European Review for Medical and Pharmacological Sciences 2016; 20: 4607-4611

Effect of nitric oxide inhalation for the treatment of neonatal pulmonary hypertension

H.-W. WU, Z.-G. LI, G. LIU, G.-Z. LU, H.-Y. LIANG

Department of Neonatal Medicine, Xuzhou Children's Hospital, Xuzhou, Jiangsu, China

Abstract. – OBJECTIVE: To investigate the effect of nitric oxide (NO) inhalation for the treatment of neonatal pulmonary hypertension.

PATIENTS AND METHODS: Eighty-six patients with neonatal pulmonary hypertension who were treated for the first time Xuzhou Children's Hospital from January 2013 to January 2016 were selected and randomly divided into the observation group and control group, with 43 cases each. Patients in the control group were treated with high-frequency oscillatory ventilation, while those in the observation group were treated with high-frequency oscillatory ventilation combined with inhalational NO therapy. The therapeutic effects were compared.

RESULTS: Over time, fraction of inspired oxygen (FiO_2) of patients in both groups decreased, and the FiO_2 levels of patients in the observation group at the different time points were lower than those of the control group; oxygen pressure (PaO_2) and oxygen saturation (SpO_2) showed an upward trend; the PaO_2 and SpO_2 levels in the observation group were higher than those of the control group at all time points. Oxygenation index (OI) increased, and the OI levels of the observation group at each time point were higher than those of the control group. Pulmonary artery pressure decreased at each time point, and the levels in the observation group were lower than those of the control group. The differences were statistically significant ($p < 0.05$). The duration of mechanical ventilation, duration of oxygen therapy, and mortality in the observation group were significantly lower than those of the control group, and the differences were statistically significant ($p < 0.05$).

CONCLUSIONS: Using NO inhalation to treat neonatal pulmonary hypertension can significantly improve oxygen supply, reduce pulmonary artery pressure, shorten treatment time, and reduce mortality. It is, therefore, worthy of clinical application.

Key Words:

Nitric oxide, Neonatal pulmonary hypertension, Inhaled oxygen concentration, Oxygenation indicators.

Introduction

Neonatal pulmonary hypertension (PPHN) commonly results from right-to-left shunting of blood. It is characterized by pulmonary vascular resistance and increased pulmonary artery pressure in the conversion process from fetal circulation to ectopic circulation[1]. The causes include pneumonia, pulmonary vascular spasm, asphyxia, respiratory distress syndrome, meconium aspiration, maternal urinary tract infection, and drug use during pregnancy[2]. The clinical manifestations include hypoxemia, severe cyanosis, and cardiac dysfunction[3]. High-frequency oscillatory ventilation can more effectively reduce lung injury of newborn infants compared with normal frequency ventilation. Nitric oxide (NO) is a selective pulmonary vasodilator that can relax smooth muscle[4,5]. Administering NO to the lungs of infants by high-frequency oscillatory ventilation can prevent alveolar collapse, reduce pulmonary vascular resistance, and improve lung capacity, and has been widely used for the treatment of PPHN[6-8]. In this study, PPHN was treated with high-frequency oscillatory ventilation combined with NO inhalation, and satisfactory results were obtained.

Patients and Methods

Patients

Eighty-six cases of neonatal PPHN admitted to Xuzhou Children's Hospital from January 2013 to January 2016 were consecutively selected according to the following criteria 1. Infants whose pulmonary artery systolic pressure was > 4.0 kPa or mean pulmonary arterial pressure was > 2.67 kPa; 2. X-ray examination showed hilus pulmonis artery expansion, enhanced beat, pulmonary arteries with thin-walled peripheral branches, and enlargement of the right ventricle;

Corresponding Author: Zhenguang Li, MD; e-mail: zhenguangli29@163.com

3. No other congenital developmental malformations and parents signed the informed consent. The exclusion criteria included: (1) Pneumothorax and hemorrhagic disorders; (2) Cyanotic congenital heart disease; (3) Poor treatment effects, relatively severe conditions, and estimation of poor prognosis.

Infants were randomly divided into the observation group and control group, with 43 cases each. In the observation group, there were 22 males and 21 females, aged 7-28 d, (average of 14.6 ± 6.5 d) and weighed 2.5-4.8 kg, (average of 2.8 ± 1.3 kg). There were 17 cases of severe pneumonia, 12 cases of amniotic fluid meconium inhalation, seven cases of pulmonary hyaline membrane disease, four cases of premature birth and three cases of bronchial pulmonary dysplasia. In the control group, there were 19 males and 24 females, aged 5-28 d, (average of 13.7 ± 5.8 d) and weighed 2.3-4.9 kg, (average of 2.8 ± 1.5 kg). There were 16 cases of severe pneumonia, 11 cases of amniotic fluid meconium inhalation, six cases of pulmonary hyaline membrane disease, six cases of premature birth, and four cases of bronchial pulmonary dysplasia. Comparisons of general parameters between the two groups showed no statistically significant differences ($p > 0.05$).

Methods

Hospitalized infants underwent respiratory tract cleaning, and mouth and nasal secretions were aspirated. Infants with inhaled amniotic fluid or meconium were treated by tracheal intubation to aspirate the fluids. Each infant was then injected with 1 ml sterile saline at a suitable temperature and supplied with oxygen for 30. The washing liquid was then aspirated. Infants in the control group were placed in an incubator, and body temperature was maintained within the normal range. A syringe was used to draw surfactant suspensions. Pulmonary surfactants were administered three times according to different body positions as follows: infants in the supine position were injected slowly with half of the amount of drug through a thin silicone tube in the tracheal catheter, and then received a quarter of the amount of drug in the right lateral and left lateral positions, respectively. To distribute drugs evenly in alveoli and to avoid overflow, the infants were supplied with oxygen for ventilation for 3 min. Infants were then placed under mechanical ventilation by high-frequency oscillatory ventilation.

Infants in the observation group, in addition to high-frequency oscillatory ventilation, were administered inhalational decompressed NO at a concentration of 800 ppm, which was added to the output loop of the ventilator (before the humidifier). The initial treatment dose of each infant was 20 ppm and they were observed every 15 min. The infants with ineffective inhalation were given an additional dose of 5 ppm per administration, and the maximum did not exceed 80 ppm. After 6 h of valid inhalation, the dose the infants received was reduced by 5 ppm every 30 min, and finally to 6 ppm.

Observational Indicators

The 2 h, 12 h, and 24 h fraction of inspired oxygen (FiO_2) after treatment, indexes of blood gas analysis, including arterial partial pressure of oxygen (PaO_2) and blood oxygen saturation (SpO_2), oxygenation index (OI), pulmonary artery pressure, duration of mechanical ventilation, duration of oxygen therapy and mortality were compared. It is well established that OI = PaO_2 / FiO_2. Doppler echocardiography was used to detect the regurgitation velocity, and tricuspid regurgitation V values were derived. Pulmonary artery pressure = 4 × V2 + 5 mmHg, and the average values were calculated after two measurements.

Statistical Analysis

SPSS19.0 software (Inc. Chicago, IL, USA) was used for statistical analysis. Measurement data are presented as a mean ± standard deviation. Comparisons between groups were by independent sample *t*-test. The different time points were compared using One-way ANOVA test followed by Post Hoc Test (LSD). Count data are presented as rate and were tested by χ^2. $p < 0.05$ was taken as statistically significant.

Results

Comparison of FiO_2 at Different Time Points

Over time, FiO_2 of the two groups decreased, and the FiO_2 levels in the observation group were lower than those of the control group at the different time points. The differences were statistically significant ($p < 0.05$) (Table I).

Comparison of Blood Gas Indexes at the Different Time Points

Over time, PaO_2 and SpO_2 in both groups increased, and the levels of PaO_2 and SpO_2 in the

Table I. Comparison of FiO_2 at different time points (%).

Group	Treatment 2 h	12 h	24 h	F	*p*
Observation group	52.0 ± 16.3	42.3 ± 12.5	31.7 ± 11.3	10.236	0.000
Control group	71.3 ± 18.7	58.6 ± 12.6	43.6 ± 12.7	12.625	0.000
t	6.248	5.968	5.457		
p	0.023	0.026	0.030		

observation group were higher than those in the control group at the different time points. The differences were statistically significant ($p < 0.05$) (Table II).

Comparison of OI at the Different Time Points

Over time, the OI in both groups increased. The OI levels in the observation group were higher than those of the control group at the different time points, and the differences were statistically significant ($p < 0.05$) (Table III).

Comparison of Pulmonary Artery Pressure at the Different Time Points

Over time, pulmonary artery pressure in both groups increased. Pulmonary artery pressure in the observation group was lower than in the control group at the different time points, and the differences were statistically significant ($p < 0.05$) (Table IV).

Comparison of Duration of Ventilatory Support, Time of Oxygen Therapy, and Death Rate

The duration of ventilatory support, time of oxygen therapy, and death rates in the observation group were lower than those in the control group, and the differences were statistically significant ($p < 0.05$) (Table V).

Discussion

The neonatal pulmonary vascular system is generally unstable. The maturation of endothelial cell function, release of vasoactive mediators, vascular wall remodeling, and smooth muscle cell differentiation are involved in the maturation process. Neonatal pulmonary hypertension is also known as persistent fetal circulation[9].

It is caused by a variety of factors including the risk factors of the perinatal period, such as maternal anemia, fever, lung disease, diabetes mellitus, the use of aspirin and non-steroidal an-

Table II. Comparison of blood gas indexes at the different time points.

Group	PaO_2 (mmHg)					SpO_2 (%)				
	Treatment 2 h	12 h	24 h	F	*p*	Treatment 2 h	12 h	24 h	F	*p*
Observation group	54.5 ± 8.6	61.3 ± 7.5	67.7 ± 8.6	8.632	0.000	65.7 ± 8.3	74.6 ± 7.5	81.7 ± 9.8	7.629	0.000
Control group	48.8 ± 9.5	54.7 ± 8.7	60.6 ± 6.5	8.967	0.000	51.6 ± 8.6	63.5 ± 9.7	71.8 ± 9.5	7.854	0.000
t	5.241	5.374	5.417			5.357	5.425	5.438		
p	0.026	0.023	0.020			0.022	0.020	0.020		

Table III. Comparison of OI at the different time points (mmHg).

Group	Treatment 2 h	12 h	24 h	F	*p*
Observation group	223.5 ± 42.3	267.9 ± 52.7	352.4 ± 72.6	7.628	0.000
Control group	202.6 ± 45.6	258.9 ± 54.3	296.3 ± 64.9	7.325	0.000
t	4.243	4.635	5.367		
p	0.035	0.030	0.024		

Table IV. Comparison of pulmonary artery pressure at the different time points (mmHg).

Group	Treatment 2 h	12 h	24 h	F	*p*
Observation group	46.5 ± 5.6	29.4 ± 6.4	15.7 ± 5.0	8.629	0.000
Control group	58.8 ± 7.4	39.5 ± 7.3	35.6 ± 6.3	7.524	0.000
t	5.348	5.634	6.167		
p	0.026	0.020	0.015		

ti-inflammatory drugs during pregnancy, meconium-stained amniotic fluid, perinatal asphyxia, and fetal distress. Greater gestational age is associated with higher incidence[10]. Neonatal pulmonary hypertension results in the inhibition of the production of NO. Stability of pulmonary vessels is achieved through the formation of vascular complexes and NO. Simultaneously, the decline in the secretion of endothelial diastolic factors in the pulmonary vasculature aggravates the injury of endothelial cells, which induces shrinkage of the vasculature. Furthermore, this increases interaction between endothelial cells, macrophages, and neutrophils, which promotes thrombosis, and in turn aggravates endothelial cell injury, usually with the characteristics of resistance of the pulmonary circulation and increasing pressure[11].

The Treatment of Neonatal Pulmonary Hypertension

The traditional treatment for neonatal pulmonary hypertension is the administration of vasodilator drugs combined with inhalation of high concentrations of oxygen, and mechanical ventilation[12]. At present, treatment with NO inhalation is widely used. NO is produced by endothelial cells and low bioavailability of NO is the pathological basis of vascular pulmonary hypertension[13]. Inhaled NO can disperse to vascular smooth muscle cells, and soluble guanylate cyclase can increase the levels of NO, which causes specific expansion of the pulmonary vasculature[14]. NO has allosteric effects on hemoglobin, which increases the exchange of oxygen and carbon dioxide, and causes blood flow distribution from oxygenation tissue to hypoxic tissue, which improves systemic and pulmonary circulation[15]. Regarding therapy with high-frequency oscillatory ventilation combined with NO inhalation, inhalation of NO when alveoli are inflated can effectively reduce pulmonary vascular resistance. The dose of NO is not significantly associated with the clinical effectiveness[16], and high concentrations of inhalational NO can cause indirect toxicity to the nervous system and red blood cells, which can easily result in methemoglobinemia[17]. Similarly, NO can inhibit collagen-induced platelet aggregation and adenosine diphosphate expression, which prolong bleeding time[18]. Therefore, to reduce the prevalence of adverse reactions, the maximum clinical dose should not exceed 80 ppm, and patients should be closely observed. If the conditions of the patients improve, the dose should be gradually reduced[19].

Over time in the present work, FiO_2 in both groups decreased, and FiO_2 levels of patients in the observation group at the different time points were lower than those in the control group.

PaO_2 and SpO_2 showed an increasing trend, and the PaO_2 and SpO_2 levels in the observation group were higher than those of the control group at all time points.

OI increased, and the OI levels in the observation group at each time point were higher than those of the control group; pulmonary artery

Table V. Comparison of duration of ventilatory support, time of oxygen therapy, and death rate.

Group	Cases	Duration of ventilatory support (d)	Time of oxygen therapy (d)	Death rate [n (%)]
Observation group	43	4.5 ± 1.2	8.7 ± 1.7	3 (7.0)
Control group	43	7.4 ± 1.5	10.5 ± 1.8	10 (23.3)
t/χ^2		6.216	6.415	4.440
p		0.013	0.010	0.035

pressure decreased, and was lower in the observation group compared with the control group at all time points. The differences were statistically significant. The duration of mechanical ventilation, duration of oxygen therapy, and mortality in the observation group were significantly lower than those of the control group.

Conclusions

NO inhalation for the treatment of neonatal pulmonary hypertension can significantly improve oxygen supply, reduce pulmonary artery pressure, shorten treatment time, and reduce mortality. It is, therefore, worthy of clinical application.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Lakshminrusimha S, Mathew B, Leach CL. Pharmacologic strategies in neonatal pulmonary hypertension other than nitric oxide. Semin Perinatol 2016; 403: 160-173.
2) Catteruccia M, Verrigni D, Martinelli D, Torraco A, Agovino T, Bonafé L, D'Amico A, Donati MA, Adorisio R, Santorelli FM, Carrozzo R, Bertini E, Dionisi-Vici C. Persistent pulmonary arterial hypertension in the newborn (PPHN): a frequent manifestation of TMEM70 defective patients. Mol Genet Metab 2014; 111: 353-359.
3) Teixeira-Mendonça C, Henriques-Coelho T. Pathophysiology of pulmonary hypertension in newborns: therapeutic indications. Rev Port Cardiol 2013; 32: 1005-1012.
4) Chen L, Xiao J, Li Y, Ma H. Ang-(1-7) might prevent the development of monocrotaline induced pulmonary arterial hypertension in rats. Eur Rev Med Pharmacol Sci 2011; 15: 1-7.
5) Mercanoglu G, Safran N, Ahishali BB, Uzun H, Yalcin A, Mercanoglu F. Nitric oxide mediated effects of nebivolol in myocardial infarction: The source of nitric oxide. Eur Rev Med Pharmacol Sci 2015; 19: 4872-4889.
6) Peyter AC, Delhaes F, Diaceri G, Menétrey S, Tolsa JF. Perinatal nitric oxide therapy prevents adverse effects of perinatal hypoxia on the adult pulmonary circulation. Biomed Res Int 2014: 949361.
7) Postolow F, Fediuk J, Nolette N, Hinton M, Dakshinamurti S. Hypoxia and nitric oxide exposure promote apoptotic signaling in contractile pulmonary arterial smooth muscle but not in pulmonary epithelium. Pediatr Pulmonol 2011; 46: 1194-1208.
8) Dhillon R. The management of neonatal pulmonary hypertension. Arch Dis Child Fetal Neonatal Ed 2012; 97: F223-F228.
9) Sood BG, Wykes S, Landa M, De Jesus L, Rabah R. Expression of eNOS in the lungs of neonates with pulmonary hypertension. Exp Mol Pathol 2011; 90: 9-12.
10) Simpson CM, Smolich JJ, Shekerdemian LS, Penny DJ. Urotensin-II contributes to pulmonary vasoconstriction in a perinatal model of persistent pulmonary hypertension of the newborn secondary to meconium aspiration syndrome. Pediatr Res 2010; 67: 150-157.
11) Steinhorn RH. Neonatal pulmonary hypertension. Pediatr Crit Care Med 2012; 11 (2 Suppl): S79-S84.
12) Vargas-Origel A, Gómez-Rodríguez G, Aldana-Valenzuela C, Vela-Huerta MM, Alarcón-Santos SB, Amador-Licona N. The use of sildenafil in persistent pulmonary hypertension of the newborn. Am J Perinatol 2012; 27: 225-230.
13) Cavallaro G, Agazzani E, Andaloro L, Bottura C, Cristofori G, Mussini P, Sacco F, Compagnoni G. Sildenafil and nitric oxide inhalation in neonatal pulmonary hypertension. Three case reports. Pediatr Med Chir 2008; 30: 149-155.
14) Chester M, Seedorf G, Tourneux P, Gien J, Tseng N, Grover T, Wright J, Stasch JP, Abman SH. Cinaciguat, a soluble guanylate cyclase activator, augments cGMP after oxidative stress and causes pulmonary vasodilation in neonatal pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 2011; 301: L755-L764.
15) Coates EW, Klinepeter ME, O'Shea TM. Neonatal pulmonary hypertension treated with inhaled nitric oxide and high-frequency ventilation. J Perinatol 2008; 28: 675-679.
16) van der Horst IW, Reiss I, Tibboel D. Therapeutic targets in neonatal pulmonary hypertension: linking pathophysiology to clinical medicine. Expert Rev Respir Med 2008; 2: 85-96.
17) Filippi L, Serafini L, Gozzini E, Poggi C, Moroni M, Fiorini P. Persistent pulmonary hypertension of the newborn refractory to inhaled nitric oxide and prostacyclin, responsive to neuromuscular blockade. Minerva Pediatr 2011; 63: 233-235.
18) Mersal A, Attili I, Alkhotani A. Severe neonatal pulmonary hypertension secondary to antenatal maternal diclofenac ingestion reversed by inhaled nitric oxide and oral sildenafil. Ann Saudi Med 2007; 27: 448-449.
19) Hunter CJ, Dejam A, Blood AB, Shields H, Kim-Shapiro DB, Machado RF, Tarekegn S, Mulla N, Hopper AO, Schechter AN, Power GG, Gladwin MT. Inhaled nebulized nitrite is a hypoxia-sensitive NO-dependent selective pulmonary vasodilator. Nat Med 2004; 10: 1122-1127.