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Effect of pulmonary surfactant combined with mechanical ventilation on oxygenation functions and expressions of serum transforming growth factor-beta1 (TGF-β1) and bone morphogenetic protein 7 (BMP-7) of neonatal respiratory distress syndrome

L.-P. WANG, Q.-H. MAO, L. YANG

Neonatal Department, Jining No.1 People's Hospital, Shandong, China

Abstract. – OBJECTIVE: To investigate and discuss the effect of early treatment with pulmonary surfactant (PS) on oxygenation functions in neonates with acute respiratory distress syndrome (ARDS), to understand the expression trend of serum transforming growth factor-beta 1 (TGF-β1) and bone morphogenetic protein 7 (BMP-7) in children with neonatal respiratory distress syndrome (NRDS), and to provide help for early prevention and treatment of NRDS.

PATIENTS AND METHODS: All the children were treated with mechanical ventilation; among them, 25 NRDS children who were given PS within 12 h after birth were selected as PS group, and 25 NRDS children who were never given PS were selected as conventional mechanical ventilation (CMV) group. Enzyme-linked immunosorbent assay (ELISA) was used to detect the expressions of serum TGF-β1 and BMP-7 in the two groups of children and monitor their oxygenation function indexes in 0, 1, 3, and 7 d after birth, respectively.

RESULTS: The content of serum TGF-β1 and BMP-7 in children of both PS group and CMV group trended to be higher at 1 d after birth while it was decreased at 7 d after birth compared with that in other days. The TGF-β1 content at 3 and 7 d after birth and the BMP-7 expression level at 7 d after birth in CMV group were significantly higher than those in PS group ($p<0.05$). After treatment, the values of oxygenation index (OI) and respiratory index (RI) at different time points (6, 12, 24, 48 h) in PS group were lower than those in CMV group ($p<0.05$). The mechanical ventilation duration in PS group (81±25 h) was decreased compared with that in CMV group (102±24 h); the oxygenation time in PS group (99±37 h) was less than that in CMV group (122±28 h); the number of cases of complications in PS group and CMV group was 3 (12%) and 6 (24%), respectively, and the effective rates of treatment were 96.0% and 84.0%, respectively ($p<0.05$).

CONCLUSIONS: Early application of PS combined with mechanical ventilation can remarkably improve lung oxygenation and compliance, suppress inflammatory responses, and effectively treat the NRDS. Monitoring the changes of serum BMP-7 and TGF-β1 is very important for treatment and prognosis assessment of the NRDS.

Key Words

Pulmonary surfactant, Respiratory distress syndrome, Oxygenation function, Neonates, TGF-β1, BMP-7.

Introduction

Neonatal respiratory distress syndrome (NRDS) is manifested by the clinical symptom that progressive dyspnea occurs just in several hours after birth. If it is not treated in time, the children patients used to from respiratory failure[1]. Various kinds of inducing factors can increase the permeability of alveolar capillary membrane and cause alveolar edema, which can reduce pulmonary surfactant (PS) and decrease lung compliance. The formation of extensive atelectasis and intrapulmonary shunt eventually lead to hypoxemia[2]. As PS combined with mechanical ventilation has been widely applied in clinical practices to treat NRDS, the survival rate of preterm infants is increased significantly[3,4]. It is important for early prediction and prognosis assessment of the NRDS to detect the changes of some cytokines or enzymes in serum, which has been proven by relevant scientific research[5]. Transforming growth factor-beta1 (TGF-β1), a member of the TGF-β family, is mainly originated from fibrocytes and epitheliums; it can damage lung functions through serious imbalance in body caused by signal transduction *in vivo*. Bone morphogenetic protein 7 (BMP-7) can regulate cell proliferation and differentiation and resist fibrotic effect of TGF-β1[6]. This research

Corresponding Author: Qinghua Mao, MD; e-mail: 793411023@qq.com

detected the effect of early use of PS combined with mechanical ventilation on NRDS children as well as the expression levels of serum TGF-β1 and BMP-7 and oxygenation functions, and analyzed its relationship with children's prognosis, hoping to provide clues for early prevention and control of NRDS in clinic.

Patients and Methods

Patients

A total of 50 neonates, who needed treatment with mechanical ventilation from October 2014 to June 2016 in our hospital, was enrolled. All the neonates were definitely diagnosed with NRDS and had the following features: (1) dyspnea occurred within 6 hours after birth; (2) blood gas analysis indicated hypoxemia[7]; (3) chest radiographic changes were at Grade II or above. Exclusion criteria were as follows: neonates with severe congenital heart disease, respiratory system abnormalities, intrauterine infection, aspiration pneumonia, primary PS deficiency or congenital pulmonary hypoplasia. This work was checked and approved by the Ethics Committee of our hospital and signed informed consent was obtained from the parents of children.

Research Methods

25 NRDS children who were treated with mechanical ventilation combined with PS were selected as PS group, and 25 NRDS children who were never given PS were selected as conventional mechanical ventilation (CMV) group. PS (bovine lung phospholipid injection, CR Double-Crane Pharmaceuticals Co., Ltd. Beijing, China) was administered to children at a dose of 70 mg/kg within 12 h after birth. Symptomatic and supporting therapy was applied in both groups.

Observation Indexes

3 mL venous blood of the two groups of children was withdrawn at 0, 1, 3, 7 d after birth, respectively, and enzyme-linked immunosorbent assay (Biotek microplate reader, BD Company, Franklin Lakes, NJ, USA) was used to measure the content of TGF-β1 and BMP-7. Blood gas analyses were monitored before and 6, 12, 24 and 48 h after mechanical ventilation (Babyloog 8000 plus Type ventilator, Dräger, Lubeck, Germany), the oxygenation index (OI) and respiratory index (RI) were calculated and the therapeutic effects were observed.

Table I. Comparisons of general information of the two groups (n=25, $\bar{x}$±s).

Group	Gestational age (week)	Birth weight (g)	Male/ female (case)
PS group	36.7±1.4	2638±230	15/10
CMV group	36.4±1.3	2699±250	12/13

Note: Comparisons between the two groups, $p>0.05$.

Statistical Analysis

SPSS 20.0 software (SPSS Inc. IBM, Armonk, NY, USA) was used for analysis and processing of the test data. The measurement data were presented as mean ± standard deviation ($\bar{x} \pm s$), *t*-test was used for comparisons between the two groups, and analysis of variance was used for multiple group comparison. Comparison between groups was done using One-way ANOVA test followed by LSD (Least Significant Difference). Percentage (%) was used to express the enumeration data and x^2-test was used for data analysis. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of General Clinical Information

By comparing sex, gestational age and birth weight of the two groups, the differences were not statistically significant ($p>0.05$) (Table I).

Comparisons of Oxygenation Functions in the Two Groups of Neonates Before and After Treatment

Before treatment, OI and RI values of the ARDS neonates in the two groups were almost equal ($p>0.05$). After treatment, the OI and RI values at different time points in PS group were lower than those in CMV group ($p<0.05$) (Table II-III).

Comparisons of Serum TGF-β1 and BMP-7 Expressions in Both Groups

The content of serum TGF-β1 and BMP-7 in children of both PS group and CMV group trended to be higher at 1 d after birth while it was decreased at 7 d after birth compared with that at other days. The TGF-β1 content at 3 and 7 d after birth and the BMP-7 expression level at 7 d after birth in CMV group were significantly higher than those in PS group ($p<0.05$) (Table IV-V).

Table II. Comparisons of OI changes in the two groups. (n=25, $\bar{x}$±s).

OI	PS group	CMV group
Before treatment	11.9±2.4	12.1±2.5
6 h after treatment	8.6±2.6$^{\Delta}$	9.9±2.2$^{*\Delta}$
12 h after treatment	7.9±2.1$^{\Delta}$	9.0±2.3$^{*\Delta}$
24 h after treatment	6.9±2.0$^{\Delta}$	8.2±1.8$^{*\Delta}$
48 h after treatment	5.9±1.7$^{\Delta}$	7.1±1.4$^{*\Delta}$

Note:*indicates comparisons with PS group at the same time point, p<0.05; $^{\Delta}$indicates comparisons with 0 d in the same group, p<0.05.

Table III. Comparisons of RI changes in the two groups (n=25, $\bar{x}$±s).

RI	PS group	CMV group
Before treatment	6.1±2.6	5.8±1.8
6 h after treatment	2.7±0.9$^{\Delta}$	3.3±1.1$^{*\Delta}$
12 h after treatment	2.3±0.7$^{\Delta}$	2.9±1.0$^{*\Delta}$
24 h after treatment	2.0±0.6$^{\Delta}$	2.4±0.7$^{*\Delta}$
48 h after treatment	1.5±0.3$^{\Delta}$	1.9±0.4$^{*\Delta}$

Note:*indicates comparisons with PS group at the same time point, p<0.05; $^{\Delta}$indicates comparisons with 0 d in the same group, p<0.05.

Table IV. Expressions of serum TGF-β1 in two groups at different time points. (n=25, $\bar{x}$±s).

Group	TGF-β1 (ng/ml)			
	0 d	1 d	3 d	7 d
PS group	37±7	40±6	41±4	37±4
CMV group	37±5	44±4$^{\Delta}$	46±5$^{*\Delta}$	47±4$^{*\Delta}$

Note:*indicates comparisons with PS group at the same time point, p<0.05; $^{\Delta}$indicates comparisons with 0 d in the same group, p<0.05.

Table V. Expressions of serum BMP-7 in two groups at different time points. (n=25, $\bar{x}$±s).

Group	BMP-7 (pg/mL)			
	0 d	1 d	3 d	7 d
PS group	46±6	48±4	49±4	44±5
CMV group	47±5	50±5	52±4	51±4*

Note:*indicates comparisons with PS group at the same time point, p<0.05.

Comparisons of Clinical Treatment

The mechanical ventilation duration in PS group [(81±25) h] was decreased compared with that in CMV group [(102±24) h], and the oxygenation time in PS group [(99±37) h] was less than that in CMV group [(122±28) h]; those results showed that the treatment effect in PS group was better than that in CMV group (p<0.05) (Figure 1).

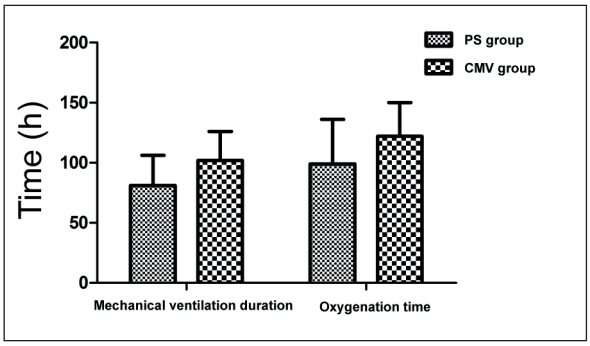

Figure 1. Comparisons of mechanical ventilation duration between PS group and CMV group.

After treatment, 14 cases were cured, 7 were effective and 4 were dead in CMV group, and the effective rate was 84.0%; in PS group which was treated in combination with PS, the number of cases of cured, effective and dead were 20, 4 and 1, respectively, and the effective rate was 96.0%. The treatment outcomes in PS group were significantly higher than those in CMV group (p<0.05) (Table VI). The number of cases of complications in PS group and CMV group were 3 (12%) and 6 (24%), respectively, and the effective rates of treatment were 96.0% and 84.0%, respectively (p<0.05).

Discussion

The major pathophysiologic features of NRDS are hypoxemia, absolute or relative deficiency of PS and declined lung compliance[8,9]. Mechanical ventilation can reverse atelectasis and improve oxygenation functions, but hyperventilation can also cause lung injury[10]. PS is secreted by type II alveolar epithelial cells, of which the physiological functions include (1) maintaining stability of alveolar volume, (2) preventing atelectasis and (3) preventing pulmonary edema. PS applied in clinical practice has the characteristics of palmitic

Table VI. Comparisons of treatment outcomes in two groups. (n=25, $\bar{x}$±s).

Group	Cured	Improved	Dead	Effective rate
PS group	20	4	4	96.0%
CMV group	14	7	1	84.0%*

Note:*indicates comparisons with PS group, p<0.05.

acid and other water-soluble liquid. As the immune systems and lung functions of the neonates are underdeveloped, when PS deficiency is caused by various reasons, the alveoli collapse and then atelectasis, pulmonary edema and lung membrane are formed; therefore, progressive dyspnea occurs very easily[11]. Understanding the pulmonary ventilation-perfusion coordination by monitoring respiratory mechanics using ventilator treatment can help diagnose diseases rapidly and assess the application effects of intervention techniques. As pulmonary arterial oxygen tension/fraction of inspired oxygen (PaO_2/FiO_2) can reflect patients' hypoxia under oxygen inhalation as well as the injury of pulmonary vascular bed and alveoli, it can be used as an effective indicator for evaluating the diagnosis and treatment effects of ARDS. Halliday et al[12] put forward OI (PaO_2/FiO_2) for the first time, which had simple calculation and could reflect intrapulmonary shunt. RI is relatively less influenced by breathing patterns, ventilation modes and fractions of inspired oxygen, thus it can objectively reveal the status of pulmonary gas exchange. Decreased RI value suggests that patients are getting better. As a protective preparation for lung, PS can be used to treat respiratory failure in neonates[13]; Donn et al[14] have also carried out clinical studies on PS treatment of other serious respiratory diseases. PS combined with mechanical ventilation has been widely applied in clinical practices to treat NRDS in recent years[15]. The results of this study showed that, after early treatment on neonates with ARDS using PS combined with mechanical ventilation, the values of OI and RI in PS group were decreased compared with that in CMV group; the mechanical ventilation duration in PS group (81±25 h) was lower than that in CMV group (102±24 h), and the oxygenation time in PS group (99±37 h) was less than that in CMV group (122±28 h). It indicates that PS can re-expand the atrophic alveoli by reducing the surface tension, improve ventilation and gas exchange, enhance oxygenation functions and remarkably shorten the mechanical ventilation duration and oxygenation time. Also, it was observed in this research that cases of complication in PS group and CMV group were 3 (12%) and 6 (24%), respectively, and the effective rates of treatment were 96.0% and 84.0%, respectively. The differences between the two groups were statistically significant ($p<0.05$); it shows that children's safety factors and prognosis can be improved after PS is applied. Incontrollable pulmonary fibrosis, which is caused by imbalance between synthesis and degradation of extracellular matrix (ECM), is the main cause of death of ARDS. TGF-β1, on the one hand, as a kind of precipitation accelerator of ECM, can increase ECM synthesis while decrease its degradation. On the other hand, it can chemotactically accumulate neutrophils and fibroblasts and stimulate the release of inflammatory factors[16]. BMP-7 is a kind of multifunctional secretory protein, which participates in regulation of normal physiological activities and fibrosis changes together with TGF-β1. Myllarniemi et al[17] have reported that BMP-7 also participates in cardiac and pulmonary fibrosis. Some studies[18,19] show that the concentration of TGF-β1 in bronchoalveolar lavage fluid declines significantly after recombining with BMP-7, of which the reduction degree depends on the dose of BMP-7. Therefore, BMP-7 can antagonize the fibrotic effect of TGF-β1[20]. We found that the content of serum TGF-β1 and BMP-7 in children of both PS group and CMV group trended to be higher at 1 d after birth while it was decreased at 7 d after birth compared with that at other days. The TGF-β1 content at 3 and 7 d after birth and the BMP-7 expression level at 7 d after birth in CMV group were significantly higher than those in PS group ($p<0.05$). In the initial phase of inflammatory response, increased TGF-β1 expression can lead to compensatory increase of BMP-7 expression in the body, and BMP-7 expression decreases along with the progression of disease and function limitation of cells secreting BMP-7. Furthermore, active proteins in PS can inhibit the pulmonary inflammatory responses in children by lowering the TGF-β1 level, thus further relieving the disease[21,22]. In CMV group, however, inflammatory responses were not contained forcefully; therefore, it was observed that the BMP-7 content at 7 d after birth in PS group was significantly lower than that in CMV group. It suggests that supplement of exogenous BMP-7 to children is conducive to reversing the state of NRDS.

Conclusions

Early application of PS combined with mechanical ventilation to treat NRDS can remarkably improve lung compliance, enhance the oxygenation functions, suppress pulmonary inflammatory responses, reduce lung injury and effectively improve children's quality of life. Monitoring the changes of serum BMP-7 and TGF-β1 in children is very important for treatment and prognosis assessment of the NRDS.

Conflict of Interest

The authors declared no conflict of interest.

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