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Beraprost as initial pharmacologic treatment for pulmonary hypertension related to left to right shunt congenital heart disease.

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Abstract

Pulmonary arterial hypertension is a common complication of uncorrected left-to-right shunt congenital heart disease. Beraprost have been used widely to treat pulmonary arterial hypertension in adult. However, the efficacy of the drug in Indonesian children has not been investigated. This study aim is to evaluate the efficacy of Beraprost in treating pulmonary arterial hypertension related to left-to-right shunt congenital heart disease. A randomized control trial was used in this study between April to September 2017 in Cardiology outpatient clinic of Dr. Soetomo General Hospital. Subjects aged 2-12 years with pulmonary arterial hypertension randomly received Beraprost 0.35 mcg/kg eight hourly for 12 weeks. Efficacy was evaluated by echocardiography and adverse effect was monitored. Data were analysed by statistical software using t-test and Mann Whitney test with significance level set to 0.05. All procedures were approved by hospital ethics committee and registered at the ClinicalTrials.gov. Twenty two children were recruited into the study. Resolution of Beraprost in decreasing pulmonary arterial pressure was -21.32 ± 11.06 mmHg (p=0.034). Adverse effects reported were headache. As conclusion, Beraprost is effective and safe as initial pharmacologic treatment in treating pulmonary arterial hypertension related to left to right shunt congenital heart disease.

Keywords: Beraprost, Pulmonary arterial hypertension, Congenital heart defect, Left-to-right shunt.

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Introduction

Congenital Heart Disease (CHD), particularly uncorrected left-to-right shunt, frequently cause increase in Pulmonary Artery (PA) pressure and are a significant contributor to morbidity and mortality. In France, 4%-15% of patients with congenital heart disease may develop Pulmonary Arterial Hypertension (PAH) [1]. Reports from the Pediatric Outpatient Clinic of Dr. Soetomo General Hospital, Surabaya, Indonesia 2015 showed that 11% of children with an uncorrected left-to-right shunt CHD ultimately develop PAH [2].

The occurrence of PAH results in surgical impropriety and also influences the prognosis after surgery. Various new drugs of different classes have been used in patients with PAH, including phosphodiesterase inhibitors, endothelin receptor antagonists and prostacyclin agonists [3]. However, oral drugs available in Indonesia are limited to Sildenafil and Beraprost. Sildenafil has been used as a paediatric anti-PAH drug in America since 2000. Beraprost has been employed as a single therapy in adult PAH since 1996 and has proven to result in pulmonary vasodilatation [4,5].

According to a report from the Pediatric Outpatient Clinic of Dr. Sutomo General Hospital, patient compliance with Sildenafil therapy is only 60% owing to the high frequency of administration (four times daily) and high cost. Beraprost is an effective single-dose oral preparation and is administered three times daily; it is available at a lower cost than Sildenafil [6]. Till date, the efficacy of Beraprost as an anti-PAH in children has not been widely evaluated. This investigation examines the efficacy of Beraprost in lowering PA pressure in paediatric PAH associated with a left-to-right shunt congenital heart defect.

Methods

Study design

This study was a randomised controlled, single-blind group study. All procedures were reviewed and approved by the Hospital Ethical Committee no. 225/Panke.KKE/III/2017 and registered at the ClinicalTrials.gov with identifier number NCT03431649.

Patients

Inclusion criteria included children aged 1-14 years with PA pressure >45 mmHg, diagnosed with a congenital heart defect (Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD), Patent Ductus Arteriosus (PDA) or combination) who agreed to

participate in this study. Exclusion criteria were chromosome abnormalities, those suffering from chronic pulmonary disease and connective tissue disease, HIV infection and undergoing interferon therapy.

Study compounds

Products examined in this study were Beraprost (Dorner® tablet 20 mcg, Astellas), at a dose of 0.35 mcg/kg every 8 hours.

Randomisation and blinding

Randomisation was performed using a computer-generated randomised list. Blinding of the participants was not possible owing to the difference in treatment dosage. The doctor performing the evaluation was not involved in treatment allocation and remained blinded to the type of medication received by the participants.

Evaluation

Pulmonary arterial pressure was evaluated using non-invasive Doppler echocardiography performed by a paediatric cardiologist consultant; using the TR jet velocity and Bernoulli equation, with an assumed right atrium pressure of 6.7 mmHg. Heart rate, blood pressure and peripheral oxygen saturation were measured by physical examination. Adverse events were also recorded.

Statistical analysis

Differences in PA pressure were analysed using dependent t-test, whereas other parameters were assessed using Wilcoxon rank sum test and Mann–Whitney U-test. All tests were considered two-tailed with significance level set to 0.05.

Results and Discussion

In total, 22 children participated in this study. All the patients included in the analysis received oral Lisinopril of 0.1 mg/kg/day and Furosemide 1 mg/kg/day as standard therapy. The key novel finding of this investigation is that Beraprost caused a great decrease in PAP. This may be owing to Beraprost's function in inhibiting platelet aggregation mediated by cAMP, and its impact on vasoconstriction and chemotactic leukocytes (Table 1).

Variables	Beraprost			
	Pre-treatment	Post-treatment	p-value	Delta
Age (years)	6.07 ± 4.10			
Sex [N(%)]				
Male	6 (27.3)			
Female	16 (72.7)			
Body weight (Kg)	15.72 ± 8.23			
Defect types [N(%)]				
VSD	7 (31.8)			
ASD	7 (31.8)			
PDA	3 (13.6)			
VSD + ASD	3 (13.6)			
VSD + PDA	1 (4.5)			
ASD + PDA	0			
VSD+ASD +PDA	1 (4.5)			
Defect size				
Small	1 (4.5)			
Moderate	8 (36.4)			
Large	13 (59.1)			
PA pressure (mmHg)	80.45 ± 18.84	58.71 ± 17.56	< 0.001	-21.32 ± 11.06
Heart rate	106 (80-142)	103 (88-136)	0.001	-6 (-34 – 0)
Blood Pressure				
Systolic	100 (80-120)	99.5 (70-110)	0.017	0 (-15 - -10)
Diastolic	60 (50-80)	60 (40-70)	0.027	0 (-10 – 5)
SpO2 (%)	97 (91-98)	98 (93-99)	< 0.001	1 (0-4)
Adverse events: [N(%)]				
Blood pressure reduction	13 (59.1)			
Headache	1 (4.5)			
Dizzy				
Flushing				
Bleeding				
Allergic reaction				

Table 1. Efficacy of Beraprost in lowering PA pressure. ASD: Atrial Septal Defect; Kg: kilograms; PA: Pulmonary Artery; PDA: Patent Ductus Arteriosus; SpO2: Peripheral Oxygen Saturation; VSD: Ventricular Septal Defect.

Thrombotic lesions found in blood vessels indicate that platelet dysfunction is a potentially pathophysiological process that occurs in PAH. Beraprost activates adenylyl cyclase and increases cAMP levels.[7,8]

Limsuwan observed that oral intake of Beraprost in children with severe PAH related to CHD for 6 months resulted in substantial improvement in pulmonary hemodynamics and a reduction in the pulmonary-to-systemic vascular resistance ratio; however, it did not show a change in PAP or vascular resistance. Crucially, measurements of PAP in Limsuwan's investigation were obtained via a right-heart catheterisation technique, whereas this study used echocardiography with 88% sensitivity, 83% specificity, and 86% accuracy as a diagnostic tool for PAH [9]. Previous investigations have also reported

that Beraprost showed clinical improvement in the 6-Minute Walk Test (6-MWT) [6,10-12].

Subjects (63.64%) also experienced a decrease in systemic blood pressure that was not classified as hypotension or shock. Adverse reactions are usually mild or moderate, transient, and correlate with dosing [13,14]. To our knowledge, this investigation was the first RCT performed in Surabaya that evaluates the efficacy of Beraprost in decreasing PA pressures [15]. It must be acknowledged that the measurement of PAP in this study (e.g. echocardiography) is not considered the gold-standard assessment tool for the assessment or diagnosis of PAH. However, a right-heart catheterisation is not commonly used in our country owing to limited human resource and cost. Beraprost is a safe anti-PAH preparation to use in pediatric care.

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PAGE 1

PAGE 2

PAGE 3