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Original Article

Effects of Myocardial Phosphodiesterase 5 Inhibitors on the Left Ventricular Function in Patients With Heart Failure: A Randomized Clinical Trial

Mohammad Garakyaraghi[1], MD; Mohsen Samadi[1], MD; Masoumeh Sadeghi[2], MD; Mahshid Givi*[1], PhD

ABSTRACT

Backgrounds: Myocardial phosphodiesterase 5 (PDE5) inhibitors are documented for use in various disease states. The efficacy of PDE5 inhibitors is less determined in heart failure patients without pulmonary hypertension. The aim of the present study was to evaluate the efficacy of PDE5 inhibitors in heart failure patients without pulmonary hypertension.

Method: Seventy-six cases with heart failure were participated in this study. The selection criteria were systolic heart failure according to the New York Heart Association (NYHA) functional classifications I and IV, echocardiographically determined left ventricular ejection fraction less than 50%, and stability for at least 3 months. The participants were randomly divided into case and control groups. Both case and control groups received 50 mg of sildenafil and a placebo for 3 months, respectively. Transthoracic echocardiography (TTE) was performed using the Vingmed 800 CSF. All the ejection fraction measurements were done using the Simpson method. Before the initiation of the trial and then 3 months afterward, TTE was obtained from the participants. Changes in the functional class and the left ventricular ejection fraction before and after the trial were assessed and the data were analyzed using SPSS, version 16.

Results: In the case group, the ejection fraction after the trial with an average of 41.53 ± 7.53 was considerably more significant than that before the trial with an average of 37.92 ± 6.92 ($P < 0.001$). The findings also showed that sildenafil inhibited PDE5 and the development of the NYHA IV when given for 90 days. As a result, sildenafil significantly improved the left ventricular ejection fraction.

Conclusions: PDE5 inhibitors are effective in the treatment of heart failure patients without pulmonary hypertension. ***(Iranian Heart Journal 2018; 19(1):61-67)***

KEYWORDS: Heart failure, Left ventricular ejection fraction, PDE5I

[1] Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, IR Iran.
[2] Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, IR Iran.

***Corresponding Author:** Mahshid Givi, PhD
Email: mahshid.givi65@gmail.com **Tel:** 09132011496

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Heart failure is a common disease worldwide, with a prevalence rate of about 8.8% of the general population. [1] It seems that the prevalence of heart failure is set to increase due to the current therapies for myocardial infarction, valvular heart diseases, and arrhythmias. Therapeutic agents such as angiotensin-receptor blockers, angiotensin-converting-enzyme inhibitors, and beta-blockers enhance the quantity and quality of life in patients with heart failure. [2, 3]

There is substantial evidence about the role of oxidative stress in the pathogenesis and outcome of patients with heart failure. Increased myocardial phosphodiesterase 5 (PDE5) is associated with oxidative stress. [4] In animal models of mice and rats, pressure overload has been associated with increased PDE5. [4, 5] These data demonstrate that superoxide dismutase can have a protective role against heart failure progression through the cessation of the PDE5 function. [4] It has been noted that there is a small amount of PDE5 in the normal myocardium, but its level increases in myocardial hypertrophy and chronic cardiomyopathy. [5] The histological analysis of samples taken from patients with heart failure compared with transplanted hearts shows elevated levels of PDE5 just in the failed but not transplanted myocardial tissue. [6] Thus, the administration of PDE5 inhibitors seems to be beneficial in the treatment of patients suffering from heart failure. These compounds have been used widely for the treatment of erection dysfunction. Several clinical trials have confirmed the safety and efficacy of these compounds. The administration of these agents has not been associated with increased rates of cardiovascular events even in patients with heart failure or coronary artery disease. It seems that these agents are safe in simultaneous usage with other cardiovascular agents such as nitrates. Sildenafil and tadalafil are the 2 agents approved for the treatment of pulmonary arterial hypertension. [6] Previous research has also introduced these agents for the treatment of such conditions as heart failure, hypertension, myocardial infarction and Raynaud's phenomenon. [7, 8]

In patients suffering from heart failure, PDE5 inhibitors can improve hemodynamic conditions and clinical parameters, which could persist for several weeks. Some of these changes are indexed as enhanced oxygen uptake, decreased peripheral vascular resistance and aortic stiffness, decreased infarct size in animal investigations, augmented walking distance, improved depression score, and enhanced quality of life. [2, 9, 10] Sildenafil enhances the contractile power of hypertrophied myocytes and prevents myocardial tissue rearrangement. Improvement of hemodynamic properties by sildenafil and its beneficial effects on pulmonary artery pressure, dyspnea score, and aerobic state of patients persist for 4 weeks and 6 months, respectively. [11, 12] Most of the findings vis-à-vis the efficacy of sildenafil are driven from small trials. The efficacy of PDE5 inhibitors is less determined in heart failure patients without pulmonary hypertension.

Therefore, the current study aimed at evaluating the efficacy of PDE5 inhibitors in heart failure patients with no pulmonary hypertension.

METHOD

The present study was a randomized double-blinded placebo-controlled clinical trial. The study population was comprised of patients referred to Isfahan Cardiovascular Research Center in Iran. Seventy-six cases with heart failure were randomly selected from the patients. The inclusion criteria consisted of systolic heart failure according to the New York Heart Association (NYHA) functional classifications I and IV, echocardiographically determined left ventricular ejection fraction (LVEF) less than 50%, and stability for at least 3 months. The exclusion criteria comprised

pulmonary hypertension, drug intolerance, and side effects such as hypotension.

The patients included were subsequently divided into case and control groups based on a simple random sampling. Informed consent was obtained from all the participants. Both case and control groups received 50 mg of sildenafil and a pill containing cellulose with exact similarity to sildenafil in terms of size and shape as a placebo for 3 months, respectively. Transthoracic echocardiography (TTE) was performed using a Vingmed 800 CSF. All the EF measurements were done using the Simpson method. Before initiation and 3 months after the trial, TTE was obtained from the participants. Changes in the functional class and the LVEF before and after the trial were assessed.

Statistical Analysis

The collected data were analyzed with SPSS, version 16, using the independent samples *t*-test, paired sample *t*-test and the χ^2 test—with a significance level of less than 0.05.

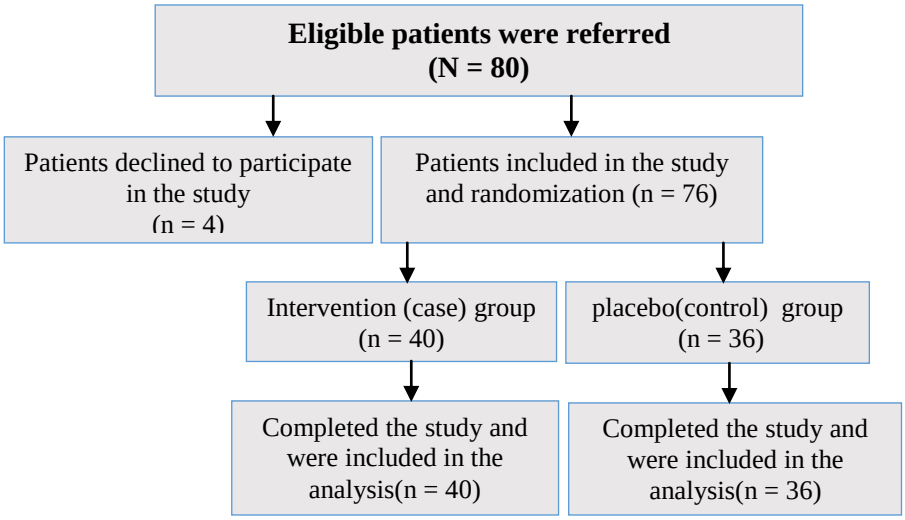

Figure 1. Progress through the phases of the trial from enrolment to follow-up and data analysis.

RESULTS

The current study comprised 76 participants, divided into 2 groups of case (n = 40) and control (n = 36) randomly. A total number of 59 participants in the study were male (35 in the case group and 24 in the control group), and 17 were females (5 in the case group and in 12 in the control group).

The average age of all the participants was 63.16 ± 8.67 years: 65.35 ± 9.06 years in the case group and 60.66 ± 7.59 years in the control group; no significant difference was observed in this regard (P = 0.366). The mean age in the males was 63.72 ± 9 years (65.85 ± 9.33 in the case group and 60.47 ± 7.56 in the control group; P = 0.328). Additionally, the mean age in the female patients was 61.24 ± 7.34 years (61.8 ± 6.41 in the case group and 61 ± 7.95 in the control group; P = 0.491). The results showed that there was no significant difference between the males and females apropos their mean age (P > 0.05). In addition, the findings revealed that there were no significant differences between the 2 groups in terms of the history of various conditions such as diabetes, hypertension, coronary artery disease, hyperlipidemia, myocardial infarction, revascularization, PET or DV, ICD or CID, and stroke (P > 0.05). However, the 2 groups had

significantly different distributions with respect to gender (P = 0.03) and chronic renal failure (P = 0.046) (Table 1).

The baseline EF level in the case and control groups was not significant (36.38 ± 6.95 vs 36.38 ± 8.9; P = 0.105). The comparison of the mean values before and after the trial revealed a significant increase in the EF in the case group (37.92 ± 6.92 vs 41.53 ± 7.53; $P \leq 0.001$); nonetheless, this difference was not significant in the control group (36.39 ± 8.9 vs 36.47 ± 8.62; P = 0.772). In addition, the percent change in the EF was 0.27 ± 1.63 in the placebo group and 9.91 ± 8.46 in the case group ($P < 0.001$).

Table 1. Demographic characteristics and underlying disease or condition of the participants

Variable	Variable Components	Treatment Group (n=40)	Placebo Group (n=36)	Total	*P*
Age(y)	total (mean±SD)	65.35±9.06	60.66±7.59	63.16±8.67	0.180 ø
	male (mean±SD)	65.85±9.33	60.47±7.56	63.72±9	0.491 ø
	female(mean±SD)	61.8±6.41	60.47±7.56	61.24±7.34	0.328 ø
Sex	Male	35(59.3%)	24(40.7%)	59(100%)	0.03 *
	Female	5(29.4%)	12(70.6%)	17(100%)	
Hypertension	No	24(52.2%)	22(47.8%)	46(100%)	0.229 *
	Yes	12(40%)	18(06%)	30(100%)	
Diabetes	No	22(45.8%)	26(54.2%)	48(100%)	0.617 *
	Yes	14(51.9%)	13(48.1%)	27(100%)	
Coronary artery disease	No	4(44.4%)	5(55.6%)	9(100%)	0.614 *
	Yes	27(45.8%)	32(54.2%)	59(100%)	
Hyperlipidemia	No	18(43.9%)	23(56.1%)	41(100%)	0.598 *
	Yes	17(50%)	17(50%)	34(100%)	
Peripheral vascular disease	No	27(42.9%)	37(57.8%)	64(100%)	0.140 *
	Yes	5(71.4%)	2(28.6%)	7(100%)	
Stroke	No	34(48.6%)	36(51.4%)	70(100%)	0.216 #
	Yes	1(20%)	4(80%)	5(100%)	
Myocardial infarction or revascularization	No	1(25%)	3(75%)	4(100%)	0.617 #
	Yes	35(48.6%)	37(51.4%)	72(100%)	
Chronic renal failure	No	31(44.3%)	39(55.7%)	70(100%)	0.046 #
	Yes	4(100%)	0(0%)	4(100%)	
PET or DVT	No	35(49.3%)	36(50.7%)	71(100%)	0.999 #
	Yes	0(0%)	1(100%)	1(100%)	
ICD or CID	No	35(48.6%)	37(51.4%)	72(100%)	0.495 #
	Yes	0(0%)	2(100%)	2(100%)	

ø Independent *t*-test, * $\chi 2$ test # Fisher exact test

Table 2. Distribution of the NYHA class on the first day (day 0) and the last day (day 90) of the study in the case and control groups

Patients		Case			Control		
		Day 0 (n=40)	Day 90 (n=40)	*P*	Day 0 (n=36)	Day 90 (n=36)	*P*
LVEF (%)	*NYHA I	0(0%)	0(0%)	0.115#	3(08.33%)	3(08.33%)	0.868#
	NYHA II	31(77.5%)	37(92.5%)		22(61.11%)	25(69.44%)	
	NYHA III	8(20%)	3(07.5%)		10(27.77%)	7(19.44%)	
	NYHA Iv	1(02.5%)	0(0%)		1(02.79%)	1(02.79%)	

NYHA, New York Heart Association; LVEF, Left ventricular ejection fraction

According to the NYHA classes, during the study, 6 (15.0%) patients in the case group had an improvement in their condition, but changes in the NYHA levels between the first and the last follow-ups were not statistically significant (P = 0.115). On the other hand, only 3 (8.3%)

patients showed improvement in the control group, and the changes in the NYHA levels were not statistically significant (P = 0.868) (Table 2).

The drug's side effects including headache and dyspepsia in the intervention group were observed sporadically during the study period (each only in 1 patient). The reported side effects in the placebo group consisted of headache (in 3 patients); dyspepsia (in 2 patients); and epistaxis, flushing, or erythema (each in 1 patient). There were no signs of other side effects.

DISCUSSION

The results of the current study revealed that long-term treatment with the PDE5 inhibitor sildenafil significantly improved the LV diastolic function and improved clinical status in stable heart failure patients with a reduced LVEF and no pulmonary hypertension.

It is important to note that that these effects were observed in a group of patients treated with a background therapeutic regimen adhering to the current recommended guidelines. In addition, minor adverse effects reported by the patients indicated that long-term sildenafil was well-tolerated.

Cyclic nucleotides (cAMP and cGMP) are important second-messenger regulators of the cardiovascular function and modulate acute and chronic stress responses in the heart. Nevertheless, myocardial cGMP levels are tightly regulated by the balance between production via guanylate cyclase and hydrolysis via phosphodiesterase (PDE). The role of the cGMP-specific type 5 PDE in the heart under stress condition remains incompletely understood, but selective inhibitors of PDE5 have improved the function of pressure-overloaded and right and left ventricles in rodents. [13, 14]

A recent intriguing suggestion proposes that sildenafil and increased cGMP activity in protein kinase G may help LV cardiomyocyte relaxation because of the phosphorylation of the giant protein titin. [15] According to recent observations, LV dilation develops through transgenic models that overexpress PDE5 in myocytes and explanted failing human hearts show a high LV PDE5 expression. [16]

Previous studies have shown that RV hypertrophy in rats with pulmonary hypertension induced by monocrotaline is prevented via PDE5 inhibition by sildenafil. [17] Previous studies have also found that PDE5 inhibition by sildenafil reduces right ventricular hypertrophy in patients with pulmonary arterial hypertension. [18] Sildenafil is well-known as a potent pulmonary artery vasodilator; as a result, it lowers pulmonary artery resistance and pressure as well as right ventricular afterload in both rats and humans. [19, 20]

There is a suggestion that another mechanism, which inverses the functional contractile abnormalities of failing myocytes, may be a modulatory protection against sympathetic nervous system activation. The LV contractile state was not measured in the present study. However, as the LVEF indicated, the overall LV performance increased over time. This effect together with improved cardiac chamber geometry highly supports the idea that—as is the case for blockers and RAS inhibitor agents, the effects of long-standing PDE5 inhibition are not pharmacological but biological. This is further strengthened when observing that the acute administration of sildenafil makes no improvement in the LV relaxation even at the time of assessing the diastolic function with catheter-based measurements. [21]

In a previous study, PDE5 had a significant role in LV failure patients with cardiomyocyte-specific overexpression of bovine PDE5.

In conclusion, PDE5 inhibitors are effective in the treatment of heart failure patients without pulmonary hypertension.

Study Limitations

There are some limitations to the present study. First, despite the clear ability of sildenafil

shown in improving Doppler-validated indices of the LV filling pressure and relaxation, a specific catheter-based study should be designed to demonstrate actual substantiation of PDE5 inhibition as modulator of the ventricular diastolic properties in the human heart failure. Second, since the number of the examined cases was small, the echocardiographic measures of the morphological changes of the cardiac chambers did not allow a significant definition of the fine changes occurring during remodeling in progress. Such a limitation precludes an exact definition of the time the reverse left atrial and LV remodeling process starts and coincides with changes in diastolic reserve. Moreover, a significant portion of the patients in this study had already taken and tolerated PDE5 inhibitors well. In fact, the study of a pure PDE5 inhibitor population would have provided more convincing data on tolerability. It is also worth noting that possibly because the population of systolic heart failure patients in this study was a highly selected one and was tightly monitored (every month) over a 3-month period, it exhibited a low rate of hospitalization. As a result, the present subset of patients may significantly differ from the general heart failure population followed up in the community.

CONCLUSIONS

To sum up, PDE5 inhibitors are effective in treating heart failure patients without pulmonary hypertension. The findings showed that the long-term use of sildenafil was well tolerated in our patients with heart failure. Therefore, as the first evidence reported in human beings, this therapeutic regimen promoted a sustained significant improvement in the LV functional properties and the cardiac geometry. Such effects provided a better functional capacity and clinical status. However, further work is needed to confirm findings observed with this therapeutic strategy and to clarify the significance and clinical impact of these effects on the natural history of heart failure.

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