RESEARCH PAPER

Effectiveness and Safety of Intravenous Iloprost for Severe Persistent Pulmonary Hypertension of the Newborn

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Objective: The aims of this study were to determine the effectiveness (oxygenation), safety (hemodynamic status) and short term outcomes of intravenous iloprost (IVI) administration as a rescue therapy in severe persistent pulmonary hypertension of the newborn (PPHN).

Design: Retrospective medical records review.

Setting: Tertiary neonatal intensive care unit at Songklanagarind Hospital, Songkhla Province, Hat Yai, Thailand.

Participants: Newborns who received IVI as an adjunctive therapy for treatment of severe PPHN, as defined by an oxygen index (OI) of >20 and without response to conventional therapies.

Main Outcome Measures: The change of OI and alveolar-arterial oxygen difference before and after commencement of IVI.

Results: 33 neonates with severe PPHN at a median gestation of 39 weeks and a baseline OI of 40 (range, 21-101) received IVI. The median OI and alveolar-arterial oxygen difference had a statistically significant decrease after 2 hours of treatment and continued to decline thereafter (P<0.05). All infants received one or more inotropic medications and volume expanders to provide blood pressure support with no statistically significant difference of blood pressure and heart rate before and after IVI treatment. The mortality rate was 15.2%, all of them had initially severe hypoxemia with a median OI of 53.6.

Conclusions: IVI may be effective in improving oxygenation and should be considered as a rescue therapy for infants with severe PPHN, especially in a limited resource environment with no inhaled nitric oxide available. Systemic hypotension may be a cause for concern.

Keywords: *Newborn, Persistent fetal circulation syndrome, Prostacyclin; Pulmonary Hypertension.*

Persistent pulmonary hypertension of the newborn (PPHN) is a life-threatening neonatal pathology with high mortality [1] and high neurologic disability [2]. The primary goal of treatment for PPHN is selective pulmonary vasodilation. Inhaled nitric oxide (iNO) therapy is effective [3], but is not available in developing countries. Alternative, less expensive treatments are being sought. Iloprost, a stable analog of endogenous prostacyclin, has been used successfully in its intravenous and aerosolized forms for treating adults and children with pulmonary hypertension (PH). Aerosolized prostacyclin was found to be a potent pulmonary vasodilator in patients with acute respiratory failure, exerting preferential vasodilatation in well-ventilated lung regions [4]. In patients with PH who deteriorated while being treated with aerosolized iloprost substantial improvement in exercise capacity was seen after switching to continuous intravenous iloprost (IVI) [5]. The inhaled route of administering iloprost has fewer side-effects than the intravenous approach and obviates the need of a permanent central venous access [6-9]. The objectives of this study were to determine the oxygenation, hemodynamic status and short term outcome of IVI.

METHODS

A retrospective medical records review was performed in newborns who received IVI as an adjunctive therapy for treatment of PPHN between December 2007 and December 2011 at the neonatal intensive care unit of Songklanagarind Hospital which is the major tertiary care institution in southern Thailand. Patient selection was based upon a diagnosis of PPHN by echocardiography with evidence of a structurally normal heart and suprasystolic pulmonary hypertension, with right-to-left intracardiac shunting [10]. Exclusion criteria included the presence of other anomalies (including congenital heart disease, congenital diaphragmatic hernia, and lung hypoplasia syndromes) or chromosomal anomalies and infants who were not diagnosed by echocardiography. The study was approved by the Ethics Committee Board of Prince of Songkla University and informed consent was obtained from the parent or guardian before starting the IVI.

The primary outcome was the effect of IVI on oxygenation [decreased oxygen index (OI) and alveolar-arterial oxygen difference ($AaDO_2$)] and hemodynamic status (blood pressure, heart rate and needed inotropic medications and volume expanders) over a 72-hour period after commencement of treatment. Secondary outcomes included the mortality rate, duration of ventilatory support and bronchopulmonary dysplasia (BPD).

All infants who were diagnosed as having PPHN were treated with the conventional therapies including HFOV, inotropic therapy such as dobutamine, dopamine, epinephrine or norepinephrine and sedation, because of the non-availability of ECMO and iNO. Infants with severe PPHN, as defined by an OI of >20 at the time of diagnosis, who did not respond to the conventional therapies were considered for administration of IVI (Ilomedin, Bayer Schering Pharma, Spain). The starting dose for IVI was between 0.5 and 3.0 ng/kg/minute with maintenance doses of 1-10 ng/kg/minute. The dosage was titrated according to the clinical response and increased in increments of 0.5-1 ng/kg/minute. The IVI was prepared and diluted with isotonic saline solution resulting in a 1 mcg/ml solution. It was administered through a central vein using a pump system. The dosage was titrated up sufficiently to achieve substantial clinical improvement while maintaining adequate systemic blood pressure for infants responding to treatment. These infants were defined as the responder group. If the infants did not respond to IVI as indicated by no improvement in OI or PaO_2 after commencement of IVI within 12-24 hours they were defined as the non-responder group and another pulmonary vasodilator was administered. IVI was discontinued if clinical deterioration occurred, defined by refractory hypotension not responding to volume expander or inotropic agents [11]. After oxyge-nation improvement, indicated by an improvement in OI (OI<10), the IVI was tapered off by 0.5-1 ng/kg/minute and finally discontinued. The decisions to commence or adjust an alternative inotropic agent and to wean assisted ventilation or supplemental oxygen treatment depended on the discretion of the attending neonatologist. Concomitant drug therapy consisted of sedatives, analgesics and antibiotics or other vasodilators as required, adjusted to the individual needs of each infant.

The demographic data and information on various study characteristics was collected from hospital records. The time of IVI commencement, minimum and maximum dose, and duration of treatment were also obtained. The definition of BPD was defined as a need for supplemental oxygen for at least 28 days and times of point assessment were at 36 weeks' postmenstrual age for babies born before 32 weeks' gestational age or at 56 days of life for babies born at or beyond 32 weeks' gestational age or discharged home, whichever came first [12]. Cranial ultrasonography was performed at the first and fourth week by the pediatrics radiologist and was classified into 4 grades of severity [13]. Hearing screening tests were performed using the otoacoustic emission technique (MADSEN AccuScreen, AURICAL, GN Otometrics, UK) at the time of discharge.

Statistical analysis: The data and clinical parameters were expressed as mean (SD) or median (range). The Epicalc package in R Software version 2.13.1 was used for statistical analysis. The Wilcoxon rank-sum test and Fisher's exact test were used to compare the difference between the responder and non-responder of iloprost-treated severe PPHN. Since the data were not normally distributed, the Wilcoxon signed-rank test was applied to compare before and after IVI application with OI, SpO_2, PaO_2, $AaDO_2$, blood pressure and heart rate. A $P<0.05$ was considered statistically significant.

RESULTS

During the study period, 41 and 35 infants were diagnosed as PPHN and severe PPHN, respectively, who needed the IVI treatment. Thirty-three (33/35, 94.3%) infants were diagnosed as PPHN by echocardiography and enrolled in the study. There were no dropout cases during the study period due to severe hypotension not responding to inotropic agents or volume expander. 16 (48.5%) were referred from other hospitals. The most common etiology of the PPHN was meconium aspiration syndrome (MAS) (n=18, 54.6%) (***Table* I**).

The medians (ranges) of OI, PaO2 and SpO2 before treatment were 40 (21-101), 35 (16-210) and 79 (20-99), respectively. IVI induced significant improvement ($P<0.05$) in OI, PaO2 and SpO2 compared with the baseline at 2 hours and thereafter following initiation of treatment ***(Fig.* 1*a)***. The median (range) $AaDO_2$ decreased with statistical significance from 621 (605-633) to 597 (415-619) mmHg after 2 hours of infusion ($P=0.02$) (***Fig.* 1*b***). Twenty-two (66.8%) infants were responders and 11 were non-responders. The mortality rate was 15.2% and all of them initially had severe hypoxemia with a median OI of 53.6. Among the mortality cases, 3 infants (3/5, 60%) were referred from other hospitals. Five infants (5/33, 15.2%) demonstrated pneumothorax and three of these infants died. ***Table* II** shows comparison of various characterstics between the non-responder group and the responder group.

Before starting IVI, 22 (66.7%), 8 (24.2%), 2 (6.1%), 3 (9.1%) infants needed dopamine, dobutamine, epinephrine and norepinephrine, respectively, to provide blood pressure support. During IVI treatment, 32 (96.9%), 22 (66.7%), 11 (33.3%) and 17 (51.5%) infants needed

TABLE I BASELINE CHARACTERISTIC OF STUDY SUBJECTS

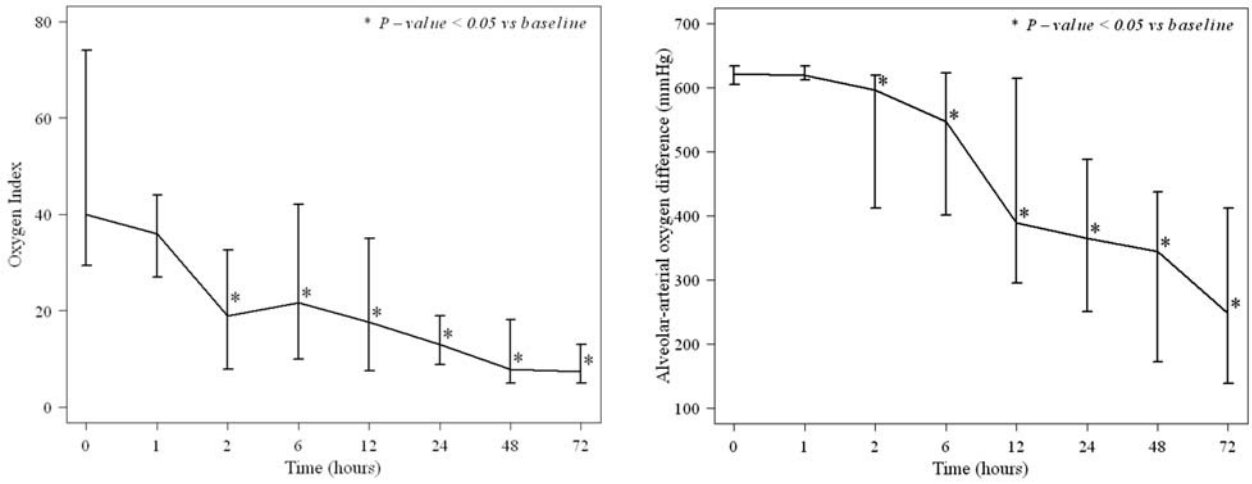
Male/female, (*n*)	22/11
Birthweight, g	3,120 (1,600-4,310)
Gestational age, wk,	39 (30-44)
Apgar score: 1 min; 5 min	6 (1-10); 8 (1-10)
Cesarean section, *n* (%)	23 (69.7)
Primary cause of PPHN, No. (%)	
Meconium aspiration syndrome	18 (54.6)
Pneumonia	12 (36.4)
Sepsis	2 (6)
Idiopathic pulmonary hypertension	1 (3)
Age at start of Iloprost (h)	26 (5-104)
Minimum dose of Iloprost, ng/kg/min	1 (0.5-3)
Maximum dose of Iloprost, ng/kg/min	4 (2.0-10)
Duration of Iloprost, h	97 (11-480)

All values median (range), unless specified.

dopamine, dobutamine, epinephrine and norepinephrine, respectively. There was a statistically significant increase in the number of infants who needed inotropic medications after the start of IVI treatment (P<0.01). After starting IVI, 21 (65.6%) infants needed any new inotrope, 12 (57.1%), 6 (28.6%), 3 (14.3%) of infants needed an additional 1, 2 and 3 more inotropic medications, respectively. The median (range) time interval between starting IVI and the need for any new inotrope was 13 (1-39) hours. During IVI treatment, only one (3%) infant never needed a volume expander. Before starting IVI, 27 (81.8%) infants needed a volume expander and after IVI administration 19 (57.6%) infants needed a volume expander to provide normal blood pressure. There was no statistically significant difference in the number of infants who needed a volume expander after IVI treatment (P=0.17). The median (range) time interval between starting IVI and the need for a volume expander was 16 (2-64) hours. There were no statistically significant differences of blood pressure and heart rate before and after IVI treatment under inotropic medications and volume expander therapies (P>0.05). Five surviving infants (5/28, 17.9%) were diagnosed only as mild BPD. All of the surviving infants had a normal hearing screening test at discharge and no infant discharged home with oxygen support. No other complications such as fever, facial flushing, cholestasis jaundice, renal insufficiency, neonatal seizure or abnormal heart disease were observed. Cranial ultrasonography was performed in 26 of 28 surviving infants, and was reported as severe intraventricular hemorrhage in one infant.

DISCUSSION

Iloprost is a synthetic analogue of the natural prostacyclin (PGI_2) with a plasma half-life of 20–30 minutes. Iloprost has been shown to decrease pulmonary vascular resistance by inhibiting adenylate cyclase, thus increasing the intracellular cyclic adenosine monophosphate (cAMP) level. Furthermore, iloprost has been linked to rapid decreases in atrial natriuretic peptide and cyclic guanosine monophosphate (cGMP) levels and increased pulmonary clearance of big endothelin-1 in pulmonary hypertension patients. These mechanisms are thought to be involved in the vasodilatory actions of iloprost [14,15]. Continuous intravenous infusion is more effective than inhaled iloprost [6]; however, no specific dosage is available for the neonatal age group. The dosage and interval usage in



(*a*) (*b*)

FIG. 1 (*a*) *Oxygen index and (b) Alveolar-arterial oxygen difference of neonates with PPHN before and after intravenous iloprost administration.*

TABLE II RISK FACTORS OF THE RESPONDER OF ILOPROST-TREATED SEVERE PPHN

	Responders (n = 22)	*Non-responders (n = 11)*
Birth weight, g	3,185.4 (453.7)	2,998.7 (660.8)
Sex, male, *n* (%)	15 (68.2)	7 (63.6)
Gestational age, wk	38.6 (2.6)	38.8 (3.8)
#Age at start‡, h	26 (24, 35)	30 (13, 39.2)
#Minimum dosage‡ ng/kg/min	1 (0.5, 1)	1 (1, 1.5)
#Maximum dosage‡, ng/kg/min	3.5 (2, 4)	5 (3.5, 5.2)
#Duration‡, h	108 (37.5, 167.8)	111 (40.2, 135)
$AaDO_2$ before treatment	614 (22.7)	603 (74.6)
Oxygen index before treatment	47.6 (28.5)	53.6 (27.3)
Tension pneumothorax, *n*(%)	3 (13)	2 (16.6)
Duration on HFOV, d	9.2 (7.2)	13.7 (17.5)
Duration on conventional ventilator, d	8.7 (6.3)	8.2 (10.9)
Duration of hospitalization, d	27.3 (17.1)	18.9 (14.1)
$Death, *n*(%)	1 (2.1)	4 (36.4)
Cause of PPHN, n(%)		
Meconium aspiration syndrome	12 (54.5)	6 (54.5)
Pneumonia	8 (36.4)	4 (36.4)
Sepsis	2 (9.1)	0 (0)
Idiopathic PHN	0 (0)	1 (9.1)

#Median (range);Other values in mean (SD); $P=0.01; ‡Iloprost; PPHN- Persistent pulmonary hypertension of newborn.

this study were derived from children with pulmonary hypertension secondary to congenital heart disease [16,17]. Other doses are also reported in literature [8,9]. The side effect of inhaled iloprost was severe bronchoconstriction in two patients without prior history of lung disease [18].

Iloprost affects vascular tone by mediating the incremental levels of cAMP. This effect is complementary to the increased cGMP levels produced by sildenafil. Because prostacyclin and sildenafil have two different second messenger systems, their simultaneous usage is likely to produce vasodilatation when single drug therapy fails [14]. The high mortality rate of IVI in combination with sildenafil in this study could be from the selection of severe cases with unresponsiveness from IVI. Oral beraprost sodium, an oral PGI_2 analog, was reported as an adjunctive therapy in infants with PPHN [25]. Oral sildenafil and beraprost sodium could be an adjunctive therapy with IVI. PPHN has a significantly wide spectrum of severity. The initial OI in the infants enrolled reflects, at least in part, the degree of illness severity and the high risk for mortality in these infants, particularly without iNO and ECMO. The median OI before the start of treatment in this study was higher than in the other studies in PPHN infants with intravenous sildenafil (27.7) [19] and intravenous milrinone with iNO (28.1) [22]. No infant with mild or moderate PPHN was entered into this study. Furthermore, several studies in children and adults with pulmonary hypertension secondary to heart disease have shown that IVI can affect systemic hypotension by dilatation of arterioles and venules [16,17]. In this study, all infants developed systemic hypotension that required one or more inotropic medications or a volume expander to provide blood pressure support which is different than studies of intravenous sildenafil [23] or intravenous milrinone with iNO [22].

This study had several limitations. This was a retrospective study with a small number of patients limited to the enrollment of PPHN infants diagnosed by echocardiogram and a lack of complete long term follow-up visits for growth and neurodevelopmental outcomes. As the study did not have a control group, the effect of confounders need to be considered. Further, clinical pharmacokinetic studies and optimal dosing on large neonatal populations using randomized clinical studies are warranted to study IVI in neonates with severe PPHN to evaluate the safety, efficacy and long-term outcomes after treatment with IVI, both in areas with and without widespread availability of alternative therapies like iNO. Our preliminary data indicate that IVI can improve oxygenation and could be an adjunctive therapy for PPHN in situations where iNO or ECMO is not available.

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Contributors: WJ: designed the study, collected data, drafted the paper, conducted the laboratory tests, analyzed the data, wrote the manuscript and revised the manuscript for important intellectual content. She will act as guarantor of the study; AT, GM, PC and SD: drafted of the manuscript. The final manuscript was approved by all authors.

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WHAT IS ALREADY KNOWN?

- The standard treatment of severe pulmonary hypertension of the newborn is inhaled nitric oxide (iNO).

WHAT THIS STUDY ADDS?

- Intravenous iloprost continuous infusion could be a promising therapy for severe pulmonary hypertension of the newborn as an adjunctive therapy in case iNO or ECMO is not available.

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