The Effect of Oral Sildenafil Therapy on Health-Related Quality of Life in Adults with Pulmonary Arterial Hypertension related to Uncorrected Secundum Atrial Septal Defect: A Quasi Experimental Study

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Abstract

Background: Assessment of health-related quality of life (HRQoL) are often measured as an important patient-reported outcome (PRO) in clinical studies. Pulmonary arterial hypertension (PAH) is a common complication of atrial septal defect (ASD). This study aimed to compare the HRQoL of PAH related uncorrected secundum ASD at pre and post therapy with oral sildenafil therapy.

Methods: We conducted quasi experimental study at Sardjito General Hospital Yogyakarta since April 2016 to August 2017. Adults with PAH related uncorrected secundum ASD, listed on Congenital Heart Disease and Pulmonary Hypertension (COHARD-PH) registry, and met the inclusion and exclusion criteria were recruited as subject. Interview was done at pre and 12 weeks post oral sildenafil therapy 3 x 20 mg using the EQ-5D-3L questionnaire. Statistical analysis was done using paired T-test to determine the differences of EQ5D utility and EQVAS score at pre and post therapy.

Results: A total of 18 adult patients with PAH related to uncorrected secundum ASD were enrolled in this study (83.33% female; mean age 38.72 ± 10.81 years old). The most frequent reported problems pre therapy were pain/discomfort (83%) and anxiety/depression (78%). Paired T-test results showed the mean value of EQ5D utility score pre and post therapy were 0.558 and 0.664 post therapy (p:0.014; 95% CI 0.024-0.187). Meanwhile, the mean of EQ-VAS pre and post therapy were 65 and 71.67, respectively (p:0.005; 95% CI 2.32-11.02).

Conclusion: The administration of oral sildenafil therapy 3 x 20 mg during 12 weeks in adult patients with PAH related uncorrected secundum ASD gives better HRQoL.

Background

Pulmonary Artery Hypertension (PAH) is a common complication of congenital heart
disease which mostly happen on patients with left to right shunt, such as atrial septal defect (ASD). Uncorrected left to right shunt may increase pulmonary pressure which can lead to vascular remodeling and dysfunction. Thus, it is responsible for progressive increase of pulmonary vascular resistance and right heart pressure.\(^1\) Based on disease registry of PAH on ASD patients in Sardjito General Hospital Yogyakarta, out of 123 adult ASD patients, 74% among them had PAH.\(^2\) Post (2013) mentioned that PAH was found in 9–35% secundum ASD, including those who have or have not corrected.\(^3\) PAH symptoms such as activity-induced dyspnea, dizziness, cough, chest pain, palpitation, and peripheral edema may impact the physical mobility and emotional status that could worsen the patients’ health related quality of life (HRQoL).\(^4\) HRQoL is a parameter of personal satisfaction in living affected by health status, such as physical capacity, cognitive ability, working relations, emotional and spirituality. It is subjective, multidimensional, and temporary.\(^5\) To date, only few data showed a potential output from patient-reported outcome (PRO) in showing the prognosis of PAH. PRO is a patient’s health parameter measured by themselves which includes HRQoL, that is a functional effect of disease and therapy consequences by patient’s judgement.\(^6\) Meta-analysis of 4 researches on safety and efficacy of sildenafil therapy for ≥ 12 weeks in patients with PAH concludes that sildenafil significantly decrease clinical deterioration events and increase 6 minutes’ walk test distance, WHO functional class, hemodynamic parameters and HRQoL compared to placebo.\(^7\) HRQoL improvement has been reported in PAH patients with the specific therapy, but it does not show consistency in all of the researches.\(^5\) Thus, we aim to investigate whether there are HRQoL differences before and after sildenafil therapy in adult patients with PAH related uncorrected secundum ASD.
Methods

Study Design

We conducted a quasi-experimental research in Sardjito General Hospital Yogyakarta from April 2016 to August 2017. The subject included in this research was adult patients (age ≥ 18 years) with PAH and uncorrected secundum ASD who had been registered on COHARD-PH registry and signed the informed consent. Secundum ASD was diagnosed by trans thoracic echocardiography and trans esophageal echocardiography, meanwhile PAH was diagnosed by right heart catheterization. Exclusion criteria were other congenital heart defect, WHO NYHA functional class I, had received specific therapy for PAH, pregnancy, had received nitrates, or chronic pulmonary diseases. Estimated sample needed was 19 subjects.

Demography and clinical data; such as age, gender, WHO functional class, marital status, comorbid disease, and other therapy; were recorded in case report form. Subject filled HRQoL questionnaire before and 12 weeks after receiving oral sildenafil 3 × 20 mg.

Instrument to measure HRQoL was generic questionnaire EuroQol-5 Dimensions 3 Levels (EQ-5D-3L) which had been proven for its validity and reliability. Repeated follow ups were conducted to evaluate the side effect and dose adjustment towards the clinical condition.

Echocardiography Evaluation

Trans thoracic echocardiography was performed by experienced technician and verified by cardiologist consultants. Bubble test was performed when interatrial defect was not clear on echocardiography examination. Bubble test and trans esophageal echocardiography was conducted by cardiologist consultant.

Right Cardiac Catheterization

Right cardiac catheterization was performed by a cardiologist through standard operating procedure in Sardjito General Hospital Yogyakarta, using angiography machine Xper
Cardio Physiomonitoring 5 hemodynamic monitors (Philips, USA). Saturation and pressure were measured on every location using oximeter (Avoximeter® 1000E, USA).

Questionnaire EQ-5D-5L Data Sampling

Questionnaire data sampling was performed by trained enumerator. Data sampling was performed through (1) Subject was given a thorough explanation about the questionnaire filling, (2) Subject filled the questionnaire, (3) Subject was allowed to ask questions, (4) Subject could be assisted on reading and filling questionnaire, if needed.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows 22.0. Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as percentages. Comparative analysis for paired categorical variables (before and after therapy) was performed for every EQ5D dimension using McNemar and Wilcoxon test. Comparative analysis to compare the EQ5D and EQ-VAS utility score before and after therapy was performed using paired T-test. Consequent analysis was performed to find the correlation between factors that influence difference between utility score of EQ5D and EQ-VAS. The analysis was performed using Mann Whitney test due to abnormal data distribution. p value < 0,05 was considered statistically significant.

Results

A total of 22 patients were included in the study subjects. During the study, 4 subjects were dropped out (one subject died in a local hospital about a week after starting sildenafil therapy, two subjects did not resume the study at the 4th week due to loss to follow up, and one subject only followed the study until the 8th week because of health insurance issues) and were not analyzed further. We obtained 18 patients who could follow the study for 12 weeks. During the study, there were 2 subjects (11.11%) who reported dizziness after taking sildenafil 3 x 20 mg. Because of that, the sildenafil dose was reduced to 2 x 20 mg and the dizziness improved. This is considered a mild side effect which improved after dose reduction.

Subjects were predominantly women with 83.33% (15) subjects being women. Mean age of subjects was 38.72 ± 10.81 years old. All of the subjects were symptomatic, 72.22% (13) subjects were in WHO functional class II and 27.78% (5) were in WHO functional class III. The majority of subjects were married (83.33%), 3 of whom had no children and 2 were widowed. Subjects working in the formal sector were 5 (27.78%) while the other 13 were unemployed (72.22%).

Other comorbid diseases were present in 2 subjects (11.11%) with one subject diagnosed with atrial fibrillation and one subject diagnosed with ischemic heart disease,
whereas 16 subjects (88.89%) were not accompanied by other diseases. A total of 10 subjects (55.56%) did not receive supportive PAH therapy (furosemide, digoxin, spironolactone, warfarin) and 8 subjects (44.44%) treated with supportive PAH therapy. Table 1 showed basic characteristics of PAH subjects with uncorrected ASD II who received sildenafil 3x20 mg for 12 weeks.

| Variable                  | Value (n=18) |
|---------------------------|--------------|
| Age (years)               | Mean ± SD    |
|                           | 38.72 ± 10.81|
| Gender                    | Woman, n (%) |
|                           | 15 (83.33)   |
|                           | Men, n (%)   |
|                           | 3 (16.67)    |
| WHO Functional Class      | II, n (%)    |
|                           | 13 (72.22)   |
| Marital Status            | Not married, n (%) |
|                           | 3 (16.67)    |
|                           | Married, with children, n (%) |
|                           | 10 (55.56)   |
|                           | Married, no children, n (%) |
|                           | 3 (16.67)    |
|                           | Widowed, n (%) |
|                           | 2 (11.11)    |
| Occupation                | Housewives, n (%) |
|                           | 11 (61.11)   |
|                           | Civil servant, n (%) |
|                           | 2 (11.11)    |
|                           | Private employee, n (%) |
|                           | 3 (16.67)    |
|                           | College student, n (%) |
|                           | 1 (5.56)     |
|                           | Unemployed, n (%) |
|                           | 1 (5.56)     |
| Comorbid disease          | None, n (%)  |
|                           | 16 (88.89)   |
|                           | Present, n (%) |
|                           | 2 (11.11)    |
| Other therapy             | No therapy, n (%) |
|                           | 10 (55.56)   |
|                           | Furosemide, n (%) |
|                           | 8 (44.44)    |
|                           | Digoxin, n (%) |
|                           | 7 (38.89)    |
|                           | Spironolactone, n (%) |
|                           | 1 (5.56)     |
|                           | Warfarin, n (%) |
|                           | 1 (5.56)     |
|                           | Aspirin, n (%) |
|                           | 1 (5.56)     |

SD: Standard Deviation

The subjects were divided into three groups; which were no-problem group, moderate problem group, and severe problem group at the time before and after sildenafil therapy. Based on the patients’ report, the most common problems were pain/discomfort (83%), anxiety/depression (78%), usual activities limitations (39%), mobility problem (44%), and self-care (17%). Figure 1 showed that the most reported severe problems were pain/discomfort (72% moderate and 11% severe problems), followed by anxiety/depression (67% moderate and 11% severe problems), and usual activities limitations (33% moderate problems and 6% severe problems). After receiving 3 x 20 mg sildenafil therapy for 12 weeks, those severe problems were no longer reported by the subjects.

Comparative analysis of paired categorical variables (before and after therapy) were performed for each EQ5D dimensions. The proportion difference before and after therapy between ‘no problem group’ and ‘problems group’ in walking ability dimension (p=0.375) and self-care dimension (p=1.0) were analyzed with McNemar test. The p value <0.001 was considered to be significant. While the proportion difference before and after therapy between ‘no problem group’ and ‘problem group’ in usual activities dimension (p=0.655), pain/discomfort dimension (p=0.46), and anxiety/depression dimension (p=0.07) were analyzed with Wilcoxon test. This showed an improvement in the health status of all five dimensions of EQ5D but the differences before and after the 3 x 20 mg sildenafil therapy for 12 weeks were not statistically significant.Figure 2 showed the average utility score were increased from 0.558 ± 0.209 (before the sildenafil therapy) to 0.664 ± 0.121 (after sildenafil therapy). Moreover, Figure 3 showed that the mean of EQVAS score also increased from 65 ± 13.06 (before therapy) to 71.67 ± 15.53 (after therapy).Comparative analysis before and after therapy was performed using paired T test because of the normal data distribution from Shapiro-Wilk test. The result was shown in table 2. The p value of EQ5D utility score were 0.014 (95% CI; 0.024 to 0.187) while p value for EQ-VAS
score were 0.005 (95% CI 2.32 to 11.02). Thus, there were statistically significant of mean difference of EQ5D and EQVAS utility scores before and 12 weeks after oral sildenafil therapy.

| Time               | EQ5D Utility Score |       |       |       |       |
|--------------------|--------------------|-------|-------|-------|-------|
|                    | Mean (SD)          | Difference (SD) | Mean 95% CI | p     |
|                    |                    |        | Lower | Upper |       |
| Before treatment   | 0.558±0.209        | 0.105±0.164 | 0.024  | 0.187 | 0.014*|
| After treatment    | 0.664±0.121        |        |       |       |       |

| Time               | EQ-VAS Score |       |       |       |       |
|--------------------|--------------|-------|-------|-------|-------|
|                    | Mean (SD)    | Difference (SD) | Mean 95% CI | p     |
|                    |              |        | Lower | Upper |       |
| Before treatment   | 65±13.06     | 6.67±8.75 | 2.32  | 11.02 | 0.005*|
| After treatment    | 71.67±15.53  |        |       |       |       |

SD: standard deviation; EQ5D: EuroQoL-5 Dimensions; EQ-VAS: EuroQoL-Visual Analogue Scale,

* p < 0.05; 95% CI

The subjects studied were the same subjects who performed HRQoL measurements twice, before and after therapy. Factors influencing changes in EQ5D and EQ-VAS utility scores were analyzed by a re-grouping subjects based on these factors, such as sex group (male and female), age (> 38 years and ≤ 38 years), education level (low and high), marital status (married and not married), employment status (employed and unemployed), other therapies (with and without other therapies), and comorbidities (with and without coexisting illness).

There was an increase of EQ5D and EQ-VAS utility score after oral sildenafil therapy in all of the sub groups. The EQ5D and EQ-VAS utility score differences were calculated in each sub-group and were analyzed using Mann Whitney test due to abnormal data distribution. p value <0.05 is considered statistically significant. From Table 3, there was no statistically significant difference between all factors affecting HRQoL to the difference of EQ5D and EQ-VAS utility scores.

Table 3. Factor affecting EQ5D utility score and EQ-VAS score difference
### Table

| Variable                        | Utility Score Difference | P       | EQ-VAS Score Difference | P       |
|---------------------------------|--------------------------|---------|-------------------------|---------|
| Gender                          |                          |         |                         |         |
| Male, n = 3                     | 0.011±0.018              | 0.083   | 11.67±7.64              | 0.242   |
| Female, n = 15                  | 0.001±0.109              |         | 16.67±5.77              |         |
| Age                             |                          |         |                         |         |
| < 38 y.o, n = 9                 | 0.089±0.114              | 0.656   | 4.44±9.17               | 0.119   |
| ≥ 38 y.o, n = 9                 | 0.122±0.210              |         | 10±7.50                 |         |
| Education status                |                          |         |                         |         |
| Low, n = 2                      | 0.254±0.530              | 1.000   | 15±7.10                 | 0.166   |
| High, n = 16                    | 0.062±0.042              |         | 6.25±8.47               |         |
| Marital Status                  |                          |         |                         |         |
| Married, n = 15                 | 0.052±0.034              | 0.339   | 13.33±11.55             | 0.460   |
| Not Married, n = 3              | 0.185±0.160              |         | 5±13.23                 |         |
| Occupation                      |                          |         |                         |         |
| Employed, n = 5                 | 0.027±0.045              | 0.091   | 9±7.42                  | 0.443   |
| Unemployed, n = 13              | 0.494±0.460              |         | 4±8.9                   |         |
| Other treatment                 |                          |         |                         |         |
| With treatment, n = 8           | 0.192±0.208              | 0.089   | 5±9.64                  | 0.249   |
| No treatment, n = 10            | 0.051±0.050              |         | 8.13±8.43               |         |
| Comorbid disease                |                          |         |                         |         |
| With comorbid disease, n=2      | 0.099±0.140              | 0.944   | 2.5±3.54                | 0.511   |
| Without comorbid disease, n=16  | 0.106±0.171              |         | 10±14.14                |         |

Description: Mann Whitney test analysis results showed p value> 0.05 in all sub groups. This means that there is no statistically significant difference between the factors affecting HRQoL to the difference of EQ5D utility score and EQ-VAS score, * p <0.05.

## Discussion

Based on the data, we found that the mean age of subjects diagnosed as PAH in uncorrected secundum ASD was 38.72 years. These results are in accordance with the study of Haque et al. (2015) which stated that PAH development in secundum ASD mostly occurred in the third decade. Vogel et al. (1999) noted that the incidence of PAH in secundum ASD were increased in patients at the age of 18 to 40 year old. The majority of the subjects of this study were female (83.33%) which similar to the previous study. Euro Heart Survey registry also support this findings. They concluded that the incidence of PAH in female ASD was 76.6%, higher than male patients. All subjects have many problems in various EQ5D dimensions before starting the specific PAH therapy. In general, subjects reporting their best performance were on the self-care dimension and their worst were on pain/discomfort dimension. Severe problems experienced by 11% of subjects on the dimension of pain/discomfort and anxiety/depression while 6% of the subjects felt severe problems on performing daily
activities. These three dimensions were also the most frequently reported problems by the study subjects. This result is in accordance with the study by Thompson et al. (2001) in Germany who found that the best performance of both primary and secondary PAH patients was experienced in the self-care dimension while the worst performance was reported on the dimension of daily activity. In this study, 20% of subjects experienced severe problems while performing daily activities and less than 10% experienced severe problems in other dimensions. Mychaskiw et al. (2010) examined the health status of PAH patients in the subjects of SUPER 1 clinical trial. The data from the study found similar to previous studies, moderate to severe problems occurring mostly in the dimensions of daily activity (77%), while the least happened in self-care dimensions (24%).

After 12 weeks of treatment, severe problems are no longer experienced in the dimensions of pain/discomfort, anxiety/depression, and usual activities. The percentage of subjects who did not had any complain in all the 5 dimensions of EQ5D were increased. Dimensions of pain/discomfort, anxiety/depression, and usual activities had the most common complaints reported by the study subjects. The severity of each EQ5D dimension problem were decreased. In line with these results, Pepke-Zaba et al. (2008) proved in his study that improvement was achieved in all dimensions of EQ5D after 12 weeks of sildenafil therapy. A clinical trials by Pepke-Zaba et al. (2008) found that the utility score mean statistically significantly changed about 0.10 ± 0.04 and EQ-VAS 8 ± 2. The study also showed similar results with the mean difference utility score of 0.105 ± 0.164 and EQ-VAS 7.22 ± 8.613. The difference also proved statistically significant with p value 0.014 (95% CI 0.024 to 0.187) for utility score and p 0.005 (95% CI 2.32 to 11.02) for EQ-VAS score. Based on the
above statistically, there is a difference of average EQ5D utility score and significant EQ-VAS score before and after sildenafil 3 × 20 mg therapy for 12 weeks.

Determination of drug effects on HRQoL is an important component in evaluating the effect of drugs on clinical outcomes and health care. Several previous studies that evaluated HRQoL after sildenafil administration showed results that are consistent with this study. Study by Sastry et al. (2004) in the population of primary lung hypertensive patients (n = 22) mentioned that there was an increase in dyspnea and fatigue components assessed by cardiac failure questionnaire after sildenafil therapy (dose 3 × 25 mg, 3 × 50 mg and 3 × 100 mg) for 12 weeks. Another study by Wong et al. (2007) involving 19 HAP patients (idiopathic, connective tissue disease, CHD with a shunt) also evaluated HRQoL for 3 months after sildenafil therapy (dose 3 × 25 mg and 3 × 50 mg) using SF-36 questionnaire. In the study there was an increase in scores on physical, social, and health dimensions in general. Tay et al. (2011) studied 12 patients with Eisenmenger syndrome who were given sildenafil 3 × 20 mg therapy. The questionnaire used in this study was a questionnaire specific disease to the pulmonary hypertension population, namely Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). The results also show an improvement in HRQoL after 3 months of therapy.

Demographic factors such as age, sex, marital status, education level, and employment status have an influence on HRQoL. A systematic review by Gu et al. (2016) who assessed factors affecting HRQoL of PAH patients to explain that HRQoL is influenced by demographic characteristics (such as living alone, decreased social support), mental health (such as anxiety, depression, stress), physical health (such as exercise and symptomatic capacity), and pharmacologic therapy. In this study, the mean utility score of subjects aged < 38 years was lower than subjects aged ≥ 38 years, but the mean EQ-
VAS score was the opposite where the difference was not statistically significant. Study by Matura et al. (2014) who examined the difference in severity of symptoms and HRQoL of young, middle, and older PAH patients concluded that the decrease in HRQoL component was experienced by all age groups, but the younger age group had slightly better physical function compared to other groups. PAH more often affects young patients, active professional workers, who are mostly women. Symptom severity, complex therapy, or psychological stressors result in the patient having difficulty being able to work as under normal conditions. This resulted in job losses resulting in disrupted economic conditions and social isolation.

Nilsson (2012) explains that female patients often exhibit lower HRQoL scores than men because of the way of thinking to assess the health of women and men differently. Women are more inclusive, more emphasizing on the matter though on the same thing, and prefer the emotional factors that are not always related to the disease. While men tend to assess disease, lifestyle, and functional ability as important. Another possibility of women having lower HRQoL is due to poorer living conditions and or more vulnerable social roles (sex studies). Accordingly, in this study average utility scores and female EQ-VAS subjects were lower than men, although the difference between them was not statistically significant.

Nilsson (2012) mentioned that in a group of unmarried / single patients had a low HRQoL. Similarly, in this study the mean utility scores and EQ-VAS of unmarried subjects were lower than those married although not statistically meaningful. Self-life and minimal social support are associated with a worse HRQoL emotional dimension score. In contrast, active work is associated with a better HRQoL physical dimension score. According to the results of the review, in this study average utility scores and EQ-VAS group subjects that
did not work were lower than those that worked although they were not statistically significant.

Delcroix and Howard (2015) published an article review on the burden of PAH disease and its impact on quality of life. It was explained that PAH patients who aged > 50 years old were reported to have more comorbid illnesses such as ischemic heart disease, coronary artery disease, hypertension, atrial fibrillation, diabetes, and hypothyroidism than younger patients. The presence of comorbidities results in delayed diagnosis of PAH in older patients. The higher burden of comorbidities also contributes to the lower survival rates of older PAH patients in the UK and Ireland, which is about 3 times higher than the younger population (≤ 50 years) with fewer comorbidities and better training capacity. In line with this, in this study, the average EQ5D utility score and EQ-VAS of subjects with comorbidities were lower than without comorbidities although not statistically significant. Supportive therapies (such as diuretics, digoxin, oral anticoagulants, or oxygen) are one of the PAH patient’s management strategies mentioned in the management guidelines of PAH ESC 2015. Right heart failure leads to fluid retention, increased central venous pressure, hepatic congestion, ascites, and peripheral edema. Clinical experience shows the benefits of diuretics to reduce fluid retention symptoms, but no randomized trials have been associated with diuretic use in PAH patients. Diuretic therapy is recommended in PAH patients with signs of right heart failure and fluid retention, with recommendation class Ic. While additional aldosterone antagonist therapy may be considered along with monitoring of plasma electrolyte levels and renal function to prevent the occurrence of hypokalemia and the effects of intravascular volume depletion resulting in pre-renal failure.

Digoxin may increase cardiac output in idiopathic PAH patients although its efficacy is unknown in long-term administration. This drug can be used also in PAH patients with
atrial tachyarrhythmia to reduce ventricular rate. Lader et al (2003) undertook a sub-study of a Digitalis Investigation Group (DIG) clinical trial to assess the effect of digoxin therapy on HRQoL heart failure patients with sinus rhythm. A total of 589 patients with heart failure (ischemic, idiopathic, hypertensive) were sub-subjects with routine diuretic and ACE inhibitors. A total of 298 subjects were treated with digoxin and 291 subjects received placebo. Several instruments are used to assess HRQoL dimensions such as the Medical Outcomes Study Short Form-36 (MOS SF-36), Ladder of Life, Centers for Epidemiologic Studies-Depression Scale (CES-D), Spielberger State Anxiety Inventory, Spielberger State Anger Inventory, and MLHFQ. HRQoL measurements were performed at the start of the study, followed up 4 months, and 12 months. The results of this study concluded that in the subset of DIG clinical trial population the digoxin therapy had no effect on HRQoL of heart failure patients with sinus rhythm.

On postmortem examination of idiopathic PAH patients found high prevalence of vascular thrombotic lesions. In addition, the abnormalities of the coagulation and fibrinolysis pathways in the PAH patient population have also been reported. Oral anticoagulants are administered to PAH patients with consideration of these as well as an increased risk of venous thromboembolism (heart failure and immobilization). The benefits of oral anticoagulant therapy are limited to idiopathic PAH patients, hereditary PAH, and PAH caused by anorexigen (recommendation class IIb). This is largely derived from retrospective studies with data from only one study center. While the results of registry and randomized clinical trials are randomized and inconclusive. Currently evidence of efficacy and safety of anticoagulant drugs in PAH patient populations is limited. The clinical guidelines do not recommend routine anticoagulant treatment in Eisenmenger syndrome patients and suggest that this therapy may be given in cases of atrial
fibrillation and pulmonary artery thrombosis without major haemorrhage.\textsuperscript{24}

In this study 44.44\% (8) subjects received other therapy, including PAH support therapy. A subject (5.56\%) was treated with oral furosemide if necessary, six (33.34\%) subjects treated with oral furosemide 1 × 20 mg and oral digoxin 1 × 0.125 mg, and a subject (5.56\%) with accompanying atrial fibrillation received oral support therapy in the form of furosemide 1 × 40 mg, digoxin 1 × 0.125 mg, spironolactone 1 × 25 mg, and warfarin 1 × 2 mg. The total subjects receiving furosemide were 44.44\% (8), digoxin 38.89\% (7 subjects), 5.56\% spironolactone (1 subject), and 5.56\% warfarin (1 subject). The mean EQ5D utility score and the EQ-VAS group of subjects with other therapies were lower than without comorbidities although not statistically significant.

This is in line with cross-sectional studies by Zlupko et al. (2008) that evaluate HRQoL PAH patients with various etiologies such as idiopathic, familial, systemic sclerosis, CHD, human immunodeficiency virus (HIV), liver disease, anorexigen, and obstructive pulmonary venous disease. A total of 93 subjects who were recruited received epoprostenol therapy (28\%), bosentan (49\%), calcium channel blockers (47\%), sildenafil (3\%), digoxin (33\%), diuretics (57\%) and warfarin (49\%). The HRQoL evaluation was measured by a specific PAH disease questionnaire (MLHF-PH) and from the results of the evaluation we found a severe HRQoL disorder in all subjects. There were no differences in HRQoL subjects treated with diuretics, digoxin, and oxygen in these populations.\textsuperscript{25}

Conclusion

This study concluded that oral sildenafil therapy 20 mg three times per day for 12 weeks in PAH patients due to uncorrected secundum ASD is statistically significant to improve HRQoL.

Abbreviations
Declarations

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Authors’ contributions

FH, PPRG, ABH, DWA, and LKD participated in concepting and designing the study. FH participated in the collecting of data. PPRG, ABH, DWA, and LKD participated in the analysis and interpretation of data. FH wrote the draft of the manuscript. All authors critically revised the manuscript and approved the final version to be published.

Authors’ information

Not Applicable.

Availability of data and materials

Data can be shared upon contact with the correspondence author.

Competing interests

The authors declare that they have no competing interests.

Consent for Publication

Not applicable

Ethical Approval

Patients provided written informed consent to participate in the study. This study was
ethically approved by the ethical commission of biomedical research Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta and permission from the Director of Dr. Sardjito General Hospital Yogyakarta. Patients provided written informed consent to participate in the study.

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Figures
Comparison of health status based on five-dimensional EQ5D in adult patients with PAH due to uncorrected secundum ASD before and after sildenafil therapy 3x20 mg for 12 weeks.
Figure 2

The mean EQ5D utility score before and after 12 weeks of oral sildenafil therapy 3 x 20 mg in adult patients with PAH due to uncorrected secundum ASD has been shown to be statistically significant. * p <0.05; 95% CI.
Figure 3

The mean of EQ-VAS score before and after 12 weeks of oral sildenafil therapy 3 x 20 mg in adult patients with PAH due to uncorrected secundum ASD proved to be statistically significant. * p <0.05; 95% CI