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Original Research

Influenced CD cells and ICAM-1 by pulmonary surfactant combined with high-frequency oscillatory ventilation and its effects on immune function in children with neonatal respiratory distress syndrome

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Abstract: This study aimed to explore the clinical efficacy of pulmonary surfactant combined with high-frequency oscillatory ventilation (HFOV) on neonatal respiratory distress syndrome (NRDS) and its influence on immune function in children. Children admitted to our hospital from March 2017 to March 2019 who received HFOV combined with pulmonary surfactant therapy as a research group. Sixty-two children received conventional nasal continuous positive pressure combined with pulmonary surfactant therapy as a control group. Clinical efficacy, blood gas and immune function of patients were compared between the two groups. The clinical efficacy of the research group was better than that of the control group ($P< 0.050$). PaO_2 and PaO_2/FiO_2 were both higher after treatment ($P< 0.050$). $CD3^+$ and NK cells in the research group were higher than those in the control group, while $CD8^+$ cells and ICAM-1 were lower than those in the control group ($P< 0.050$). $CD3^+$, $CD4^+$ and NK cells decreased in both groups after treatment, while $CD8^+$ cells and ICAM-1 increased ($P< 0.050$). HFOV combined with pulmonary surfactant has significant clinical efficacy and high safety on NRDS, and has a certain protective effect on children's immune function. Hence, it is worthy of being the first choice for the clinical treatment of NRDS in the future.

Key words: HFOV; NRDS; Nasal continuous positive pressure. Pulmonary surfactant; T-lymphocyte subsets.

Introduction

Neonatal respiratory distress syndrome (NRDS), also known as hyaline membrane disease, refers to symptoms such as dyspnea and respiratory failure occurring shortly after birth (1). At present, NRDS is believed to be mainly caused by the progressive alveolar collapse caused by a lack of alveolar surfactant (2). Within 4-12h of birth, NRDS can cause progressive dyspnea, moaning, cyanosis, etc. and respiratory failure in more severe cases (3). According to statistics, the current clinical morbidity of NRDS is about 3.5/1000,000 (4). In recent years, continuous research has revealed that the morbidity of NRDS is increasing year by year (5). NRDS children are usually premature infants. As a self-limiting disease, the lung maturity of NRDS children who survive for more than three days increases, and the possibility of recovery increases (6). However, the death of the seriously ill usually occurs within three days. According to statistics, the fatality rate of NRDS is 24.0% (7). Faced with the increasingly serious NRDS, it is particularly important to seek effective treatment for improving the prognosis of newborns.

Surfactant replacement therapy is very important in NRDS clinically, and its treatment strategy mainly uses nasal continuous positive airway pressure ventilation or nasal cavity ventilation (8). However, high-frequency oscillatory ventilation (HFOV) is used as a lung-protective ventilation strategy clinically and is usually a rescue plan used after mechanical ventilation fails (9). And Sklar et al. (10) pointed out that HFOV had a very crucial efficacy on adult acute respiratory distress syndrome. At present, no clinical study has confirmed the value of HFOV as the preferred treatment for NRDS. Therefore, we suspect that the clinical application value of HFOV combined with pulmonary surfactant is better than that of traditional mechanical ventilation. Therefore, this study provides reference and guidance for future clinical treatment of NRDS by analyzing the effects of two NRDS treatment methods and comparing their effects on the immune function of children.

Materials and Methods

General data

A total of 127 children with NRDS admitted to our hospital from March 2017 to March 2019 were selected as the research objects, 65 of whom received HFOV combined with pulmonary surfactant therapy as the research group, while another 62 children received conventional nasal continuous positive pressure combined with pulmonary surfactant therapy as the control

group. This experiment was approved by the Ethics Committee of our hospital, and all the above research subjects signed informed consent by their immediate family members.

Inclusion and exclusion criteria

Inclusion criteria were as follows: gestational age < 34 weeks, shortness of breath, cyanosis and three depression sign after birth, PEEP ≥ 7 cm, FIO_2>60%, PO_2<50mmHg, $PaCO_2$>60mmHg, or PH<7.25. NRDS was confirmed by imaging examination. Exclusion criteria were as follows: children with severe congenital heart disease, infection, shock and tumor diseases; instrument ventilation < 24h; children with severe asphyxia or drug allergy; children who gave up by their family members during the treatment; children who were transferred to another hospital.

Methods

The research group was treated with HFOV, SLE5000 infant ventilator was used, HFOV mode was selected, and the initial adjustment parameters were as follows: frequency 10-15Hz (1Hz=60 times/min), mean airway pressure (MAP) 10-15cm H_2O, and amplitude 20-40cm H_2O. It was appropriate that the contour above the umbilicus was obviously vibrated, or the diaphragm surface of chest radiograph was located at the 8th to 9th posterior ribs (FIO_2 04-1.0). The percentage of inspiratory time was 0.5. When the results of blood gas were normal (MAP < 8cm H_2O, FIO_2 < 0.4), we adopted normal frequency ventilation instead. The control group received nasal continuous positive pressure therapy and CPAP aspirator. The initial parameters were 3-5cm H_2O, PIOW 6-8L/min, PaO_2 60-80mmHg and $PaCO_2$ 40-50mmHg. After blood gas returned to normal, oxygen was absorbed by hood instead. Both groups were treated with pulmonary surfactant and were given 70mg/kg of creosote (CR DOUBLE-CRANE Pharmaceutical Co., Ltd., SFDA Approval No. H20052128). Drugs were dissolved at room temperature before use, then they were inhaled with a syringe and injected into children through tracheal intubation. The respiratory secretions were cleaned before intubation, the total dose was divided into four doses and injected in the order of recumbent, right recumbent, left recumbent and semi-recumbent, and the administration time for each time was 10-15s. At the same time, they were pressurized and ventilated by resuscitation balloon (40-60 times/min, 1-2min).

Observation indicators

Main indicators

Clinical efficacy of children in the two groups was as follows: after treatment, breathing was stable, moaning disappeared, and the X-ray examination of clear lung texture was determined to be markedly effective; after treatment, breathing was stable, moaning disappeared, and X-ray examination of improvement of abnormal shadow was determined to be effective. The symptoms did not improve after treatment and were judged invalid if they did not meet the above criteria. Effective treatment rate = (markedly effective + effective)/total number ×100%. The incidence rate of adverse reactions was as follows: adverse reactions occurred during the treatment of children, and the incidence rate of adverse reactions was calculated = number of adverse reactions/total number ×100%. Changes in the function of blood gas before and after treatment included PaO_2, $PaCO_2$, and PaO_2/FiO_2.

Secondary indicators

Changes of immune function of children in the two groups were as follows: T-lymphocyte subsets including $CD3^+$, $CD4^+$, $CD8^+$, and NK cell percentage were detected by flow cytometry (BD canto II) before treatment (T0), 3 days after treatment (T1), and 7 days after treatment (T2). Enzyme-linked immunosorbent assay (ELISA) was used to detect intercellular cell adhesion molecule-1 (ICAM-1) in the serum of children, and the kit was purchased from Shanghai Hengfei Biotechnology Co., Ltd. (SEA548Po-1). The total hospitalization time of children in the two groups and the 30-day survival of children in the two groups was recorded.

Statistical methods

The results of this experiment were analyzed by SPSS24.0 statistical software (Shanghai Yuchuang Network Technology Co., Ltd) and all graphical results were drawn by Graphpad8 (Shenzhen Qiruitian Software Technology Co., Ltd). The counting data were expressed in the form of (rate), and a chi-square test was used for comparison between groups. The measurement data were expressed in the form of (mean±standard deviation), the comparison between groups adopted T-test, and repeated measures analysis of variance and Bonferroni back testing were used for comparison among multiple time points. The survival rate was calculated by the Kaplan-Meier method and compared by the Log-rank test, and P < 0.050 was considered to be a statistically significant difference.

Results

Comparison of general data

The gestational age, Apgar score, body mass, gender, mode of delivery, classification of chest X-ray film, family medical history, family environment and whether the two groups were only children were compared, and there was no significant difference (P > 0.050), as shown in Table 1.

Comparison of clinical efficacy

Comparing the clinical efficacy of children in the two groups, it was found that the effective cure rate of the research group was 92.31%, significantly higher than that of the control group (79.03%) (P=0.032), as shown in Table 2.

Comparison of the incidence rate of adverse reactions

Comparing the incidence rate of adverse reactions between the two groups, it was found that the incidence rate of adverse reactions in the research group was 6.15%, significantly lower than that in the control group (19.35%) (P=0.025), as shown in Table 3.

Table 1. Comparison of general data of children in the two groups n (%).

	Research group (n=65)	Control group (n=62)	t or X^2	*P*
Gestational age (weeks)			1.209	0.229
	32.21±1.24	31.95±1.18		
Apgar score (5min after birth)			0.823	0.412
	2.95±0.64	3.04±0.59		
Body mass (kg)			0.259	0.796
	2.07±0.42	2.09±0.45		
Gender			0.361	0.548
Male	37 (56.92)	32 (51.61)		
Female	28 (43.08)	30 (48.39)		
Mode of delivery			0.362	0.548
Eutocia	44 (67.69)	45 (72.58)		
Cesarean	21 (32.31)	17 (27.42)		
Classification of chest X-ray film			0.107	0.948
Grade II	38 (58.46)	38 (61.29)		
Grade III	17 (26.15)	15 (24.19)		
Grade IV	10 (15.38)	9 (14.52)		
Family medical history			0.074	0.785
Yes	5 (7.69)	4 (6.45)		
No	60 (92.31)	58 (93.55)		
Family environment			0.127	0722
Cities and towns	54 (83.08)	50 (80.65)		
Countryside	11 (16.92)	12 (19.35)		
Only child			0.480	0.488
Yes	60 (92.31)	55 (88.71)		
No	5 (7.69)	7 (11.29)		

Table 2. Comparison of clinical efficacy of children between the two groups n (%).

	Research group (n=65)	Control group (n=62)	X^2	*P*
Markedly effective				
	42 (64.62)	30 (48.39)		
Effective				
	18 (27.69)	19 (30.65)		
Ineffective				
	5 (7.69)	13 (20.97)		
Effective cure rate (%)			4.597	0.032
	92.31%	79.03%		

Table 3. Comparison of incidence rates of adverse reactions in children from the two groups n (%).

	Research group (n=65)	Control group (n=62)	X^2	*P*
Multiple organ failure				
	0 (0.00)	1 (1.61)		
Pneumorrhagia				
	1 (1.54)	1 (1.61)		
Pneumonia				
	1 (1.54)	3 (4.84)		
Pulmonary fibrosis				
	1 (1.54)	3 (4.84)		
Respiratory tract infection				
	1 (1.54)	4 (6.45)		
Incidence rate (%)			5.022	0.025
	6.15	19.35		

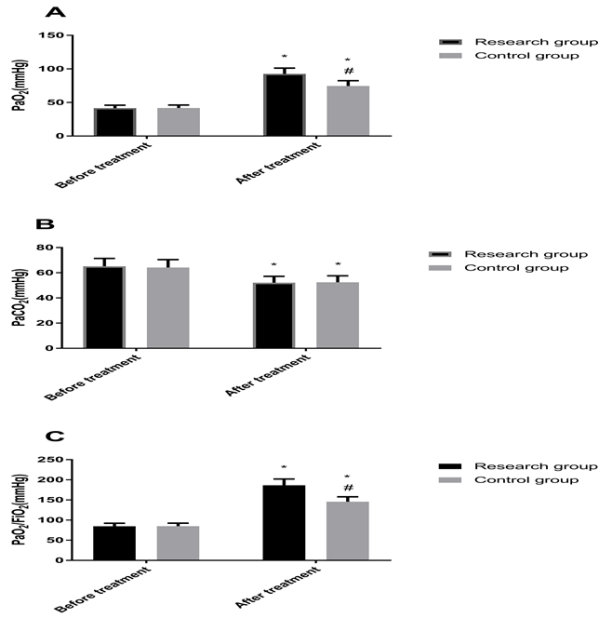

Figure 1. Changes in the function of blood gas before and after the treatment of children in the two groups. A. Comparison of PaO_2 before and after treatment between the two groups. B. Comparison of $PaCO_2$ before and after treatment between the two groups. C. Comparison of PaO_2/FiO_2 before and after treatment between the two groups. * represented that compared with the same group before treatment, P was less than 0.050. # represented that compared with the research group after treatment, P was less than 0.050.

Comparison of changes in the function of blood gas

Before treatment, PaO_2, $PaCO_2$ and PaO_2/FiO_2 of children in the two groups showed no significant difference ($P > 0.050$). After treatment, PaO_2 and PaO_2/FiO_2 of children in the two groups increased compared with before treatment, while $PaCO_2$ decreased ($P < 0.050$). There was no significant difference in $PaCO_2$ between the research group and the control group after treatment ($P > 0.050$), while PaO_2 and PaO_2/FiO_2 were higher than those in the control group after treatment ($P < 0.050$), as shown in Figure 1.

Changes of T-lymphocyte subsets

Comparing the changes of T-lymphocyte subsets of children between the two groups, it could be seen that $CD3^+$, $CD4^+$, $CD8^+$, NK cells, ICAM-1 and $CD4^+$ cells had no significant difference at T0 in the research group ($P > 0.050$). At T1, $CD3^+$ and NK cells of children in the two groups were higher than those in the control group, $CD8^+$ cells and ICAM-1 were lower than those in the control group ($P< 0.050$). At T3, $CD3^+$, $CD4^+$ and NK cells were higher than those in the control group, $CD8^+$ cells and ICAM-1 were lower than those in the control group ($P< 0.050$). $CD3^+$, $CD4^+$ and NK cells decreased in both groups after treatment, $CD8^+$ cells and ICAM-1 increased ($P < 0.050$). More details were shown in Figure 2.

Comparison of prognosis

The total hospitalization time in the research group was (22.53±5.47)d, and there was no significant difference between the research group and the control group (23.81±3.27)d ($P> 0.050$). The 30-day mortality of children in the research group was 9.23%, and there was no significant difference between the 30-day mortality

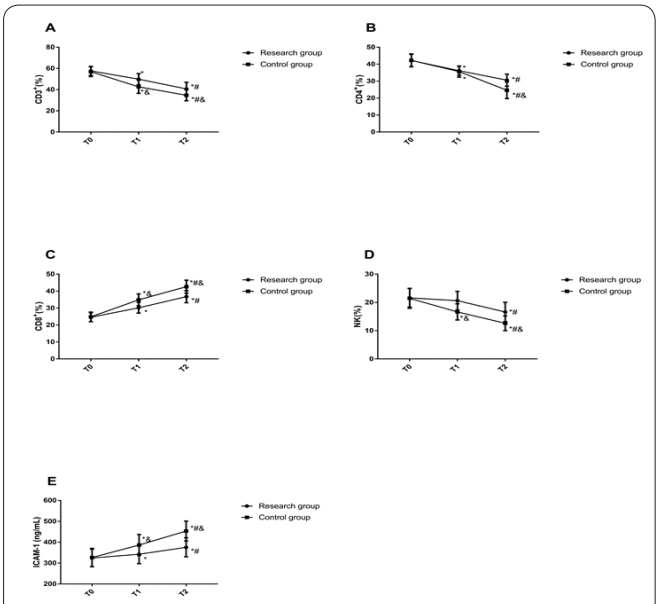

Figure 2. Changes of immune function in the two groups during treatment. A. $CD3^+$ cell changes during treatment. B. $CD4^+$ cell changes during treatment. C. $CD8^+$ cell changes during treatment. D. NK cell changes during treatment. E. ICAM-1 cell changes during treatment. * represented that compared with T0 in the same group, P was less than 0.050. # represented that compared with T1 in the same group, P was less than 0.050. & represented that compared with the research group at the same time after treatment, P was less than 0.050.

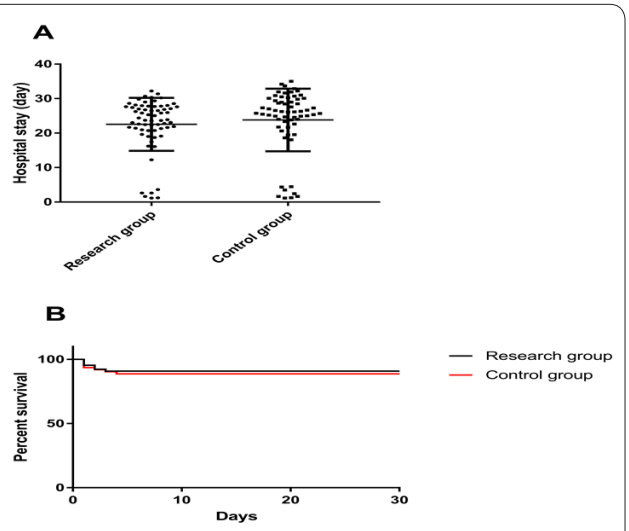

Figure 3. Comparison of prognosis of children between the two groups. A. Comparison of total hospitalization time of children between the two groups. B. B) 30-day survival curve of prognosis in children form the two groups.

of children in the control group (11.29%) ($P > 0.050$). More details were shown in Figure 3.

Discussion

NRDS is one of the most common causes of neonatal respiratory failure, usually occurring in premature infants (11). The early fatality rate of newborns is extremely high, and the effect of treatment by injection of pulmonary surfactant alone is not good and may cause a further increase in mortality (12). In addition, severe NRDS, hypoxemia and acidosis cause continuous contraction of smooth muscle in pulmonary arterioles, which can greatly increase the incidence rate of pulmo-

nary hypertension (13). Therefore, choosing a treatment that can rapidly improve hypoxemia in the early stage of NRDS is the key to determine the prognosis of children. Although traditional nasal continuous positive pressure therapy can reduce the prevalence rate of children to a certain extent, lung injury and complications of different degrees are easy to occur in the treatment process (14). HFOV, as a protective ventilation strategy, adopts tidal volume higher than normal ventilation frequency and lower limit of hell, and can independently control ventilation and oxygen (15,16). In order to improve the effective treatment rate of NRDS, we recommend joint therapy of HFOV and pulmonary surfactant as the first choice in clinical practice, and then made corresponding experimental analysis.

The experimental results indicated that the effective cure rate of children in the research group treated with HFOV combined with pulmonary surfactant was higher than that of children in the control group treated with nasal continuous positive pressure combined with the pulmonary surfactant, and the incidence rate of adverse reactions in the research group was lower than that of the control group, suggesting that HFOV had higher application value in NRDS treatment and higher safety than traditional treatment. This was also consistent with Ethawi et al. (17) who studied the efficacy of HFOV on pulmonary dysfunction of premature infants, which could be used as our evidence. In the past, many studies confirmed the efficacy of pulmonary surfactant on NRDS (18-20). Therefore, we will not repeat them in this article, instead, we will focus on the differences in the efficacy of children caused by two ventilation methods. We speculated that this might be related to HFOV's higher mean arterial pressure (MAP). HFOV can reduce the pressure fluctuation in the airway, make the lung in a high lung volume mode to collect more alveoli, and then keep the alveoli in a more uniform ventilation state, and reduce the chances of inflammation and exudation in children (21). When Laviola et al. explored the effect of HFOV on the pig model of respiratory distress syndrome, they found that its PaO_2 increased significantly (22). However, comparing the changes in the function of blood gas before and after treatment of children between the two groups, we discovered that PaO_2 and PaO_2/FiO_2 in the research group were higher than those in the control group. PaO_2 refers to the tension generated by oxygen molecules dissolved in plasma in the physical state, which determines the oxygen partial pressure of inhaled gas and the functional state of external respiration (23). The increase of PaO_2 in children from the research group signified that HFOV had the ability to supply oxygen to children more fully, reduce the surface tension of alveoli, enhance compliance and improve ventilation as well as air exchange functions.

In order to further understand the influence of HFOV on NRDS, we detected the changes of T-lymphocyte subsets of children in the two groups and found that $CD3^+$, $CD4^+$, NK cells decreased and $CD8^+$ cells increased after the treatment started of children in the two groups, suggesting that both ventilation methods had a certain influence on the immune function of children. In the process of mechanical ventilation, tracheal intubation, closed sputum suction and mechanical invasion will cause greater damage to the lung tissue of neonates who are not yet fully developed, and lung tissue may also be damaged to a certain extent under hyperoxia (24). Moreover, Doi et al. (25) also verified that mechanical ventilation had a certain effect on human immune function, which would be more significant in newborns. However, we found that the decrease of immune function in the research group was lower than that in the control group during the treatment process, which also showed that HFOV had stronger protection for neonatal immune function. Hence, we speculated that the reason might be similar to the above part. Under HFOV ventilation, airway resistance and ventilation pressure of lung tissue were reduced, effectively increasing residual air volume in lung to prevent alveolar atrophy (26), so as to avoid the air pressure, volume, atelectasis and other injuries that were easy to occur under the ventilation environment of the instrument, and the immune function of children could be kept in a relatively stable state.

Furthermore, we further detected the ICAM-1 concentration of children in the two groups and discovered that the research group was also lower than the control group during the treatment process. ICAM-1 is one of the members of immunoglobulin superfamily and is currently recognized as a key substance for antigen-presenting cells to bind to T cells (27). The elevated level can inhibit the anti-tuberculosis immunity of the body (28). Therefore, it is suggested that HFOV combined with pulmonary surfactant therapy has extremely high application value in the future clinical treatment of NRDS. However, comparing the prognosis of children in the two groups with 30 days of survival, it was found that there was no significant difference between the two groups, and the death situation was basically distributed in the first 3 days, which was also consistent with the pathological conditions of NRDS (29-43).

This study was designed to compare the application value of HFOV and conventional nasal positive pressure ventilation combined with pulmonary surfactant in the treatment of NRDS. However, there are still deficiencies due to effective conditions. For example, the protective mechanism of HFOV on immune function cannot be clearly understood without in vitro experiments, and the pulmonary surfactant is not the only one used in this article, but ventilation therapy and pulmonary surfactant have close interaction in the treatment process, so it is not excluded that other active substances may have different efficacy, which will also be analyzed as a research focus in the future. We will conduct a more in-depth and comprehensive discussion on the above deficiencies as soon as possible to obtain the best experimental results.

To sum up, HFOV combined with pulmonary surfactant has significant clinical efficacy and high safety on NRDS, and play a certain protective role in the immune function of children, which is worthy of being the first choice for clinical treatment of NRDS in the future.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

LS and QS conceived and designed the study. LS, WC and YQ were responsible for the collection, analysis and interpretation of the data. WC drafted the manuscript. LS revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Fourth Hospital of Harbin Medical University. Signed written informed consent was obtained from the patients and/or guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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