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Clinical and Hemodynamic Effect of Sildenafil in Patients with Left Sided Heart Failure Complicated with Pulmonary Hypertension

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Abstract

Background: The prognostic role of Pulmonary arterial hypertension (PH) and RV dysfunction in LV HF provides the rationale for targeting PH as a new option in both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Therefore, we conducted the present randomized controlled trial in order to assess the clinical and hemodynamic effects of sildenafil in patients with left-sided HF complicated with PH.

Methods: The current study enrolled 120 patients who were randomly divided into Sildenafil group included 60 patients received sildenafil therapy in addition to standard treatment of HF and control group included 60 patients received standard treatment of HF only. All patients had left sided HF complicated with severe PH.

Results: Notably, at six months of follow-up, the sildenafil led to statistically significant improvements in the 6 MWT; this improvement was significantly higher in Sildenafil group than control group and patients on sildenafil had a significantly higher frequency of NYHA's improvement (41(71.9%) vs.16(29.1%); P=0.01) in comparison to the control group. In addition sildenafil led to a higher reduction in mPAP than the control group (p=0.02).

Conclusion: Sildenafil is safe and an effective treatment option for patients with left-sided HF complicated by PH.

Keywords: Sildenafil; Pulmonary hypertension; Left sided HF

Introduction

Pulmonary Hypertension (PH) is a frequent condition, which may occur as a consequence of pulmonary vascular disease, chronic left heart or lung disease, pulmonary embolism, or other aetiologies. Among the various PH groups, PH associated with left heart failure (HF) represents by far the most common form of PH. In fact, left heart diseases (LHD) account for 65-80% of PH cases [1].

The prognostic impact of PH and RV dysfunction in LV HF provides the rationale for targeting PH as a potential additional treatment option in both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Treatment of PH in addition to established HF therapies may appear to be a promising approach. Targeted therapies approved for the treatment of PAH include endothelin receptor antagonists (ERAs), prostanoids, phosphodiesterase type 5 inhibitors (PDE5i), and stimulators of soluble Guanylate Cyclase (sGC). Randomized Controlled Trials (RCTs) investigating the efficacy and safety of ERAs and prostanoids have shown no benefit, or PH therapies have even proved harmful [2].

More recent studies have focused on targeting the NO pathway in patients with PH-LHD. The PDE-5 inhibitor sildenafil has been advocated as a first-line drug for treating PAH. It is a potent, orally active, and selective inhibitor that has been widely used in monotherapy and combination therapy for adults with PAH. Several meta-analyses of drug therapies to treat PAH have been carried out, and they suggest that sildenafil is safe and effective [3].

Nevertheless, there is a scarcity in the published literature regarding the impact of sildenafil onhemodynamic parameters in patients with left-sided HF complicated with PH. Therefore, we conducted the present randomized controlled trial in order toassess the clinical and hemodynamic effects of sildenafil in patients with left-sided HF complicated with PH.

Methods

Our study enrolled 120 patients who were recruited from the Cardiology department of Aswan University Hospital during the period from June 2018 to June 2019. All the patients had chronic heart failure NYHA class (III-IV) and severe pulmonary hypertension despite of intensive medical TTT of heart failure, patients with moderate to severe mitral stenosis , aortic stenosis, prosthetic valve, congenital heart disease with left to right shunt, Chronic obstructive pulmonary disease, chronic renal failure, Connective tissue disease, previous history of pulmonary embolism and hyperthyroidism were excluded from the study then patients divided into two groups sildenafil group included 60 patients who received sildenafil 20 mg three times daily's for 3 ms plus HF treatment and control group included 60 patients received HF treatment only.

All the patients were subjected to clinical assessment including: Signs and symptoms of heart failure and questionnaire of quality of life (Figure 1).

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	No	Very Little				Very Much
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

Figure 1: Minnesota living with heart failure.

Electrocardiography

Twelve leads resting ECG were done for all patients to detect rhythm, detect any ischemic changes or arrhythmias.

Echocardiography

Images was obtained with left lateral decubitus using Philips Healthcare (Philips xmatrixiE 33) data acquisition was done in parasternal and apical views using (X5-1) transducer. Standard M-mode, 2D and Doppler blood flow measurements were performed and 3 consecutive beats were saved in cineloop format in RV focused apical 4-chamber view.

Left Atrial (LA) volume was measured from apical 4- and 2-chamber views [4]. LV end-diastolic volume and EF were calculated by Simpson biplane method from apical imaging planes [4]. Cardiac chamber volumes were indexed to body surface area.

Pulsed Doppler was used to record transmitral flow in the apical 4-chamber view [5]. Sample volume was placed at the tips of mitral valve leaflets. Peak early diastolic flow velocity (E), peak flow velocity of atrial contraction (A), and their ratio (E/A) were measure at their maximum amplitude. Pulsed-wave tissue Doppler (PW-TDI) early diastolic annular velocities (E′) were acquired at the septal and lateral annular sites. The ratio between transmitral (E) velocity and (E′) velocity (E/E′) was calculated.

Right Atrial (RA) pressure estimation was based on interrogation of the Inferior Vena Cava (IVC) diameter and dispensability and pulsed-wave Doppler interrogation of the hepatic vein flow, and it was scored as 5 (normal sized IVC with>50% respiratory collapse and systolic forward predominant flow on hepatic vein Doppler), 10 (borderline/normal sized IVC with>50% respiratory collapse and equal degrees of systolic and diastolic forward flow on hepatic vein Doppler), 15 (enlarged IVC with>25% respiratory collapse and predominant diastolic forward flow on hepatic vein Doppler), or 20 mm Hg (enlarged IVC with minimal or no collapse and solely diastolic forward flow or systolic flow reversal on hepatic vein Doppler) according to the Mayo Clinic protocol [6].

Mean pulmonary artery pressure

A coaxial TR jet is identified in parasternal long axis (RV inflow), parasternal short axis, or apical 4-chamber view with the help of color Doppler. PA systolic pressure was estimated from the peak continuous-wave Doppler velocity of tricuspid valve regurgitation plus the estimated RA pressure. No patient had 2D or Doppler evidence of pulmonary valve stenosis or RV outflow tract obstruction.

Mean PAP can be approximated from the Systolic PAP (SPAP) using the following formula: mPAP=0.61*SPAP+2 mmHg [7].

The best TR signal is often "off-axis," in-between parasternal and apical windows. An RV-focused or fore shortened 4-chamber view might give the best signal [6]. Sometimes, subcostal long and short axis windows provide the optimal signal and incident angle.

6-minute walk test

The walk test was performed in an indoor corridor 15 m long. Patients were instructed to walk the corridor from one end to the other, as many times as possible, in the permitted time. The test was performed under the control of a physician who encouraged the patients using phrases like 'you are doing well' or 'you are doing a good job'. The patient can stop or slow down at any time and then resume walking, depending on his/her degree of fatigue. At the end of the 6min, we measured the total distance walked by the patient. The following parameters were monitored before and after the test: arterial pressure, heart rate and oxygen saturation.

Follow up

After a total period of 3 months of treatment, a second physical examination, questionnaire of quality of life (Minnesota living with heart failure questionnaire), 6 minute walk test, echocardiography were performed.

Results

Our study enrolled 120 patients who were recruited from the Cardiology department of Aswan University hospital during the period from June 2018 to June 2019, all the patients had chronic heart failure NYHA class (III-IV) and severe pulmonary hypertension despite of intensive medical TTT of heart failure then patients divided into two groups Sildenafil group included 60 patients who received sildenafil 20 mg three times daily for 3 ms and control group included 60 patients received HF treatment only. During follow up 3 patients were died from sildenafil group and 5 patients were died from control group. Mean age of sildenafil group was 57.87 ± 8.83 years and majority (58.2%) of them was males. Out of sildenafil group 29 (50.9%), and 25

(43.9%) patients were DM and HTN, respectively. mean age of control group was 57.87 ± 8.83 years and majority of them (64.9%) also, was males 25 (45.5%), and 27 (49.1%) patients of control group were DM and HTN, respectively. Both groups had insignificant differences as regarding baseline data (p>0.05) (Table 1).

	Control group (n= 55)	Sildenafil group(n = 57)	P value
Age (year)	58.18 ± 9.91	57.87 ± 8.83	0.86
Sex			0.29
Male	32 (58.2%)	37 (64.9%)	
Female	23 (41.8%)	20 (35.1%)	
Diabetes mellitus	25 (45.5%)	29 (50.9%)	0.35
Hypertension	27 (49.1%)	25 (43.9%)	0.34

Table 1: Demographic data of study groups.

Data was expressed in form of frequency (percentage), mean (SD). P value was significant if<0.05.

As regarding baseline NYHA, it was noticed that majority (47.3% of placebo group and 50.9% of sildenafil group) had NYHA class III with insignificant differences between both groups (P=0.56). Follow up NYHA showed that 23 (40.4%), 22 (38.6%) and 12 (21.1%) patients of sildenafil group had NYHA class I, II and III respectively while 32 (58.2%) and 23 (41.8%) patients of placebo group had NYHA class II and III, respectively with significant differences between both groups (P=0.03).

It was noticed that baseline and follow up NYHA class had insignificant difference in placebo (P=0.06) but there was significant difference in case of sildenafil group (P=0.03). Also, sildenafil group had significant higher frequency of NYHA's improvement (41 (71.9%) vs.16 (29.1%); P=0.01) in comparison to placebo group (Table 2).

	Control group (n = 55)	Sildenafil group (n=57)	P1 value
Baseline NYHA			0.56
I	3 (5.5%)	2 (3.5%)	
II	22 (40%)	18 (31.6%)	
III	26 (47.3%)	29 (50.9%)	
IV	4 (7.3%)	8 (14%)	
Follow up NYHA			0.03
I	0	23 (40.4%)	
II	32 (58.2%)	22 (38.6%)	
III	23 (41.8%)	12 (21.1%)	
P2 value	0.06	0.04	
NYHA improvement	16 (29.1%)	41 (71.9%)	0.01

Table 2: Comparison between the two study groups as regard NYHA class.

p value was significant if<0.05 (P1 compared between both groups while P2 compared baseline with follow up data of same group), NYHA: New York heart association.

It was noticed that both group had insignificant difference as regarding baseline 6 MWT (339.19 ± 61.89 vs. 353.20 ± 53.64 m; P=0.20) but sildenafil group had significantly higher follow up 6MWT (401.54 ± 79.14 vs. 358.56 ± 42.39; P=0.01). As regarding comparison baseline and follow up 6MWT I each group it was noticed that follow up 6 MWT was significantly higher in comparison to baseline data **(Table 3).**

	Control group (n = 55)	Sildenafil group (n = 57)	P1 value
Six minute walk test			
Baseline (m)	353.20 ± 53.64	339.19 ± 61.89	0.2
Follow up (m)	358.56 ± 42.39	401.54 ± 79.14	0.01
P2 value	0.34	0.01	

Table 3: Comparison between the two study groups as regard 6 MWT.

Data was expressed in form of mean (SD). P value was significant if<0.05 (P1 compared between both groups while P2 compared baseline with follow up data of same group).

Both groups had insignificant differences as regarding baseline ejection fraction. Also, both groups had insignificant differences as regarding baseline septal e` (15.86 ± 6.07 vs. 16.65 ± 3.66; P=0.40) and lateral e` (18.79 ± 3.21 vs. 17.89 ± 3.31; P=0.14) but both parameters were significantly lower in sildenafil group during follow up (P<0.05). Comparing baseline and follow up data, lateral e`and septal e`were significantly decreasing during follow up in sildenafil group only (Table 4).

	Control group (n= 55)	Sildenafil group (n= 57)	P1 value
Ejection fraction (%)	46.94 ± 18.91	46.28 ± 17.76	0.66
Septal e`			
Baseline	15.86 ± 6.07	16.65 ± 3.66	0.4
Follow up	16.25 ± 5.78	13.53 ± 3.26	0.02
P2 value	0.15	0.01	
Lateral e`			
Baseline	18.79 ± 3.21	17.89 ± 3.31	0.14
Follow up	19.25 ± 2.43	15.45 ± 3.92	0.01
P2 value	0.13	0.01	

Table 4: Ejection fraction, Septale and Lateral e in both groups.

Data was expressed in form of mean (SD). P value was significant if<0.05 (P1 compared between both groups while P2 compared baseline with follow up data of same group).

Pulmonary artery pressure (mPAP) had insignificant difference between both groups at baseline (43.05 ± 7.63 vs. 43.59 ± 9.66 mmHg; P=0.55) but it was significantly decreased, during follow up, in sildenafil group (43.05 ± 7.63 vs. 39.40 ± 8.74 mmHg; P=0.02) in comparison to control group. There was significant change in mean PAP during follow up in comparison to baseline in sildenafil group only (P=0.01) (Table 5).

	Control group (n= 55)	Sildenafil group (n= 57)	P1 value
Mean PAP (mmHg)			
Baseline	42.58 ± 8.28	43.59 ± 9.66	0.55
Follow up	43.05 ± 7.63	39.40 ± 8.74	0.02
P2 value	0.56	0.01	

Table 5: Comparison between both groups as regard means PAP.

Data was expressed in form of mean (SD). P value was significant if<0.05 (P1 compared between both groups while P2 compared baseline with follow up data of same group) (PAP: Pulmonary Arterial Pressure).

Discussion

The prognostic impact of PH and RV dysfunction in LV HF provides the rationale for targeting PH as a potential additional treatment option in both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Treatment of PH in addition to established HF therapies may appear to be a promising approach [2].

Nevertheless, there is a scarcity in the published literature regarding the impact of sildenafil on hemodynamic parameters in patients with left-sided HF complicated with PH. Therefore, we conducted the present randomized controlled trial in order to assess the clinical and hemodynamic effects of sildenafil in patients with left-sided HF complicated with PH.

The current study enrolled 120 patients who were recruited from the Cardiology Department of Aswan University Hospital. During follow up two patients were lost and six patients died. So, finally, we had 112 patients who were randomly divided into:

Sildenafil group included 57 patients received sildenafil therapy plus traditional HF treatment.

Control group included 55 patients received traditional HF treatment.

Age and male gender are established risk factors for HF and PH. Males aged 60 years and older are more likely than younger people to suffer from cardiovascular disease, including HF. In addition hypertension, obesity, diabetes, hyperlipidemia and metabolic syndrome are common comorbidities in HF [8]. In the present study, the mean age of patients in both groups was almost 58 years and the majority of them were males. Moreover, up to 50% of the patients had one or more comorbidities, most commonly hypertension and diabetes.

HF is a clinical syndrome, characterized by exercise intolerance and/or signs of congestion in the presence of a cardiac condition (congenital or acquired) [1]. While the New York Heart Association (NYHA) functional classification is a validated tool in the clinical setting to assess the severity of chronic HF in patients with left ventricular dysfunction [9].

In the present study, the baseline six minutes walking test (6MWT) in the sildenafil group was 339.19 ± 61.89 m which was not significantly different from that of the control group. Notably, at 3 months of follow-up, the sildenafil led to statistically significant improvements in the 6MWT; this improvement was significantly higher in Sildenafil group than the control group. Such improvements were apparently reflected on the New York Heart Association (NYHA) functional classification in which patients on sildenafil had a significantly higher frequency of NYHA's improvement (41 (71.9%) vs. 16 (29.1%); P=0.01) in comparison to the control group. The increase in 6MWT was an independent predictor for improvement in the NYHA class.

In concordance with our findings, Lewi et al. tested the hypothesis that sildenafil would lower pulmonary vascular resistance and improve exercise capacity in patients with HF complicated by PH. Thirty-four patients with symptomatic HF and PH were randomized to 12 weeks of treatment with sildenafil (25 to 75 mg orally 3 times daily) or placebo. Sildenafil treatment was associated with improvement in 6MWT (29 m versus placebo; P=0.047) and Minnesota living with Heart Failure score (-14 versus placebo; P=0.01). Subjects in the sildenafil group experienced fewer hospitalizations for HF and a higher incidence of headache than those in the placebo group without incurring excess serious adverse events [10].

Similarly, Wu et al. evaluated the effect of sildenafil on PH associated with chronic left HF. Twenty patients with PH and left HF were divided into treatment group (10 cases, with an oral dose of sildenafil 75 mg daily for 8 weeks) and placebo group (10 cases, with the treatment of cardiac glycosides, diuretics, an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, and beta-blockers). The walking distance in the 6-minute walk test (6-MWT) was significantly increased after treatment when compared with the placebo group [11].

In patients with PH treated with pulmonary vasodilators, a continuation of therapy is conditional on the demonstration of treatment effect. As the risk and cost of performing Right Heart Catheterization (RHC) make this test unattractive for 6-month follow-up, echocardiography represents an accessible and feasible real-world tool for follow-up assessments and risk stratification in PH [12].

Elevation in the mean pulmonary artery pressure (mPAP) of at least 25 mmhgat rest, as assessed by echocardiography, is the hallmark for the diagnosis of PH. Therefore, a significant fall of mPAP represents one of the main goals in the treatment of PH [13]. In the present study, patients in the sildenafil group showed a statistically significant reduction in the mPAP at follow-up (P=0.01). Moreover, sildenafil led to a higher reduction in mPAP than the placebo group (P=0.02). The reduction in mPAP was an independent predictor for improvement in the NYHA.

In agreement with our findings, Wang et al. performed a systematic review and meta-analysis to evaluate the safety and efficacy of using sildenafil for ≥ 12 weeks to treat) PH. Randomized controlled trials (RCTs) of sildenafil therapy in patients with PH published through May 2013 were identified by searching PubMed, the Cochrane Library, Embase, relevant websites, and reference lists of relevant studies. Meta-analysis was carried out with subsets of 4 trials involving 545 patients. Sildenafil therapy significantly reduced Mpap relative to placebo [14].

Sastry et al. performed a randomized, double-blind, crossover design, to compare the efficacy of sildenafil with placebo in patients with pulmonary hypertension PH. Twenty-two patients completed the study. With sildenafil, the pulmonary artery systolic pressure decreased significantly at the end of follow-up [15].

Similarly, Singh et al. evaluated the efficacy of oral sildenafil in PH patients. This was a randomized, double-blind, placebo-controlled crossover study. Twenty patients were randomized to receive placebo or sildenafil for 6 weeks and. The results showed that the mPAP improved from the baseline (P<.0001) after treatment with sildenafil [16].

Early diastolic mitral annular tissue velocity (E′) was reported to have a good correlation with left ventricular filling pressure and can be used to diagnose diastolic dysfunction [17]. Our analysis showed that sildenafil results in statistically significant reductions in lateral e`and septal e` at the end of follow-up. Moreover, patients on sildenafil had significantly lower lateral e`and septal e` than control group. Lateral e′ was an independent predictor for improvement in 6MWT. Such findings highlight the positive impact of sildenafil in left ventricular diastolic function of PH patients.

In concordance with our findings, Guazzi et al. assessed the effect of sildenafil on RV functions among patients with pulmonary hypertension and RV burden with the phosphodiesterase-5 inhibitor sildenafil PH and HFpEF. Forty-four patients were randomly assigned to placebo or sildenafil (50 mg thrice per day). At 6 months, there was no improvement with placebo, but sildenafil mediated significant improvements in mean septal e′, lateral e′, E/ e′ ratio, and other parameters of LV diastolic function [18].

Mikhail et al. investigated the use of sildenafil in patients with PH. Ten patients (8 females, mean age 34.5 ± 3.3 years) with PH commenced on oral sildenafil 50 mg t.d.s. The echocardiographic findings showed trend towards improvement in LV diastolic function [19].

Conclusion

Sildenafil is safe and an effective treatment option for patients with left-sided HF complicated by PH. The present study showed that sildenafil significantly improved the clinical outcomes of PH, as evident by six minutes walking distance test and NYHA class.

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