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Sildenafil Improves Right Ventricular Function, Exercise Capacity, and Quality of Life in Patients with Biventricular Dysfunction: Results from a Randomised Study

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ABSTRACT

Background: Phosphodiesterase-5 (PDE-5) inhibitors have shown beneficial effects in heart failure owing to their propensity to dilate the pulmonary vasculature, enhance the right ventricular contractility, and improve the ventricular interdependence. However, their effect in biventricular failure remains unclear. We evaluated the effect of sildenafil, a selective PDE-5 inhibitor, on ventricular function, exercise capacity, and quality of life (QoL) in patients with biventricular dysfunction.

Methods: Patients aged 18 years or older with pulmonary hypertension secondary to biventricular dysfunction, despite optimal medical therapy were randomised to receive either sildenafil 20 mg thrice a day or placebo for 3 months. Clinical investigations such as coronary angiogram, 6-minute walk distance (6MWD), Minnesota Living with Heart Failure questionnaire (MLHFQ), 2D echocardiogram (2D ECHO), right and left ventricular ejection fraction by first pass radionuclide scan and right heart hemodynamics were performed at baseline and at 3 months.

Results: 38 patients aged ≥18 years with biventricular dysfunction (<40%) were included in the study. Sildenafil significantly improved the right ventricular ejection fraction (RVEF), right ventricular systolic pressure and 6-minute walk distance ($p < 0.05$) as compared to the placebo group. There were fewer hospitalizations for heart failure in the sildenafil group as compared to placebo group (2 vs. 5; $p < 0.05$). No significant differences in the occurrence of adverse events was noted amongst the two groups except for headache, which was more frequent in the sildenafil group.

Conclusion: Sildenafil has a beneficial effect on right ventricular function, exercise capacity, and QoL in patients with biventricular dysfunction with secondary pulmonary hypertension.

Keywords: Heart Failure (HF), Pulmonary Vascular Resistance (PVR), 6-Minute Walk Distance (6MWD), Right Ventricle Ejection Fraction (RVEF)

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INTRODUCTION

Heart failure (HF) remains a global health priority by affecting approximately 26 million people worldwide.[1] Owing to increased longevity of population, it accounts for high morbidity and mortality in India. Pulmonary hypertension (PH) is a common complication of left heart failure that is reported in 65-80% of patients which in turn may lead to right ventricular (RV) failure.[2-4] In patients with heart failure, an increase in PH has shown to positively correlate with higher mortality rate.[5] Therapies targeted at reducing pre-capillary pressure and improving pulmonary arterial pressure may provide a reasonable approach to appropriately manage RV impairment. Phosphodiesterase (PDE)-5, the predominant isoform of PDE in the pulmonary vasculature that hydrolyzes intracellular cyclic GMP, has emerged as an important therapeutic target. Inhibition of PDE5 by sildenafil has shown to improve RV dysfunction in patients with primary pulmonary hypertension.[6-10]

Acute administration of sildenafil has shown to improve the endothelium-dependent flow-mediated vasodilation in patients with chronic HF.[11] Furthermore, sildenafil has shown to improve the exercise ventilation and aerobic efficiency via endothelium-mediated attenuation of exercising muscle in chronic HF.[11] Thus, by targeting multiple hemodynamic processes sildenafil may improve functional capacity and ameliorate symptoms in HF patients. In a randomized trial, sildenafil has shown to significantly reduce pulmonary pressure; improve RV function and 6-minute walk distance (6MWD); and decrease serum levels of N-terminal pro b-type natriuretic peptide (NT-proBNP).[12] Nevertheless, there is a paucity of evidence on sildenafil treatment for biventricular failure.

The present study aimed to evaluate the benefits of sildenafil treatment in patients with secondary pulmonary artery hypertension associated with biventricular dysfunction.

PATIENTS AND METHODS

This prospective, single-blind, randomized, placebo-controlled trial was carried out at the Postgraduate Institute of Medical Education Research, Chandigarh, a tertiary care institute in Northern India. Patients aged 18 years or older with pulmonary hypertension secondary to biventricular dysfunction (<40%), despite optimal medical therapy were included in the study. Patients were required to have non-revascularizable coronary artery disease and the reversible causes of cardiomyopathy was ruled out. Patients were excluded if they had co-morbidities that affects the pulmonary artery pressure and RVEF, e.g., chronic obstructive pulmonary disease, connective tissue disorder, chronic thromboembolic pulmonary hypertension, valvular heart disease, or obstructive sleep apnea.

Patients fulfilling the inclusion and exclusion criteria were randomised (1:1) using computer generated random numbers to receive either sildenafil 20 mg thrice a day or placebo for 3 months in a blinded fashion. All clinical investigations were performed at baseline and at 3 months. Investigations included coronary angiogram, 6MWD, Minnesota Living with Heart Failure questionnaire (MLHFQ), 2D echocardiogram (2D ECHO), right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) by first pass radionuclide scan and right heart hemodynamics. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is one of the most widely used health-related QoL questionnaires for patients with heart failure (HF). It is a questionnaire containing 21 questions with scores ranging from 0 to 5 and provides scores for physical and emotional dimensions along with a total score. Primary endpoints were improvement in 6-MWD, RVEF, LVEF and RV systolic pressure (RVSP). Secondary endpoints were improvements in QoL by MLHFQ and the New York Heart Association (NHYA) class. The study was conducted according to the ethical principles stated in the latest version of Helsinki Declaration, and the applicable guidelines for good clinical practice (GCP). Ethics approval was obtained from the institutional ethics committee and written informed consent was obtained from individual patient.

All data were presented as mean ± SD. Paired Student t- test was applied to test the pre- and post-intervention values within each group for continuous variables that were demonstrated to be normally distributed by the Wilk-Shapiro test. Unpaired student t test was applied for between- group comparisons of normally distributed continuous variables. A probability value ≤ 0.05 was accepted as statistically significant.

RESULTS

A total of 250 dilated cardiomyopathy patients were screened and assessed for biventricular dysfunction by 2D ECHO and radionucleotide study. Of the 250 patients screened, 212 patients were excluded as they did not meet the eligibility criteria (RVEF >40%, n=192; reversible etiology, n=10; and comorbid conditions affecting pulmonary artery pressure, n=10). 38 patients were eligible for the study and were randomly assigned to receive either sildenafil 20 mg thrice daily (n=19) or placebo (n=19). Baseline clinical and demographic characteristics are presented in Table 1 which were similar between the two treatment groups. A majority of the patients (>60%) presented with NYHA class III in both the groups. All patients were receiving the maximal tolerable doses of ACE inhibitors, beta- blockers, and diuretics.

Table 2 presents the comparison of radionuclide and 2D echo parameters at baseline and after 12 weeks of treatment. Compared to placebo, sildenafil treatment over three months significantly improved mean RVEF (mean change from baseline, 5.7 ±1.9 % vs. 1.57 ±1.0 %; p=0.0001). Similar improvements were observed in RVSP (mean change from baseline, -10.9±3.95 mm Hg vs. -2±3.11 mm Hg; p=0.0001) and 6MWD (change from baseline, 106.8 ±44.7 m vs. 4.2 ±8.2 m; p=0.0005) with sildenafil treatment as compared to placebo. However, sildenafil treatment did not alter LVEF at 12 weeks (p=0.08).

QoL measured by the MLHFQ (52.6±10.9 vs. 52.4±10) and proportion of patients in each NYHA class was similar in the two groups at baseline (Table 1). At the end of the 12-week treatment period, there were significant improvements in the sildenafil group in MLHFQ (p=0.0001) and in NYHA functional class; whereas, there was no change in QoL in the placebo group (Table 3).

There were no deaths during this study. Hospitalization for HF exacerbation were fewer in the sildenafil group compared with placebo (2 vs. 5; p<0.05) (Table 4). There were no significant differences in the occurrence of adverse events in the two treatment groups except for headache which occurred in 36% of patients in the sildenafil group as compared to 10% in the placebo group. No patients reported visual disturbances during the study.

DISCUSSION

In this randomized, single-blind, placebo-controlled study we found that treatment with the PDE5 inhibitor, sildenafil, for 12 weeks improved RV function, RVSP, 6MWD, and QoL, but did not alter LVEF in patients with biventricular dysfunction. Sildenafil was generally well tolerated and associated with fewer hospitalizations for HF when compared to placebo.

Several groups have proposed possible theories to explain the mechanism underlying the beneficial effect of sildenafil on RV function.[13-14] The most plausible one is improvement in RV function mediated by reduction in pulmonary artery pressure. In a study by Kleinsasser A et. al, 34 patients with symptomatic HF and pulmonary hypertension were randomized to 12 weeks of treatment with sildenafil (25 to 75 mg orally 3 times daily) or placebo.[13] The study results

showed that all doses of sildenafil caused significant increases in intrapulmonary shunt flow, with a marked decreases in partial pressure of oxygen (PaO2) and a significant increase in cardiac index (CI).

In a randomized study by Lewis GD et. al, in patients with symptomatic HF and pulmonary hypertension, type 5 phosphodiesterase inhibition with sildenafil showed an improved peak VO2, reduced VE/ ventilatory response to CO2 output (VCO2) slope, and a selective pulmonary vasodilation during rest and exercise. [15] The improvement in exercise capacity with sildenafil was accompanied by a reduction in pulmonary vascular resistance (PVR). Further, patients with the highest PVR at baseline showed the greatest improvement in exercise capacity with sildenafil treatment. Thus, the improvement in RV function observed in the present study is likely due to the after load reduction. This is supported by the finding that there was a significant improvement in RVEF in patients who had severe pulmonary hypertension.

In a double blind, placebo controlled, randomized clinical trial by Guazzi et al., 48 patients with heart failure with preserved ejection fraction (heart failure signs and symptoms, diastolic dysfunction, ejection fraction ≥50%, and pulmonary artery systolic pressure >40 mm Hg) were randomly assigned to placebo or sildenafil (50 mg thrice per day) for a period of 1 year. [16] The results showed an improvement in pulmonary pressure and vasomotility, RV function and dimension, left ventricular relaxation and distensibility and lung interstitial water metabolism. Another study by Guazzi et al.,45 HF patients (NHYA class II-III) were randomly assigned to placebo or sildenafil (50 mg three times per day) for 1 year, with assessment of LVEF, diastolic function, geometry, cardiopulmonary exercise performance, and quality of life at 6 months and 1 year showed improved LV diastolic function and cardiac geometry, functional capacity, and clinical status with sildenafil. [17]

In a placebo controlled study by Guazzi et al., PDE5 inhibition in HF patients with exercise oscillatory breathing (EOB) demonstrated the dual advantage of improving functional capacity and modulating the EOB pattern.[18] In a double-blind, placebo controlled clinical trial by Behling A et al., sildenafil administration for four weeks showed improvement in functional capacity, ventilatory efficiency, oxygen uptake kinetics, and pulmonary hypertension in stable outpatients with CHF.[19] The results observed in our study are in line with all these previously published reports.

In the present study, we report improvements in NYHA functional class and MLHFQ similar to previous studies with sildenafil. In a similar study by Lewis GD et. al, phosphodiesterase 5 inhibition with sildenafil showed improvement in exercise capacity and quality of life in patients with systolic HF with secondary pulmonary hypertension.[20] Improvement in 6MWD and QoL in HF patients is mainly dependent on peak VO2 achieved during exercise, which in turn consists of two components, cardiac output and oxygen extraction. Thus, QoL in HF patients is indirectly dependent on cardiac output. Given the association between cardiac output and RV contractile function, the improvements in QoL with sildenafil are primarily due to the improvement in RVEF.

In the present study there were no changes in LVEF, despite significant improvement in RV function. This may suggest that sildenafil specifically impacts pulmonary hemodynamics and not systemic vascular resistance. However, it must be noted that patients had received heart failure therapy prior to the study. The use of sildenafil in left ventricular systolic dysfunction is not common in general practice. The only randomized trial that demonstrated a beneficial role for sildenafil was a small sample study.[20] Hence, larger well-designed clinical trials to evaluate the benefits and risks of using sildenafil as an adjuvant to HF therapy seems warranted.

CONCLUSION

This is the first randomized controlled trial conducted in India which evaluated the effect of sildenafil in biventricular dysfunction. Overall, sildenafil had a beneficial effect on RV hemodynamics, 6MWD, and QoL in patients with biventricular dysfunction with secondary pulmonary hypertension. The results need to be confirmed in a larger, preferably, multicentre study.

LIMITATIONS

Firstly, this study had a small sample size. Secondly, owing to the short treatment duration, long-term effects of sildenafil could not be evaluated. Changes in hemodynamics after exercise were not assessed due to resource constraints. All patients were prescribed a low dose level of the study drug (sildenafil 20 mg thrice daily) as it was difficult to ensure regular biweekly follow-up visits for dose titration at an outpatient clinic. Lastly, since minimal dose of the drug was used possible benefits and risks with higher doses could not be ascertained.

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Table 1: Baseline characteristics of study participants

Characteristics	Sildenafil (N=19)	Placebo (N=19)
Age (mean ±SD, years)	45.7±14.1	42.2±12.3
Gender (%)		
Male	10 (52.6%)	10 (52.6%)
Female	9 (47.4%)	9 (47.4%)
NYHA class, %		
II	5 (26.3%)	5 (26.3%)
III	12 (63.2%)	13 (68.4%)
IV	2 (10.5%)	1 (5.3%)
Number of patients with pharmacotherapy for HF		
Diuretics	19 (100%)	19 (100%)
ACE/ARB	19 (100%)	19 (100%)
Beta-blockers	19 (100%)	19 (100%)
Spironolactone	19 (100%)	19 (100%)
Digoxin	10 (52.6%)	11 (57.9%)

RVEF % (mean ±SD)	26±4.2	26±4.0
LVEF %	23.1±6.3	23.2±5.7
RVSP, mm Hg	55.2±7.8	55.6±7.8
6MWD, mts	245.3±87.5	250±84.1
MLHFQ	52.6±10.9	52.4±10.1

ACE indicates angiotensin-converting enzyme; ARB- angiotensin receptor blockers; HF, heart failure; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; 6MWD, 6-minute walk distance; RVEF, right ventricular ejection fraction; RVSP, right ventricular systolic pressure

Table 2: Comparison of Radionuclide and 2D ECHO parameters at baseline and after 12 weeks of treatment

Variables	Sildenafil (N = 19)				Placebo (N = 19)				p-value for between group comparison
	At baseline	At 12 weeks	Mean change from baseline	p-value	At baseline	At 12 weeks	Mean change from baseline	p-value	
RVEF % (mean ±SD)	26±4.2	31.7±3.9	5.7±1.99	0.00	26±4.0	27.57±4.1	1.57±1.0	0.59	0.0001
LVEF %	23.1±6.3	23.4±6.1	0.31±0.74	0.08	23.2±5.7	23.46±4.2	0.26±0.45	0.08	0.80
RVSP, mm Hg	55.2±7.8	44.3±5.5	-10.9±3.95	0.00	55.6±7.8	53.6±5.2	-2±3.11	0.42	0.0001
6MWD, mts	245.3±87.5	352.1±78.5	106.8±44.7	0.0001	250±84.1	254.2±78.7	4.2±8.2	0.80	0.0001

Values are mean± SD unless otherwise indicated.
LVEF, left ventricular ejection fraction; 6MWD, 6-minute walk distance; RVEF, right ventricular ejection fraction; RVSP, right ventricular systolic pressure.

Table 3: Comparison of quality of life by MLHFQ and number of patients in each NYHA functional class at baseline and at 12 weeks

Variables	Sildenafil (N = 19)			Placebo (N = 19)		
	At baseline	At 12 weeks	p-value	At baseline	At 12 weeks	p-value
MLHFQ	52.6±10.9	34.3±10.2	0.0001	52.4±10.1	52.2±9.6	0.76
NYHA class						
I	0	5	0.005	0	0	1
II	5	10		5	5	
III	12	4		13	13	
IV	2	0		1	1	

MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heat Association

Table 4: Adverse events

Event, n (%)	Sildenafil (N=19)	Placebo (N=19)
Death	0	0
Hospitalizations for HF exacerbation	2* (10.5%)	5 (26.3%)
Headache	7* (36.8%)	2 (10.5%)
Dyspepsia	5 (26.3%)	3 (15.8%)
Flushing	3 (15.8%)	1 (5.3%)
Visual disturbances	0	0
Myalgia	2 (10.5%)	1 (5.3%)

*p<0.05 v/s placebo; HF-heart failure

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