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Original Article

Sildenafil for pulmonary hypertension due to left-to-right shunt after corrective procedure

Dyahris Kuntartiwi[1], Piprim B. Yanuarso[2], Sudigdo Sastroasmoro[2]

Abstract

Background Pulmonary arterial hypertension (PAH) is a common complication seen in those with a left-to-right shunt congenital heart defect (CHD). Corrective procedures by surgery or catheterization are the therapies of choice for reversible PAH. Since morbidity and mortality due to PAH after correction is high, sildenafil has been used as a selective vasodilator of the pulmonary artery, in order to decrease pulmonary arterial pressure.

Objectives To evaluate the effect of sildenafil on pulmonary arterial pressure and clinical outcomes after left-to-right shunt CHD corrective procedures.

Methods Left-to-right shunt patients aged < 18 years scheduled for corrective treatment were randomized in a double-blind fashion, to receive either oral sildenafil or placebo, given on days 3 to 30 after the corrective procedure. Clinical and pulmonary arterial pressures were evaluated by echocardiography before, 3 days after, and 30 days after the corrective procedure.

Results From July 2013 to June 2014, 36 patients were included in the study: 17 in the placebo and 19 in the sildenafil groups. There were no differences in pulmonary arterial pressure or in clinical outcomes after corrective procedure between the two groups. There were no adverse events during the treatment.

Conclusion Sildenafil has little effect on decreasing pulmonary arterial pressure, as most of our subjects seem to have hyperkinetic PAH. As such, pulmonary arterial pressure returns to normal soon after corrective procedures. **[Paediatr Indones. 2015;55:257-62]**.

Keywords: *pulmonary arterial hypertension, left-to-right CHD, corrective procedure, sildenafil*

Pulmonary hypertension, also known as pulmonary arterial hypertension (PAH), is a common complication in those with left-to-right shunt congenital heart disease (CHD). In children, 50% of PAH cases are caused by CHD, especially due to large left-to-right shunts.[1,2] The PAH is defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest, pulmonary capillary wedge pressure ≥ 15 mm Hg, and pulmonary vascular resistance index (PVRI) ≥ 3 Wood units, as confirmed by right heart catheterization at baseline.[3]

Corrective procedures by surgery or catheterization are the therapies of choice for reversible PAH. Since morbidity and mortality due to PAH after correction is high, many recent studies have been done on the pathology and pathobiology of PAH, as well as the introduction of vasodilator therapy. Sildenafil, a phosphodiesterase type 5 inhibitor, increases the accumulation of cyclic guanosine monophosphate (cGMP) through the nitric oxide (NO) pathway. As a selective vasodilator, sildenafil has been used broadly and proven effective for the adult population, but studies have been limited on its tolerability, efficacy,

From the Department of Child Health, Brawijaya University Medical School/Dr. Saiful Anwar Hospital, Malang, East Java[1] and University of Indonesia/Dr. Cipto Mangunkusumo Hospital, Jakarta[2], Indonesia.

Reprint requests to: Dyahris Koentartiwi, Dr. Saiful Anwar General Hospital, Jl. Jaksa Agung Suprapto 2, Malang, East Java. Tel/fax: +62341.332440/+62341.332440. Email : risty.kuntartiwi@gmail.com.

and safety for pediatric PH.[4] Our aim was to evaluate the effect of sildenafil on pulmonary arterial pressure and clinical outcomes after left-to-right shunt CHD corrective procedures.

Methods

We conducted a double-blind, randomized, placebo-controlled trial from July 2013 to June 2014 at Integrated Cardiovascular Unit, Dr. Cipto Mangunkusumo Hospital, Jakarta. Randomization was done by block permutation. Subjects in the placebo group received oral saccharum lactis, while those in sildenafil group received oral sildenafil at doses based on body weight (**Table 1**), for 30 days after the corrective procedures were performed.

Table 1. Sildenafil dosage based on body weight

Body weight	Oral sildenafil dose, 3x daily
≤8 kg	5 mg
8 to ≤20 kg	10 mg
> 20 to 45 kg	20 mg
≥45 kg	40 mg

We included pulmonary hypertension patients due to left-to-right shunt, aged < 18 years who were scheduled for corrective procedures by transcatheter intervention or surgery. Written informed consent was obtained from subjects' parents or guardians. Subjects received either oral sildenafil or placebo, given from days 3 to 30 after the corrective procedure was performed. We excluded patients with suspected syndrome or pulmonary stenosis patients. Pulmonary hypertension criteria by echocardiography were defined to be pulmonary artery systolic pressure (PASP) ≥ 25 mm Hg and/or maximal velocity tricuspid regurgitation (Vmax TR) ≥ 2.8 m/second.[5] We performed echocardiography measurements to estimate PASP by measuring the inferior vena cavae (IVC) diameter to approximate right atrial pressure (RAP) using M-mode at a subcostal view, and color Doppler-mode at the tricuspid valve in an apical four-chamber view to measure the regurgitated tricuspid jet as Vmax TR. We used the following formula to estimate PASP: PASP = 4 $(Vmax_{TR})^2$ + RAP. We also measured other hemodynamic parameters such as cardiac index (CI), transannular plane systolic excursion (TAPSE), diastolic function (E/A ratio), and left ventricular ejection fraction (LVEF). In addition, we assessed post-operative clinical outcomes. Echocardiography was performed by our pediatric cardiologist at Integrated Cardiovascular Unit Dr. Cipto Mangunkusumo Hospital. This study was approved by the Ethics Research Committee of the University of Indonesia Medical School/Dr. Cipto Mangunkusumo Hospital, Jakarta.

The primary outcomes were pulmonary artery systolic pressure (PASP) after corrective procedure (day 3) and PASP after oral sildenafil (day 30). The secondary outcomes were hemodynamic parameters (CI, TAPSE, E/A ratio, and LVEF). Length of stay in the intensive care unit (ICU), length of ventilator use, and length of hospital stay were also recorded.

We used independent T-test for normally distributed numerical data, otherwise, we used Mann-Whitney test. A P value < 0.05 was considered to be statistically significant. Statistical analysis was performed using *SPSS 15* software.

Results

This study was performed from July 2013 to June 2014. One patient was excluded because she died after catheterization. Eleven patients underwent interventional catheterization, resulting in complete closure in 10 patients, and residual patent ductus arteriosus (PDA) in 1 patient. Of the 25 patients who underwent surgery, only one patient had residual PDA. The placebo group had 17 subjects and the sildenafil group had 19 subjects.

We performed history-taking, as well as physical and echocardiographic examinations, before and after the corrective procedure, as well as 30 days after treatment. Baseline data on the characteristics of subjects can be found in **Table 2**, which also shows no significant differences in echocardiography results between the placebo and sildenafil groups before the corrective procedures.

In this study, we found decreased PASP and Vmax TR after corrective procedure and after treatment for 30 days in both groups of subjects. However, there were no significant differences in Vmax TR, PASP, or PASP/sBP between the placebo and sildenafil groups (**Table 3**).

Table 2. Characteristics of subjects before corrective procedure

Characteristics	Placebo (n=17)	Sildenafil (n=19)
Median age (range), years	6 (2 months-17 years)	4 (6 months-8 years)
Median body weight (range), kg	13 (5.4 – 36)	11.5 (5 – 36)
Gender, n		
Male	8	7
Female	9	12
Functional class, n		
I	2	5
II	13	11
III	1	3
IV	1	0
Type of left-to-right shunt, n		
VSD	8	6
ASD	1	7
PDA	8	4
Combination	0	2
Corrective procedure, n		
Interventional catheterization	6	5
Surgery	11	14
Flow ration, n	9	6
Echocardiographic measurements		
Median Vmax TR (range), m/second	3.3 (2.8-5.5)	3.5 (3-4.2)
Median PASP (range), mmHg	53.5 (41.4-131)	59 (46-80.6)
Median PASP/sBP (range)	0.5 (0.4-1.3)	0.6 (0.5-0.9)
Median CI (range), L/minutes/m^2	5.6 (2.3-12.6)	4.8(2-13.4)
Median E/A ratio (range)	1.2 (1.1-1.5)	1.2 (0.8-1.7)
Median EF (range), %	68(36-78)	67.4 (56-86)
Median TAPSE (range), mm	16 (9-25.3)	16.3 (12-26)

VSD=ventricular septal defect; ASD=atrial septaldefect; PDA=patentductus arteriosus; VmaxTR= maximal velocity tricuspid regurgitation, PASP=pulmonary arterial systolic pressure, sBP= systolic blood pressure, CI=cardiac index, E=early inflow mitral filling, A=late inflow mitral filling, EF=ejection fraction, TAPSE= tricuspid annular plane systolic excursion

Table 3. Echocardiographic data day 1(I) or day 30 (II) after corrective procedure and treatment

Variables	Placebo (n=17)	Sildenafil (n=19)	P value
Median Vmax TR (range), m/second			
I	2.5 (1.7-3.8)	2.6 (1.1-3.3)	0.66
II	1.9 (1.1-2.9)	1.8 (1-4.2)	0.33
Median PASP (range), mmHg			
I	35 (21-67.8)	37 (14.8-53)	0.66
II	24.4 (14.8-436)	23 (14-80.6)	0.33
Median PASP/sBP (range)			
I	0.3 (0.2-0.7)	0.4 (0.2-0.5)	0.70
II	0.3 (0.2-0.5)	0.23 (0.2-0.9)	0.26
Median CI (range), L/min/m^2			
I	4.8 (2-8.9)	4.6 (2.1-.7.4)	0.53
II	4.2 (2.1-8.3)	4.6 (1.9-6.9)	0.70
Median ratio E/A (range)			
I	1.2 (1-1.5)	1.2 (1.1-1.6)	0.52
II	1.2 (1-1.9)	1.3 (1.1-1.6)	0.31
Median TAPSE (range), mm			
I	15 (7-23)	16 (7-24,3)	0.10
II	16 (9-22)	16 (8-20)	0.21
Median EF (range), %			
I	60 (37-78)	65 (31-78)	0.35
II	62 (33-88)	63 (45-88)	0.57

Mann-Whitney test

CI=cardiac index; EF=ejection fraction, TAPSE=tricuspid annular plane systolic excursion, sBP=systolic blood pressure, PASP=pulmonary arterial systolic pressure, TR=tricuspid regurgitation, I=examination between days 1 to 3, II=examination on day 30

There were also no significant differences in the other hemodynamic parameters (CI, TAPSE, E/A ratio, and LVEF) between the placebo and sildenafil groups after corrective procedure and after treatment for 30 days **(Table 3)**. No patients died after 30 days of treatment. No improvement in functional class occurred in 2 patients in the placebo group, and in 4 patients in the sildenafil group (data not shown). Median lengths of hospital stay, ICU stay, and ventilator use were not significantly different between the placebo and sildenafil groups after corrective procedure **(Table 4)**.

No patients died after the study, nor did any fatal reactions occur during this study. No diarrhea, nausea or vomiting were observed in our patients after the treatment. We found epistaxis in 1 patient, headache in 1 patient, and flushing in 1 patient, all of which were in the sildenafil group.

Table 4. Clinical outcomes after corrective procedure

Variables	Placebo (n=17)	Sildenafil (n=19)	P value
Median length of ICU stay (range), days	1 (0-9)	1 (0-1)	0.57
Median length of ventilator use (range), days	1 (0-8)	1 (0-1)	0.38
Median length of hospital stay (range), days	5 (1-97)	5 (2-11)	0.53

ICU=intensive care unit

Discussion

The VSD and PDA were the most common left-to-right shunt CHDs in this study, similar to that of an epidemiological study from a Dutch registry.[6] The pathophysiology of PAH associated with left-to-right shunts depends on the diameter of the defect and magnitude of the shunt. The PAH more frequently occurs in post-tricuspid valve shunts, such as PDA and VSD.[7] In our study, the minimum age in the both groups was < 12 months. Hyperkinetic PAH is likely in large left-to-right shunt CHDs in those < 1 year of age.[8] Some patients in our study underwent corrective procedures at ages ≥ 6 years. Large left-to-right shunt CHDs leave the distal pulmonary artery chronically exposed to higher blood pressures. Shear stress due to increased blood flow and pressure on the pulmonary artery causes it to remodel and vasoconstrict due to unbalanced vasodilator and vasoconstrictor mediators. These processes cause reactive PAH or immediate PAH after corrective procedures.[9,10,11] In children who undergo corrective procedures before 1 year of age, the pulmonary artery returns to normal within 2-3 months after correction.[8]

Median Vmax TR, PASP, and PASP/sBP were not significantly different between groups after correction and after treatment, because all parameter values decreased after closure of the left-to-right shunt CHDs, either by transcatheter intervention or surgery. A sildenafil study done by Palma *et al.* was conducted in PAH patients who underwent elective surgery. Patients received pre-operative and post-operative sildenafil or placebo, resulting in a significant reduction in pulmonary arterial pressure in the sildenafil group.[4] A separate double-blind, randomized, placebo-controlled trial was performed in children aged 1-17 years with PAH. The sildenafil group had significantly decreased PAP, using a range of sildenafil doses based on body weight and compared to a placebo group after 16 weeks of treatment.[12] In our study, there were no significant differences in PASP between groups after 30 days of treatment, because PASP had already decreased in all patients after the corrective procedure but before treatment, regardless of procedure type, interventional catheterization or surgery. The response to treatment could have been due to PAH severity, as well as duration of PAH, though we did not know the time of PAH onset in our subjects.

The CI parameter can be used to predict prognosis and severity of PAH. The CI < 2.1 L/min/m^2, RAP ≥ 10 mmHg, and central venous oxygen saturation <64% are predictive of a poor prognosis.[13] Median CI was not significantly different between groups after 30 days of treatment. After the defect was closed, sildenafil did not effect a decrease in cardiac output, since PAP became lower after the corrective procedure. Right heart failure before the defect was closed was due to a large left-to-right shunt and the magnitude of the shunt. An E/A ratio < 1 is indicate severe PAH. Usually, systolic and diastolic volume are reduced but systolic and diastolic function remain good in such patients.[5] Since there was no systolic

and diastolic dysfunction in PAH due to left-to-right shunt, sildenafil had no effect on left ventricular contraction. In addition, a TAPSE parameter of < 15 mm and RAP > 15 mmHg are indicative of a poor prognosis.[14] The median TAPSE after treatment was not significantly different between groups. Sildenafil had no effect on systolic function of the right heart because all TAPSE values in the study were normal. Seven patients suspected of having pulmonary vascular obstructive disease (PVOD) underwent diagnostic catheterization to evaluate their response to a vasodilator (oxygen) test. All patients had high flow PAH, low resistance, and were reactive to the oxygen test. These observations indicate that all patients had hyperkinetic PAH. All subjects then underwent surgery, and no PAH was observed during subjects' ICU stays.

Median lengths of ICU stay, ventilator use, and hospitalization were not significantly different between groups after corrective procedures. Length of ICU stay was very short because no patients had reactive or immediate PAH after corrective procedures. The range of length of hospital stay was wide because one patient was intubated for 4 weeks due to pneumonia and 1 patient stayed for more than 6 weeks due to infective endocarditis.

Flushing, headache, and abdominal discomfort were found in the sildenafil group, consistent with another study in children who received sildenafil for 16 weeks of treatment.[12] These side effects occur due to vasodilatation in parts of the body other than the pulmonary artery. They may be mild or moderate, transient, and correlated with doses of sildenafil.[15]

In our study, the smaller sample size was due to a technical error; the actual sample size should have been 46 patients. Another limitation of our study was that we included PAH patients with left-to-right shunt CHDs of all ages, which may have led to wide variations in hyperkinetic and obstructive PAH. In addition, echocardiography data was measured by another pediatric cardiologist elsewhere, whereupon made some evaluations were not performed on the proper day after treatment, and some data were incomplete. Not all patients had FR and PVRI data which showed the severity of the left-to-right shunt CHD in both groups. Furthermore, most of our subjects appeared to have had hyperkinetic PAH prior to their procedures, which would explain the lack of difference between groups on days 1-3 after procedure,

In hyperkinetic PAH, closure of the defects decreases pulmonary artery pressure.[9] Though medial hypertrophy and non-occlusive intimal proliferation is typically found in hyperkinetic PAH, these entities are reversible following CHD correction.[10,11]

In conclusion, there were no differences in pulmonary artery pressure or length of hospital stay between the sildenafil and control groups after the corrective procedure. A double-blind, randomized, placebo-controlled trial with more subjects, older subjects, 12-16 weeks of treatment, or groups divided based on PVRI, is needed to clarify the post-operative effects of sildenafil.

Conflict of interest

None declared.

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