

## Inhaled iloprost in the treatment of pulmonary hypertension in very low birth weight infants: a report of two cases

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### Abstract

We treated 2 very low birth weight (VLBW) infants with respiratory distress syndrome suffering from refractory hypoxic respiratory failure complicated with severe pulmonary hypertension with inhaled iloprost. The first infant was an 800 gram male and the second case was a 920 gram

female. Echocardiography revealed a right to left shunt through patent duct in the first case; suprasystemic pulmonary arterial pressure was estimated by using tricuspid regurgitation of moderate severity in the second case. Inhaled iloprost was started in those infants when conventional therapies including the administration of exogenous surfactant and high-frequency oscillatory ventilation failed.

After the commencement of therapy, the clinical condition of the infants improved dramatically. Pulmonary arterial pressure returned to normal levels within five days. We suggest that inhaled iloprost may be helpful by improving oxygenation and reducing the need for aggressive mechanical ventilation in some cases of severe hypoxaemic respiratory failure in VLBW infants.

**Keywords:** Refractory hypoxic respiratory failure, Inhaled iloprost, Echocardiography, Exogenous surfactant.

## Introduction

Pulmonary artery hypertension (PAH) in preterm infants is characterized by an altered vasoreactivity with a marked pulmonary hypertension, which can lead to a right-to-left shunting of blood across the patent ductus arteriosus and foramen ovale. Preterm neonates with respiratory distress syndrome (RDS) may have elevated pulmonary vascular resistance soon after birth and this may be related to underdevelopment, including a decrease in the cross-sectional area and an abnormal muscularization of the pulmonary vasculature.<sup>1</sup> In the clinical setting, the preterm or very low birth weight (VLBW) infant may manifest severe hypoxaemia, even after initial improvement following endotracheal surfactant instillation. This hypoxaemia often can be prolonged and unresponsive to conventional medical treatment and increasing respiratory support. Pulmonary artery hypertension may be a possible explanation and has been reported in preterm infants with RDS by many investigators.<sup>2</sup>

Inhaled iloprost recently has been introduced in the treatment of pulmonary hypertension, especially in adults. Iloprost is a stable prostacycline (PGI<sub>2</sub>) analogue with vasodilatory, anti-inflammatory and vascular remodeling properties. The systemic use of iloprost has been limited for causing hypotension in children and adults. Similar to nitric oxide (NO), when used by the inhaled route it selectively dilates pulmonary vessels and improves oxygenation.<sup>3</sup> A few case reports have demonstrated the effectiveness and safety of inhaled iloprost in preterm infants, including extremely

preterm ones and term infants with persistent pulmonary hypertension (PPHN) refractory to inhaled NO (iNO).<sup>3-8</sup> Currently the use of inhaled iloprost has not been approved for premature neonates, and its therapeutic efficacy in this group remains controversial. Herein, we report the use of inhaled iloprost in treating pulmonary hypertension in two VLBW infants with RDS unresponsive to conventional treatment.

## Case Reports

### Case-1:

An 800 gram male infant was delivered spontaneously at 27 weeks gestation. Apgar scores were 5 at 1 minute and 8 at 5 minutes. The infant developed respiratory distress and required intubation in the first hour. Chest radiography on admission showed diffuse opacities in both lung fields, but laboratory findings were normal. The diagnosis was RDS and surfactant was applied 2 hours after birth. Initially, sufficient oxygenation was achieved on conventional ventilation, with approximately 40-50% inspired oxygen (FiO<sub>2</sub>). At the age of 8 hours, the patient deteriorated rapidly. Systemic arterial hypotension developed and in spite of increasing the inspired oxygen to 100% with conventional ventilation, the transcutaneous oxygen saturation (SaO<sub>2</sub>) decreased to 62%. We commenced high-frequency oscillatory ventilation (HFOV) with 100% oxygen. Surfactant was repeated 8 hours after birth. High dose vasopressors had been used for systemic hypotension. Treatment with surfactant, hyperventilation, and the elevation of systemic blood pressure had failed to improve oxygenation (SaO<sub>2</sub> 65-70%). Patient had an arterial oxygen tension (PaO<sub>2</sub>) / FiO<sub>2</sub> ratio <60 despite optimum ventilator settings during at least 16 hours (Table). His clinical course was consistent with pulmonary hypertension. Echocardiography revealed a right to left shunt over a patent arterial duct (Figure-1). Inhaled iloprost was started at a dose of 1 mcg/kg for each inhalation with 120-minute periods between inhalations. Iloprost was diluted with sodium chloride and administered endotracheally by an ultrasonic nebulizer integrated into the

**Table: Timeline showing changes in oxygenation parameters and pulmonary artery systolic pressure.**

Timeline: from the birth (hour)	FiO <sub>2</sub>	PaO <sub>2</sub> (mmHg)	PAO <sub>2</sub> / FiO <sub>2</sub> ratio	OI	MAP (cmH <sub>2</sub> O)	PASP (mmHg)
	case 1 / case 2	case 1 / case 2	case 1 / case 2	case 1 / case 2	case 1 / case 2	case 1 / case 2
1	80 / 80	50 / 52	62.5 / 65	30 / 26.7	20 / 18	
4	50 / 50	64 / 68	128 / 136	11.7 / 10.25	15 / 14	
8	100 / 100	54 / 50	54 / 50	40.7 / 46	22 / 23	
24*	100 / 100	52 / 52	52 / 52	44.23 / 44.23	23 / 23	75 / 77
48	75 / 70	68 / 72	115 / 118	18.75 / 16.50	17 / 17	40 / 47
72	55 / 50	77 / 80	160 / 160	9.2 / 8.13	13 / 13	30 / 24
96	30 / 35	86 / 85	286 / 243	3.4 / 4.5	10 / 11	24 / 24

\*Therapy with inhaled iloprost was started; FiO<sub>2</sub>: Fraction of inspired oxygen; PaO<sub>2</sub>: Partial pressure of oxygen; OI: Oxygenation index; MAP: Mean alveolar pressure; PASP: Pulmonary artery systolic pressure.



Figure-1: Color doppler demonstrates right to left shunting at the ductal level.

ventilator system. Oxygen saturation was normalized within 12 hours ( $\text{SaO}_2 > 90\%$ ). Control echocardiography the following day showed a complete conversion of right to left ductal shunting. Pulmonary artery systolic pressure was measured as 40 mmHg while systemic pressure was 70 mmHg. On the third day, the pulmonary to systemic pressure ratio decreased under the ratio of  $\frac{1}{2}$ . The administration of iloprost decreased the oxygenation index (OI;  $((\text{FiO}_2 \times \text{mean airway pressure})/\text{PaO}_2) \times 100$ ) from 44.23 to 3.4 and increased the ratio of  $\text{PaO}_2$  to  $\text{FiO}_2$  from 52 to 286 (Table). The dose of iloprost was halved and then stopped on the fourth day. Echocardiography revealed normal pulmonary artery pressure on the fifth day and the patient began to be weaned from the ventilator. Clinical, haematologic, biochemical and radiological studies before discharge from the neonatal intensive care unit did not reveal any side effects of iloprost.

### Case-2:

A 920 gram female infant was delivered by emergency caesarean section for uncontrolled hypertension and spontaneous premature rupture of membranes at 28 weeks gestation. The mother had not received any antibiotics during pregnancy. The infant developed respiratory distress soon after birth. Chest x-ray revealed hazy, ground glass opacities consistent with RDS. Surfactant was applied. Despite effective conventional ventilation, her clinical condition deteriorated within hours. Oxygen saturation decreased to 60% with 100%  $\text{FiO}_2$ . The systemic arterial blood pressure was 35 mmHg at the same time. Treatment with a second dose of surfactant, high frequency oscillation and elevation of systemic blood pressure to 68 mmHg had failed to improve oxygenation ( $\text{SaO}_2$  remained below 70%). The  $\text{PaO}_2/\text{FiO}_2$  ratio was below 60 despite optimum ventilator settings during at least 16 hours (Table).

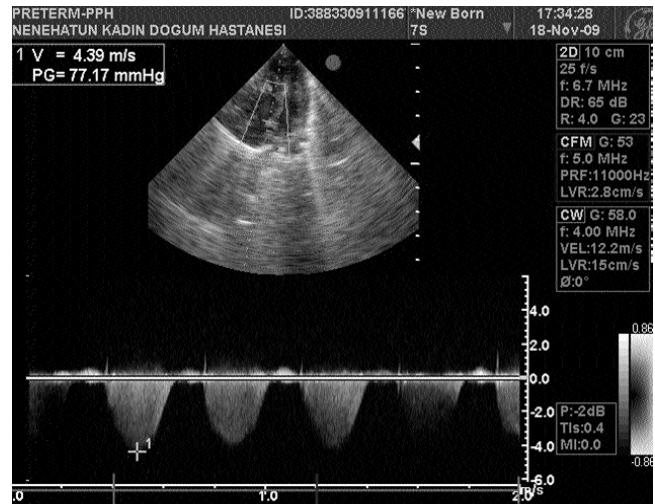


Figure 2: Pulmonary artery systolic pressure was estimated as at least 77 mmHg by using tricuspid regurgitation jet.

Echocardiography on the second day of life revealed tricuspid regurgitation of moderate severity. Pulmonary artery systolic pressure calculated by using tricuspid regurgitation jet was 77 mmHg (Figure-2). Suprasystemic pulmonary arterial hypertension was diagnosed and inhaled iloprost was started at a dose 1 mcg/kg. Oxygen saturation increased to 90% after the commencement of treatment. Pulmonary artery systolic pressure at control echo was measured as 47 mmHg while systemic pressure was 70 mmHg. On the third day, pulmonary arterial pressure was 24 mmHg. Inhaled iloprost therapy decreased the OI from 44.23 to 4.5 and increased the  $\text{PaO}_2/\text{FiO}_2$  ratio from 52 to 243 (Table). The dose of iloprost was halved and then stopped on the fourth day. The patient was weaned from the ventilator on the sixth day. The post-weaning period was non-eventful. We observed no side effects on blood pressure or on homeostasis.

### Discussion

This report describes our experience with the use of inhaled iloprost as a rescue therapy for severe hypoxemia in 2 VLBW infants who were on maximal mechanical ventilator support.

Currently, the mainstay of treatment and the recommended pulmonary vasodilating agent for PPHN is iNO. Nitric oxide acts by relaxing the vascular smooth muscle cells (SMCs) by increasing cGMP levels through the guanylate cyclase pathway. Although iNO therapy has improved the clinical course and outcomes of many infants, pulmonary hypertension can be refractory to iNO, suggesting the need for additional approaches to severe pulmonary hypertension. Alternatively, PGI<sub>2</sub> acts on the vascular SMCs by activating adenylate cyclase. Several studies demonstrated that inhaled PGI<sub>2</sub> rapidly improved oxygenation in infants

with PPHN and hypoxaemia refractory to iNO,<sup>3-8</sup> probably through an alternative cyclic adenosine monophosphate-mediated vasodilatation.

The reports on the use of inhaled iloprost in the treatment of PPHN in term or near term infants show good results. De Luca et al. reported two neonates treated with inhaled iloprost for PPHN, one with diaphragmatic hernia and one associated with an aneurysm of the vein of Galen. Both patients were refractory to iNO. A dose of 1 mcg every 4 hours was reported to be sufficient for improvement in oxygenation.<sup>4</sup> Chotigeat et al. reported one case of PPHN of the neonate that had hypoxia despite high frequency oscillation, inotropic drugs and oral sildenafil. Aerosolized iloprost was given through the nasotracheal tube and induced significant improvement in oxygenation.<sup>5</sup>

To our knowledge, only one report has been made on the use of inhaled iloprost in VLBW infants. Eifinger et al. treated 4 preterm neonates with 2 µg/kg iloprost per dose for a total of 44 to 65 doses.<sup>7</sup> The time elapsed between doses was 60 to 180 minutes. Oxygenation improved and echocardiography showed reduction in pulmonary pressure. We achieved similar results with the use of 1mcg/kg inhaled iloprost for each dose with 180 minutes between doses. The pulmonary artery pressure declined to normal levels and the patients were weaned from the ventilator in a couple of days. We did not detect any side effects that could be attributed to inhaled iloprost.

Several vasodilator agents have been shown to decrease pulmonary vascular resistance, but their use was limited by concomitant decreases in systemic vascular resistance and worsening of intrapulmonary shunt. Intravenous prostacyclin is a potent, dose-dependent vasodilator. However, vasodilatation is nonselective, resulting in both systemic hypotension and an increase of ventilation/perfusion mismatch in nonventilated areas. Therefore several investigators studied the effect of inhaled PGI<sub>2</sub> on the lung vasculature.<sup>9,10</sup> They demonstrated pulmonary vasodilation together with reduced shunt-flow, improved mismatch of pulmonary perfusion and ventilation with redistribution of pulmonary blood flow to well-ventilated areas and improved arterial oxygenation without repercussions on the systemic circulation.

We started inhaled iloprost as a first-line therapy in both of the cases. In our settings, NO is unavailable, so we could not use this agent in the treatment. Preterm infants are vulnerable and any change in their environment may have

detrimental effect. For that reason, we avoided conventional agents like magnesium sulfate or tolazoline. Recent studies have yielded good results on the use of intravenous sildenafil in the treatment of PPHN of the neonates. But no reports have been made on the use of this agent in VLBW infants.

Echocardiography is the only method for the diagnosis of PPHN in neonates. Mostly, the tricuspid regurgitation is used for the estimation of pulmonary artery systolic pressure, and pulmonary regurgitation is used for the estimation of pulmonary artery diastolic pressure. Sometimes, there may not be any valvular regurgitation for the estimation of pulmonary artery pressure. In such a situation, right to left shunt through a patent ductus arteriosus may clearly demonstrate supra-systemic pulmonary arterial hypertension in a cyanotic neonate. We detected suprasystemic pulmonary arterial pressure by observing right to left shunt through patent ductus in one of our cases.

## Conclusion

Our clinical experience indicates that inhaled iloprost is a promising therapy for pulmonary hypertension unresponsive to conventional treatment in VLBW infants. In view of our findings, we believe that further studies with larger group should be conducted to fully elucidate the safety and efficacy of inhaled iloprost in comparison with other vasodilator drugs in VLBW infants.

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