0.05). After treatment, there was no evident change in TNF-α and IL-6 in the OG, and the two indexes in the CG were evidently enhanced (P<0.05), and the two indexes in the OG were lower than that in the CG (P<0.05). However, IL-10 in the two groups of children was evidently decreased after treatment, and IL-10 in the OG was evidently higher than the CG (P<0.05). See **Figure 4**.

Table 2. Clinical efficacy [n (%)]

Group	N	Markedly effective	Effective	Ineffective	Total effective rate (%)
Control group	45	15 (33.33)	20 (44.44)	10 (22.23)	75.56
Observation group	45	22 (48.89)	20 (44.44)	3 (6.67)	90.91
χ^2 value	-	-	-	-	4.341
P value	-	-	-	-	0.037

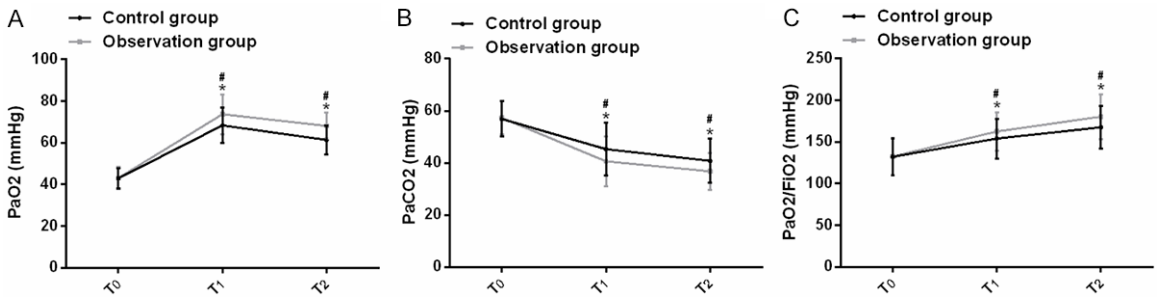

Figure 1. Arterial blood gas indexes of two groups of children. A. PaO_2 in the OG increased significantly and then decreased after treatment, but it was always significantly higher than that in the CG. B. $PaCO_2$ in the OG decreased significantly after treatment and was significantly lower than that in the CG. C. PaO_2/FiO_2 in the OG increased significantly after treatment and was significantly higher than that in the CG. Note: compared with the CG, *P<0.05; compared with T0, #P<0.05.

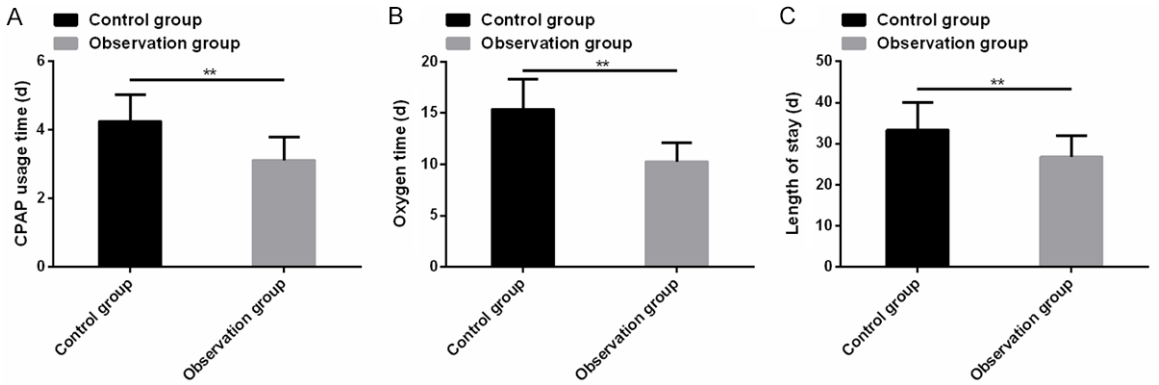

Figure 2. Treatment time of two groups of children. A. CAPA usage time in the OG was significantly shorter than that in the CG. B. The oxygen time of the OG was significantly shorter than that of the CG. C. The length of stay of the OG was significantly shorter than that of the CG. Note: ** indicates P<0.01.

The oxidative stress index of BUD combined with PS was better

There was no evident difference in GSH-Px, SOD, MDA and other oxidative stress indexes between the OG and CG before treatment (P>0.05). After treatment, GSH-Px and SOD were evidently increased, and the two indexes in the OG were higher than CG (P<0.05). However, MDA was evidently decreased after treatment, and MDA in the OG was lower than the CG (P<0.05). See **Figure 5**.

Discussion

NRDS is a common reason for premature infants to enter into the neonatal intensive care unit, which has a certain threat to the life of premature infants [21]. BUD and AMB are both therapeutic drugs for lung diseases, and they can formed into nanoporous particles to break through the resistance of lung mucus and have full effect [22]. PS is currently recognized as a NRDS replacement therapy, but the efficacy and safety of combination therapy

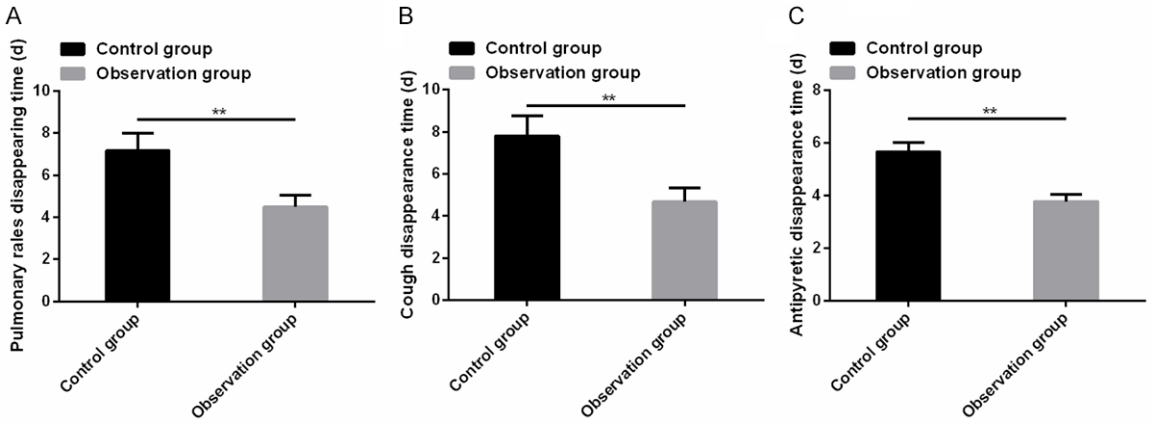

Figure 3. Symptom recovery time of two groups of children. A. The disappearance time of pulmonary rales in the OG was significantly shorter than that in the CG. B. The cough disappearance time in the OG was significantly shorter than that in the CG. C. The antipyretic disappearance time of the OG was significantly shorter than that of the CG. Note: ** indicates P<0.01.

Table 3. Complications, deaths and repeated drug use rates

Items		Control group (n=45)	Observation group (n=45)	χ^2 value	*P* value
Complication	Pneumonia	2 (4.44)	1 (2.22)	-	-
	Leukomalacia	2 (4.44)	0 (0.00)	-	-
	ROP	3 (6.67)	0 (0.00)	-	-
	IVH	1 (0.00)	1 (2.22)	-	-
	Total	8 (17.78)	2 (4.44)	4.050	0.044
Death		4 (8.89)	0 (0.00)	4.186	0.041
Repeated medication		8 (17.78)	3 (6.67)	2.589	0.108

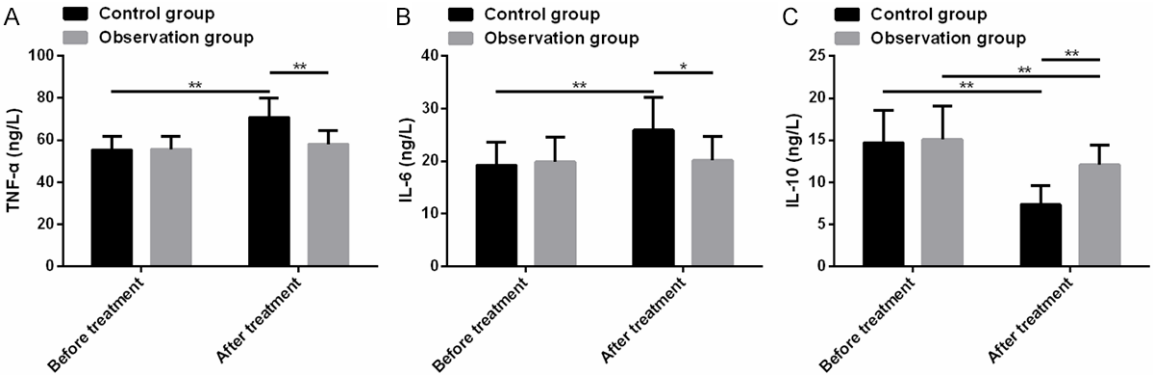

Figure 4. Inflammatory indexes of two groups of children. A. TNF-α in the OG had no significant change after treatment and was significantly lower than that in the CG. B. IL-6 in the OG had no significant change after treatment and was significantly lower than that in the CG. C. IL-10 level in the OG decreased significantly after treatment and was significantly higher than that in the CG. Note: * indicates P<0.05, ** indicates P<0.01.

have yet to be proven [23]. This study focused on the combination therapy of BUD or AMB both combined with PS for NRDS treatment, and explore the best combination therapy for NRDS.

In our study, BUD with PS combination therapy was used in the CG and AMB with PS combination therapy was used in the OG. The results showed that the total effective rate of the OG was higher than that of the CG (90.91% VS

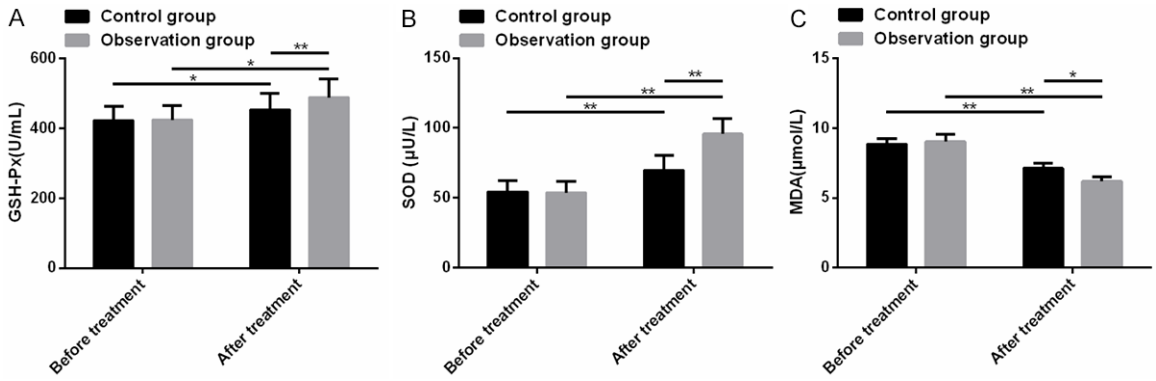

Figure 5. Oxidative stress index of two groups of children. A. GSH-Px in the OG increased significantly after treatment and was significantly higher than that in the CG. B. SOD in the OG increased significantly after treatment and was significantly higher than that in the CG. C. MDA in the OG decreased significantly after treatment and was significantly lower than that in the CG. Note: * indicates $P<0.05$, ** indicates $P<0.01$.

75.56%), indicating that AMB combined with PS was superior to BUD combined with PS in the treatment of NRDS. Then, arterial blood gas index data showed that the OG had higher PaO_2, PaO_2/FiO_2 and lower $PaCO_2$ at the last observation point (12 h after medication), suggesting that AMB and PS combination therapy was more conducive to improving hypercapnia and hypoxemia, so that the systemic oxygen metabolism of the children tended to be normal. In the treatment and symptom recovery of the two groups of children, the OG showed shorter CPAP usage time, oxygen time, length of stay, pulmonary rales disappearance time, cough disappearance time and fever reduction disappearance time, indicating that AMB combined with PS was more conducive to shortening the treatment time of NRDS children and accelerating the recovery of normal signs of children. Studies have shown that pneumonia, leukomalacia, ROP, IVH are common clinical complications of NRDS in children, and repeated PS administration is a valid choice for children with NRDS whose remission is not optimistic for the first time [24-26]. Our research results showed that the total complication rate, mortality rate and repeated medication rate of the OG were evidently lower than those of the CG, suggesting that the treatment strategy of the OG had higher safety and performance price ratio. Although BUD is helpful to improve the early lung maturity of premature infants, there may be complications such as ROP, which is also confirmed in our study [27]. In the research of Bishr et al. [28], AMB could reduce cisplatin-induced hepatorenal toxicity by inhibiting p-JNK/p-ERK pathway, and the main mechanism of action was to inhibit apoptosis, inflammation and oxidative stress injury, which may be the explanation for AMB combined with PS to have higher safety.

We also explored the effects of two treatment strategies on inflammation and oxidative stress in children with NRDS. Studies have shown that TNF-α and IL-10 may be involved in the pathological effects of cytokine gene polymorphism in children with NRDS. IL-10-1082 may be used as a risk identification marker for NRDS, and the expression level of IL-6 in serum is significantly positively correlated with the disease severity of children with NRDS [29, 30]. Studies have reported that oxidative stress is also involved in the pathological process of lung injury in children with NRDS, which is related to the oxygen supplement, mechanical ventilation, inflammation, and infection, and it can overload the detoxification capability of children's antioxidant defense system [31]. Ahmed [32] et al. and Hamid [33] et al. pointed out that children with NRDS showed lower antioxidant enzyme GSH-Px, SOD activity and higher MDA level than normal premature infants, indicating that inhibiting oxidative stress and improving the body's antioxidant defense capability may help alleviate the illness of NRDS in children. Our research results showed that the OG showed lower TNF-α, IL-6, MDA and higher IL-10, GSH-Px, SOD levels after treatment, suggesting that AMB-PS therapy for children with NRDS was helpful to inhibit inflammatory environment and oxidative stress in the body.

The research has finally come to an end, but there is still room for improvement. First of all, we can increase the clinical sample size and improve the accuracy of research results. Secondly, we can increase the observation of long-term efficacy and further verify the long-term efficacy of the two treatment strategies. Furthermore, we can also increase molecular targeted studies of the two therapeutic strategies and explore their specific mechanisms of action.

To sum up, AMB combined with PS has a higher curative effect in the treatment of children with NRDS, and is conducive to improving safety, promoting body recovery, inhibiting inflammation and oxidative stress, and has good clinical promotion value.

Disclosure of conflict of interest

None.

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