

Sildenafil Improves Six-minute Walk Distance in Chronic Obstructive Pulmonary Disease: A Randomised, Double-blind, Placebo-controlled Trial

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ABSTRACT

Background. Sildenafil has been found to improve exercise capacity and haemodynamic parameters in patients with various pulmonary disorders. This study was undertaken to evaluate its efficacy in severe chronic obstructive pulmonary disease (COPD).

Methods. In this double-blind, randomised, placebo-controlled study, 37 patients with severe COPD received either sildenafil or placebo for 12 weeks. Distance covered in six-minute walk test (6MWD) was taken as primary end-point. Pulmonary artery pressure (PAP) was measured as secondary end point.

Results. Thirty-three patients (15 in sildenafil arm and 18 in placebo arm) completed the study. Non-parametric tests were used for comparison. There was significant increase in 6MWD from baseline after three months of follow-up in sildenafil users (median change in distance covered in six-minute walk test (Δ 6MWD)=190m) as compared to placebo users (Δ 6MWD=0m, $p < 0.05$). The PAP decreased significantly ($\chi^2=14.94$, $p < 0.05$) in sildenafil group after three months, while it did not change significantly among placebo group ($\chi^2=3.84$, $p > 0.05$).

Conclusion. Sildenafil improved 6MWD and PAP in patients with severe COPD.

This trial has been registered with Indian Council of Medical Research (ICMR) Trial Registry. [CTRI Registry Number: CTRI/2009/091/000017] [Indian J Chest Dis Allied Sci 2011;53:81-85]

Key words: Six-minute walk test, COPD, Sildenafil, Pulmonary hypertension.

INTRODUCTION

Activity limitation and dyspnoea are the primary symptoms of chronic obstructive pulmonary disease (COPD) and progress as the disease advances, contributing to reduced quality of life. Exercise capacity in COPD can be evaluated by measuring the distance covered in six-minute walk test (6MWD). This test is simple to perform, cheap and reproducible. Six-minute walk test has been shown to be a better test of functional capacity and predictor of mortality in patients with COPD.^{1,2}

Various factors, such as ventilation perfusion mismatch, skeletal muscle abnormality as a result of systemic inflammatory condition, right ventricular overload for pulmonary vascular changes and simple de-conditioning of right heart, can result in reduced exercise capacity in patients with COPD.³

Pulmonary arterial hypertension (PAH) is a common complication during the course of COPD and is an important predictor of mortality.⁴ Endothelial dysfunction and decreased concentration of endothelium derived nitric oxide may play an important role in the development of PAH in patients having COPD.⁵ Sildenafil improves nitric oxide induced relaxation of smooth muscles of pulmonary arteries through blockage of type 5 phosphodiesterase (PDE5), and therefore, it has potential of reducing pulmonary artery pressure (PAP).

Long-term administration of sildenafil has been shown to improve exercise capacity, dyspnoea and haemodynamics in patients with symptomatic PAH.^{6,7} In a preliminary report of six patients of COPD it was shown that sildenafil improved 6MWD and haemodynamic parameters.⁸ However, in a recent study,⁹ sildenafil failed to improve stroke volume and 6MWD in patients of COPD with and

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without PAH. This emphasises the need for further studies, and therefore, we studied the efficacy of sildenafil regarding 6MWD, dyspnoea and PAH in patients with severe COPD.

MATERIAL AND METHODS

In this randomised, double-blind, placebo-controlled trial in which ambulatory patients having severe or very severe COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification were recruited if they had past history of smoking of at least 20 pack years and had pulmonary artery systolic pressure of more than 40mmHg as measured by Doppler echocardiography. The patients were enrolled for duration of one year. The primary outcome of the study was to evaluate the effect of sildenafil in improving 6MWD. Improvement in PAP was taken as secondary outcome of the study. Patients were not included if they had: acute exacerbation of COPD in last month, history of bronchial asthma or more than 12% increase in forced expiratory volume in the first second (FEV₁) with bronchodilator, history of primary cardiac disease or documented ischaemic heart disease, use of nitrates or other vasodilator throughout the study period, haemoglobin less than 12g/dL, any severe concomitant disease, evidence of PAH due to any other cause, such as pulmonary thromboembolism, human immunodeficiency virus (HIV), scleroderma, congenital heart disease and de-compensated right or left heart failure.

Informed consent from all the subjects and permission from the Research Review Board of the institute was obtained.

Thirty-seven patients enrolled in this double-blind, placebo-controlled study were randomised into two groups. One group was administered oral sildenafil in the dosage 20mg three times a day and another group was administered identical placebo. Patients were followed up for the next 12 weeks. They were assessed at baseline, after four weeks and after completion of the study by measuring 6MWD and PAP. They were on, inhaled anti-muscarinic, long-acting beta agonists, inhaled corticosteroids and sustained release theophylline one month before the enrollment in the study and same medicines were continued during the study. None of the patients were on regular oral steroids or domiciliary oxygen therapy.

In 6MWD test patients were asked to walk at a sub-maximal effort for six minutes as per the protocol.¹⁰ Heart rate, oxygen saturation and dyspnoea as per the Borg scale before and after the walk were noted. Distance covered at the end of the test was recorded.

The PAP was measured by two-dimensional echocardiography with colour Doppler, a reliable, non-invasive investigation to screen for PAH. Values above 40mmHg are highly specific for detection of PAP.¹² It was used to measure PAP on the basis of presence of tricuspid regurgitation and pressure was calculated by modified Bernoulli equation.¹³ Single investigator performed all the echocardiography testing.

Sildenafil and placebo were dispensed according to random allocation of computer generated code. Drug was dispensed by an unblinded coordinator, who dispensed the drug to blinded coordinator, who gave it to the subjects. The study design is depicted in flow chart shown in the figure.

Statistical Analysis

The Shapiro Wilk statistical test indicated that the assumption of normality had been violated ($p < 0.05$); therefore, non-parametric tests were used for comparison. Mann-Whitney U-test was applied for comparison of Δ 6MWD between sildenafil and placebo at one-month and at three-month follow-up. Friedman's ANOVA was applied for within group comparison of PAP.

RESULTS

Thirty-seven patients were enrolled in the study. Among 33 patients who completed the study, 18 received placebo and 15 were given sildenafil. The number of severe and very severe COPD patients in sildenafil arm was eight and nine, respectively and in the placebo arm were nine and eleven, respectively (Figure). The baseline parameters of the study group are given in table 1.

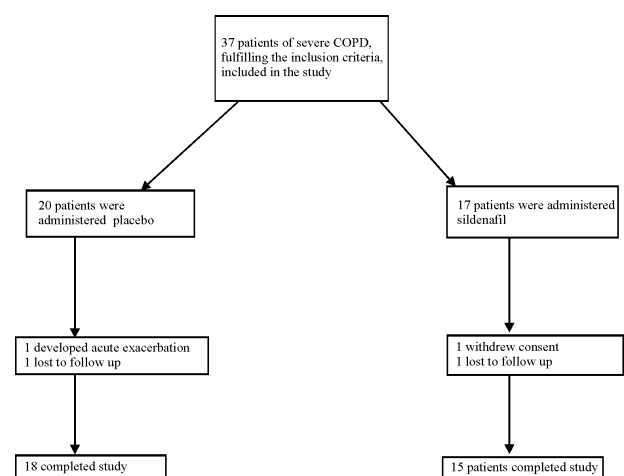


Figure. Flow chart of patient recruitment to the study.

Table 1. The baseline characteristics of the patients in sildenafil and placebo groups

Characteristic	Sildenafil	Placebo
Age	60.7±8.5	63.6±6.7
FEV ₁ % predicted (m)	32.5±11.1	28.5±7.5
6MWD (m)	268.9±139.9	323.1±165.6
PAP (mmHg)	52.7±11.9	47.8±13.4

All data are expressed as mean±SD

FEV₁=Forced expiratory volume in the first second;
6MWD=Distance covered in six minute walk test
PAP=Pulmonary artery pressure (mmHg); SD=Standard deviation

Patient receiving sildenafil (median=266m) did not seem to differ in 6MWD test from placebo (median=365m) at baseline (Mann-Whitney U=113.50, p>0.05). There was significant increase in 6MWD from baseline after one month follow-up in sildenafil group (Δ 6MWD median=190m) compared to placebo users (Δ 6MWD median=15m, Mann-Whitney U=60.00, p<0.05). Similarly, there was significant increase in 6MWD from baseline after three months follow-up in sildenafil users (Δ 6MWD median=190m) compared to placebo users (Δ 6MWD median=0, Mann-Whitney U=35.50, p<0.05) (Table 2).

Friedman's ANOVA was applied separately for sildenafil group and placebo for comparison of PAP at baseline, after one month follow-up and after three months follow-up.

Table 2. Change in distance covered in six-minute walk (6MWD) test and pulmonary artery pressure (PAP) in sildenafil and placebo groups

Time Point	Change in 6MWD (metres)				PAP (mmHg)			
	Sildenafil		Placebo		Sildenafil		Placebo	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Baseline	—	—	—	—	53±12	48	48±13	43
4 weeks	150±123	190	24±117	15	47±17	36	45±14	40
12 weeks	191±127	190	39±87	0	41±8	30	44±12	32

After three months of therapy in sildenafil group, PAP was significantly decreased ($\chi^2=14.94$, p<0.05) whereas there was no significant change in placebo group ($\chi^2=3.84$, p>0.05). Wilcoxon test were used to follow up this finding. A Bonferroni correction was applied and so all effects were reported at a 0.025 level of significance. The PAP in sildenafil users did not significantly change from the baseline to one month (p>0.025); however, there was significant change from baseline to three months (p<0.025) (Table 2).

Four patients, two in each group did not complete the study. In the sildenafil arm, one patient withdrew

consent as he developed epigastric discomfort and another was lost to follow up. In the placebo arm one patient developed acute exacerbation, within one month of therapy and another was lost to follow up.

Headache was the most common side effect with sildenafil. Other adverse effects noted were epigastric pain or discomfort, headache, paresthesias, and numbness.

DISCUSSION

In our study sildenafil has shown to improve the 6MWD test and a decrease in PAP. Similar increase in 6MWD was found in a study of four patients with COPD and three patients with idiopathic pulmonary fibrosis (IPF) who were administered sildenafil 50mg three times daily for eight weeks. The study concluded that sildenafil may have a role for selected patients with COPD and IPF who have pulmonary hypertension.¹⁴ In some recent studies,¹⁵⁻¹⁸ sildenafil proved to have a role for selected pulmonary and cardiac patients with pulmonary hypertension. It improved exercise capacity and haemodynamic parameters in these patients.¹⁵⁻¹⁸ Interestingly, sildenafil was found helpful in weaning off three patients of acute exacerbation of COPD from ventilator.¹⁹ They had repeated failures of breathing trials. Reduction in PAP was proposed as a mechanism helpful in these patients.

However, in another study done in patients with PAH, sildenafil when administered for three months,

improved the 6MWD, World Health Organization (WHO) functional class of dyspnoea even without any significant improvement in PAP.²⁰ These results suggest a possibility that apart from effect on PAP sildenafil might have an additional effect on physical endurance and functional class of dyspnoea.

In a previous study,⁸ the change in 6MWD was observed to be 82±26 metres. As the alpha error of the above-mentioned study was 0.05 and the desired power 80%, the sample size determined was adequate to obtain a significant result.

Our study showed a modest improvement in PAP in sildenafil group at the end of the study. The

improvement in distance 6MWD in our study was out of proportion to the improvement in PAP. The mean increase in the 6MWD at the end of 12 weeks in patients on sildenafil was 190.66 metres, while in patients on placebo, mean increase in distance was 38.89 metres. These results lead us to think that factors other than improvement in PAP might be responsible for this finding. This notion is further supported by yet another study which suggested that sildenafil may help all COPD patients, even those not diagnosed with full blown PAH.²¹

Increased contractility of right ventricle (RV) in setting of RV hypertrophy is commonly observed in severe COPD patients. Recently, it has been proposed that sildenafil reverses remodelling of RV^{22,23} and may improve breathing capacity as PDE type 5 inhibition also has been implicated in reversing bronchoconstriction.²⁴ Transformation of pulmonary fibroblast to myofibroblast, mediated by transforming growth factor-beta (TGF- β), plays an important role in various pathophysiologic events related to COPD and IPF. It has been shown that combining sildenafil with the guanylyl cyclase activator suppresses TGF- β induced differentiation and may affect the course of the disease.²⁵

In contrast to our results, a recent study⁹ on 15 COPD patients (9 with PAH and 6 without PAH), a three months course of oral sildenafil failed to show improvement in stroke volume and exercise capacity. Different effects of sildenafil probably can be explained on the basis of severity of COPD disease in the recruited patients. Mean FEV₁ in that study⁹ was 49% of predicted while patients in our study had mean FEV₁ of 32.5% only. Baseline mean 6MWD was 269 metres in our study in comparison to 385 metres in their study. Probably these results suggest that sildenafil is effective in patients with more severe COPD.

CONCLUSIONS

Sildenafil increased the 6MWD significantly. The drug reduced PAP in patients with severe COPD.

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REFERENCES

1. Brown CD, Benditt JO, Sciarba FC, Lee SH, Crineq GJ, Morenifar Z, *et al*. Exercise testing in severe emphysema: association with quality of life and lung function. *COPD* 2008;5:117-24.
2. Budweiser S, Heidtkamp F, Jorres RA, Heinemann F, Arzt M, Schroll S, *et al*. Predictive significance of six minute walk distance for long term survival in chronic hypercapnic respiratory failure. *Respiration* 2008;75:418-26.
3. Macintyre NR. Mechanism of functional loss in patients with chronic lung disease. *Respir Care* 2008;53:1177-84.
4. Weitzenblum E, Hirth C, Ducolone A, Mirhom R, Rasaholinjanahary J, Ehrhart M. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 1981;36:752-8.
5. Naeija R, Barbera JD. Pulmonary hypertension associated with chronic obstructive lung disease. *Crit Care* 2001;5: 586-9.
6. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Robin LJ, Badesch D, *et al*. Sildenafil citrate for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148-57.
7. Sheth A, Park JE, Ong YE, Ho TB, Madden BP. Early hemodynamic benefit of sildenafil in patients with coexisting chronic thromboembolic pulmonary hypertension and left ventricular dysfunction. *Vascular Pharmacol* 2005;42:41-5.
8. Alp S, Skrygan M, Schmidt WE, Bastian A. Sildenafil improves hemodynamic parameters in COPD: an investigation of six patients. *Pulm Pharmacol Ther* 2006;19:386-90.
9. Rietema H, Holverda S, Bogaard HJ, Marcus JJ, Smit HT, Westerhof N, *et al*. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *Eur Respir J* 2008;31:759-64.
10. ATS Committee on proficiency standards for clinical pulmonary function laboratories. ATS statement: Guideline for six minute walk test. *Am J Respir Crit Care Med* 2002;166:111-7.
11. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.
12. Mcgoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA *et al*. Screening, early detection, and diagnosis of pulmonary arterial hypertension. *Chest* 2004;126:14s-34s.
13. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation* 2001;104:2797-802.
14. Madden BP, Allenby M, Loke TK, Seth A. A potential role for sildenafil in the management of pulmonary hypertension in patients with parenchymal lung disease. *Vascular Pharmacol* 2006;44:372-6.
15. Madden BP, Sheth A, Wilde M, Ong YE. Does sildenafil produce a sustained benefit in patients with pulmonary hypertension associated with parenchymal lung and cardiac disease? *Vascul Pharmacol* 2007;47:184-8.
16. Lewis GD, Shah R, Shazad K, Camuso JM, Pappagianopoulos PP, Hung J, *et al*. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation* 2007;116:1555-62.
17. Keogh AM, Jabbour A, Hayward CS, Macdonald PS. Clinical deterioration after sildenafil cessation in patients with pulmonary hypertension. *Vasc Health Risk Manag* 2008;4:1111-3.
18. Michelhaus ED, Tymchak W, Noga M, Webster L, Wu XC, Lien D, *et al*. Long term treatment with oral sildenafil is safe and improves functional capacity and hemodynamics in patients with pulmonary arterial hypertension. *Circulation* 2003;108:2066-9.
19. Stanopoulos I, Manolakoqlou N, Pitsiou G. Sildenafil may facilitate weaning in mechanically ventilated COPD

- patients: a report of three cases. *Anaesth Intensive Care* 2007;35:610-3.
20. Wong RC, Koh GM, Choong PH, Yip WL. Oral sildenafil therapy improves health related quality of life and functional status in pulmonary arterial hypertension. *Int J Cardiol* 2007;119:400-2.
 21. Holverda S, Rietema H, Bogaard HJ, Westerhof N, Postmus PE, Boonstra A, *et al.* Acute effects of sildenafil on exercise pulmonary hemodynamics and capacity in patients with COPD. *Pulm Pharmacol Ther* 2008;21:558-64.
 22. Nagendran J, Archer SL, Soliman D Gurtu V, Moudgil R, Haromy A, *et al.* Phosphodiesterase type 5 is highly expressed in hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improve contractility. *Circulation* 2007;116:238-48.
 23. Van Wolferen SA, Boonstra A, Marcus JT, Marques KM, Bronzwaer JG, Postmus PE, *et al.* Right ventricular reverse remodelling after sildenafil in pulmonary hypertension. *Heart* 2006;92:1860-1.
 24. Charan NB. Does sildenafil also improve breathing? *Chest* 2001;120:305-6.
 25. Dunkern TR, Feurstein D, Rossi GA, Sabatini F, Hatzelmann A. Inhibition of TGF-beta induced lung fibroblast to myofibroblast conversion by phosphodiesterase inhibiting drugs and activators of soluble guanylyl cyclase. *Eur J Pharmacol* 2007;572:12-22.

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