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The clinical effects of combined use of inhaled nitric oxide at early stage to cure severe respiratory failure in neonates

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Abstract. – OBJECTIVE: To observe the clinical effects of combined use of inhaled nitric oxide at the early stage to cure severe respiratory failure in neonates.

PATIENTS AND METHODS: 45 cases of neonates with severe respiratory failure, who were admitted to the neonatal intensive care unit (NICU) of XuZhou Children's Hospital from November 2014 to February 2016, were selected as objects of study, namely the iNO treatment group. On the basis of conventional treatment and mechanical ventilation, all of them were treated with the combined use of iNO at the early stage. The arterial blood gas index, respiratory function index and other indexes of those children were observed before iNO treatment and 1 h, 6 h, 12 h and 24 h post-treatment. 31 cases of newborns with severe respiratory failure admitted to the NICU of the same hospital from July 2013 to August 2014 were analyzed and selected as the control group. The cases in this group met the same criteria as those administered the iNO treatment. Comparisons were made between both groups in terms of the duration of ventilator support, complications during treatment, oxygen supply time, hospital stay and other data.

RESULTS: When treated after 1 h, 6 h, 12 h and 24 h, the pH value, arterial oxygen and carbon dioxide partial pressure of children in the iNO inhalation group significantly improved compared to those before treatment, and the difference was significant ($p<0.05$). When treated after 6, 12 and 24 h, the inspired oxygen concentration and oxygenation values of children significantly decreased compared to before treatment ($p<0.05$). When treated after 6, 12, and 24 h, the mean airway pressure of children was less than that before treatment and the difference was statistically significant ($p<0.05$). When treated after 1 h, 6, 12, 24 h, the arterial alveolar oxygen partial pressure ratio of children was greater than that before treatment and the difference was significant ($p<0.05$). When treated after 24 h, the pulmonary artery pressure of children significantly decreased compared to before treatment ($p<0.05$). Compared to the control group, the complications during the treatment, the respirator use time, oxygen supply time, length of stay and the mortality of children in the iNO treatment group were significantly decreased.

CONCLUSIONS: Mechanical ventilation, combined with iNO therapy, can effectively improve the respiratory function and arterial blood gas index of neonates with severe respiratory failure, improve the oxygenation, reduce complications and improve the quality of rescue, which is worthy of promotion.

Key Words:
Respiratory failure, Newborns, Nitric oxide, Mechanical ventilation.

Introduction

Severe respiratory failure is an important cause of neonatal death, and it is very common in the neonatal intensive care unit (NICU)[1,2]. With the development and progress of NICU respiratory support technology, conditions of the majority of children with respiratory failure have been effectively alleviated through the positive airway care and mechanical ventilation, but such treatments fail to alleviate conditions of some children, particularly in alleviating hypoxia symptoms and restoring normal oxygenation; the mortality of these children is relatively high. Nitric oxide (NO) is a type of vasoactive substance produced and released by endothelial cells with a wide range of physiological activity, and it is a selective pulmonary vasodilator[3]. NO can relax the pulmonary vascular smooth muscle and bronchial smooth muscle, reduce pulmonary arterial pressure and airway pressure, relieve lung inflammation caused by endotoxins, reduce the release of inflammatory cytokines and the media, and prevent the occurrence and excessive development of immune injury and inflammatory reaction. European and American countries have

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administered inhaled nitric oxide (iNO) treatment in the treatment of pulmonary hypertension, pulmonary fibrosis, persistent pulmonary hypertension of newborn (PPHN), acute hypoxic respiratory failure, respiratory distress syndrome (RDS) and other diseases. In 2013, the Affiliated Children's Hospital of Xuzhou Medical College introduced the inhaled nitric oxide therapy device. The device is used in cases of severe neonatal respiratory failure treatment and it has achieved good clinical results, which are summarized as follows.

Patients and Methods

Patients

Neonates with severe respiratory failure that were admitted to neonatal intensive care unit (NICU) of XuZhou Children's Hospital from November 2014 to February 2016 were selected as subjects of study. Practical Neonatology provides references to the indications of neonates' ventilation machinery and diagnostic criteria of complications[4]. Severe respiratory failure criteria includes: when conventional mechanical ventilation lasts for more than 4 h and the fraction of inspired oxygen (FiO_2) is more than 50%, the arterial partial pressure of oxygen (PaO_2) is less than 50 mmHg (1 mmHg = 0.133 kPa), the transcutaneous arterial oxygen saturation ($TcSaO_2$) is less than 0.85, and (or) the oxygenation index (OI) of blood gas analysis within 6 h is more than 15[5]. Exclusion criteria: children whose respiratory or digestive tract have severe congenital malformations; children whose mechanical ventilation lasted less than 24 h; children with severe congenital heart disease or severe left ventricular failure; children with bleeding disorders or bleeding tendency, and severe anemia. This study was approved by the Ethics Committee of XuZhou Children's Hospital. Signed written informed consents were obtained from the guardians of all participants before the study. 45 cases were included in the treatment group. Those 45 cases were treated with the conventional treatment of mechanical ventilation and the combined use of iNO treatment. The arterial blood gas index, respiratory function index and outcome indicators of all children were observed before and after 1, 6, 12, and 24 h of treatment. Also, newborns with severe respiratory failure that were admitted to NICU of the same hospital from July 2013 to August 2014 were selected as the control group. The cases in this group met the same criteria as those in the group with iNO treatment and there were 31 cases of control patients in total. The mechanical ventilation duration, complications during the treatment, oxygen supply time and length of stay of both groups were compared. General information of the two groups is shown in Table I. According to statistical analysis, the differences between both groups in gender, birth weight, gestational age, admission age, primary disease and average OI before treatment were not statistically significant ($p>0.05$), and these data were comparable.

Methods

Methods of two Conventional Treatment Groups

Both groups were treated with mechanical ventilation therapy and lung protective ventilation strategy. The initial adjustment value of the ventilator parameters were based on the blood gas analysis of children and the parameters were adjusted according to the curative effects. At the same time, attention was paid to thermal insulation, nutritional support and homeostasis maintenance. Dopamine and other vasoactive drugs were used to ensure stable cardiovascular function. For primary disease, surfactant was routinely used for RDS, antibiotics was used for lung infections, pneumothorax was timely treated with thoracentesis or chest drainage, ibuprofen was used to close the ductus arteriosus, patients with gastrointestinal bleeding or neonatal necrotizing enterocolitis (NEC) needed to fast and were treated with gastrointestinal decompression.

Methods of iNO Treatment Group

After children were admitted to the hospital and once the clinical and blood gas analysis were in line with criteria of severe respiratory failure, the hospital explained the disease condition to families of the children. If the families signed the informed consent, then their children were included into the iNO treatment group. The initial concentration of iNO was 15 ppm, with the basis of $TcSaO_2 \geq 90\%$. 30-60 min after iNO inhalation, if $TcSaO_2$ increased more than 10% and PaO_2 increased more than 10 mmHg (1 mmHg = 0.133 kPa), then the results were determined to be valid (otherwise determined to be invalid). Then, iNO concentration was reduced to 2-3 ppm, and the invalid ones kept increasing 2-3 ppm until PaO_2 and $TcSaO_2$ remained stable. iNO concentration

Table I. General information on two groups of children.

General information (n=45)	iNO treatment group (n=31)	Control group	t/x^2	p
Number of cases			0.250	>0.05
Male	31	23		
Female	14	8		
Age when admitted (d)	20.33±9.56	22.78±10.11	1.073	>0.05
Birth weight (g)	2303±903	2411±812	0.534	>0.05
Gestational age (week)	34.43±5.67	35.17±5.83	1.300	>0.05
Average OI when admitted	28.66±9.79	27.03±7.96	0.768	>0.05
Primary disease (cases)	0.570	>0.05		
Respiratory distress syndrome	23	14		
Tire class aspiration syndrome	8	5		
Asphyxia	5	5		
Pneumonia/sepsis	9	7		

and FiO_2 were gradually reduced at intervals of 6 to 12 h after the children's condition ameliorated. When iNO reduced to 3 ppm, if FiQ was less than or equal to 30% and TcSaQ was greater than or equal to 90%, and such condition lasted for 12 h, then iNO treatment was stopped. The highest concentration of iNO inhaled by one child was 30 ppm. Due to serious complications, the child's families abandoned the treatment. The average effective iNO concentration was (10.97±3.01) ppm. The longest duration of iNO inhalation was 96 h, and the average iNO inhalation duration was (52.66 ± 25.17) h. During treatment, the NO_2 level was monitored, and platelet function and blood coagulation functions were monitored regularly.

Observing the Indexes

The indexes of respiratory function of all children were observed before and 1, 6, 12, and 24 h after treatment. The arterial blood gas indexes included pH value, PaO_2 and $PaCO_2$. The respiratory function indexes included FiO_2, mean airway pressure (MAP), OI, pulmonary pressure and arterial alveolar oxygen partial pressure ratio (a/A). [$OI = 100 \times MAP \times FiO_2/PaO_2$, $a/An = PaO_2/(713 \times FiO_2 - PaCO_2/0.8)$]. Complications may occur during observation and treatment, such as pulmonary hemorrhage, pneumothorax, gastrointestinal bleeding/NEC and multiple organ damage. Comparison and observation of both groups were made in terms of duration of mechanical ventilation, complications during treatment, oxygen supply time, mortality and average length of stay, etc.

Statistical Analysis

SPSS19.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis and measurement data were expressed by mean±standard deviation (x±s). Comparisons between both groups were tested by the *t*-test. Comparisons of repeated measurement data between both groups were analyzed by ANOVA. The enumeration data was tested by the X^2-test. $p \leq 0.05$ indicated that the difference was statistically significant.

Results

The Arterial blood gas Index

We compared the pH value, PaO_2, $PaCO_2$ of the iNO treatment group before and after 1, 6, 12, and 24 h of treatment; the differences were statistically significant ($p<0.05$). The pH value after 6, 12, and 24 h of treatment were greater than that before treatment. The value of PaO_2 1, 6, 12, and 24 h after treatment was greater than that before treatment. The PaO_2 value after 1, 6, 12 and 24 h of treatment was greater than before. The $PaCO_2$ value after 1, 6, 12, and 24 h of treatment was less than before; the differences were statistically significant ($p<0.05$, Table II).

The Respiratory Function Indexes

We compared the FiO_2, OI and MAP of children in the iNO treatment group before and after 6, 12, and 24 h of treatment; the difference was statistically significant ($p<0.05$). The FiO_2, OI and MAP 6, 12, and 24 h after treatment were less than before. The a/A after 1, 6, 12, and 24 h of treatment were greater than before. The pulmonary arterial pressure after treatment decreased compared to that before treatment; all differences were statistically significant ($p<0.05$, Table III).

Table II. A comparison of arterial blood gas of children in iNO treatment group between before and after treatment (x±s).

Period	pH value	$PaCO_2$	PaO_2
Before treatment	7.090.115	68.44±6.75	35.42±6.74
1 h after treatment	7.13±0.09	51.90±4.67	50.23±5.88
6 h after treatment	7.28±0.07	47.82±6.18	55.03±4.96
12 h after treatment	7.33±0.07	44.49±5.51	59.79±6.11
24 h after treatment	7.35±0.05	41.25±3.99	65.73±5.22
F-value	48.32	27.79	59.67
p-value	<0.05	<0.05	<0.05

Compared to the data before treatment, $p<0.05$.

Table III. The respiratory function comparison of children in iNO treatment group between before and after treatment.

Period	FiO2(%)	MAP (mmH_2O)	OI	a/A	Pulmonary artery pressure
Before treatment	89.82±15.13	16.73±3.54	28.66±9.79	0.08±0.03	59.32±17.78
1 h after treatment	87.66±16.56	16.89±2.97	27.82±8.86	0.11±0.05	-
6 h after treatment	60.92±13.9	14.47±2.83	19.90±4.71	0.17±0.04	-
12 h after treatment	51.33±10.78	13.53±1.96	13.65±2.99	0.20±0.07	-
24 h after treatment	45.37±10.15	13.02±2.25	11.57±2.48	0.23±0.50	29.75±7.56
F-value	55.47	10.98	22.63	79.33	5.53
p-value	<0.05	<0.05	<0.05	<0.05	<0.05

Compared to the data before treatment, $p<0.05$.

Table IV. Comparison of outcomes of two groups of children.

Clinical outcomes	iNO treatment group	Control group	t/x^2	*p*-value
Duration of mechanical ventilation	93.55±25.17	117.8±30.42	3.794	<0.05
Complications (cases)				
Pneumothorax	2	9	4.890	<0.05
Gastrointestinal bleeding/NEC	10	18	4.530	<0.05
Pulmonary hemorrhage	1	5	4.090	<0.05
Multiple organ injury	14	23	4.560	<0.05
Duration of oxygen supply (h)	127.7±29.11	149.9±33.39		<0.05
Days of hospitalization	15.7±3.5	20.9±4.9	4.985	<0.05
Number of deaths (cases)	4	10	4.470	<0.05

Clinical Outcomes of Children in the two Groups

In the iNO therapy group, pneumothorax was present in 2 cases, gastrointestinal bleeding / NEC was present in 10 cases; there was 1 case of pulmonary hemorrhage and 14 cases of multiple organ injuries. In the control group, there were 9 cases of pneumothorax, 18 cases of gastrointestinal bleeding/ NEC, 5 cases of pulmonary hemorrhage and 23 cases of multiple organ damages. The complications of iNO treatment group were reduced compared to the control group. The duration of mechanical ventilation, oxygen supply time and length of stay of children on iNO was significantly decreased compared to those of the control group. 4 children in iNO treatment group died after leaving treatment, and 3 children of those were effectively treated by iNO, but they had severe neurological complications (intracranial hemorrhage, severe asphyxia, severe meconium aspiration). The remaining patient suffered from a pulmonary hemorrhage during treatment, and parents withdrew treatment; the mortality was 8.8%. In the control group, 10 cases of children died after leaving treatment, and the mortality was 32.2%. The differences between both groups were statistically significant ($p<0.05$, Table IV).

Discussion

The neonatal respiratory failure (NRF) is a prominent cause of neonatal deaths, and is the most common critical illness in NICU. Clark[6] found that RDS was the most common cause on NRF in children that were at a gestational age ≥ 34 weeks, followed by meconium aspiration syndrome (MAS), pneumonia/sepsis and wet lung. Furthermore, the lower the gestational age, the higher the incidence of RDS. Multi-center epidemiological surveys in China show that the respiratory disease is the most common cause of NRF, among which RDS was the most common cause. Other causes include hypoxic-ischemic encephalopathy, a variety of congenital malformations and primary or secondary pulmonary hypertension[7]. In the past 20 years, due to the advancement of mechanical ventilation in neonates NRF applications, the mortality rate of NRF has been greatly reduced. The domestic neonatal mortality rate for those on mechanical ventilation reduced from 63.1% in the 1980s to about 20% in the 21st century[1]. However, the symptoms of hypoxia in some children with severe NRF failed to be alleviated by mechanical ventilation, and therefore, required higher ventilator parameters such as high concentrations of oxygen and high-pressure mechanical ventilation in order to maintain normal blood gas levels. The survival rate of these neonates is still relatively low, and there were often more complications that seriously influence clinical outcomes and result in a poor prognosis. Several reasons account for this included the severity of the primary disease, collapse of the lung caused by surfactant consumption, release of inflammatory mediators, the reduction of secretion of endogenous NO, pulmonary arterial hypertension caused by the pulmonary artery spasm, barotrauma caused by the use of mechanical ventilation, and lung injury aggravated by volume injury. Therefore, the treatment effects of mechanical ventilation alone are not satisfactory[8,9]. iNO therapy is a newly developed respiratory support system that has emerged in recent years. A large number of studies have demonstrated that NO plays an important role in the pathophysiology of many diseases. Clinical trials in China and abroad have found that NO can be used to reduce reperfusion injury caused by ischemic lung transplantation, selectively reduce heart transplantation and pulmonary arterial resistance of patients with congenital heart disease, as well as cure severe hypoxic respiratory failure, high altitude pulmonary edema and acute respiratory distress syndrome[10,11]. iNO therapy equipment was introduced into this Department in 2013 for the intention of early intervention of severe NRF. Once the children met the diagnostic criteria of severe respiratory failure, and the oxygenation index of conventional mechanical ventilation, which lasted for more than 4 h, was still not ideal, patients were started on the iNO treatment as soon as possible. Studies have shown that with early use of iNO auxiliary ventilator support therapy, the duration of mechanical ventilation, oxygen supply time and length of stay, were significantly less than those of the control group. In addition, the morbidity and mortality rate of children in the iNO treatment group were significantly lower than those of the control group; differences were statistically significant. Therefore, it is suggested that the early combined use of iNO adjuvant treatment can effectively cure neonates with severe neonatal respiratory failure. It can also significantly shorten the time of respiratory support, reduce complications and improve the success rate. There were no abnormal changes in patients' 24-h ambulatory blood pressure, platelet function and blood coagulation function during iNO treatment. NO is a type of vasoactive substance produced and released by endothelial cells. It has a wide range of physiological activities and belongs to fat-soluble gas molecules. iNO can easily and quickly penetrate the airways and through the cell membrane of lung vascular smooth muscle cells. iNO combines with and activates the intracellular guanylate enzymes, thereby enhancing the levels of cyclic guanosine monophosphate (cGMP), and then selectively relaxing pulmonary blood vessels by acting as a vasodilator, reducing pulmonary artery pressure, improving ventilation/perfusion ratio, and improving heart function. In addition, NO can activate membrane Na^+-K^+-ATP on the enzyme, relaxing the airway smooth muscle and the airway, and increasing ventilation. NO comes into the blood through the pulmonary capillary, where it combines with hemoglobin and rapidly becomes inactivated. Therefore, there is no systemic vascular dilation and the impact on peripheral blood pressure is small. Under the impact of NO, the ventilation/perfusion ratio of lungs tends to be reasonable, and the oxygenation efficiency is relatively improved, so as to reduce the required concentration of inhaled oxygen and improve blood pressure; this can alleviate hypoxia hyperlipidemia to some extent[12]. Furthermore, the

experiment showed that through the process of releasing pro-inflammatory mediators induced by the inhibiting nuclear factor-κB (NF-κB), iNO can reduce the neutropenia accumulation in the lung so as to reduce the lung inflammation and improve the function of the surfactant[13,14].

Conclusions

This study shows that the pH value and PaO_2 of children in the observation group after 6, 12 and 24 h of iNO treatment were greater than those before treatment, and $PaCO_2$ was less than that before treatment. The FiO_2, MAP, and OI after 6, 12 and 24 h of treatment were less than those before treatment, and a/A after 1, 6, 12 and 24 h of treatment was greater than that before treatment. The average pulmonary artery pressure significantly decreased 24 h after treatment. A series of results suggest that the combination of respiratory support and iNO can improve arterial blood gas indexes and respiratory function indexes of neonates with severe respiratory failure, lead to a reduction in pulmonary hypertension, and improve oxygenation. After the administration of iNO, the oxygenation function of children in the iNO treatment group can be rapidly improved, FiO_2 and ventilation pressure are significantly reduced, so as to avoid or reduce high oxygen and high pressure ventilation in lung injury. Due to the shortening of duration of mechanical ventilation and intubation, the prevalence rate of secondary infection of lungs is significantly reduced.

iNO can shorten the course of disease, improve prognosis and increase the cure rate, which is why it is worthy of clinical promotion.

Conflict of interest

The authors declare no conflicts of interest.

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