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Comparison of inhaled nitric oxide and aerosolized iloprost in pulmonary hypertension in children with congenital heart surgery

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Abstract

Background: *Pulmonary arterial hypertension is of importance in congenital cardiac surgery as being a significant cause of morbidity and mortality. Although therapy options are limited, inhaled nitric oxide (NO) is used as a standard therapy. The present study aimed to compare inhaled NO and aerosolized iloprost in children with secondary pulmonary hypertension who underwent congenital cardiac surgery.*

Methods: *Sixteen children included in the study were randomized into either inhaled NO or aerosolized iloprost group. For both groups, the observation period terminated at 72 h after cardiopulmonary bypass.*

Results: *There was no significant difference between the groups in terms of mean age, weight, cross clamp time, pump time, and extubation time. No significant change was observed in the arterial tension and central venous pressure of both groups before the operation, 30 min after the pump, 45 min after the pump, and after extubation, whereas an increase was observed in the heart rate and cardiac output, and a decrease was observed in the pulmonary artery pressure. The mean values at the above-mentioned time points showed no difference between the groups. No serious adverse event and mortality was detected.*

Conclusions: *Both inhaled NO and aerosolized iloprost were found to be effective and comparable in the management of pulmonary hypertension.* (Cardiol J 2012; 19, 4: 387–394)

Key words: pulmonary hypertension, nitric oxide, aerosolized iloprost

Editorial p. 335

Introduction

Pulmonary hypertension, a life-threatening disease, is characterized by vasoconstriction and progressive remodeling of the pulmonary arterial wall causing right ventricular failure and death. Congenital heart disease is responsible for pulmonary hypertension in children in approximately 50% of cases [1]. Generally, correction of cardiac malformation could not be carried out in patients with congenital heart disease and severe pulmonary arterial hypertension. Recently, understanding the pulmonary arterial hypertension pathogenesis has led to the development of therapeutic approaches for pulmonary arterial hypertension including the uses of endothelin receptor antagonists [2], prostacyclin analogs [3], and phosphodiesterase-5 inhibi-

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tors [4]. Nitric oxide (NO) is biologically identical to endothelium-derived relaxing factor, which has been shown to mediate vascular dilatation. When released, NO diffuses into the vascular smooth muscle cells and activates the soluble guanylate cyclase. Activation of soluble guanylate cyclase increases the concentration of cyclic guanosine monophosphate and initiates a cascade of events resulting in smooth muscle relaxation. Several evidences indicate that NO is an important mediator of pulmonary vascular tone [5]. Therefore, inhaled NO, as a selective pulmonary vasodilator, has been the treatment of choice for controlling pulmonary hypertension after cardiac surgery. The use of inhaled NO leads to an improvement in pulmonary hypertension and a decrease in the ratio of pulmonary artery pressure to systemic artery pressure [5, 6].

Various methods have been tried to enhance the effect of NO in children with congenital heart disease. The effect of NO can be enhanced by precise patient selection, supplemental agents, and gradual withdrawal [6].

Prostacyclin induces a stimulation of adenylatcyclase by binding to specific membrane receptors (IP-receptors) and other receptors that are localized on the cell surface or in the nucleus. The result is an increase of the cyclic 3', 5'-adenosin monophosphate (cAMP) level. Increase of the 'second messenger' cAMP in the muscle cells activates the calcium pumps and thus makes the calcium stream out of the cytoplasm, increased intracellular cAMP level inhibits the myosin kinases. This results in vasorelaxation with a reduction of vessel resistance and an increased blood flow. Iloprost has a similar pharmacological profile to endogenous PGI2. This has been shown through tests with several animal species, in healthy human test subjects and also in patients [7]. The elimination half-life of inhaled iloprost is 20–30 min; it is selective for pulmonary vasculature and used as a specific vasodilator [8].

The aim of the present study was to compare the acute hemodynamic effects of aerosolized iloprost and inhaled NO in secondary pulmonary hypertension in children undergoing congenital heart surgery.

Methods

Sixteen children with severe pulmonary arterial hypertension (pulmonary arterial/aortic pressure ratio, greater than 0.7) who underwent cardiac surgery at our institution for congenital cardiac defects between September 2009 and November 2011 were enrolled in the present study. Only patients who fulfilled the diagnostic criteria of the National Institutes of Health Registry for primary pulmonary hypertension were included [1]. The study was approved by the Ethical Committee of our hospital. Informed consent was obtained from the relatives of the patients. Patients older than 24 months and/or echocardiographic and clinical findings suggestive of fixed pulmonary hypertension (forexample; right heart enlargement, normal or decreased pulmonary artery flow velocity on echocardiogram, quite precorium with no clinical signs of significant left to right shunting) underwent cardiac catheterization and assessment of pulmonary vascular reactivity testing using inhaled 100% oxygen.

Surgical and anesthetic procedure

In the present study, surgical management was standardized. We carried out intracardiac repair through a median sternotomy with standard cardiopulmonary bypass using bicaval cannulation, moderate hypothermia (at 24–26°C), and antegrade extracellular cardioplegia. All patients were normoventilated by pressure-controlled ventilation during weaning from extracorporeal circulation with a Servo Ventilator 300/NO-A (Servo 300; Siemens, Munich, Germany); they were then transferred to the intensive care unit on this ventilator. For all patients, end-tidal CO_2 was kept at 35–40 mm Hg. Patients were ventilated with 100% oxygen for 30 min and FIO2 was then decreased accordingly monitoring individual arterial pO2 values. Positive end-expiratory pressure was kept at 5 cmH_2O.

Patients were randomized to receive either aerosolized iloprost (iloprost group) or inhaled NO (NO group) by an independent monitor using a computer-based scheme. Iloprost and NO were administered immediately after cardiopulmonary bypass and before heparin reversal. Iloprost (Ilomedin, Schering AG, Schlieren, Switzerland) was administered at a dose of 0.5 μg/kg every 90 min for a minimum of 72 h using an ultrasound nebulizer (MaQuet, Germany). The nebulizer was connected to the distal inspiratory part of the respiratory circuit. Nitric oxide (Westfalen-Gas, Germany) was administered at a dose of 20 parts per million (ppm) using a commercially available system for NO application and concentration measurement (Draeger NODOMO®, Dräger, Lübeck, Germany).

The observation period was terminated at 72 h after cardiopulmonary bypass for both groups. In the NO group, inhaled NO was also administered for at least 72 h after cardiopulmonary bypass if weaning was not possible. Nitric oxide or iloprost treatment was then continued on an individual ba-

sis, if clinically required. The endpoints were as follows: 1) cumulated mean pulmonary arterial pressure and pulmonary artery pressure to systemic artery pressure as measured with arterial lines during the observation period, 2) duration of mechanical ventilation (in hours) until weaning from the respirator.

Hemodynamic monitoring

Hemodynamic monitoring was performed in the intensive care unit. A 5 F to 8 F introducer sheath was placed into the right or left internal jugular vein according to the age and weight of the patients. Chest X-ray or fluoroscopy was used to verify the correct positioning of the catheter. A 24 G catheter was inserted into the radial artery, or a 2 F catheter was inserted into a femoral artery for systemic arterial pressure monitoring. Either a Swan-Ganz catheter through the superior vena cava or a 3 F catheter directly inserted surgically to the main pulmonary artery was used for direct pulmonary artery pressure monitoring. Transducers were positioned at the midaxillary line and zeroed at atmospheric pressure. Pulmonary arterial pressure, systemic arterial pressure, and right atrial pressures were continuously monitored. Cardiac output was measured using Fick principle. Heart rate and transcutaneous arterial oxygen saturation were also continuously monitored. Arterial and mixed-venous blood samples were obtained simultaneously to determine the partial pressure of oxygen, partial pressure of carbon dioxide, pH, base excess, and oxygen saturation (ABL 520, Radiometer, Copenhagen).

Statistical analysis

Statistical calculations were performed using the Number Cruncher Statistical System 2007 Statistical Software program for Windows (NCSS Statistical Systems, Kaysville, Utah, USA). Standard descriptive statistics were performed and expressed as mean and standard deviation. Groups were compared using the Mann-Whitney U test. In each treatment group repeated measures of Friedman test was used to determine the differences in measurement at each time point. When p less than 0.05, Dunn's multiple comparisons tests were used for pairwise comparisons. A p value less than 0.05 was considered statistically significant.

Results

There was no significant difference between NO and iloprost groups in terms of mean age, weight, cross clamp time, pump time, and extubation time (Table 1).

Nitric oxide and iloprost groups were compared in terms of arterial tension, central venous pressure, heart rate, pulmonary arterial pressure, ratio of pulmonary artery pressure to systemic artery pressure, and cardiac output values before the operation (preoperative), 30 min after the pump, 45 min after the pump, and after extubation. No difference was found between the groups in terms of the mean values of these parameters at the above-mentioned time points (Table 2). Although there was a trend towards reduction of the pulmonary artery pressure in the NO group 45 min after the pump it did not reach to statistical significance ($p = 0.064$). Moreover, when the changes in the mean values of these parameters were evaluated, no significant changes were found in arterial tension and central venous pressure values at all time points in both groups (Fig. 1). A statistically significant change was observed in the heart rate, cardiac output, pulmonary arterial pressure, and ratio of pulmonary artery pressure to systemic artery pressure values in both groups at all time points. As compared to the preoperative values, an increase was observed in heart rate and cardiac output values in both NO and iloprost groups, whereas a decrease was observed in pulmonary arterial pressure and ratio of pulmonary artery pressure to systemic artery pressure values (Figs. 2, 3).

Paired comparisons revealed that heart rate values at the time points of 45 min after the pump and after extubation were significantly higher as compared to the preoperative heart rate value in the NO group. In the iloprost group, heart rate value at the time point of after extubation was significantly higher than the preoperative heart rate value and heart rate value at the time point of 45 min after the pump. In the NO group, cardiac output values at the time points of 30 min after the pump, 45 min after the pump, and after extubation were significantly higher than the preoperative cardiac output value. In the iloprost group, cardiac output values at the time points of 45 min after the pump and after extubation were significantly higher than the preoperative cardiac output value there were no severe complications associated with catheter testing or drug administration. Both treatments (inhalation of NO and iloprost) were generally well tolerated. During inhalation of NO or iloprost, no side effect was observed in any patient. Moreover, there was no evidence of rebound pulmonary hypertension following administration of NO or iloprost. No serious adverse events were observed during the

Table 1. Age, weight, cross clamp time, pump time, and extubation time in the nitric oxide and iloprost groups.

	Diagnosis	Age [month]	Weight [kg]	Cross clamp time	Pump time	Extubation time
Nitric oxide group		33.63 ± 33.27	10.25 ± 5.5	73.38 ± 55.89	99.25 ± 71.23	4.88 ± 5.14
Patient 1	Ventricular septal defect, pulmonary hypertension	84	21	24	50	1
Patient 2	Ventricular septal defect, pulmonary hypertension	72	15	32	40	1
Patient 3	Atrioventricular canal defect	1	5	50	60	2
Patient 4	Total anomalous pulmonary venous return, ventricular septal defect, atrioventricular septal defect	18	8	90	127	10
Patient 5	Atrioventricular septal defect	6	8	67	75	6
Patient 6	Atrioventricular septal defect	60	12	60	87	2
Patient 7	Ventricular septal defect, pulmonary hypertension	24	8	62	93	2
Patient 8	Truncus arteriosus	4	5	202	262	15
Iloprost group		38.5 ± 25.67	11.6 ± 8.41	50.25 ± 11.65	73.38 ± 40.76	3.38 ± 4.31
Patient 1	Ventricular septal defect, pulmonary hypertension	72	16	50	60	1
Patient 2	Ventricular septal defect, pulmonary hypertension	24	10	36	52	2
Patient 3	Atrioventricular septal defect	24	8	48	55	2
Patient 4	Ventricular septal defect, atrial septal defect, total anomalous pulmonary venous return	18	8	40	64	2
Patient 5	Atrioventricular septal defect	4	3	70	173	14
Patient 6	Atrioventricular septal defect	60	30	62	68	2
Patient 7	Ventricular septal defect, pulmonary hypertension	36	12	41	50	2
Patient 8	Truncus arteriosus	70	6	55	65	2
P		**0.597**	**0.790**	**0.400**	**0.400**	**0.728**

Data are presented as mean ± standard deviation or number, where appropriate.

Table 2. Mean values of the parameters before the operation, after the pump and after extubation in the nitric oxide and iloprost groups.

	Nitric oxide group	Iloprost group	P
Arterial tension			
Preoperative	54.13 ± 9.27	62.25 ± 17.58	0.318
30 min after the pump	60.63 ± 9.09	53.25 ± 8.17	0.092
45 min after the pump	59.50 ± 4.78	61.38 ± 12.04	0.598
After extubation	69.00 ± 17.24	73.75 ± 9.50	0.878
Central venous pressure			
Preoperative	9.25 ± 2.25	11.00 ± 1.51	0.079
30 min after the pump	11.00 ± 3.30	11.25 ± 2.92	0.205
45 min after the pump	9.75 ± 3.01	9.25 ± 3.37	0.789
After extubation	8.38 ± 2.83	8.75 ± 3.45	0.874
Heart rate			
Preoperative	111.75 ± 14.96	110.88 ± 14.96	0.999
30 min after the pump	123.63 ± 29.73	124.50 ± 21.21	0.563
45 min after the pump	122.75 ± 15.15	119.63 ± 12.14	0.563
After extubation	132.00 ± 19.82	139.13 ± 15.91	0.563
Cardiac output			
Preoperative	2.50 ± 0.34	2.86 ± 0.60	0.248
30 min after the pump	3.21 ± 0.60	3.17 ± 0.54	0.172
45 min after the pump	3.54 ± 0.82	3.39 ± 0.54	0.227
After extubation	3.48 ± 0.64	3.31 ± 0.72	0.528
Pulmonary arterial pressure			
Preoperative	45.75 ± 14.66	47.00 ± 9.52	0.713
30 min after the pump	42.25 ± 11.37	37.38 ± 4.10	0.494
45 min after the pump	31.13 ± 5.03	34.75 ± 4.95	0.064
After extubation	32.50 ± 6.19	36.75 ± 6.27	0.222
Ratio of pulmonary artery pressure to systemic artery pressure			
Preoperative	0.82 ± 0.16	0.82 ± 0.14	0.832
30 min after the pump	0.70 ± 0.19	0.71 ± 0.10	0.599
45 min after the pump	0.52 ± 0.06	0.57 ± 0.05	0.084
After extubation	0.49 ± 0.13	0.47 ± 0.05	0.636

observation period (72 h after cardiopulmonary bypass). Patient 2 in the iloprost group had thrombocytopenia (less than 70 000 platelets/μL) at day 4 after cardiopulmonary bypass, which did not need to be treated because spontaneously improved. No mortality was noted during the observation period. After the observation period, one in-hospital death was observed in the NO group; the patient died 14 days after surgery due to chronic respiratory failure.

Discussion

In children, pulmonary hypertension associated with congenital heart diseases is a major cause of postoperative morbidity and mortality. Thus, management of pulmonary hypertension after cardiac surgery is of great importance [9]. On the other hand, therapy options are limited in children. Introduction of pulmonary-specific vasodilators into medical practice has led to a significant increase in the quality of life and life expectancy in these patients; however, controversy still exists about the management of pulmonary arterial hypertension. Many reports have suggested the use of inhaled NO to treat pulmonary hypertension after cardiac repair in congenital heart disease. Miller et al. [10] reported the effect of inhaled NO at a concentration of 10 ppm, and propagated the use of prophylactic NO because NO reduced the risk of pulmonary hypertensive crisis after intracardiac repair. In their study, Day et al. [11] used inhaled NO at a concentration of 20 ppm in 20 patients; however, they failed to demonstrate its beneficial effects on

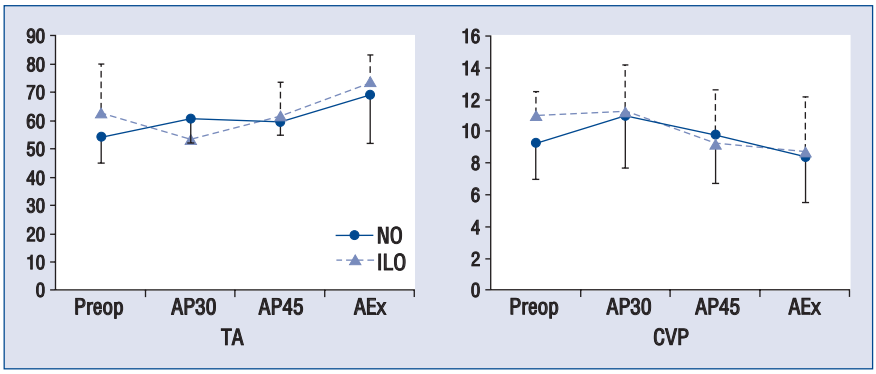

Figure 1. Changes in arterial tension and central venous pressure values in the inhaled nitric oxide (NO) and aerosolized iloprost groups; Preop — preoperative value; AP30 — 30 min after discontinuation of cardiopulmonary bypass; AP45 — 45 min after discontinuation of cardiopulmonary bypass; AEx — after extubation; ILO — ilomedin; TA — tension arterial; CVP — central venous pressure.

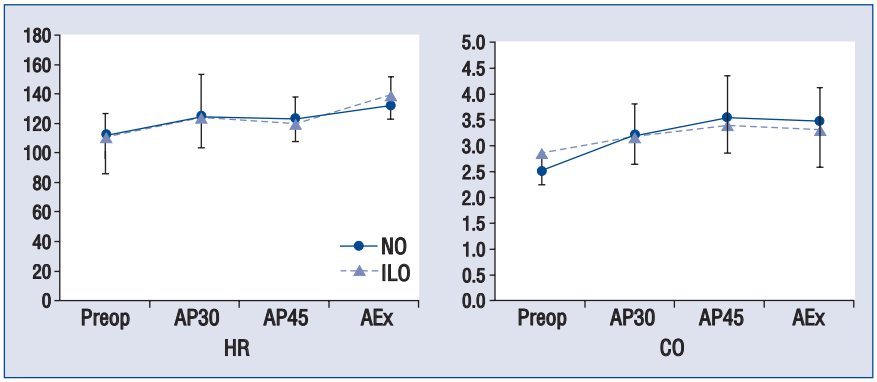

Figure 2. Changes in heart rate and cardiac output values in the inhaled nitric oxide (NO) and aerosolized iloprost groups; Preop — preoperative value; AP30 — 30 min after discontinuation of cardiopulmonary bypass; AP45 — 45 min after discontinuation of cardiopulmonary bypass; AEx — after extubation; ILO — ilomedin; HR — heart rate; CO — cardiac output.

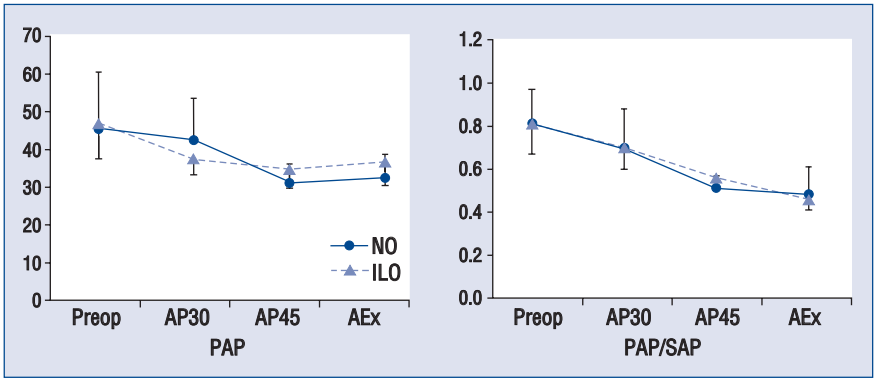

Figure 3. Changes in pulmonary artery pressure and pulmonary artery pressure to systemic artery pressure values in the inhaled nitric oxide (NO) and aerosolized iloprost groups; (Preop — preoperative value; AP30 — 30 min after discontinuation of cardiopulmonary bypass; AP45 — 45 min after discontinuation of cardiopulmonary bypass; AEx — after extubation; ILO — ilomedin; PAP — pulmonary artery pressure; SAP — systemic arterial pressure.

pulmonary hemodynamics after correction for congenital heart disease. However, limitations associated with inhaled NO include inadequate prevention of pulmonary hypertensive crisis, possible fatal rebound pulmonary hypertension after discontinuation of NO, and requirement of a more complex delivery system to administer the agent [12, 13].

Clinical studies comparing standard NO therapy with other pharmacological agents or evaluating different agents are being conducted [14–16]. There are limited studies regarding the use of inhaled iloprost therapy especially in children with pulmonary hypertension. Limsuwan et al. [8] reported inhaled iloprost to be an effective drug for postoperative pulmonary hypertensive crisis in children undergoing congenital cardiac surgery. Aerosolized iloprost was given by using an oxygen jet nebulizer (Delphenius™, Italy) connected to the endotracheal tube. Depending on the therapeutic efficacy the administered iloprost dosage was stepwise increased. The initial dosage was 250 ng/kg over 10 min. If no significant response was observed, the dose was firstly increased to 1000 ng/kg nebulized over 10 min and subsequently to the maximal dosage of 2000 ng/kg over 10 min every 30 min up to 5 times [8]. Loukanov et al. [15] recently compared inhaled NO with aerolized iloprost for treatment of pulmonary hypertension in children after cardiopulmonary bypass surgery. They used inhaled iloprost at 0.5 μg/kg every 2 h for a minimum of 72 h using an ultrasound nebulizer. The inhaled iloprost dose of 0.5 μg/kg was used in our study as well in order to achieve reported theoretical alveolar deposition of 250 ng/kg since it is known from previous studies that administration effectiveness is about 50%. Inhaled iloprost selectively induces a decrease in pulmonary vascular pressure with minor effects on the systemic circulation, which is an advantage in acute pulmonary hypertensive crisis. Inhaled iloprost decreases the ventilation-perfusion mismatch due to delivery only to ventilated lung segments. This effect may cause an increase in oxygen saturation in patients with hypoxia [17].

Responses to NO and iloprost are highly selective, and mediator pathways of these vasodilators are different and independent. Although different messenger pathways are activated, the final pathway leads to smooth muscle cell relaxation [18]. Loukanov et al. [15] reported no difference between the groups regarding the frequency of pulmonary hypertensive crisis, mean pulmonary arterial pressure and duration of mechanical ventilation. We also found no significant difference between the effects of NO and iloprost on hemodynamic parameters in children with secondary pulmonary hypertension who underwent congenital cardiac surgery. No serious side effects and no mortality during the treatment were observed. Neither NO nor iloprost caused a significant change in the arterial tension and central venous pressure values, whereas they caused an increase in the heart rate and cardiac output values and a decrease in the pulmonary arterial pressure and ratio of pulmonary artery pressure to systemic artery pressure values. Contrary to some previous reports [19, 20], no changes were observed in systemic artery pressure values during iloprost inhalation in the present study. This may be attributed to the different characteristics of the aerosol sprays and different intrapulmonary deposition characteristics between intubated and non-intubated patients.

Conclusions

Children with pulmonary hypertension and congenital heart disease, both inhaled NO and aerosolized iloprost are effective to selectively reduce pulmonary arterial pressure. Nebulization of iloprost may be advantageous over inhalation of NO due to the fact that it is not associated with toxic reactions and iloprost is easily administered by nebulizer as compared with complex delivery system required for NO. The patients were administered either inhaled NO or aerosolized iloprost; the results were found to be comparable. In conclusion, neither NO nor iloprost caused a significant change in the arterial tension and central venous pressure values, whereas they caused an increase in the heart rate and cardiac output values and a decrease in the pulmonary arterial pressure and ratio of pulmonary artery pressure to systemic artery pressure values; no difference was found between the groups in terms of these effects.

Conflict of interest: none declared

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