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Impact of Phosphodiesterase-3 Inhibitor and Prostacyclin Analogue Combination on Pulmonary Hemodynamics in Acyanotic Congenital Heart Disease Patients with Pulmonary Hypertension: A Randomized Controlled Trial

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Abstract

Background: Acyanotic congenital heart disease (ACHD) with left-to-right shunting frequently presents with pulmonary hypertension, especially in developing countries where treatment options are often limited and costly. Cilostazol, a phosphodiesterase-3 inhibitor, has vasodilatory and inotropic effects, but its impact on pulmonary vascular resistance (PVR) and pulmonary blood flow (Qp) in this condition remains unclear. The aim of this study was to evaluate the effect of adding cilostazol to standard beraprost therapy on PVR and Qp in patients with ACHD complicated by pulmonary hypertension.
Methods and Results: This double-blind randomized controlled trial involved 40 subjects with ACHD and pulmonary hypertension. Participants were assigned to receive either cilostazol plus beraprost or placebo plus beraprost for three months.
In the cilostazol+beraprost group, PVR significantly decreased from 11.1±11.8 to 10.1±10.9 Wood units (P=0.001), while Qp showed no significant change (11.5±6.49 vs. 13.3±9.34 L/min; P=0.128). The beraprost-only group showed a smaller decrease in PVR (11.1±13.2 vs. 10.6±12.8 Wood units; P=0.006), but a significant increase in Qp (15.9±17.6 vs. 17.1±18.8 L/min; P=0.007). The E/e ratio for right ventricle diastolic function improved significantly only in the combination group.
Conclusion: Adding cilostazol to beraprost reduces pulmonary artery pressure without significantly increasing pulmonary blood flow, possibly by improving right ventricular diastolic function in ACHD patients with pulmonary hypertension.**(International Journal of Biomedicine. 2025;15(2):273-278.)**

Keywords: congenital heart disease • pulmonary hypertension • phosphodiesterase inhibitor • prostacyclin analogue

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Abbreviations

6MWT, 6-minute walk test; **ACHD**, acyanotic congenital heart disease; **ASD**, atrial septal defect; **BPS**, beraprost; **CLZ**, cilostazol; **DBP**, diastolic blood pressure; **HR**, heart rate; **LVOT**, left ventricular outflow tract; **PA**, pulmonary artery; **aPTT**, activated prothrombin time; **mPAP**, mean pulmonary artery pressure; **PDA**, patent ductus arteriosus; **PASP**, pulmonary artery systolic pressure; **PH**, pulmonary hypertension; **PVD**, pulmonary vascular disease; **PVR**, pulmonary vascular resistance; **PVRi**, pulmonary vascular resistance index; **Qp**, pulmonary blood flow; **RVOT**, right ventricular outflow tract; **SVR**, systemic vascular resistance; **SBP**, systolic blood pressure; **VSD**, ventricular septal defect.

Introduction

Uncorrected congenital heart disease with left-to-right shunting can progressively lead to pulmonary hypertension (PH) and, ultimately, pulmonary vascular disease (PVD).[1,2] The persistent increase in pulmonary blood flow induces structural remodeling of the pulmonary vasculature and sustained activation of vasoactive mediators, resulting in progressive vasoconstriction. As pulmonary vascular resistance (PVR) rises and eventually exceeds systemic vascular resistance (SVR), the shunt may reverse to a right-to-left direction, leading to systemic desaturation and clinical cyanosis.[3] At this advanced stage, surgical closure of the defect becomes contraindicated.

The "treat-and-repair" strategy has gained increasing attention.[4,5] This approach involves administering pulmonary vasodilators to reduce PVR before defect closure. Patients demonstrating a favorable hemodynamic response are considered for surgery, with studies showing improved long-term outcomes compared to those who remain uncorrected.

In low- and middle-income countries, such as Indonesia, a significant number of patients with acyanotic congenital heart disease (ACHD) present at a late stage with established PH.[6] Data from a single-center registry in Indonesia reported that 66.9% of congenital heart disease patients presented with concurrent PH.[7] However, access to pulmonary vasodilator therapies remains limited. Available agents are often costly and not fully covered by national health insurance schemes.

Cilostazol (CLZ), a phosphodiesterase-3 (PDE-3) inhibitor with vasodilatory and inotropic properties, has been shown in prior studies to reduce pulmonary artery pressure.[8-10] However, its effect on PVR, particularly when added to standard therapy such as beraprost (BPS), remains unclear in the context of congenital heart disease-associated pulmonary hypertension.

The objective of this study was to evaluate the effect of adding cilostazol to standard beraprost therapy on pulmonary vascular resistance and pulmonary blood flow in patients with ACHD complicated by pulmonary hypertension.

Methods

Study Design

This research was conducted as a randomized, double-blind, placebo-controlled trial employing a pre/post test design to assess the impact of adding cilostazol to standard BPS therapy in ACHD patients with left-to-right shunting complicated by pulmonary hypertension. The double-blind methodology ensured that participants and investigators were unaware of group assignments, reducing potential bias. Randomization was utilized to distribute confounding variables evenly across the treatment groups. The intervention spanned three months, providing adequate duration to evaluate changes in PVR and blood flow. This study was conducted at Dr. Kariadi Central General Hospital in Semarang, Indonesia.

Participants

The study population consisted of patients diagnosed with ACHD with left-to-right shunting complicated by PH, confirmed via right heart catheterization (RHC) with a mean pulmonary artery pressure (mPAP) exceeding 20 mmHg. Patients were excluded if they exhibited PVR greater than SVR, were taking medications such as ketoconazole, omeprazole, or erythromycin, or had comorbid conditions, including chronic obstructive pulmonary disease, connective tissue disorders, genetic abnormalities, obstruction of the LVOT or RVOT, or active bleeding.

Study Procedure

All subjects provided written informed consent before enrollment and were randomly assigned to two groups: CLZ + BPS or BPS + placebo. Each participant received an identity number to maintain the blinding of researchers regarding group allocation. Echocardiography examinations were performed at baseline and after 3 months to assess outcomes.

Intervention

The treatment group received CLZ 100 mg twice daily in addition to standard BPS therapy for three months. The control group received a placebo alongside BPS therapy for the same duration.

Statistical Analysis

Data were analyzed using GraphPad Prism v. 10. Baseline characteristics were summarized as frequencies and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. Paired t-tests or Wilcoxon signed-rank tests were applied as appropriate to evaluate differences between pre- and post-intervention measurements within the same group. Statistical significance was defined as a *P*-value of 0.05 or less.

Results

A total of 40 patients were enrolled and randomly assigned to two groups: 20 patients received a combination therapy of CLZ and BPS, while the remaining 20 were treated with BPS alone. The baseline characteristics of both groups are detailed in Table 1.

Most participants were female, with ages spanning from their twenties to fifties. Atrial septal defect (ASD) was identified as the most common form of congenital heart disease among the cohort. At baseline during right heart catheterization, mPAP ranged between 51 and 55 mmHg, accompanied by a mean PVR ranging from 4.9 to 6.12 Wood units. The average descending aortic oxygen saturation was recorded at 93%. No statistically significant differences in baseline parameters were observed between the two groups.

Echocardiographic assessments conducted on the same day as catheterization and repeated three months post-intervention revealed that both treatment arms experienced a significant decrease in PVR (Table 2).

Pulmonary blood flow (Qp) remained stable in the combination therapy group; however, a notable increase was detected in patients receiving only beraprost (Table 3).

Table 1.

Baseline characteristics of the study subjects.

Variables	BPS + CLZ (n=20)	BPS + placebo (n=20)	*P*-value
Age, years	34.0 (24.5-50.0)	30.0 (21.3-39.3)	0.285
Gender, n(%)			
Male	2(10)	4(20)	0.661
Female	18(90)	16(80)	
Sildenafil medication, n(%)			
Yes	9(45	11(55)	0.527
No	11(55)	9(45)	
Body weight, kg	44.5(38.3-55)	43.5(38.3-55.8)	0.931
Body height, cm	155(149-160)	155(151-160)	0.577
Body mass index, kg/m^2	17.7(16.7-22.7)	19.2(15.8-23.1)	0.920
Body surface area, m^2	1.42 ± 0.176	1.43 ± 0.188	0.816
WHO functional class (n)			
Class 1	3	1	>0.999
Class 2	12	14	
Class 3	5	5	
Class 4	0	0	
6MWT, m	270 ± 60.3	267 ± 49.8	0.845
SBP, mmHg	108 ± 13.8	106 ± 14.1	0.622
DBP, mmHg	69.4 ± 12.2	65.5 ± 11	0.296
HR, bpm	84.9 ± 11.5	86.4 ± 12.4	0.684
Regularity of HR			
Regular	19	18	>0.999
Irregular	1	2	
ACHD type (n)			
ASD	15	14	>0.999
VSD	3	3	
PDA	2	3	

Abbreviations: 6MWT, 6-minute walk test; ACHD, acyanotic congenital heart disease; ASD, atrial septal defect; BPS, beraprost; CLZ, cilostazol; DBP, diastolic blood pressure; HR, heart rate; PDA, patent ductus arteriosus; SBP, systolic blood pressure; VSD, ventricular septal defect.

Evaluation of right ventricular function demonstrated a significant reduction in RV E/e′ ratio after three months within the combination group, suggesting an improvement in diastolic function. Conversely, no meaningful change was noted for this parameter among those treated solely with beraprost (Table 4).

Table 1 (continued).

Baseline characteristics of the study subjects.

Variables	BPS + CLZ (n=20)	BPS + placebo (n=20)	*P*-value
Right heart catheterization			
mPAP, mmHg	51 ±2 1.2	55.2 ± 26	0.374
PASP, mmHg	81.4 ± 31.2	85.1 ± 38.7	0.354
PVR, Wood units	6.12(1.06-46.8)	4.91(0.29-46)	0.799
PVRi	4.41(0.1-40.8)	3.58(0.19-32)	0.862
PVR/SVR	0.16(0.01-1.09)	0.145(0.01-1.59)	0.941
Flow ratio (FR)	2.66 ± 1.55	2.31 ± 1.07	0.117
PA saturation, %	83.6(67.1- 89.9)	81(67.1-91.1)	0.774
Aorta saturation, %	93.3 ± 3.22	93.6 ± 3.18	0.829
Mixed Vein, %	65.2 ± 6.46	64.2 ± 6.15	0.615
Hemoglobin, g/dL	13.7 ± 2.66	14.3 ± 1.48	0.384
Hematocrite, %	43.1 ± 6.57	43.7 ± 5.02	0.725
Creatinine, mg/dL	0.861 ± 0.192	0.890 ± 0.175	0.621
Actual aPTT, sec	30.6 ± 2.64	32.0 ± 3.78	0.180
Control aPTT, sec	30.6(29.9-31.3)	31.2(30.1-32.1)	0.185

Abbreviations: BPS, beraprost; CLZ, cilostazol; aPTT, activated prothrombin time; mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; SVR, systemic vascular resistance; PA, pulmonary artery;

Table 2 .

PVR pre- and post-intervention.

PVR, Wood units				
	Baseline	After 3 months	Delta	*P*-value
BPS+CLZ	11.1 ± 11.8	10.1 ± 10.9	-1.05 ± 1.48	0.001$^{\gamma}$
BPS	11.1 ± 13.2	10.5 ± 12.4	-0.655 ± 1.02	0.003$^{\gamma}$
Delta				0.372$^{\chi}$
$^{\gamma}$ *Wilcoxon test;* $^{\chi}$ *Mann Whitney test*				

Table 3.

Qp pre- and post-intervention.

Qp, L/min				
	Baseline	After 3 months	Delta	*P*-value
BPS+CLZ	11.50 ± 6.49	13.30 ± 9.34	1.76 ± 2.84	0.128$^{\delta}$
BPS	15.90 ± 17.60	18.70 ± 23.30	2.84 ± 6.77	<0.001$^{\gamma}$
Delta				0.337$^{\chi}$
$^{\delta}$ *Paired t-test;* $^{\gamma}$*Wilcoxon test;* $^{\chi}$ *Mann-Whitney test*				

Table 4.

RV E/e' ratio pre- and post-intervention.

E/e' ratio				
	Baseline	After 3 months	Delta	*P*-value
BPS+CLZ	7.84 ± 3.21	6.79 ± 2.30	-1.06 ± 2.24	0.048[δ]
BPS	7.87 ± 3.31	6.73 ± 4.19	-1.15 ± 5.77	0.199[γ]
Delta				0.792[φ]
[γ] Wilcoxon test; [δ] Paired t-test; [φ] Unpaired t-test				

Throughout the study duration, adverse events were monitored monthly. Minor side effects such as headaches and palpitations occurred comparably across both groups without statistically significant differences. Importantly, all participants completed the study without discontinuing their assigned therapies (Table 5).

Table 5.

Profile of adverse symptoms reported in each treatment group.

Symptoms	BPS + CLZ (n)	BPS + placebo (n)	*P*-value
Cephalgia	12	6	0,.61
Palpitation	8	8	
Nausea	1	1	
Vertigo	0	1	

Discussion

The average age of subjects with ACHD and PH in this study was 30 years, with a predominance of female patients, most of whom had atrial septal defects. This demographic profile is consistent with data from the COHARD-PH registry in Indonesia.[11] Subjects were randomized into two groups with no significant differences in baseline characteristics, ensuring comparability of outcomes. The mean systolic pulmonary artery pressure (sPAP) was 107.85±13.84 mmHg, while the mean pulmonary artery pressure (mPAP) was 55±26 mmHg. Baseline pulmonary vascular resistance ranged widely, from 0.29 to 46.8 Wood units. A subset of patients were on surgical waitlists, while others had been undergoing medical therapy for at least one year before repeat right heart catheterization.

The "treat-and-repair" strategy, in which patients undergo pulmonary vasodilator therapy before defect closure, has been associated with improved outcomes compared with persistent uncorrected lesions.[2,12,13] However, in Indonesia and similar settings, access to pulmonary vasodilators remains a major barrier due to limited availability and lack of insurance coverage.

Cilostazol, a PDE3 inhibitor, induces vasodilation by elevating intracellular cyclic adenosine monophosphate (cAMP) concentrations. This elevation in cAMP leads to the inhibition of myosin light chain kinase (MLCK), an essential enzyme in forming actin-myosin cross-bridges.[14,15] This study demonstrated a reduction in pulmonary vascular resistance in both treatment groups; however, the decrease was more pronounced in the combination therapy group (cilostazol plus beraprost) than in the beraprost-only group. These findings suggest a synergistic effect of the dual mechanism of phosphodiesterase-3 (PDE-3) inhibition and prostacyclin receptor activation, both of which amplify cAMP-mediated pulmonary vasodilation.[16] This aligns with previous meta-analyses showing that combination therapy provides superior hemodynamic outcomes compared to monotherapy.[17,18,19]

Pulmonary vascular resistance continues to be a crucial factor in assessing patient eligibility for defect closure. As the 2020 ESC Guidelines for the management of adult congenital heart disease outlined,[20] patients with a pulmonary vascular resistance less than 5 Wood units and a pulmonary-to-systemic flow ratio (Qp/Qs) greater than 1.5 are deemed appropriate candidates for surgical intervention. Patients with higher pulmonary vascular resistance may still be candidates if their resistance decreases adequately following targeted medical therapy, with fenestrated closure as an option.[20,21,22]

Pulmonary blood flow (Qp) increased significantly in the beraprost-only group but not in the combination group. Although both groups had uncorrected congenital heart disease and persistent left-to-right shunting, which maintains a state of volume and pressure overload in the pulmonary vasculature, only the combination therapy group showed significant improvement in right ventricular (RV) diastolic function, as reflected by a reduction in the RV E/e′ ratio. This may reflect enhanced right ventricular compliance under the influence of cilostazol. These findings are consistent with prior studies, including one by Aaid et al.,[9] which demonstrated improved left ventricular diastolic function following short-term cilostazol therapy.

Notably, this study did not follow patients through to surgical correction, and thus, the long-term outcomes of a treat-and-repair strategy could not be assessed. In addition, patients with Eisenmenger syndrome were excluded, although they may represent a subgroup with substantial potential benefit from PVR-lowering interventions.

In patients with ACHD and pulmonary hypertension, the combination of cilostazol and beraprost significantly reduced pulmonary vascular resistance without a corresponding increase in pulmonary blood flow. This favorable hemodynamic response may be partially attributed to improved right ventricular diastolic function, suggesting enhanced right ventricular compliance. These findings support the potential role of cilostazol as an adjunct to standard pulmonary vasodilator therapy in optimizing preoperative management and candidacy for defect closure in resource-limited settings.

Ethical Considerations

This study was reviewed and approved by the Ethics Commission for Health Research at the Faculty of Medicine, Diponegoro University (No. 994/EC/KEPK-RSDK/2022). All participants signed written informed consent prior to inclusion in accordance with ethical standards protecting human subjects.

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Competing Interests

The authors declare that they have no competing interests.

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