



Original Article

The Combination of Oral PDE5-Inhibitor (Sildenafil) And Oral Prostacyclin Analogue (Beraprost) Therapy for Increasing Quality of Life in Adults with Pulmonary Arterial Hypertension Related to Uncorrected Secundum Atrial Septal Defect

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ABSTRACT

Background : Sildenafil, an oral phosphodiesterase type-5 inhibitor, has vasodilatory effects through a cyclic guanosine 3,5-monophosphate-dependent mechanism, whereas beraprost, an oral prostacyclin analog, induces vasorelaxation through a cAMP-dependent mechanism. This combination has often used but there was little detailed study on it

Objectives : To investigate whether the combination of oral sildenafil and beraprost is superior to sildenafil alone in in adult patients with Pulmonary Arterial Hypertension (PAH) related uncorrected secundum Atrial Septal Defect (ASD).

Methods : Patients with secundum ASD who developed PAH divided into two group. Group A received oral sildenafil 3x40 mg and oral beraprost 3x20 mcg. Group B received oral sildenafil only 3x40 mg in a 12-week. Health-related quality of life (HRQoL) was recorded by patients using the Medical Outcomes Study 36-item short form (SF-36) questionnaires at baseline and after 12 of therapy. Therapy adherence was achieved through a series of phone calls and a four-weekly hospital visit. Every normal follow-up appointment included an examination of side effects and a dosage modification based on the clinical situation

Results: We didn't found any significant of proportion different in cofounding factor between groups. Compared with Group B, Group A had better functional capacity, limitation to physical health, energy fatigue, pain, and health change (P=0.00, P=0.03, P=0.044, P=0.026, P=0.008, respectively).

Conclusion: Combination between oral sildenafil therapy 40 mg three times per day and beraprost 20 mcg two times per day significantly increase the HRQoL in PAH patients in uncorrected secundum ASD compared sildenafil alone

1. Introduction

Pulmonary arterial hypertension (PAH) is a term used to classify a variety of conditions that have in common an injury to the pulmonary vasculature that produces elevations in pulmonary arterial pressure. PAH is a common (9–35%) consequence of congenital heart disease that primarily affects patients with a left-to-right shunt, including an atrial septal defect (ASD) that has or has not been repaired. It is characterized by vascular remodeling, elevated pulmonary vascular resistance, and raised pulmonary arterial pressure.¹ PAH had twice risk of mortality, three times risk of a cardiac event, and five times chance of ICU admission in ASD patients. Patients with PAH caused by uncorrected ASD are currently managed in tertiary care centers, where the development of advanced specific medications is expected to increase prognosis.^{2,3}

ASD patients who developed PAH could have symptom that reduced their quality of life such as dyspnea on effort, hemoptoe, dizziness, chest pain, palpitation, and peripheral edema. It's impact on physical mobility and mental state that might deteriorate the patients' health related quality of life (HRQoL).⁴ HRQoL is an indicator of personal satisfaction with one's life that is influenced by one's health condition, such as physical stamina, learning function, working relationships, emotional well-being, and spirituality. It is subjective, multifaceted, and transient. Quality of life in various chronic illnesses may be assessed using specialized and validated questionnaires such as the Short-Form 36 Health Survey (SF-36). This evaluation is highly repeatable, well-known, non-invasive, and extensively utilized survey is available in a variety of languages.^{4,5}

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Sildenafil, an oral phosphodiesterase type-5 inhibitor, causes vasodilation via a cyclic guanosine 3', 5'-monophosphate-dependent pathway, whereas beraprost, an oral prostacyclin analog, generates vasodilation via a cAMP-dependent function. When compared to treatment with either medication alone, combined treatment with sildenafil and beraprost exhibited additive effects on increases in plasma cAMP and cyclic guanosine 3', 5'-monophosphate levels, resulting in additional improvement in pulmonary hemodynamics.⁶ The combination of sildenafil and epoprostenol (intravenous prostacyclin analogue), however, has demonstrated synergistic effects. The PACES trial evaluated the benefit of sildenafil in patients on background epoprostenol therapy. This study included a total of 267 patients and randomized patients to sildenafil or placebo. Sildenafil improved 6MWD by 28.8 meters (95% CI, 13.9 to 43.8 meters), and there were improvement in cardiac index and reductions mean PA pressures. Combined therapy yielded improvement in quality of life and time to clinical worsening although there were increased rates of headaches and dyspepsia.⁷

HRQoL improvement has been reported in PAH related uncorrected ASD patients with the specific therapy, but it does not show consistency in combination of oral PDE5 inhibitor and oral prostacyclin analogue. Thus, we aim to investigate whether there are HRQoL differences between sildenafil mono therapy and combine with oral prostacycline analogue (Beraprost) in adult patients with PAH related uncorrected secundum ASD.

2. Method

This was an observational prospective cohort study undertaken in the Saiful Anwar General Hospital, a Tertiary Hospital associated with Universitas Brawijaya in Malang, East Java, Indonesia. Adult patients (more than 18 years) with PAH and uncorrected secundum ASD who had enrolled on the Saiful Anwar-PH registry and signed the informed consent form were included in this study. Transthoracic echocardiography and transesophageal echocardiography were used to identify secundum ASD, whereas right cardiac catheterization was used to diagnose PAH. Exclusion criteria included failing to complete follow-up, having another congenital heart defect, being in WHO NYHA functional class I, being pregnant, or having chronic pulmonary illnesses. In case report form, demographic and clinical data such as age, gender, WHO functional class, marital status, and concomitant illness were collected. Subjects completed an HRQoL questionnaire before and after receiving the optimum dose of oral sildenafil 3x40 mg (Group B) or in conjunction with an oral prostacycline analogue (Beraprost 3x20mcg) (Group A). Therapy adherence was achieved through a series of phone calls and a four-weekly hospital visit. Every normal follow-up appointment included an examination of side effects and a dosage modification based on the clinical situation.

2.1. Assessment of HRQoL

HRQoL in varied cardiac situations was assessed using the Short Form Survey (SF)-36 questionnaire. The HRQoL assessment was carried out to assess physical functioning, physical health limitations, emotional problems, energy/fatigue, emotional well-being, and social functioning.

2.2. Right heart catheterization (RHC)

After TTE and/or TOE were verified as ASD and recorded, right heart catheterization (RHC) was simulated in all individuals. Before treatments, cardiology experts performed RHCs on non-sedated patients using conventional techniques. The RHC's goal was to compute hemodynamics, diagnose pulmonary artery hypertension (PAH), and

assess the septal defect/shunt repair procedure. The flow rate was calculated using the formula pulmonary blood flow (Qp)/systemic blood flow (Qs) = (aorta saturation - mixed vein (MV) saturation)/(pulmonary vein (PV) saturation-pulmonary artery (PA) saturation). The MV saturation was calculated as ((3 x superior vena cava saturation) + inferior vena cava saturation)/4. The pulmonary vascular resistance index was used to develop the formula (mPAP-mean left atrial pressure (mLAP) (or mPAWP)/Qp) (PVRi). A Qp was calculated using the formula: O₂ intake (ml/min)/ (1.36x10xhemoglobin level x ((PV saturation-PA saturation)/100)).⁷ The PVR was calculated using the PVRi/body surface area. The PAH diagnosis was established when mPAP was 25 mmHg, PVR was greater than 3 WU, and PAWP or mLAP was greater than 15 mmHg.⁸ Eisenmenger syndrome is characterized when Qp/Qs = 1 and PVRi > 8 WU.m2. A vasoreactivity test was done on a subset of individuals (discretion by cardiologist consultants). The vasoreactivity result was determined using established recommendations (reduction in PVR > 20% and final PVRi 6 WU.m2).⁹ Shunt correctability was defined as patients with appropriate defect anatomy (surgery and/or device), Qp/Qs > 2, and PVRi 6 WU.m2.⁸ Blood was drawn from each patient through venipuncture in peripheral veins and during RHC. Cuvettes analysis was used to measure the blood Gases analysis sample. The hemoglobin and hematocrit levels were determined using a standard hemocytometer.

2.3. Statistical Analysis

The mean/median is used to represent continuous variables (interquartile range). Numbers and percentages are used to represent categorical variables. For comparisons between SF-36 domain subgroups, the Independent T-test was utilized (symptoms, activities and quality of life). Subgroups were established for continuous variables based on their median values. All statistical analyses were carried out utilizing the SPSS software, version 21 (SPSS Institute, Inc; Cary, North Carolina). If $p < 0.05$, the results were significant.

3. Result

Forty-four patients were included to the analysis from the Saiful Anwar Pulmonary Hypertension Registry between January 2019 until December 2020. As of 31 December 2020, at diagnosis, the mean age was 30.4 ± 8.2 years, The main symptoms were dyspnea on effort (35.9%), easily fatigued (16.3%), chest pain/discomfort (10.8%) and palpitations (9.3%). 20 patients got Sildenafil 3x40 mg, and 24 patients got combination between beraprost 3x20 mcg and sildenafil 3x40 mg. We didn't found any significant of proportion different in Comorbid condition between groups.

Hemodynamic variables obtained during RHC (Table 2), that found no significant different level of hemodynamic variable between group. We found that, there were significant increasing for quality of live in group A compared with group B, there were significant different in physical functioning, Limitation to physical health, Energy fatigue, Pain, and health change ($P=0.00$, $P=0.03$, $P=0.044$, $P=0.026$, $P=0.008$, respectively).

4. Discussion

The mean age of patient with ASD who developed PAH was similar to other studies, stated that PAH development in secundum ASD mostly occurred in the third decade. Incidence of PAH in secundum ASD were increased in patients at the age of 18 to 40 years old.¹⁰ Dyspnea on effort was the most common symptom in this study, and its similar with previous studies stated that the most common symptom in uncorrected ASD who developed PAH was breathlessness due to volume overload of the right ventricle (RV).¹¹

Tabel 1. Clinical Characteristics.

Clinical Characteristics	Sildenafil 3x40mg + Beraprost 3x20mcg (Group A) N= 24	Sildenafil 3x40mg (Group B) N = 20	P
Age (Years)	31.9±12.7	31.73±13.56	0.48
Sex Female	86.2%	84.3%	0.95
NYHA III-IV	6.9%	8.4%	0.21
Presenting Symptoms			
DOE	67.2%	82.9%	0.04
Palpitation	14.3%	17.2%	0.64
Syncope	8.6%	10.3%	0.73
Orthopneu	5.2%	8.1%	0.36
Chest Pain	4.3%	5.2%	0.81
PND	10%	12.1%	0.70
Hemoptysis	3.4%	6.9%	0.48
Abdominal Distension	2.9%	5.2%	0.65
Edema	10.3%	18.6%	0.18
Dizziness	5.2%	4.3%	0.81
Comorbid Condition			
Obesity	5.2%	4.3%	0.81
Atrial fibrillation	2%	4.2%	0.23
Diabetes	3.4%	2.8%	0.92
Cancer	1.7%	0%	0.94
Family History	17.2%	14.2%	0.64
HRQOL (SF-36)			
Physical Function	86.95±12.07	82.16±26.24	0.042
Limitation due to physical health	82.92±34.63	82.14±25.6	0.12
Limitation due to emotional problem	84.99±34.86	84.14±25.6	0.68
Energy fatigue	82.65±14.83	74.64±18.72	0.022
Psychological health	86.17±20.61	86.19±20.60	0.88
Social Function	85.08±15.20	85.67±14.5	0.84
Pain	88.14±10.41	89.29±14.10	0.78
General health	84.15±12.14	72.62±11.42	0.012
Vitality change	86.15±12.13	71.12±14.12	0.002

Note, data were presented in mean ±SD or n (%); NYHA = New York Heart Association (NYHA) Functional Classification; DOE = Dyspnea on Exertion; PND = Paroxysmal Nocturnal Dyspnea; HRQOL (SF-36) = Short-Form Health Survey.

Table 2. Hemodynamics Variable

Value	Group A	Group B	P
Hemoglobin (g/dl)	14.2 ± 3.2	15.6 ± 2.8	0.24
Hematocrit (%)	48.2 ± 11.2	51 ± 9.8	0.48
MPAP (mmhg)	44.4±10.2	45.32±8.8	0.44
MRAP (mmhg)	8.8±4.2	9.6±2.42	0.14
LVEDP (mmhg)	11.48±3.8	12.2±2.82	0.22
PVR	6.2±1.42	6.6±1.28	0.82
Aortic Oxygen Saturation (%)	96.4 ± 2.6	93.2±1.8	0.12

Note, data were presented in mean ±SD or n (%); ,MPAP = Mean pulmonary Arterial Pressure; MRAP = Mean Right Atrial Pressure; LVEDP = Left Ventricular End-Diastolic Pressure; PVR= Pulmonary Vascular Resistance.

Table 3. Increasing Quality of Life According Group

Parameter	Group A	Group B	P
Physical Functioning	7.02±2.73	3.94±2.13	0.00
Limitation To Physical Health	6.88±12.09	0.22±13.9	0.03
Limitation To Emotional problem	2.75±3.76	1.71±13.4	0.18
Energy Fatigue	5.38±13.46	2.71±13.4	0.044
Emotional Well Being	3.81±17.15	2.41±3.92	0.48
Social Functioning	2.28±7.7	.2±4.8	0.86
Pain	6.61±13.09	0.6±7.66	0.026
General Health	2.95±7.58	2.54±4.60	0.16
Health Change	6.46±10.54	3.66±7.80	0.008

Note, data were presented in mean ±SD or n (%)

The assessment of medication effects on HRQoL is a key component in assessing the impact of medicines on clinical outcomes and health care. Several prior studies that assessed HRQoL following sildenafil and beraprost administration yielded results that were compatible with this study. Study by Joanna et al. (2008) found that after 12 weeks treatment, sildenafil-treated participants exceeded placebo-treated patients in terms of exercise ability (p 0.001). Increases in all SF-36 categories were seen in sildenafil-treated patients from baseline to week 12, with statistically significant increases in physical functioning (p 0.001), overall health (p 0.001), and vitality (p 0.05) compared to placebo-treated control individuals.¹² Nazzareno Galiè et al. (2002) stated that Patients who received beraprost increased their exercise ability and symptoms, resulting in a higher quality of life.^{13,14}

In this study, we found that combination of treatment between sildenafil and beraprost had better quality of life compared than sildenafil alone. improve HRQoL measured by Medical Outcomes Study Short Form 36 (SF-36). Patients in group A had better physical functioning, lower limitation to physical activity, less energy fatigue and less pain. SF-36 questionnaire is the most extensively used instrument for accessing HRQoL in various cardiac conditions. It can be used to accommodate eight health concepts. The improvement in the HRQoL can be achieved through several ways. Sildenafil relaxes the pulmonary vasculature via a cGMP-dependent pathway, whereas beraprost dilates the pulmonary arteries via a cAMP-dependent process. As a general pharmacologic concept, when various medicines that cause comparable effects via distinct pathways are combined, they may have additive or synergistic effects. In fact, as compared to therapy with either medication alone, the combination of oral sildenafil and beraprost substantially reduced increases in RV systolic pressure and RV/BW. These data imply that the combination of oral sildenafil and beraprost is more effective than either medication alone in preventing the development of MCT-induced pulmonary hypertension.^{13,6}

Although the drug administration significantly improves the SF-36 based on statistics, the clinical benefit cannot significant for patients. Thus, the score difference must exceed the MCID (Minimal Clinical Important Difference) that represent the minimal amount of benefit that were recognized by the patient. Using the distribution-based method, Koichi et al (2020) stated that the SF-36 MCIDs of the PCS (Physical component summery) and MCS (Mental component summery) were 5 and 5 by half the SD, and 6 and 5 by standard error of the measurement. we believe that the result can be used as a treatment consideration for pulmonary arterial hypertension cases especially in developing countries.

We noticed several limitations in this study. First the sample size was small, further study with larger number of participants might

be required. Second, we did not assess the effect of supportive treatments (such as diuretics, digoxin, oral anticoagulants), which is one of the PAH patient care methods specified in the ESC PAH recommendations.⁸ Fluid retention, elevated central venous pressure, hepatic congestion, ascites, and peripheral edema are all symptoms of right heart failure. Although clinical experience suggests that diuretics might help minimize fluid retention symptoms, there have been no randomized studies including diuretic usage in PAH patients. Diuretic treatment is advised in PAH patients who show symptoms of right heart failure and fluid retention, according to the I C recommendation class. To avoid hypokalemia and pre-renal kidney disease, aldosterone antagonist treatment, combined with plasma electrolyte levels and renal function monitoring, may be explored.⁹

5. Conclusion

This study concluded that combination between oral sildenafil therapy 40 mg three times per day and beraprost 20 mcg two times per day in PAH patients in uncorrected secundum ASD significantly improve physical functioning, Limitation to physical health, Energy fatigue, Pain, and health change resulted in increasing HRQoL compared sildenafil alone.

6. Declarations

6.1. Ethics Approval and Consent to participate

This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

6.2. Consent for publication

Not applicable.

6.3. Availability of data and materials

Data used in our study were presented in the main text.

6.4. Competing interests

Not applicable.

6.5. Funding source

Not applicable.

6.6. Authors contributions

Idea/concept: HM. Design: HM, AIN. Control/supervision: HM. Data collection/processing: HM, MRF, AIN. Extraction/Analysis/interpretation: HM, MRF, AIN Literature review: HM, MRF, AIN. Writing the article: HM, MRF, AIN. Critical review: HM. All authors have critically reviewed and approved the final draft and are

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