Paediatrica Indonesiana

VOLUME 52 January • 2012 NUMBER 1

Case Report

Inhaled iloprost as part of combination therapy for persistent pulmonary hypertension of the newborn

Heru Samudro,[1] Mulyadi M. Djer[2]

Persistent pulmonary hypertension of the newborn (PPHN) is rare, but life-threatening. If not treated, PPHN may cause respiratory failure and death in neonates.[1,2,3] PPHN often occurs in term or post-term infants with a history of difficult labor, infection or asphyxia during birth. These infants do not have adequate oxygen during labor.[3] Based on etiology, PPHN can be categorized into primary PPHN, which occurs by itself without apparent cause; or secondary PPHN, which is caused by meconium aspiration, hyaline membrane disease, neonatal sepsis with pneumonia, congenital heart abnormality, or maternal drug use (non-steroidal anti-inflammatories, methamphetamine, or selective serotonin reuptake inhibitors) during the third trimester of pregnancy.[2,4]

PPHN is defined as persistence of high pulmonary arterial pressure (P_{PA}) due to the inability of newborns' circulatory systems to adapt to breathing during birth. When a fetus is in utero, it obtains its oxygen from the maternal placenta through the umbilical cord, so the lungs need little blood supply. At that time, the blood pressure in the lungs is high, so blood in the pulmonary artery is sent to the lungs and other organs through a fetal blood vessel, the ductus arteriosus. When the baby takes its first breaths after birth, the lungs inflate and obtain oxygen, and pulmonary blood pressure falls to about 50% of the systemic arterial pressure. Oxygen and carbon dioxide are exchanged inside the lungs. Oxygenated blood then returns to the heart and is pumped to the body. Generally, the ductus arteriosus constricts and permanently closes in the first days of life. However, in babies with PPHN, pulmonary pressure remains high and the ductus arteriousus remains open, causing blood to flow back through the open ductus arteriosus towards the aorta, resembling the characteristics of fetal circulation (**Figure 1**). Ultimately, PPHN can cause life-threatening conditions such as hypoxia, cyanosis, and acidosis.[2,3,4]

In the past, the prognosis for PPHN was poor. However, with advanced medical progress we have a better understanding of biological characteristics of blood vessels and circulation in PPHN patients, and several drugs have been developed to treat the disease. Since the year 2000, there have been reliable clinical trials on the benefits of medical treatment on PPHN management, especially prostacycline and endothelin antagonists.[5,6]

Clinical presentations of PPHN include tachypnea, tachycardia, respiratory distress, and persistent bluish skin even after oxygen administration. On physical examination, grunting, retraction, cyanosis, and murmur are usually found.[2,3,5]

From the Department of Child Health, Christian University of Indonesia Medical School,[1] and University of Indonesia,[2] Jakarta, Indonesia.

Reprint requests to: Heru Samudro, Department of Child Health, Christian University of Indonesia Medical School, Jl . Let. Jend. Sutoyo, *Cawang,* Jakarta 13630 Indonesia. Email: *hsamudro@yahoo.com*

The diagnosis of PPHN is usually considered when there is hypoxemia with poor response to the administration of oxygen and positive pressure ventilation. A difference of arterial oxygen pressure (PaO_2) ≥ 15 mmHg or ≥ 10% between pre-ductal artery (right radialis artery on right thumb) and post-ductal artery (on tips of toes), measured by pulse oxymetry, indicates the presence of right to left shunting. Diagnosis may be confirmed by echocardiogram performed by a pediatric cardiologist.[3,4]

Treatment for PPHN includes conventional and extracorporeal membrane oxygenation (ECMO) therapy. Conventional treatment is performed initially by improving the underlying factors of PPHN, including administration of high concentration oxygen, treating low blood sugar level, and correcting metabolic and respiratory acidosis. In addition, infants with PPHN frequently have respiratory failure, necessitating intubation and mechanical ventilation. Also, PPHN requires administration of pulmonary vasodilator agents. Intravenous prostacycline, subcutaneous treprostinil, inhaled nitric oxide, inhaled iloprost, $MgSO_4$, oral beraprost and receptor antagonist (bosentan), as well as phosphodiesterase inhibitor (sildenafil), all show apparent benefits in patients with PPHN. Intravenous prostacycline and inhaled iloprost are potential treatments for PPHN. However, data regarding long-term effects of these medications should be further studied. A likely side effect of intravenous pulmonary vasodilator agents is hypotension. Both nitric oxide and inhaled iloprost are selective pulmonary vasodilators, which cause vasodilatation only in the pulmonary artery.

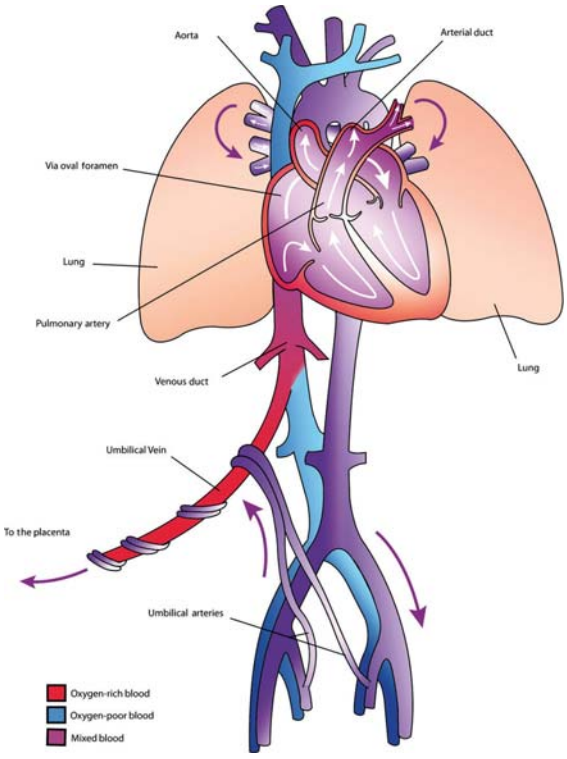

Figure 1. Right to left shunting due to PPHN results in neonates' circulation resembling fetal circulation

The other treatment, ECMO, requires surgical measures, and is only performed on PPHN cases which do not respond to conventional therapy.

This article reports the use of inhaled iloprost and oral sildenafil combination therapy as treatment for PPHN patients in the PICU/NICU at Mitra Keluarga Kelapa Gading Hospital. Inhaled iloprost has become a treatment alternative for pulmonary hypertension, especially in adults.[7-9] Several studies in Europe have shown that this drug is also beneficial for treating PPHN.[10-12] Iloprost is currently unavailable in the United States, but has been widely used in European countries.

Usually, the combination therapy of inhaled iloprost and oral sildenafil is used on PPHN cases which do not respond to conventional therapy (high frequency oscillation ventilation, inhaled nitric oxide, and sildenafil). Inhaled iloprost can restore the abnormal shunting into left to right shunting, thus offering significant oxygenation improvement.

The Case

First case

A male neonate was born on 22 September 2008 by Caesarean section due to fetal distress. The full-term baby had a birth weight of 2480 g and Apgar scores of 8 and 10. At 1 day of age, the patient was transferred from the regular infant ward to the perinatology ward due to cyanosis and tachypnea.

At 6 days old, the patients' general condition worsened, and he had respiratory failure. He was transferred to the NICU, intubated and put on ventilator support. Echocardiography by the pediatric

cardiologist showed pulmonary hypertension with P_{PA} of 50 mmHg. The patient was then treated with inhaled iloprost (8 x 2.5 μg) and oral sildenafil (3 x 0.75 mg). With this combination therapy, the patient showed improvement 11 day following drug administration, as demonstrated by a decrease in P_{PA} to 40 mmHg. At 25 days old (the 19th day of continued combination treatment), the infant's condition improved enough to allow extubation.

Echocardiography on day 20 of treatment showed a P_{PA} decrease to 30-40 mmHg, and on day 22 P_{PA} was 30-35 mmHg. The patient was subsequently discharged in good general condition.

Second case

A male neonate was born on 21 February 2009 by Caesarean section due to fetal distress. He was a term infant with birth weight of 3202 g and Apgar scores of 9 and 9. At 18 hours of age, the patient was transferred from the regular infant ward to the NICU due to cyanosis and tachypnea. Echocardiogram done by a pediatric cardiologist showed pulmonary hypertension, with P_{PA} of 60 mmHg and persistent ductus arteriosus. The patient was treated with inhaled iloprost (6 x 2.5 μg) and oral sildenafil (3 x 1 mg). The patient began to demonstrate improvement at 6 days old, with P_{PA} decreasing to 40-50 mmHg, and the persistent ductus arteriosus closed. At 8 days old, the P_{PA} decreased to 40 mmHg, and at 13 days old the P_{PA} was back to normal, i.e., 30 mmHg. The patient was discharged in good general condition.

Discussion

Inhaled iloprost is a synthetic prostacycline analog which can cause pulmonary artery vasodilatation and can affect platelet aggregation.[13,14]

Treatment of PPHN using inhaled nitric oxide (iNO) is expensive, while inhaled iloprost, sildenafil, and intravenous magnesium sulphate are more affordable, especially for patients in developing countries. However, intravenous magnesium sulphate can result in hypotension as a side effect. Inhaled iloprost has been used for PPHN treatment in Europe.[7] The use of this drug has been approved by the European Commission for the treatment of pulmonary hypertension in adults since 2003.[7,8,15,16]

Several studies on iloprost have been done in adults, but few studies have reported on its use in children and neonates.[10-12] This article is the first case report on the use of inhaled iloprost for PPHN treatment in Indonesian children.

Iloprost is a stable prostacycline analog which may cause a longer duration of vasodilatation.[17] If iloprost is administrated by aerosol to pulmonary hypertension patients, its vasodilatation potential resembles that of prostacycline, but with a longer effect of 30 to 90 minutes, compared to prostacycline's 15 minute effect.[9,18,19] One case in Thailand reported a patient's response to the drug to be within 30 minutes. Ten doses (15 μg) were required daily.[20] Due to its brief therapeutic effect, inhaled iloprost needs to be administered 6-12 times per day in order to maintain the desired clinical effect.[6] Mullen *et al*. recommended an inhaled iloprost dose of 2.5 μg, 6-8 times per day.[21]

In the Thai case, iloprost was given only after sildenafil treatment failed.[20] However, in both our patients, iloprost was given simultaneously with sildenafil, resulting in a good response. Moreover, the diagnosis of our second case was established earlier, thus the patient did not need mechanical ventilation. Our second case was consistent with that of Muller, who reported success with inhaled iloprost treatment for PPHN cases not needing mechanical ventilation.[22]

Combination therapy of iloprost and sildenafil may intensify the desired vasodilatation effect. In particular, it can prolong the response of pulmonary artery vasorelaxation.

We report the beneficial effect of inhaled iloprost for PPHN treatment. The conventionally accepted paradigm has been for PPHN patients to be immediately referred for maximum conventional treatment before performing ECMO.[1] However, our experience is that physicians have alternatives in treating PPHN patients, even if inhaled nitric oxide (iNO) is unavailable, such as in patients with mechanical ventilation. Iloprost is well-tolerated, economical, safe, and has been used extensively in Europe and Thailand. Moreover, earlier diagnosis of PPHN patients treated with inhaled iloprost and oral sildenafil have a better chance of not needing

mechanical ventilation. Further evaluation of iloprost through monitoring of P_{PA} improvement by way of echocardiography is recommended.

References

1. Mok O, Yates R, Tasker RC. Persistent pulmonary hypertension of the term neonate: a strategy for management. Eur J Pediatr. 1999;158:825-7.
2. Graves ED, Redmond CR, Arensman RM. Persistent pulmonary hypertension in the neonate. Chest. 1988;93: 638-41.
3. Kohnle D. Persistent pulmonary hypertension of the newborn (PPHN). EBSCO, Neonatology Children's Memorial Hospital July, 2008 [homepage on the Internet]. c2008. [cited 2011 July 5]; Available from: *http://www.empowher.com/media/reference/persistent-pulmonary hypertension-newborn.*
4. University of California Medical center. Persistent pulmonary hypertension of the newborn (PPHN). Intensive care nursery house staff manual [homepage on the Internet]. c2006 [cited 2009 May]. Available from: *http://www.ucsfhealth.org.*
5. Rashid A, Ivy D. Severe paediatric pulmonary hypertension: new management strategies. Arch Dis Child. 2005; 90:92-8.
6. Hoeper MM, Galie N, Simonneau G, Rubin LJ. New treatments for pulmonary arterial hypertension. Am J Respir Crit Care Med. 2002;165:1209-16.
7. Walmrath D, Schneider T, Pilch J, Grimminger F, Seeger W. Aerosolized prostacyclin in adult respiratory distress syndrome. Lancet. 1993;342:961-2.
8. Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, Haller M, et al. Inhaled prostacyclin (PGI2) versus inhaled nitric oxide in adult respiratory distress syndrome. Am J Respir Crit Care Med. 1996;154:1671-7.
9. Olscheski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respirat Crit Care Med. 1999;160:600-7.
10. Ehlen M, Wiebe B. Iloprost in persistent pulmonary hypertension of the newborn. Cardiol Young. 2003;13:361-3.
11. Lambert V, Serraf A, Durand P, Losay J. Aerosolized iloprost therapy in an infant with chronic pulmonary hypertension after a neonatal arterial switch operation. Arch Pediatr. 2001;8:1218-21.
12. Concheiro GA, Sousa RC, Suarez TB, Paradela CA, Ocampo CS, Antelo DJ. Inhaled iloprost: a therapeutic alternative for persistent pulmonary hypertension of the newborn. An Pediatr (Barc). 2005;63:175-6.
13. Dembinski R, Brackhahn W, Henzler D, Rott A, Bensberg R, Kuhlen R, et al. Cardiopulmonary effects of iloprost in experimental acute lung injury. Eur Resp J. 2005;25:81-7.
14. Tissières P, Nicod L, Argiroffo CB, Rimensberger PC, Beghetti M. Aerosolized iloprost as a bridge to lung transplantation in a patient with cystic fibrosis and pulmonary hypertension. Ann Thorac Surg. 2004;78:48-50.
15. Walmrath D, Scheneider T, Pilch J, Schermuly R, Grimminger F, Seeger W. Effects of aerosolized prostacyclin in severe pneumonia. Impact of fibrosis. Am J Respir Crit Care Med. 1995;151:724-30.
16. Walmrath D, Schneider T, Schermuly R, Olschewski H, Grimminger F, Seeger W. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. Am J Respir Crit Care Med. 1996;153:991-6.
17. Fitscha P, Tiso B, Krais T, Sinzinger H. Effect of iloprost on in vivo and in vitro platelet function in patients with peripheral vascular disease (PVD). Adv Prostaglandin Thromboxane Leukot Res. 1987;17A:450-4.
18. Hoeper MM, Olschewski H, Ghofrani HA, Wilkens H, Winkler J, Borst MM, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. J Am Coll Cardiol. 2000;35:176-82.
19. Gessler T, Schmehl T, Hoeper MM, Rose F, Ghofrani HA, Olschewski H, et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur Respir J. 2001;17:14-9.
20. Jaratwashirakul S. Inhaled iloprost for severe persistent pulmonary hypertension of the newborn. J Med Assoc Thai. 2007;90: 167-70.
21. Mullen PM, Wessel DL. Pharmacological treatment of pulmonary hypertension. In: Munoz R, Schmitt CG, Roth SJ, Cruz ED, editors. Handbook of pediatric cardiovascular drugs. London: Springer; 2008. p. 226-47.
22. Muller JC. Iloprost inhalation in early therapy of pediatric lung failure. Journal fur Anasthesie und Intensiv behandlung. 2007;7:150.