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**Brief communication (Original)**

# Intravenous iloprost may be an effective first-line treatment for persistent pulmonary hypertension of the newborn in limited-resource situations

Narongsak Nakwan[a,b], Jeerawan Wannaro[b], Narongwit Nakwan[c]
*[a]Neonatal Intensive Care Unit, Hat Yai Medical Education Center, Hat Yai Hospital, Songkhla, 90110, Thailand, [b]Department of Pediatrics, Hat Yai Medical Education Center, Hat Yai Hospital, Songkhla, 90110, Thailand, [c]Department of Medicine, Hat Yai Medical Education Center, Hat Yai Hospital, Songkhla, 90110, Thailand*

***Background:*** Persistent pulmonary hypertension of the newborn (PPHN) is one of the most serious conditions in neonates, and has high mortality and morbidity rates. New alternative therapies have been sought for improving survival and reducing morbidity for PPHN.
***Objective:*** To report an initial experience of using intravenous iloprost to treat infants with PPHN, and assess its effect on oxygenation and hemodynamic stability over a 96-hour study.
***Methods:*** The clinical data of infants who received intravenous iloprost as first line adjunctive therapy for PPHN at our institution between March 2009 and June 2010 were retrospectively reviewed.
***Results:*** During the study period, 10 PPHN infants received intravenous iloprost as the first line of adjunctive therapy. The median gestational age was 40 weeks (range: 38–42), and birth weight was 3,250 grams (range: 2,310–3,900 g). Intravenous iloprost was initiated at an average age of 38 ± 26 hours (median: 32 h, range: 6–79 h), with an average baseline oxygen index (OI) of 25 ± 18 (median: 18, range: 8–65). Two infants who died while receiving the intravenous iloprost were excluded from our analysis because of incomplete data. Of the 8 who survived, the baseline OI was 24 ± 20 (median: 17, range: 8–65), and the mean OIs at 24 and 72 hours following treatment were significantly improved (16 ± 18 (median: 6, range: 4–50) ($p = 0.02$), and 9 ± 5 (median: 8, range: 3–18) ($p = 0.02$), respectively). No clinically significant changes in heart rate or blood pressure were noted during the iloprost therapy. At discharge, 6 of the infants were clinically normal, and 2 were complicated with cholestatic jaundice. No neurodevelopmental or cardiopulmonary disorders were observed in the 8 surviving infants at hospital discharge or later follow-up visits.
***Conclusion:*** Intravenous iloprost may be a useful adjunctive therapy in PPHN, and should be investigated in a larger controlled study.

***Keywords:*** Iloprost, newborn infant, neonatal mortality, persistent pulmonary hypertension of the newborn

The treatment options for persistent pulmonary hypertension of the newborn (PPHN) in developing countries are generally limited to inhaled nitric oxide or extracorporeal membrane oxygenation, which are not ideal treatments and have high mortality and morbidity rates[1-2]. Various alternative treatments for PPHN such as sildenafil, bosentan, or beraprost sodium have been studied to attempt to find a way to reduce mortality in these patients within the resource limitations of most developing country settings [3-6].

Iloprost is a stable analogue of prostacyclin, which has been reported to reduce pulmonary vascular resistance and pulmonary arterial pressure in both adult and pediatric patients with pulmonary arterial hypertension [8, 9]. To date, however, there have been only a few reports on treating PPHN with aerosolized iloprost as an adjunctive treatment [10-12] and, to our knowledge, no report on using intravenous iloprost in this condition. In this study, we describe our experience of the clinical management of infants with PPHN in a developing country setting who failed to respond to

***Correspondence to:*** Narongsak Nakwan, MD, Neonatal Intensive Care Unit, Department of Pediatrics, Hat Yai Medical Education Center, Hat Yai Hospital, Songkhla, 90110, Thailand. E-mail: nnakwan@hotmail.com

conventional management with alkali therapy and/or high frequency oscillatory ventilation (HFOV), and were then given intravenous iloprost as the first line adjunctive treatment, because the initial treatment was not successful. This study was undertaken to assess the impact of this treatment, and its effect on oxygenation and hemodynamic stability over a 96-hour observation following iloprost administration.

## Materials and methods

This was a retrospective study involving infants diagnosed with PPHN from March 2009 to June 2010 who received intravenous iloprost as the first line adjunctive therapy for treatment in the neonatal intensive care unit (NICU) of Hat Yai Hospital in southern Thailand. The study was approved by the Ethics Committee of Hat Yai Hospital.

PPHN was diagnosed if the infant was noted to have refractory hypoxemia plus one of the three following conditions: (1) documented pulmonary hypertension as defined by echocardiographic evidence of elevated pulmonary pressure (right to left or bidirectional shunt), (2) a pre-to-postductal partial pressure of oxygen gradient equal to or greater than 20 mmHg, and/or (3) a pre-to-postductal pulse oximetry oxygen saturation ($SpO_2$) gradient equal to or greater than 10% [12]. Excluded from the study were: (1) infants with PPHN secondary to congenital diaphragmatic hernia or pulmonary hypoplasia, (2) infants with PPHN who had a major congenital anomaly, or cyanotic congenital heart disease, (3) infants with PPHN, but with incomplete records, and (4) infants with PPHN who received intravenous iloprost and died prior to the completion of the observations (within 96 hours after initial administration of the iloprost).

In Thailand, iloprost is only licensed for adults and children, but not infants, with pulmonary arterial hypertension, and written informed consent was therefore obtained from parents before the iloprost therapy was started on our PPHN infants. For the adjunctive therapy, iloprost (Ilomedin, 20 μg/2 mL, Schering, Berlin, Germany) was started at an intravenous dose of 2 ng/kg/min in our PPHN infants who were showing a poor response to alkali therapy and/or HFOV, which was defined by decreased pre-ductal $SpO_2$ to < 90%. A loading dose was not administered because of the potential risk of profound hypotension. An intravenous iloprost infusion was then increased stepwise after 10 to 15 minutes by 1 ng/kg/min until a positive clinical response was seen as determined by improved $SpO_2$, or until side-effects such as profound systemic hypotension or major bleeding precluded further dose escalation. The maximum dose of intravenous iloprost given to any patient was 20 ng/kg/min.

To compare the mortality outcomes between infants who received and did not receive intravenous iloprost, a matched historical control was performed. Historical control subjects were defined as infants who had been treated for PPHN at our institution prior to this study, who were very similar to our case subjects except, that they had not received intravenous iloprost as an adjunctive therapy for PPHN treatment. Control subjects were matched to case subjects at a 1:1 ratio using the computerized record system. Basic demographic data were obtained from the study and control records. Primary outcome measures, mainly oxygen index (OI), systolic blood pressure (SBP), and heart rate (HR) over a 96-hour period, at 1–2 hours before the intervention began, and at 6, 12, 24, 48, 72, and 96 hours after initiating the intravenous iloprost treatment without any other pulmonary vasodilator, were also noted.

### Statistical analysis

Data were analyzed as mean ± standard deviation or median (range: minimum–maximum). Because of the degree of non-normality in the distribution and small study population, data transformation could not be conducted to obtain statistical normality. For this lesion nonparametric statistics were used to analyze the data. A Mann–Whitney *U* test was used for continuous variables, and Fisher's exact test was used for comparisons of categorical data. The OIs, HRs and SBPs were compared at different time points using the Friedman test. If the Friedman test results showed a significant difference, the paired Wilcoxon signed-rank test was used to compare differences between baseline and serial parameters of the outcomes at 6, 12, 24, 48, 72, and 96 hours after initiation of the intravenous iloprost therapy. A $p < 0.05$ was considered statistically significant.

## Results

During the study period, 10 infants were treated with intravenous iloprost as the first line adjuvant therapy following an inadequate response in each of the study subjects to conventional treatment. **Table 1** presents the basic characteristics of the study groups.

There were no significant differences between the 10 case subjects and the 10 control subjects with regard to basic demographic characteristics, except the historical control group had a lower average birth weight than our study group ($p = 0.04$). The mortality rate in the iloprost group was lower than the historical control group, but the difference was not statistically significant (20% vs. 50%, $p = 0.35$, respectively).

The 10 infants in our study initially received intravenous iloprost at a dose of 2 ng/kg/min, with a mean age at initiation of treatment of 38 ± 26 hours (median: 32, range: 6–79), and a mean baseline OI of 25 ± 18 (median: 18, range: 8–65), a mean preductal $SpO_2$ of 73 ± 12 mmHg (median: 73, range: 47–90), a mean baseline HR of 162 ± 13 beats per minute (median: 166, range: 146–180), and a mean baseline SBP of 75 ± 10 mmHg (median: 73, range: 61–91). The mean maximum dose of intravenous iloprost was 4 ± 2 ng/kg/min (median: 4, range: 1–12), and the mean duration of iloprost treatment was 5 ± 3 days (median 5, range: 1–12).

In our study, we excluded 2 infants who received intravenous iloprost from the analysis because of uncompleted clinical data at each of time point. The first infant died from severe PPHN because of meconium aspiration syndrome with hospital duration at the age of 57 hours. He was initially treated with conventional ventilation and alkali therapy, and then changed to intravenous iloprost at 27 hours of age, with a maximum dose of 4 ng/kg/min. The baseline OI was 34, with preductal $SpO_2$ of 67%. He received dopamine and epinephrine to maintain his blood pressure at the maximum doses of 20 and 1 μg/kg/min, respectively, until he died. The other infant died from PPHN complicated with pneumothorax at an age of 24 hours. He was treated with HFOV and alkali therapy, and received intravenous iloprost beginning at 5 hours of age with a maximum dose of 2 ng/kg/min. His baseline OI was 19, with preductal $SpO_2$ of 47%. He received dopamine and epinephrine to maintain his blood pressure at the maximum doses of 20 and 1.5 μg/kg/min, respectively, until he died.

**Table 1.** Comparison of basic demographic characteristic between iloprost group and historical control subjects

| Characteristic | Iloprost group (n = 10) | Historical control group (n = 10) | *p* |
|---|---|---|---|
| Gestational age (weeks), median (range) | 40 (38–42) | 40 (37–40) | 0.18 |
| Birth weight (g), median (range) | 3,250 (2,310–3,900) | 2,850 (2,180–3,290) | 0.04 |
| Male, n (%) | 8 (80%) | 8 (80%) | 1.00 |
| Outborn, n (%) | 5 (50%) | 4 (40%) | 1.00 |
| Apgar Score at 1 min, median (range) | 8 (1–10) | 9 (1–10) | 0.97 |
| Apgar Score at 5 min, median (range) | 9 (4–10) | 9 (5–10) | 0.69 |
| SNAP-II score, median (range)□ | 38 (18–77) | 44 (16–73) | 0.94 |
| Diagnostic methods of PPHN, n (%) | | | |
| Pre-to-postductal SpO2 difference only | 8 (80%) | 6 (60%) | 0.63 |
| Echocardiography plus SpO2 difference | 2 (20%) | 4 (60%) | |
| Cause of PPHN, n (%) | | | |
| Meconium aspiration syndrome | 7 (70%) | 5 (50%) | 0.65 |
| Transient tachypnea of the newborn | 3 (30%) | 2 (20%) | 1.00 |
| Sepsis | 0 | 2 (20%) | 0.47 |
| Idiopathic PPHN | 0 | 1 (10%) | 1.00 |
| Treatment modalities, n (%) | | | |
| HFOV treatment | 9 (90%) | 5 (50%) | 0.14 |
| Alkali therapy | 10 (100%) | 10 (100%) | 1.00 |
| Duration of ventilator support (days), median (range) | 7 (1–23) | 7 (1–12) | 0.11 |
| Duration of supplemental oxygen (days), median (range) | 15 (1–25) | 11 (1–19) | 0.26 |
| Duration of inotropic therapy (days), median (range) | 8 (1–42) | 6 (1–10) | 0.23 |
| Duration of hospital stay (days), median (range) | 23 (1–40) | 16 (1–31) | 0.29 |
| Death, n (%) | 2 (20%) | 5 (50%) | 0.35 |

□score was calculated within 12 hour of admission, SNAP-II = Score for Neonatal Acute Physiology-Version II, $SpO_2$ = Preductal pulse oximetry oxygen saturation, PPHN = Persistent pulmonary hypertension of the newborn, HFOV = High frequency oscillatory ventilation

Ultimately, 8 infants received intravenous iloprost over the full 96-hour study, and their results were analyzed for the effect of the intervention on oxygenation and hemodynamic stability. Their clinical data recorded at the study time points, included OI, SBP, HR, partial pressure of oxygen, preductal $SpO_2$, supplemental oxygen, dosage of the inotropic drug, and dosage of iloprost, are presented in **Table 2**. The Freidman test revealed significant differences among OI and preductal $SpO_2$ levels ($p = 0.01$, and $p \leq 0.01$, respectively). The mean OI of the study group was 24 ± 20 (median: 17, range: 8–65) at the beginning of treatment, and in all cases there was a cumulative and significant improvement in OI as the iloprost treatment progressed, to average values of 16 ± 18 (median: 6, range: 4–50) ($p = 0.02$), and 9 ± 5 (median:

**Table 2.** Clinical data before and following data after starting intravenous iloprost in the 8 infants participating in the present study

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|---|---|---|---|---|---|---|---|---|
| **Time 0 (Pre-IVL)** | | | | | | | | |
| OI/SBP/HR | 8/70/148 | 29/79/166 | 8/74/146 | 11/67/180 | 18/63/150 | 44/91/172 | 65/61/171 | 16/80/148 |
| $PaO_2/SpO_2/FiO_2$ | 91/72/1.0 | 49/70/1.0 | 126/85/1.0 | 65/90/1.0 | 45/69/1.0 | 48/74/1.0 | 19/78/1.0 | 88/74/1.0 |
| DA/Epi | 20/NA | 12/NA | 20/1 | 20/1 | 20/0.1 | 10/1 | 20/NA | 17/NA |
| **Time 2 h** | | | | | | | | |
| OI/ SBP/HR | 14/74/160 | 5/86/134 | 24/69/163 | 14/68/170 | 23/76/168 | 40/85/167 | 29/64/179 | 4/77/180 |
| $PaO_2/SpO_2/FiO_2$ | 57/95/1.0 | 269/98/1.0 | 43/88/1.0 | 51/73/1.0 | 34/96/1.0 | 52/98/1.0 | 53/93/1.0 | 292/84/1.0 |
| DA/Epi | 20/0.1 | 15/NA | 20/1 | 20/1 | 20/1 | 20/1 | 20/0.8 | 20/NA |
| IVL | 2 | 2 | 3 | 4 | 6 | 2 | 3 | 2 |
| **Time 6 h** | | | | | | | | |
| OI/ SBP/HR | NA/80/141 | 4/71/148 | 5/76/174 | 25/89/175 | 7/84/166 | 75/84/162 | 54/82/179 | 10/112/180 |
| $PaO_2/SpO_2/FiO_2$ | NA/97/1.0 | 352/97/1.0 | 210/99/1.0 | 57/92/1.0 | 108/97/1.0 | 35/90/1.0 | 28/94/1.0 | 247/97/1.0 |
| DA/Epi | 20/0.1 | 15/NA | 10/1 | 20/1 | 20/1 | 20/1 | 20/0.9 | 20/NA |
| IVL | 2 | 2 | 3 | 4 | 7 | 6 | 3 | 3 |
| **Time 12 h** | | | | | | | | |
| OI/ SBP/HR | 10/74/160 | 5/81/125 | 13/81/168 | 33/104/170 | 10/84/154 | 48/70/163 | 50/78/166 | 7/73/156 |
| $PaO_2/SpO_2/FiO_2$ | 84/96/1.0 | 263/97/1.0 | 77/87/1.0 | 44/94/1.0 | 124/95/1.0 | 56/90/1.0 | 32/94/1.0 | 290/96/1.0 |
| DA/Epi | 20/0.1 | 15/NA | 20/1 | 20/1 | 20/1 | 20/1 | 20/1 | 20/0.3 |
| IVL | 2 | 2 | 3 | 4 | 7 | 6 | 3 | 4 |
| **Time 24 h** | | | | | | | | |
| OI/ SBP/HR | 15/70/149 | 6/64/134 | 5/70/153 | 5/89/186 | 4/88/124 | 38/74/151 | 50/78/163 | 5/73/160 |
| $PaO_2/SpO_2/FiO_2$ | 55/98/1.0 | 203/97/0.98 | 225/99/1.0 | 287/97/0.98 | 239/99/0.94 | 71/91/1.0 | 40/90/1.0 | 373/95/1.0 |
| DA/Epi | 20/0.2 | 15/NA | 20/1 | 20/1 | 20/1 | 20/1 | 20/1 | 20/0.5 |
| IVL | 3 | 2 | 4 | 4 | 7 | 6 | 6 | 4 |
| **Time 48 h** | | | | | | | | |
| OI/ SBP/HR | 3/94/166 | 8/85/126 | 18/115/155 | 14/65/140 | 27/105/160 | 21/79/136 | 49/66/164 | 19/82/154 |
| $PaO_2/SpO_2/FiO_2$ | 252/97/1.0 | 111/96/0.90 | 36/100/0.8 | 61/97/0.92 | 40/88/1.0 | 86/93/0.68 | 37/82/1.0 | 90/94/1.0 |
| DA/Epi | 20/0.3 | 20/NA | 20/1 | 20/1 | 20/1 | 20/1 | 20/1 | 20/0.7 |
| IVL | 5 | 2 | 3 | 4 | 7 | 2 | 6 | 4 |
| **Time 72 h** | | | | | | | | |
| OI/ SBP/HR | 8/97/187 | 3/52/146 | 8/86/154 | 12/86/173 | 4/67/198 | 18/70/168 | 6/68/153 | 13/79/168 |
| $PaO_2/SpO_2/FiO_2$ | 158/94/0.96 | 353/97/0.98 | 37/99/0.35 | 77/96/1.0 | 174/97/0.77 | 60/89/0.58 | 237/98/0.9 | 83/91/0.74 |
| DA/Epi | 20/0.8 | 20/NA | 20/1 | 20/1 | 20/1 | 20/0.4 | 20/1 | 20/0.7 |
| IVL | 5 | 2 | off | 4 | 7 | 2 | 6 | 4 |
| **Time 96 h** | | | | | | | | |
| OI/ SBP/HR | 35/106/168 | 5/72/134 | NA/95/132 | 4/70/174 | 3/66/164 | 10/74/126 | 37/84/177 | 4/51/164 |
| $PaO_2/SpO_2/FiO_2$ | 40/98/1.0 | 154/99/0.8 | NA/96/0.43 | 165/98/0.8 | 89/96/0.3 | 85/95/0.55 | 44/92/1.0 | 151/93/0.55 |
| DA/Epi | 20/1.5 | 20/NA | 20/0.1 | 20/1 | 20/1 | 19/Off/ | 20/1 | 20/0.6 |
| IVL | 5 | 2 | off | 4 | 4 | off | 6 | 4 |

OI = oxygen index, SBP = systolic blood pressure (mmHg), HR = heart rate (beat per minute), $PaO_2$ = arterial oxygen pressure (mmHg), $SpO_2$ = pre-ductal pulse oximetry oxygen saturation, (%) , $FiO_2$ = fraction of inspired oxygen, DA = dopamine (μg/kg/min), Epi = epinephrine ( g/kg/min), IVL = intravenous iloprost (ng/kg/min), h = hour, NA = not applicable

8, range: 3–18) ($p$ = 0.02), at 24 and 72 hours of treatment, respectively (**Figure 1A**). The average baseline preductal $SpO_2$ level was 77 ± 7%, which statistically significantly increased after the initiation of iloprost treatment at 6 hours (95 ± 3%) ($p$ = < 0.01), 12 hours (94 ± 3%) ($p$ = < 0.01), 24 hours (96 ± 3%) ($p$ = < 0.01), 48 hours (93 ± 6%) ($p$ = < 0.01), 72 hours (95 ± 4%) ($p$ = < 0.01), and 96 hours (96 ± 2%) ($p$ = < 0.01) (**Figure 1B**). There was not a statistically significant difference in preductal $SpO_2$ level at 2 hours after initiation of iloprost treatment, and no clinically significant changes in HR or SBP (**Figure 1C**) were noted during the iloprost therapy ($p$ = 0.17, and $p$ = 0.54, respectively, by Friedman test). Five infants were given dopamine and 3 infants were given epinephrine at maximum doses (20 µg/kg/min and 1 µg/kg/min, respectively), before iloprost administration. Dopamine and epinephrine were given at the maximum dosages in 3 and 4 infants, respectively, after iloprost administration. Only one infant was not given epinephrine during iloprost treatment. In the 8 surviving infants, the mean maximum dosage of iloprost was 5 ± 2 ng/kg/min (median: 5, range: 2–7), and the mean duration of iloprost treatment was 6 ± 3 days (median 6, range: 3–12).

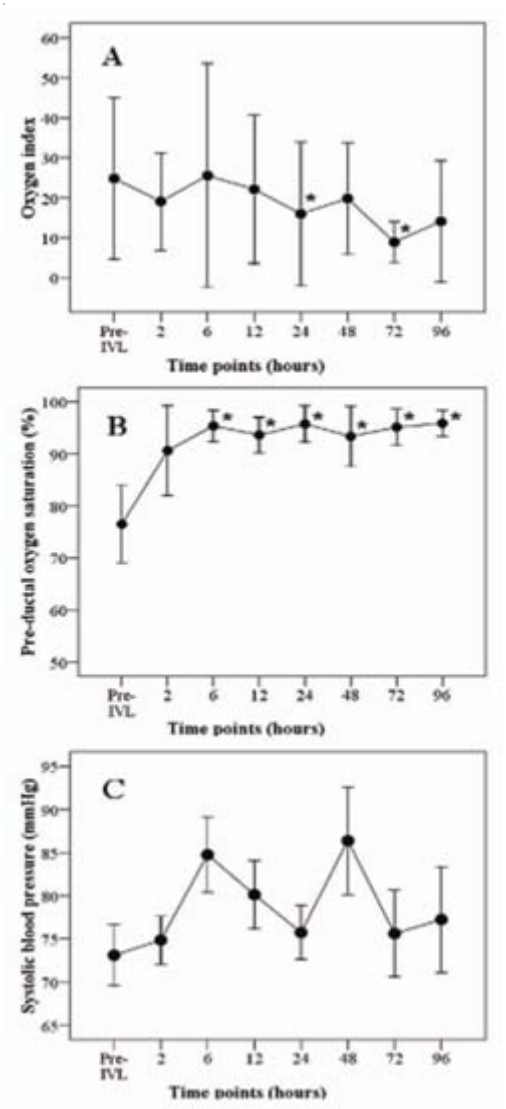


**Figure 1.** (**A**) Oxygen index, (**B**) preductal pulse oximetry oxygen saturation ($SpO_2$), and (**C**) systolic blood pressure saturation after intravenous iloprost (IVL) treatment. Data are presented as mean ± standard deviation. *$p$ < 0.05 vs. baseline.

At discharge, 6 of the infants were clinically normal, and 2 were complicated with cholestatic jaundice, which may have been caused by their feeding regimes of prolonged nothing-per-oral and intravenous parenteral nutrition. The direct/total bilirubin levels of these 2 infants were 3.0/15.0 (case 4) and 3.1/9.1 mg/dL (case 5), and both were treated with ursodeoxycholic acid until they were weaned from this at 4 months of age. There were no cases complicated with chronic lung disease, renal insufficiency, hearing loss, or heart disease. Cranial ultrasonographies and hearing tests were performed in all patients before discharge, with no abnormal findings. All study infants exhibited normal growth and developmental screening tests at follow-up visits at 6 months of age.

## Discussion

Persistent pulmonary hypertension of the newborn is a disease with a higher mortality rate in developing countries than in developed countries because of limited treatment options [2]. Various alternative treatments based on pulmonary vasodilators, including sildenafil, bosentan, and beraprost sodium, have been reported in the literature [3-6], but to date there have been no reports on the effectiveness of intravenous iloprost as an adjunctive therapy in PPHN. To our knowledge, this study is the first reporting documented beneficial effects of intravenous iloprost as an adjunctive therapy in PPHN infants in a hospital setting with limited resources and therapeutic options. The crude mortality rate of our historical control group was 50%, which was higher than the overall crude mortality rate of 20% for the iloprost group population, although because of the small number of patients in the study, the difference was not deemed statistically significant. Our study does, however, indicate that intravenous iloprost may be a useful adjunctive therapy in neonates with PPHN in situations with otherwise limited resources.

Iloprost is an effective therapy in adults and children with pulmonary arterial hypertension [7-9]. Its molecular structure is similar to prostacyclin and it works through prostacyclin receptors on the vascular smooth muscle cells [14, 15]. Epoprostenol, a chemically unstable analogue, is similar in function to prostacyclin. Epoprostenol is a potent vasodilator of the pulmonary vascular bed and inhibits platelet aggregation [15]. Epoprostenol is a relatively more stable compound than prostacyclin [16]. By comparison, iloprost has a longer half-life and is less costly than epoprostenol. Earlier studies established aerosolized iloprost as an effective treatment for PPHN because of its vasodilatation effects on the pulmonary vascular bed [10-13]. Because aerosolized administration directly delivers drugs to the lungs, and this mode of delivery is less likely to lead to systemic toxicities such as systemic hypotension, aerosolized iloprost has been used widely as an adjunctive therapy in PPHN infants. In our setting, we have tried aerosol iloprost, but with less favorable results than in the literature reports, as some of our infants had only shortened periods of improved oxygenation and some did not respond at all.

Recently, we reported a successful trial involving using an oral prostacyclin analogue (beraprost sodium) for treating PPHN [5]. We found that beraprost sodium improved oxygenation within 24 hours after administration and significantly reduced mortality. However, the use of oral forms of adjunctive drugs such as sildenafil, bosentan, or beraprost sodium in infant PPHN has been limited by the fact that newborns have a lower intestinal blood flow and thus limited intestinal absorption, which may lead to a delayed onset of action. Another study found that intravenous iloprost can be more potent than the aerosol route in relieving pulmonary vasoconstriction, and its efficacy could be continuously sustained on pulmonary vascular beds [7]. Also, the intravenous route is the administrative route of choice when it comes to emergency treatment for severe pulmonary vasoconstriction [17]. Therefore, we felt that intravenous iloprost may offer a new and improved treatment for PPHN in our setting with limited resources.

There are no recent studies on the pharmacokinetics of intravenous iloprost in neonatal populations, and we have only limited experience with establishing optimal dosing regimens for continuous intravenous iloprost in neonates, so the doses used in our patients were derived from adult patients with pulmonary arterial hypertension in previous studies at an initial dosage of 2 ng/kg/min, which was then increased stepwise after 10 to 15 minutes by 1 ng/kg/min until a positive clinical response with improved $SpO_2$ or until side-effects precluded further dose escalation [18]. In our practice, we used preductal $SpO_2$ as an indicator of when we should begin the intravenous iloprost. Following this guideline, 3 infants had $PaO_2$ of >80 mmHg before the beginning of iloprost administration,

while preductal $SpO_2$ was <90%. In the iloprost group, 8 responded to intravenous iloprost with OI and preductal $SpO_2$ significantly improved within 24 hours after beginning the high-dosage intravenous iloprost treatment, results which were similar to a report of Higenbottam et al. [18]. All 8 of our surviving infants were gradually weaned off the iloprost within 3–12 days with the mean period of receiving the maximum dosage of 5 days. Again, more detailed pharmacokinetic studies are needed to determine the optimal dosage of intravenous iloprost for newborn PPHN, and to examine the reasons a higher dosage is required in the neonatal population. However, the mechanism of action of intravenous iloprost is known to be through prostacyclin receptors present on the vascular smooth muscle cells and on the peripheral vessels [14-15]. Therefore, iloprost has a systemic vascular dilating effect, potentially resulting in systemic hypotension. In our study, most of our infants had needed an inotropic drug to maintain their blood pressure before iloprost administration. However, the increased dopamine and epinephrine given to maintain adequate blood pressure could be a risk factor indicator for an incidence of systemic hypotension, which could be an important side effect after iloprost treatment, although there was no significant decrease in blood pressure in our patients following this study. Another potential problem is that because of its antiplatelet effect, iloprost could increase the risk of intraventricular hemorrhage or bleeding [14], which could be a strong contraindication against using intravenous iloprost in certain patients. Other side effects have also been reported from iloprost use in adult patients, such as headache, diarrhea, and abdominal pain [16, 18].

There were several limitations to this study. First, the present study was a retrospective study with only a small number of patients, and thus lacked a control group to allow examination of any possible placebo effect. This is particular applies to the effects on hemodynamic measurements immediately after intravenous iloprost administration. A randomized controlled study is therefore needed to evaluate the efficacy of intravenous iloprost in PPHN. Second, in this study, the diagnosis of PPHN was not confirmed in all patients by echocardiography because of the limited availability of pediatric cardiologists at our hospital; only 2 of 10 infants had their diagnosis confirmed with echocardiography. However, we did confirm that the surviving cases did not have cyanotic heart disease as all had good oxygenation after their PPHN resolved and at their follow-up visits. Finally, this was a short term study involving only 8 patients, and longer-term survival studies are needed to more fully evaluate the therapeutic role of intravenous iloprost. However, these early data suggest that iloprost may be an effective long-term treatment (6 months) for PPHN.

In summary, we found that intravenous iloprost may be a useful adjunctive therapy in infants with PPHN, and thus may be particularly useful in the treatment of PPHN in countries with limited resources. The optimal dosing regimen of intravenous iloprost remains to be determined, and its therapeutic efficacy needs to be further evaluated in a larger study.

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