www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i6.40

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

A Study to Evaluate the Short-Term Efficacy of Oral Sildenafil Therapy in Patients of Pulmonary Arterial Hypertension

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Abstract
Objective: *The objective was to evaluate the short- term efficacy of oral Sildenafil in symptomatic patients of Pulmonary Arterial Hypertension (PAH), both primary and secondary.*
Materials and Methods: *The study involved 40 patients of PAH (n=18 for primary, n=22 for secondary PAH) of both sexes & between 12 to 75 years of age, having pulmonary arterial pressure (PAP) of more than 30 mm of Hg with NYHA class II&III symptoms. Subjects received sildenafil 50 mg 8 hourly orally, or a matching placebo for six weeks each, in a randomized, double-blind, crossover design. A run-in period of two weeks was permitted at the beginning and between two therapies. At the end of each therapy, the patients were evaluated for the study parameters i.e. distance covered in 6-minute walk test, PAP by doppler echocardiography and quality of life (QOL) assessed by 'Minnesota Living with Heart-failure Questionnaire'. Statistical analysis was done using paired & un-paired 't' test ($p<0.05$).*
Results: *The mean distance covered in 6 minute walk test improved from 283.33 ± 56.81m to 422.17 ± 79.09m ($p<0.0001$) for primary and from 353.23 ± 56.61m to 406.09 ± 59.33m ($p<0.0001$) for secondary PAH after 6 wks treatment with sildenafil. PAP decreased from 85.94 ± 11.81 mm Hg to 38.78 ± 6.90 mm Hg ($p<0.0001$) for primary and from 52.14 ± 10.26 mm Hg to 41.68 ± 9.09 mm Hg for secondary PAH. Sildenafil shows very significant improvement in functional capacity by lowering the QOL score in both primary and secondary PAH ($p<0.0001$ and $p<0.0001$ respectively). No serious side effects of drug were observed in the study.*
Conclusion: *Sildenafil significantly improves exercise capacity and quality of life and decreases the PAP in both primary and secondary PAH. Therefore, oral sildenafil may be recommended as first-line or adjunctive treatment in PAH, particularly primary one.*
Keywords: *Sildenafil, placebo, primary and secondary pulmonary arterial hypertension.*

Introduction

Pulmonary arterial hypertension (PAH) is defined as a condition characterized by a progressive elevation of mean pulmonary arterial pressure to more than 25 mm of mercury (mm Hg) at rest or to more than 30 mm Hg with exercise.[1] Most of the patients present

with exertional dyspnoea, chest pain, syncope /near syncope, fatigue and lower extremity edema progressing over months to years.

PAH is of two types, primary or idiopathic without any identifiable cause and secondary due to different diseases like connective tissue diseases (e.g. scleroderma & CREST syndrome, mixed connective tissue disease), congenital heart diseases (e.g. ASD, PDA etc.), lung diseases (COPD, ILD etc), chronic thrombotic/ embolic diseases, diseases directly affecting the pulmonary vasculature, HIV and other serious infections.[2]

The prognosis of both primary and secondary PAH is not very promising. Progressive increase in pulmonary vascular resistance (PVR) and Pulmonary Arterial Pressure (PAP) often leads to right heart failure and premature death.

The management of PAH is limited and unsatisfactory. At present the pharmacological treatment options include conventional agents (calcium channel blockers, diuretics, digoxin), vasodilators, antiproliferative agents such as prostanoids and endothelin receptor antagonists [3,4]. The above treatment options are often limited, ineffective, costly and sometimes associated with serious complications. Therefore, there is an urgent need for a cheap, safe and effective oral therapy for the patients of PAH (both primary and secondary) for both short-term & long-term benefit.

Sildenafil, by inhibiting phosphodiesterase-5 (PDE-5), which metabolises c-GMP and which is up regulated in conditions associated with PAH, could be of benefit in PAH[5,6,7] .

It enhances nitric oxide mediated pulmonary vasodilatation and is believed to have additional beneficial effects on vascular remodelling and cardiac function. Sildenafil has been documented to be beneficial in animal models of PAH[8,9,10]. Its effectiveness in patients of idiopathic and secondary PAHhas also been demonstrated in several open-label and blinded randomised clinical trials [5,11,12] .

The aim of this study was to prospectively evaluate the effect of sildenafil on pulmonary arterial pressure, exercise capacity and QOL in patients with PAH of both primary and secondary types.

Materials and Methods

The protocol along with the 'informed patient consent form' was placed to Institutional Ethics Committee, R. G. Kar Medical College, Kolkata and prior permission was taken for conducting the study. Informed written consent was taken from all patients before enrolment.

Study Design: It was a single centre, randomized, placebo-controlled, double blind, cross-over study.

Study Setting: The screening, recruitment, and cardiological investigations were carried out in the department of cardiology and preparatory ground works, randomization, blinding, drug/placebo administration, follow-up and analysis of data were carried out in the department of Pharmacology, R.G. Kar Medical College, Kolkata.

Study Population: The patients who attended the OPD or admitted in indoor of cardiology department, on the basis of inclusion and exclusion criteria (Table 1).

Sample Size: Total 40 (forty) patients

Study Duration: One year seven months.

Study Parameters:

Primary: The primary end point parameter was change in walking capacity as judged by 6-minutes walk test (6MWT) after 6 weeks of treatment.

Secondary: The secondary end points included –

i) Change in pulmonary arterial pressure (PAP) as assessed by Doppler echocardiography (PR jet / TR jet method)

ii) Change in Quality of life (QOL) score as assessed by pre-designed 'Minnesota Living with Heart- failure Questionnaire'.

Method

Patients with PAH between 12 and 75 years of age of either gender were enrolled on the basis of inclusion/exclusion criteria (Table 1) and their written informed consent was taken. All the non-permitted medications (nitrates, vasodilators etc) were withdrawn. A run-in period of two weeks was given before collecting baseline data. Routine concomitant medications including digitalis, diuretics and oral anticoagulants were allowed to continue throughout the study.

Base-line investigations were done which included resting 12lead electrocardiography (ECG), chest X-ray, trans-thoracic Doppler echocardiography, walking/exercise capacity measured by 6-min walk test (6-MWT), complete hemogram and biochemical tests (urea, creatinine, total cholesterol, fasting blood sugar level, bilirubin, SGPT).

Quality of life (QOL) was assessed using pre-designed Minnesota Living with Heart Failure questionnaire. Then randomization of the patients was done, on the basis of computer generated random numbers and subjects were allocated into two groups, either sildenafil-first group or placebo-first group.

At base-line visit, patients were given either study drug (Sildenafil citrate) or placebo according to randomization. Initially, patients were given 25 mg sildenafil and repeated after 6 hours under observation. If there was no hypotension, then they were selected to give 50 mg thrice daily and were included in the study. The patients were followed up every two weeks for six weeks. At the end of the initial six weeks, 6-MWT, PAP by Doppler echocardiography, QOL assessment and all other base-line investigations were repeated. After cross-over, the patients underwent a two weeks wash-out period and new base-line investigations including the study parameters were carried out. In the second part of the study the patients were again followed up every two weeks. This second therapy was instituted for next six weeks and final parameters were carried out. No up or down titration of the study drug was permitted through-out the study.

Statistical Analysis

The relevant data were collected in the form of mean ± standard deviation (SD) from the raw data sheets. Changes in the efficacy parameters at baseline and at the end of placebo or study drug (Sldenafil) were analyzed using paired and un-paired 't-test'. A value of $p<0.05$ was considered significant.

Results

Total 61 (sixty one) subjects were screened for the study, of which 48 (forty eight) (78.69%) were recruited after inclusion/exclusion check and necessary investigations. As it was an intention-to-treat study, all patients who have completed at least first phase of the study (i.e. first 3 follow-up visits) were included in the study. Out of 48, total 43 (forty three) subjects completed the first phase of the study and 5 patients were lost after 1st baseline, 1st follow up or 2nd follow up visits.

Among the 43 subjects included in the study, 3 subjects completed only the first phase of the study, all were from placebo-first group and were secondary type (2 patients were due to COPD and the rest was due to bronchial asthma). Within the 40 (forty) subjects who completed the whole study and received end-of-trial certification, 18 (eighteen) subjects were with primary or idiopathic type and 22 (twenty two) subjects were with secondary/ associated pulmonary arterial hypertension. Among 22 secondary PAH patients, 9 patients were due to COPD, 4 patients were due to bronchial asthma, 6 patients were due to different valvular and congenital heart diseases like ASD, 2 patients were due to interstitial lung disease (ILD) and 1 patient was due to systemic sclerosis.

Out of total 43 subjects, 28 were male and the rest were female. 40 patients received both the study drug (sildenafil) and placebo in a cross-over design and 3 patients received only placebo after randomization into placebo-first and sildenafil-first groups.

Average age of primary PAH patients was 18.25 years and of secondary PAH was 32.80 years.

Overall compliance of the study subjects was excellent.

Effect on distance covered in 6 min walk test (6MWT)

The study shows significant increase in mean distance covered in 6 minutes on horizontal surface when the patients were treated with sildenafil for 6 weeks and it was extremely significant when compared to baseline value in both primary and secondary PAH ($p<0.0001$ and $p<0.0001$ respectively), though placebo therapy did not show any significant change. The improvement with sildenafil therapy is not only highly significant but

often dramatic in primary PAH (283.33 ± 56.81m to 422.17 ± 79.09m) than secondary PAH (353.23 ± 56.61m to 406.09 ± 59.33m); 49% vs 14.96% increase over baseline respectively. Both groups taken together, the improvement in the "6-minute walk" distance was found to be 28.45% over baseline. The distance and degree of oxygen desaturation during the 6MWT correlate with prognosis in patients with primary PAH[14]. A consistent improvement in the exercise capacity was also seen with sildenafil (Table 2).

Effect on Pulmonary Arterial Pressure (PAP):

Sildenafil caused highly significant decrease in pulmonary arterial pressure after 6 weeks therapy in both primary and secondary PAH when compared with the base-line values ($p<0.0001$ and $p<0.0001$ respectively). The reduction in mean pulmonary arterial pressure was more in patients with primary PAH (mean PAP from 85.94 ± 11.81 to 38.78 ± 6.90 mm of Hg) than secondary PAH (from 52.14 ± 10.26 to 41.68 ± 9.90 mm of Hg); 54.87% vs 20.06% reduction over baseline (Table 3). Taking both groups together, sildenafil significantly decreases PAP from baseline value (40.06%).

Effect on Quality of Life Scores

Quality of life (QOL) score was assessed out of total 105 score. Reduction of QOL score signifies improvement in functional capacity of the patient. Sildenafil showed highly significant improvement in functional capacity by significantly lowering the QOL score in both primary and secondary PAH (34.54% vs 24.88%) after 6 weeks of therapy ($p<0.0001$ and $p<0.0001$ respectively). Activity was significantly greater during phase sildenafil than phase placebo (Table 4).

Adverse effect profile

There was no significant change in systolic and diastolic BP, heart rate and body weight after taking placebo or sildenafil. There were no significant or serious adverse events noted with sildenafil, necessitating withdrawal of the drug in any patient. The minor adverse effects seen with sildenafil in this study were mild headache (6 cases), dyspepsia (5 cases), dizziness (4 cases), nasal congestion (4 cases), diarrhoea-vomiting (1 case) and vertigo (3 cases) which did not require any medications. There was no single case of priapism.

Table 1 Inclusion and exclusion criteria for selection of the patients with pulmonary arterial hypertension into the study

Inclusion Criteria	Exclusion Criteria
1. Patients with PAH of both primary & secondary cause. 2. PAP is more than 30mm of Hg. 3. Patients with NYHA class II&III and are able to walk 4. Adult age group between 12 to 75 years of age.	1. Patients with renal or hepatic dysfunction. 2. Patients aged less than 12years or more than 75 years and weighing less than 30 kg. 3. Patients showing severe hypotension on test dose and with other contraindications to Sildenafil. 4. Patients with NYHA class IV symptoms, coronary heart disease, severe Hypertension. 5. Patients taking vasodilator, especially nitrates, CCBs etc. 6. Pregnancy / lactation. 7. PAH due to HIV /any severe infections

Table 2 Effects of 6-weeks therapy with Placebo and Sildenafil on 6-min walk test (6-MWT) in primary and secondary pulmonary arterial hypertension patients

(Values are distance covered in meters)

Types of PAH	Placebo Therapy	Sildenafil Therapy
Primary PAH	(n=18)	(n=18)
At Baseline	285.44 ± 61.82	283.33 ± 56.81
At End of 6 wks	282.72 ± 57.67	422.17 ± 79.09 *#
Secondary PAH	(n=25)	(n=22)
At Baseline	366.12 ± 52.93	353.23 ± 56.61
At End of 6 wks	362.56 ± 50.90	406.09 ± 59.33*#
All cases of PAH	(n=43)	(n=40)
At Baseline	332.35 ± 69.06	321.78 ± 66.12
At End of 6 wks	329.14 ± 66.45	413.33 ± 68.47 *#

Values are Mean ± SD

* $p < 0.0001$ in Student's paired t test (within group before –after comparison)

# $p < 0.0001$ in Student's unpaired t test (between group comparison after 6 wks therapy)

Table 3 Effects of 6-weeks therapy with Placebo and Sildenafil on Pulmonary Arterial Pressure (PAP) in primary and secondary pulmonary arterial hypertension patients
(Values are in mm of Hg)

Types of PAH	Placebo Therapy	Sildenafil Therapy
Primary PAH	**(n=18)**	**(n=18)**
At Baseline	85.06 ± 13.29	85.94 ± 11.81
At End of 6 wks	87.17 ± 14.32	38.78 ± 6.90 *#
Secondary PAH	**(n=25)**	**(n=22)**
At Baseline	49.16 ± 7.55	52.14 ± 10.26
At End of 6 wks	50.40 ± 9.16	41.68 ± 9.90*#
All cases of PAH	**(n=43)**	**(n=40)**
At Baseline	64.19 ± 20.62	67.35 ± 20.19
At End of 6 wks	65.79 ± 21.63	40.37 ± 8.70 *#

Values are Mean ± SD
* p < 0.0001 in Student's paired t test (within group before –after comparison)
# p < 0.0001 in Student's unpaired t test (between group comparison after 6 wks therapy)

Table 4 Effects of 6-weeks therapy with Placebo and Sildenafil on Effect on Quality of Life Scores (QOL) in primary and secondary pulmonary arterial hypertension patients
(Value of scores out of total 105)

Types of PAH	Placebo Therapy	Sildenafil Therapy
Primary PAH	**(n=18)**	**(n=18)**
At Baseline	43.72 ± 7.14	43.11 ± 13.20
At End of 6 wks	44.28 ± 11.20	28.22 ± 6.92 *#
Secondary PAH	**(n=25)**	**(n=22)**
At Baseline	36.88 ± 8.45	38.18 ± 9.27
At End of 6 wks	38.84 ± 9.14	28.68 ± 6.69*#
All cases of PAH	**(n=43)**	**(n=40)**
At Baseline	39.74 ± 8.55	40.40 ± 11.33
At End of 6 wks	41.12 ± 10.29	28.47 ± 6.71 *#

Values are Mean ± SD
* p < 0.0001 in Student's paired t test (within group before – after comparison)
# p < 0.0001 in Student's unpaired t test (between group comparison after 6 wks therapy)

Discussion

The present placebo controlled randomized study shows that sildenafil citrate is very effective in reducing the pulmonary arterial pressure and improving functional status in patients of both primary and secondary PAH, like the previous studies[11,12,13], where as placebo shows no appreciable change. We also found that sildenafil causes more reduction of pulmonary arterial pressure in primary PAH patients and less in secondary PAH, though both showed significant reduction. The changes in PAP as measured by Doppler echocardiography, though an approximate estimate, but in a crossover design, these measurements do define the beneficial effect of the drug.

It was also found that, sildenafil was very effective in improving the exercise capacity , interpreted by observing the significant increase in distance covered in 6 minutes among the patients of both primary and secondary PAH.

The functional capacity of the patients was also significantly improved by 6 weeks sildenafil therapy, detected by significant lowering in QOL score with sildenafil from the baseline.

Therefore, after 6 weeks sildenafil therapy, the improvement in exercise tolerance, functional capacity and clinical status denotes an increase in cardiac output and a decrease in pulmonary vascular resistance which is corroborative with the findings of decrease in PAP with sildenafil.[4,5]

As a result of the crossover design of the study, each patient acted as his/her own control which had minimized inter-subject variability in results. A washout period of 2 weeks between the two therapies was allowed to abolish any carryover effect of the drug in the placebo arm subsequently.

The short duration of the study, small sample size and non-invasive efficacy parameters were the limitations, though sub maximal exercise testing (6MWT) has been particularly useful in evaluating the efficacy of drug therapy and was independently related to mortality in primary pulmonary hypertension in the previous studies[11, 13, 14].

Conclusion

In conclusion our study showed that sildenafil citrate significantly improves exercise tolerance and quality of life and decreases the pulmonary arterial pressure in patients with primary and secondary PAH. In fact, there was an overall symptomatic improvement in the clinical status of all patients in all the parameters assessed. The betterment effects were more among primary PAH than the secondary

one. As the other treatment options are very costly and all are not available in the developing countries like India, oral sildenafil may be recommended as a first-line or adjunctive treatment in patients with pulmonary arterial hypertension, particularly the primary one.

It is too early to predict the long term benefits of sildenafil therapy. Further studies are needed to evaluate long-term efficacy, safety, survival advantage and its role as an adjuvant drug with other drugs in a larger sample.

Acknowledgement

We are acknowledging the support and helps of the Department of Pharmacology and Department of cardiology, R.G. Kar Medical College and Hospital, Kolkata.

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