INHALED ILOPROST TREATMENT OF PULMONARY ARTERIAL HYPERTENSION BEFORE AND AFTER THE SURGICAL REPAIR OF VENTRICULAR SEPTAL DEFECT IN CHILDREN

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is an important factor for morbidity and mortality in children with ventricular septal defect. Increased pulmonary blood flow can lead to progressive and serious structural changes in the vessel wall such as extensive intimal changes, adventitial fibrosis and loss of intraacinar arteries. Pulmonary hemodynamic parameters are used to decide whether surgical correction is indicated or not. There are limited data to define safe values considering surgical repair, but a threshold pulmonary vascular resistance of <6 Wood units after vasoreactivity testing is generally the consensus of opinion. Patients with values in the "grey zone" between 6–10 Wood units remain a particular challenge.

Prostacyclin is a pulmonary vasodilator and can be administered intravenously or via a nebuliser. Inhaled iloprost is a stable prostacyclin and can be used in children with PAH. The objective of this study was to evaluate the utility of iloprost in children with long-standing and severe PAH related to congenital heart disease at pre-post operative period.

METHODS

A prospective study was conducted between June 2008 and August 2011 among 17 children with long-standing and severe PAH secondary to congenital heart disease (15 children with VSD, 1 child with VSD-ASD, 1 child with PDA).
Various hemodynamic parameters (systolic, diastolic, and mean pulmonary and systemic arterial pressures) were measured before and after iloprost inhalation (0.5 µg/kg), and vascular resistance was determined. Responders to the iloprost test were defined as those with a decrease in both pulmonary vascular resistance (PVR) and pulmonary to systemic vascular resistance ratio (R(p)/R(s)) of > 10%.

All patients were treated by aerosolised iloprost during two weeks before surgery. After hospitalization all patients were switched to IV iloprost. Iloprost infused continuously with a portable infusion pump for two days before surgery. During iloprost therapy, echocardiographic measurements were performed routinely and the medical team decided if the patient was eligible for surgery at that moment.

All children continued to improve with IV iloprost treatment after surgery until pulmonary arterial pressure decreased less than half of systemic arterial pressure obtained from tricuspid regurgitation by echocardiography. Inhaled iloprost was discontinued when systolic pulmonary arterial pressure was ≤40 mm Hg from tricuspid regurgitation by echocardiography at follow up. First routine detailed echocardiography was performed at first month after surgery.

RESULTS

Baseline demographic and hemodynamic parameters before and after vasoreactivity test are summarized in Table 1. Median age at surgery was 4(1-17) years and 9 patients (%53) were male. At the catheterization laboratory, the baseline median PAP (MPAP), PVR, PVR/SVR were 63 (45-72) mmHg, 8.3 (6.2-11.2) WU, 0.41 (0.35-0.7) respectively. After iloprost vasoreactivity test median MPAP, PVR and PVR/SVR ratio significantly decreased to 52 (41-71) mmHg, 6.4 (5.8-10.4) WU, 0.28 (0.18-0.48) respectively (p<0.001). Pulmonary artery systolic pressure decreased to 75% of systemic arterial pressure in all patients after surgery. All the patients were administered inhaled iloprost after catheterization until the end of
surgery. Prior to surgery the median SPAP was 71 (59-89) mmHg. IV iloprost infusion continued median 4 day (2-8) in intensive care unit. Inhaler iloprost was continued median 3 months after surgery. Prior to surgery the median SPAP was 71 (59-89) mmHg and decreased significantly after surgery (p < 0.001) (Table 2). Four patients who had insignificant ASD or PFO remained opened.

Three patients suffered pulmonary hypertensive crisis (PHC) at postoperative 3th, 4th, 30th days. Pulmonary hypertensive crisis happened in recovery period from sedation in case 2 and case 3, hence sedation was continued in the following day. Case 2 and case 3, who responded to PHC treatment, had PVR/SVR ratio more than 0.3 after vasoreactivity test. One of them who did not respond to treatment had preoperative PAP: 55mmhg, PVR:7.8 WU/m², PVR/SVR: 0.39. He was discharged without any complications but died secondary to PHC due to bronchopneumonia at first month (case 11). Another patient was a 4 years old boy who had preoperative mean PAP: 72mmHg, PVR/SVR: 0.48 suffered pulmonary hypertensive crisis intraoperatively and died (case 4).

15 patients recovered well and discharged. Median follow up time was 17 (6-42) months. They didn’t have any cardiac and respiratory problems on follow-up.

After surgery median SPAP measured via tricuspid regurgitation by echocardiography was 39(28-51), 38(32-44) 35(28-40) mmHg respectively at first month, third month, last control, which decreased significantly (p<0.001).

**DISCUSSION**

Congenital heart defects with increased pulmonary blood flow or pulmonary venous congestion frequently lead to pulmonary hypertension (PH). Advances in treatment of PH during the past decade have markedly improved the survival of these patients. Children with suprasystemic PAH have increased risk of major perioperative complications, including
cardiac arrest and pulmonary hypertensive crisis. Early operation should be recommended to avoid pulmonary hypertension. PVR>7 WU and age over 5 years are considered as important risk factors for death on long term follow-up. Structural remodeling of small pulmonary arteries in PH is further accompanied by a reduced synthesis of prostacyclin. It is suggested PVR and PVR/SVR is more important than PAP on decision for corrective cardiac surgery. PVR index value of <6 WU/ m2 and PVR/SVR ratio <0.3 are widely accepted as a cut-off for operability in children with large let to right shunt.

Prostacyclin is a selective pulmonary vasodilator that can be administered via a nebulizer. Recently, iloprost, a stable carbacyclin derivative of prostacyclin with a favorable safety profile, has become established as a diagnostic tool comparable to inhaled nitric oxide for assessing the vasodilator capacity of pulmonary vessels in children with PH related to congenital heart disease. In our study; aerosolized iloprost therapy significantly reduced the pulmonary arterial pressure in patients suffering from PH before surgery of congenital heart defects. A significant reduction in pulmonary artery pressure after cardiac surgery was observed in patients with positive response to inhaled iloprost (especially PVR/SVR < 0.5). Inhaled iloprost is an important medicine for treatment PAH related to CHD, acute inhaled iloprost was as effective in selectively lowering pulmonary vascular resistance. Inhaled iloprost therapy during congenital heart surgery may influence mortality and morbidity in cases with left to right shunt and significant pulmonary hypertension. The prognosis for patients undergoing closure of large VSD with increased PVR is dependent on the age, degree of PVR and PVR/SVR. However, this is the report of a preliminary study in a small patient population. The result needs to be confirmed with larger well designed clinical trials and also long-term results should be followed.

**Key Words:** Pulmonary arterial hypertension, Iloprost, Congenital Heart Surgery