Paediatrica Indonesiana

VOLUME 51 July • 2011 NUMBER 4

Case Report

Inhaled prostacyclin for Eisenmenger syndrome complicated with miliary tuberculosis

Eva M. Marwali,[1] Novik Budiwardhana,[1] Anna U. Rahayoe[2]

Eisenmenger syndrome occurs in patients with large congenital cardiac or extracardiac left-to-right shunts. Clinically, Eisenmenger syndrome is characterized by multiple organ involvement and progressive deterioration of function over time. In the advanced stages, signs and symptoms of Eisenmenger syndrome include central cyanosis, dyspnea, fatigue, hemoptysis, syncope and right-sided heart failure. Survival of patients with Eisenmenger syndrome is generally poor, but appears to be better than that of patients with idiopathic pulmonary arterial hypertension (PAH) in a comparable functional class.[1]

The treatment strategy for patients with Eisenmenger syndrome is based mainly on empirical clinical experience rather than evidence-based medicine. The pathophysiology of pulmonary hypertension in patients with Eisenmenger syndrome is rather similar to that of idiopathic PAH. Both conditions are associated with neurohormonal imbalances of endogenous pulmonary vasodilators and vasoconstrictors. Therefore, in management of patients with Eisenmenger syndrome, the use of pulmonary vasodilating agents that have been proven to be beneficial for patients with IPAH is conceptually appealing. Long-term prostacyclin therapy improves hemodynamic features (decreased mean pulmonary artery pressure [PAP], improved cardiac index, and decreased pulmonary vascular resistance [PVR]) and quality of life in patients with congenital heart disease and PAH.[2,3,4] However, reports on the use of prostacyclin to treat acute pulmonary hypertension resulting from Eisenmenger syndrome in children are still rare. Inhaled nitric oxide (NO) was the common agent used for acute pulmonary hypertension in cardiac ICU settings. But this modality is expensive and requires specialized equipment. Inhaled prostacyclin was proposed to replace inhaled NO in treating acute pulmonary hypertension in the ICU. We present a case report on the effectiveness of inhaled prostacyclin to ameliorate acute deterioration in a patient with Eisenmenger syndrome complicated by miliary tuberculosis.

The Case

A 5-year-old boy, (weighing 16 kg) with a history of large ventricular septal defect (VSD) and Eisenmenger syndrome complicated by miliary tuberculosis, was admitted to the Cardiac Intensive Care Unit (CICU)

From the Division of Cardiac Critical Care Medicine, Department of Child Health, National Cardiovascular Center, Harapan Kita Hospital, Jakarta, Indonesia.[1] From the Division of Pediatric Cardiology, Department of Cardiology, National Cardiovascular Center, Harapan Kita Hospital, Jakarta, Indonesia.[2]

Reprint requests to: Eva M Marwali, MD, Division of Cardiac Critical Care Medicine, Department of Child Health, National Cardiovascular Center, Harapan Kita Hospital, Jakarta, Indonesia.
E-mail: *evamarwali@yahoo.com*

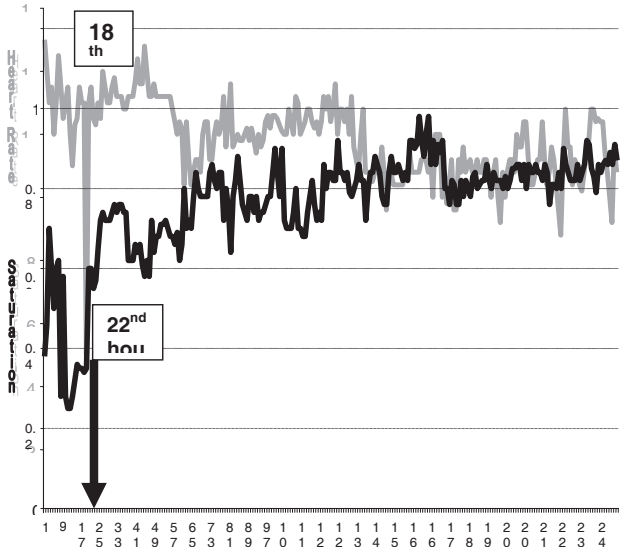

Figure 1. Heart rate and oxygen saturation.

of Harapan Kita National Cardiovascular Center, Jakarta. The patient presented with severe cyanosis and respiratory failure. He was diagnosed to have a large VSD at 2 years old. Echocardiogram showed large doubly committed subarterial VSD, right to left shunt with mild pulmonary regurgitation (PR), suggestive of pulmonary hypertension. Chest X Ray showed miliary spread of suspected pulmonary tuberculosis. Sildenafil 3 mg every 6 hours was given in the Intermediate Care Ward to treat the pulmonary hypertension, but after 4 days on sildenafil the patient deteriorated and required ventilatory support. Eighteen hours after admission to the CICU, a pulmonary hypertension crisis ensued, and cardiopulmonary resuscitation was performed for 35 minutes. Afterwards his hemodynamics improved and he was started on dobutamine 5 μg/kg/min and milrinone 0.375–0.5 μg/kg/min. Ventilation was controlled by vecuronium drip for 48 hours. Morphine infusion and intermittent midazolam were given for analgesia/sedation. Besides sildenafil, inhaled prostacyclin (Iloprost, Ventavis®) 2.5 μg every 3 hours was given for treatment of pulmonary hypertension. Iloprost was started 22 hours after admission. Iloprost 2.5 μg diluted in 2 ml 0.9% NaCl was administered through endotracheal tube (ETT) by jet nebulizer. Pulmonary tuberculosis was treated with a four-drug regimen of antituberculosis medications (INH, Rifampicin, Ethambutol and Pyrazinamide) and steroids.

After administering Iloprost, the patient's hemodynamics became stable. **Figure 1** shows increased oxygen saturation and stable heart rate.

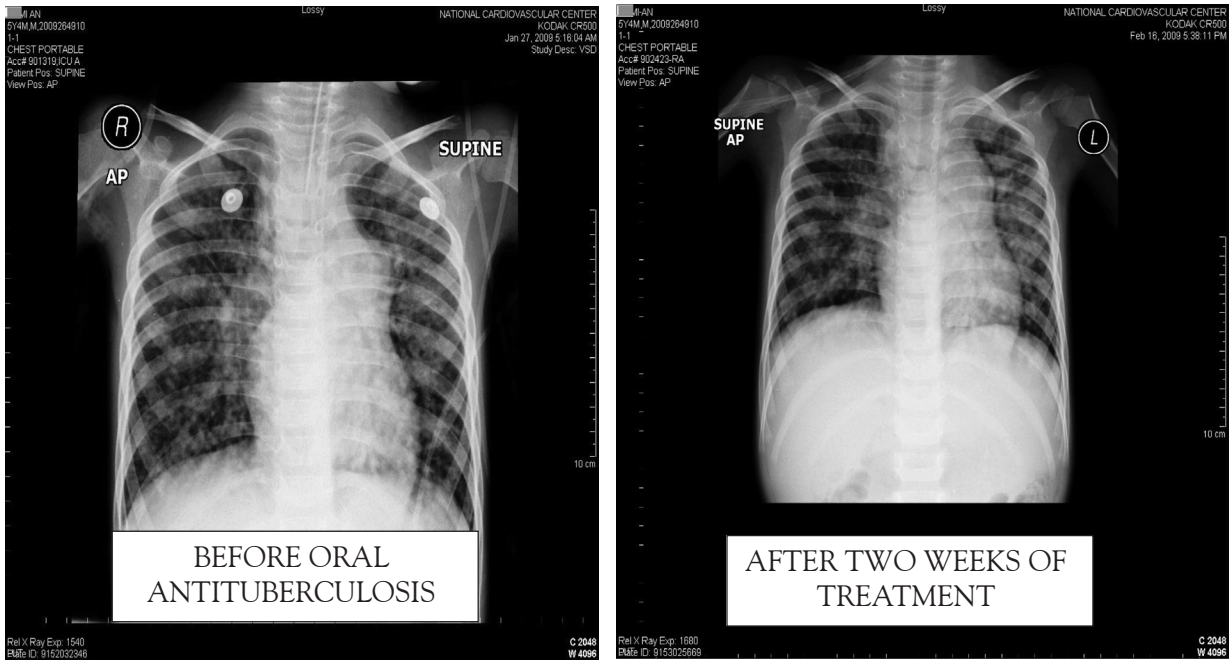

Figure 2. Chest X-ray before and two weeks after starting antituberculosis treatment showed improvement of miliary tuberculosis.

Table 1. Saturation, mean arterial pressure, mean airway pressure, oxygen index, ventilation index, $AaDO_2$, a/A PO_2 and echocardiography findings pre- and post- Iloprost commencement

Variable Mean (SD)	Pre-Iloprost	Post-Iloprost commencement			
		48 hours	96 hours	144 hours	192 hours
O_2 saturation, %	41.6 (14.6)	67.9 (8.1)	77.3 (5.9)	83.4 (5.7)	83.2 (4.3)
Mean arterial pressure, mmHg	69.8 (18.1)	78.6 (13.9)	81.8 (9.3)	78 (8.1)	86.5 (7.7)
Mean airway pressure	10.9 (2.5)	11.3 (1.1)	9.2 (0.6)	8.1 (0.1)	N/A
Oxygen index	37.2 (15.2)	32.0 (8.0)	15.5 (2.5)	9.9 (1.8)	N/A
Ventilation index	23.9 (5.1)	14.0 (3.1)	7.9 (2.8)	2.4 (0.6)	N/A
$AaDO_2$, mmHg	627 (15)	573 (87)	354 (61)	270 (26)	139 (69)
a/A PO_2, mmHg	0.04 (0.01)	0.05 (0.01)	0.1 (0.01)	0.14 (0.02	0.29 (0.05)
Echo: EF	67%	68 % (Echo 8 days after discharge from CICU)			
Mean PAP	35-40 mmHg	45-50 mmHg			

Table 1 indicates the changes in blood pressure, ventilation requirement and oxygenation before Iloprost and every 48 hours after commencement of Iloprost treatment. Pre-Iloprost blood pressure was 69.8 (SD 18.1) mmHg and increased to 86.5 (SD 7.7) mmHg after 192 hours of Iloprost treatment. Oxygenation was measured by oxygen index, arterial-alveolar oxygen difference ($AaDO_2$) and arterial-alveolar oxygen partial pressure ratio (a/A PO_2). The oxygen indices decreased from 37.2 (SD 15.2) pre-Iloprost to 9.9 (SD 1.8) after 144 hours post-Iloprost. The $AaDO_2$ decreased while the a/A PO_2 increased, indicating better oxygenation. The need for mechanical ventilation support, as well as mean airway pressure, oxygen and ventilation index decreased.

The patient was extubated on the 6th day after CICU admission and transferred to the Intermediate Care Ward after 10 days. Hemodynamically he was still supported with 5 micrograms/kg/min of dobutamine. Sildenafil and Iloprost every 3 hours were also continued for pulmonary hypertension. He was discharged from the CICU with SpO_2 of around 80% on 2 l/min nasal oxygen. Echocardiography performed 8 days after discharge from the CICU showed no change in EF (68%), but with a mean PA pressure of 45-50 mmHg. The chest X-ray showed improvement after 2 weeks of receiving oral antituberculosis medications. (**Figure 2**)

Discussion

Approximately 50% of infants with a large, nonrestrictive VSD or patent ductus arteriosus (PDA) develop pulmonary hypertension by early childhood. In this case report, the patient developed Eisenmenger syndrome at 5 years of age. His pulmonary hypertension worsened due to miliary tuberculosis. It is known that patients with pulmonary hypertension secondary to congenital heart disease are susceptible to potentially fatal pneumonia. Miliary tuberculosis in children is associated with decreased immune response, especially cellular immunity. However, we cannot conclude that pulmonary hypertension contributed to the development of miliary tuberculosis, as a correlation between miliary tuberculosis and Eisenmenger syndrome has not been reported.

Inhaled prostacycline (Iloprost) has been reported to be a successful treatment for adult chronic pulmonary hypertension. However, clinical experience with Iloprost in the pediatric population has been minimal. Three case reports documented inhaled Iloprost use in children with idiopathic PAH.[5,6,7] As evidenced in our case report, Iloprost ameliorated the acute attack of pulmonary hypertension. Inhaled NO is the most common agent used in the CICU to treat pulmonary hypertension crises. Rimensberger *et al.*[8] showed both inhaled nitric oxide (iNO) and Iloprost could significantly reduce the pulmonary-to-systemic vascular resistance ratio (Rp/Rs). In the iNO group, Rp/Rs decreased from 0.48 (SD 0.38) to 0.27 (SD 0.16), $P<0.001$, while in the Iloprost group Rp/Rs decreased from 0.49 (SD 0.38) to 0.26 (SD 0.11), $P<0.05$. Furthermore, they showed that combination therapy offered no further benefit over single drug therapy. Similarly, we observed a remarkable improvement after Iloprost treatment, without iNO. The oxygen and ventilation indices, as well as the $AaDO_2$ were

reduced after Iloprost treatment. In addition, the ratio of arterial to alveolar oxygen pressure remarkably increased. No adverse effects were observed during administration of this agent. The mean arterial pressure was even higher post-treatment compared to pre-treatment with Iloprost (pre 69.8 mmHg (SD 18.1) vs post 81.4 mmHg (SD 9.8)). This finding may be due to better cardiac function. Unfortunately, hemodynamic parameters such as CVP, PVR, and cardiac output could not be measured because of the lack of invasive monitoring and catheterization. Although echocardiography finding were largely unchanged before and after Iloprost, clinically the patient improved. We did not have echocardiography data when the patient's condition deteriorated in the ICU. However, the second study was performed after the patient was discharged from the ICU. As this patient has Eisenmenger syndrome, it was unlikely for him to have such significant decrease of pulmonary artery pressure in a very short time, unless there was improvement of his lung disease.

We used a dose of 25 ng/kg/minute for 10 minutes, maximal 2.5 μg for 10 minutes for inhaled Iloprost. Because of the patient's weight (16 kg), the calculated dose exceeded the maximal dose, 2.5 μg. As such, we used the maximal dose for 10 minutes. This dose was determined based on two hemodynamic trials by Rimensberger *et al*.[8] and Hallioglu *et al*.[9] Combination therapy has been reported to be effective for severe pulmonary hypertension. We used a combination of sildenafil and Iloprost to treat pulmonary hypertension. The treatment for miliary tuberculosis also likely had a major role for the long term recovery of this patient.

We suggest that inhaled prostacyclin (in combination with sildenafil) forms a powerful regimen to treat acute deterioration of pulmonary hypertension in Eisenmenger syndrome. Inhaled prostacyclin is less costly than NO and can be used in any center without the need for specialized equipment, as is required for NO. Further research regarding inhaled Iloprost for treatment of acute pulmonary hypertension cases is warranted.

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