

## CLINICAL RESEARCH

## Clinical Trial

# Clinical Efficacy of Sildenafil in Primary Pulmonary Hypertension

## A Randomized, Placebo-Controlled, Double-Blind, Crossover Study

B. K. S. Sastry, DM, C. Narasimhan, DM, N. Krishna Reddy, DM, B. Soma Raju, DM  
*Hyderabad, India*

<b>OBJECTIVES</b>	In a randomized, double-blind, crossover design, we compared the efficacy of sildenafil with placebo in patients with primary pulmonary hypertension (PPH). The primary end point was the change in exercise time on treadmill using the Naughton protocol. Secondary end points were change in cardiac index and pulmonary artery systolic pressure as assessed by Doppler echocardiography and quality of life (QOL) as assessed by a questionnaire.
<b>BACKGROUND</b>	Primary pulmonary hypertension is a disorder with limited treatment options. Uncontrolled studies had shown sildenafil to be beneficial in the treatment of PPH.
<b>METHODS</b>	After initial clinical evaluation, including Doppler echocardiography and treadmill exercise test, patients were randomized to placebo or sildenafil with dosages ranging from 25 to 100 mg thrice daily on the basis of body weight. The evaluation was repeated after six weeks. Then patients were crossed over to alternate therapy. Final evaluation was performed after another six weeks of treatment.
<b>RESULTS</b>	Twenty-two patients completed the study. Exercise time increased by 44% from $475 \pm 168$ s at the end of placebo phase to $686 \pm 224$ s at the end of sildenafil phase ( $p < 0.0001$ ). With sildenafil, cardiac index improved from $2.80 \pm 0.9$ l/m <sup>2</sup> to $3.45 \pm 1.1$ l/m <sup>2</sup> ( $p < 0.0001$ ), whereas pulmonary artery systolic pressure decreased insignificantly from $105.23 \pm 17.82$ mm Hg to $98.50 \pm 24.38$ mm Hg. There was significant improvement in the dyspnea and fatigue components of the QOL questionnaire. During the placebo phase, one patient died and another had syncope. There were no serious side effects with sildenafil.
<b>CONCLUSIONS</b>	Sildenafil significantly improves exercise tolerance, cardiac index, and QOL in patients with PPH. ( <i>J Am Coll Cardiol</i> 2004;43:1149–53) © 2004 by the American College of Cardiology Foundation

Primary pulmonary hypertension (PPH) is an uncommon disorder of unknown etiology characterized by progressive elevation of pulmonary vascular resistance and pulmonary artery pressure that often leads to right heart failure and death (1–3). The current management of this condition is limited and unsatisfactory and includes the use of oral anticoagulants; calcium channel blockers; continuous intravenous administration of prostacyclin, bosentan, beraprost, or iloprost; atrial septostomy; and lung transplantation (4–13).

A number of uncontrolled studies have reported the beneficial effect of sildenafil in the treatment of PPH (14–17). Sildenafil inhibits cyclic guanosine monophosphate-specific phosphodiesterase-5, an enzyme that is abundantly present in pulmonary vasculature and leads to nitric oxide-mediated vasodilatation, which in turn decreases pulmonary vascular resistance (18,19). It has been shown to be a potent pulmonary vasodilator in a lamb model of pulmonary

hypertension (20). However, no randomized controlled trial on the efficacy of sildenafil in PPH has been reported.

In this study, we report the results of a randomized, double-blind, placebo-controlled, crossover trial comparing the efficacy of sildenafil and placebo in patients with PPH. The primary end point was a change in exercise time on treadmill using the Naughton protocol. The secondary end points were changes in pulmonary artery systolic pressure and cardiac output, as assessed by echo Doppler evaluation, and change in quality of life (QOL) score, as assessed by a heart failure questionnaire (21). The study protocol was approved by Institutional Ethics Committee and Drugs Controller General of India, and all patients signed a written informed consent before randomization.

## METHODS

Patients with PPH between 12 and 65 years of age of either gender were invited to participate in the study. The following were conducted: history, physical examination, 12-lead electrocardiogram, Doppler echocardiogram, chest X-ray, arterial blood gas analysis, pulmonary function test, and a lung perfusion scan or spiral computed tomographic angiography. Patients were included in the study if they were in New York Heart Association (NYHA) functional class II to

From the Department of Cardiology, CARE Hospital, Hyderabad, India. This study has been supported and funded by CARE Foundation and was conducted in CARE Hospital, Hyderabad, India. The CARE Foundation is a not-for-profit organization and supports clinical research.

Manuscript received July 27, 2003; revised manuscript received September 25, 2003, accepted October 19, 2003.

**Abbreviations and Acronyms**

NYHA = New York Heart Association  
 PPH = primary pulmonary hypertension  
 QOL = quality of life

III, had an estimated pulmonary artery mean pressure more than 30 mm Hg on Doppler echocardiography, and were able to walk on a treadmill. Exclusion criteria included NYHA functional class IV, significant right-to-left shunt, valvular heart disease, left ventricular systolic dysfunction, systemic hypertension, secondary pulmonary hypertension, and other severe co-morbid conditions.

Doppler echocardiographic evaluation was performed on a Sonos 4500 (Hewlett Packard Company, Andover, Massachusetts) echocardiographic machine. Pulmonary artery pressures were obtained from tricuspid and pulmonary regurgitation jet velocity tracings (22,23). Cardiac output was measured from velocity time integral of aortic flow, left ventricular outflow tract diameter measured at the aortic annulus, heart rate, and a mean of five values was taken (24). Exercise time was monitored on a treadmill (Centra of Marquette Medical Systems Inc., Milwaukee, Wisconsin) using the Naughton protocol. The patient, clinical investigator, echocardiographer, and the person supervising the exercise were blinded to the patient's treatment regimen.

Quality of life was assessed using a chronic heart failure questionnaire (21). The questionnaire has a total of 16 questions, including five questions to assess dyspnea, four questions to assess fatigue, and seven questions to assess emotional function of daily living. The answers to each question may be scored from 1 (denoting worst function) to 7 (denoting best function). The maximum possible score of 108 would denote the best QOL, whereas a minimum score of 16 would denote worst QOL.

After treadmill, echo Doppler, and QOL assessment at baseline, patients were randomized to drug or placebo in a double-blind manner. Randomization was performed on the basis of computer-generated random numbers. Medication dosage was assigned on the basis of body weight, with patients weighing up to 25 kg receiving 25 mg thrice daily, those weighing between 26 and 50 kg receiving 50 mg thrice daily, and those weighing >51 kg receiving 100 mg thrice daily. Digoxin, diuretics, and oral anticoagulants were used at the clinician's discretion. No other vasodilators were allowed, and patients were specifically advised not to take nitrate preparations in any form. Patients were followed up every two weeks for six weeks. After six weeks, treadmill, Doppler echocardiography, and QOL assessment were repeated, and patients were crossed over to the alternate therapy. Patients were again followed up every two weeks for another six weeks when the final treadmill, echo Doppler evaluation, and QOL assessment were made.

**Statistical analysis.** Our earlier uncontrolled observational study had shown 40% improvement in exercise tolerance

**Table 1.** Baseline Characteristics of Study Patients (n = 22)\*

Age range (yrs)	16-55
Gender	
Male	10
Female	12
NYHA	
Class II	18
Class III	4
Duration of symptoms (months)	1-180 (30)†
Pulmonary artery systolic pressure (mm Hg)	107.36 ± 24.98
Cardiac index (l/m <sup>2</sup> )	2.83 ± 1.06
Exercise time (s)	440.09 ± 172.17
Quality of life‡	
Dyspnea	21.86 ± 6.47
Fatigue	20.38 ± 5.12
Emotional function	34.14 ± 10.38

\*Plus and minus values are means ± SD. †Median of duration of symptoms is 30 months. ‡Higher score indicates better quality of life.  
 NYHA = New York Heart Association.

with sildenafil (16). On the basis of this result, we calculated that we would require a sample size of 18 patients to demonstrate 40% improvement with 99% statistical power on the primary end point exercise capacity. We proceeded with an objective of enrolling 30 patients with an interim analysis after 20 patients completed the study. The intention-to-treat principle was applied in the analysis, and for missing observations, the last observation carried forward was done. Changes in all continuous variables measured at baseline and end of placebo or end of the study drug were analyzed using paired *t* test, and a value of *p* < 0.05 (two-sided) was considered significant.

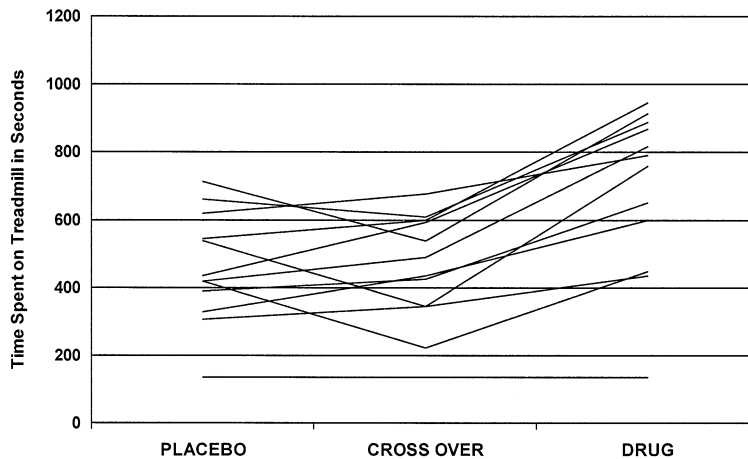
**RESULTS**

We enrolled 22 patients between September 17, 2002, and December 13, 2002. The baseline characteristics of these patients are given in Table 1. All patients had a peak pulmonary artery systolic pressure of more than 70 mm Hg and a mean pulmonary artery pressure above 30 mm Hg. Of the 22 patients, 12 were randomized first to placebo (placebo-first group) and 10 to sildenafil (sildenafil-first group).

**Table 2.** Frequency of Adverse Effects Noted With Sildenafil and Placebo During the Trial Period\*

Effect	Sildenafil	Placebo
Body aches	1	2
Backache	3	1
Headache	3	1
Insomnia	2	3
Leg pains	3	6
Numbness of hands and feet	4	1
Anorexia	3	3
Nausea and vomiting	1	5
Abdominal discomfort	3	6
Constipation	3	0
Giddiness	1	4
Syncope	0	1
Death	0	1

\*Denotes number of patients with adverse event.



**Figure 1.** Change in exercise time during the study in placebo-first group (n = 12). The y-axis shows time spent on treadmill, using Naughton Protocol, in seconds. p = 0.83 for baseline versus end of placebo phase; p < 0.001 for end of placebo phase to end of sildenafil phase.

One patient in the sildenafil first group opted out of the study one week after randomization. This was not the result of any serious adverse effect of medication. Another patient in the placebo-first group died one week after randomization. One patient had syncope at rest while receiving the placebo. All other patients tolerated sildenafil well except for minor adverse events, as noted in the Table 2. No patients discontinued the medication because of adverse events. There was no significant change in the systemic blood pressure during sildenafil therapy.

In the placebo-first group (Fig. 1), exercise time at baseline was  $459.6 \pm 164.1$  s, and it was  $452.1 \pm 165.6$  s at the end of the placebo phase. This increased significantly to  $687 \pm 243.9$  s by the end of the sildenafil phase (p < 0.0001). In the sildenafil-first group (Fig. 2), exercise time at baseline was  $451.6 \pm 189.6$  s, and it increased to  $698.1 \pm 272.9$  s at the end of the sildenafil phase (p < 0.001). By the end of the placebo phase, it decreased significantly to  $527.4 \pm 181.6$  s (p < 0.005), but compared with baseline, it was still significantly higher (p < 0.001).

In both the groups together, the exercise time increased

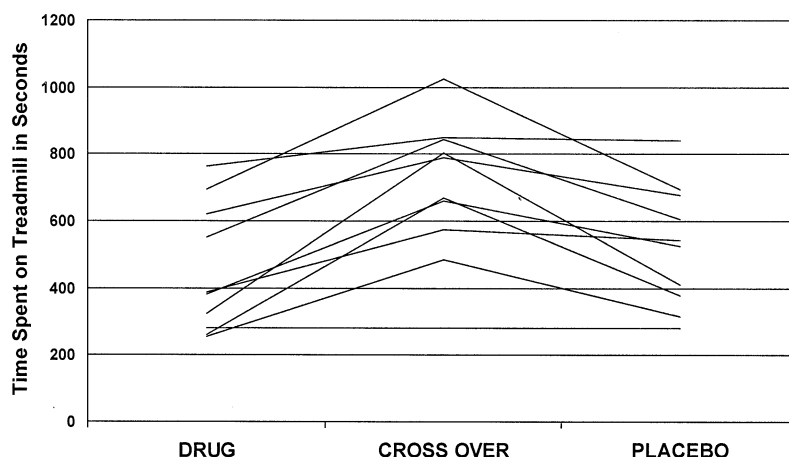
from mean of  $475 \pm 168$  s at end of placebo therapy to  $686 \pm 224$  s after 6 weeks of sildenafil therapy (p < 0.0001) (Table 3). The improvement in exercise time with sildenafil was seen in all patients (Figs. 1 and 2).

Cardiac index improved significantly from  $2.80 \pm 0.90$  l/m<sup>2</sup> at the end of placebo phase to  $3.45 \pm 1.16$  l/m<sup>2</sup> at the end of six weeks of sildenafil therapy (p < 0.0001) (Table 3). Pulmonary artery systolic pressure decreased from  $105 \pm 17$  mm Hg at the end of placebo phase to  $98 \pm 24$  mm Hg at the end of sildenafil phase, but this is not statistically significant (p = 0.09).

There was a significant improvement in the dyspnea and fatigue components of the QOL score. However, the change in the emotional function component of QOL was marginal (Table 3).

## DISCUSSION

Primary pulmonary hypertension is an uncommon disorder with few treatment options. Calcium channel blockers are useful in only the 10% to 15% of patients who respond



**Figure 2.** Change in exercise time during the study in sildenafil-first group (n = 10). The y-axis shows time spent on treadmill, using Naughton protocol, in seconds. p ≤ 0.005 for baseline versus end of sildenafil phase, for end of sildenafil versus end of placebo phase, and for baseline versus end of placebo.

**Table 3.** Comparison of Efficacy of Sildenafil With Placebo (n = 22)\*

	End of Placebo Phase	End of Sildenafil Phase	p Value
Exercise time on treadmill (s)	475.05 ± 168.02	686.82 ± 224.02	< 0.0001
Cardiac index (l/m <sup>2</sup> )	2.80 ± 0.90	3.45 ± 1.16	< 0.0001
Pulmonary artery systolic pressure (mm Hg)	105.23 ± 17.82	98.50 ± 24.38	0.09
Quality of life†			
Dyspnea	17.62 ± 5.68	21.95 ± 6.02	0.009
Fatigue	20.67 ± 5.19	22.33 ± 4.82	0.04
Emotional function	34.71 ± 10.91	37.33 ± 9.32	0.06

\*Plus minus values are means ± SD. †Higher score indicates better quality of life.

favorably to acute vasodilator challenge (4). At present, continuous intravenous infusion of prostacyclin is considered the landmark of care. This therapy significantly improves effort tolerance, decreases pulmonary vascular resistance, and increases cardiac output (5,6). In one study, the 6-min walk distance improved by an average of 32 m, compared with a decrease of 15 m in the placebo group. Cardiac output increased by 0.3 l/min/m<sup>2</sup> in the prostacyclin group, whereas it decreased by 0.2 l/min/m<sup>2</sup> in the placebo group (7). However, this therapy is expensive, tedious to administer, and may be associated with serious complications, such as sepsis.

Oral bosentan, an endothelin receptor antagonist, also has shown to improve the 6-min walk distance by 35 to 54 m compared with placebo (8) and to marginally improve cardiac output by 0.4 l/min/m<sup>2</sup> (9). Beraprost, an oral analog of prostacyclin, increased the 6-min walk distance by 45 m compared with placebo (10). Likewise, iloprost, another prostacyclin analog, increased the 6-min walk distance by 57 m (11). Mean pulmonary artery pressure was reduced by about 10% to 20%, an effect that seems superior to nitric oxide inhalation. It also caused significant improvement in clinical status. However, because of the transient effects of iloprost inhalation, 6 to 12 doses of the drug a day may be required.

Thus, overall improvement in the 6-min walk distance in these trials was 12% to 21% over a baseline of 226 to 372 m (5-11). Compared with this, oral sildenafil led to significant and often dramatic improvement in functional capacity in previous uncontrolled studies. Our earliest uncontrolled study (16) showed a mean improvement of 225 m (40% over baseline) in the 6-min walk distance. To assess the functional capacity more objectively, we chose the Naughton exercise protocol in this study and used a crossover design, with each patient acting as his or her own control. A consistent improvement in the exercise capacity was seen with sildenafil that tended to decrease upon withdrawal of the drug. However, this did not reach the baseline, suggesting some carryover effect.

Although measurement of the absolute change in cardiac output and pulmonary artery pressures by Doppler echocardiography may not be very accurate, the directional changes in these measurements are more reliable when patients act as their own controls. The improvement in cardiac index was associated with a parallel improvement in functional

capacity. The decrease in pulmonary artery systolic pressure, although insignificant, occurred while the cardiac output increased, suggesting that pulmonary vascular resistance fell. This benefit in hemodynamic parameters was associated with an improvement in dyspnea and fatigue components of QOL.

This was a short-term study that was not designed to comment on the survival advantage. However, there was one death and one episode of syncope in the placebo arm of the study. None of the patients had syncope or any other serious adverse event while receiving sildenafil. Our previous observational study showed a survival advantage with sildenafil compared with historical controls, and patients tolerated the drug for over two years without major adverse events (16).

One of the limitations of our study was that, because this was a crossover study, there should have been a washout period. In the absence of a washout period, the sildenafil effect got carried over into the placebo phase of sildenafil-first group (Fig. 2), and this would only blunt the overall beneficial effect of sildenafil. Despite this, exercise time was significantly greater with sildenafil, further confirming its superiority over placebo. Another limitation of the study was that hemodynamic evaluation was performed by non-invasive methods. However, the primary objective was to assess the change in functional capacity in the patients. Finally, the duration of the study may be considered too short, but it was associated with hemodynamic and clinical benefit. Long-term safety and survival advantage cannot be concluded from the study.

In conclusion, sildenafil significantly improves effort tolerance, cardiac output, and QOL in patients with PPH and may be a reasonable first-line therapy in these patients. However, further studies are required to establish long-term safety and efficacy of sildenafil, its additive benefit with other drugs, if any, and its role in secondary forms of pulmonary artery hypertension.

#### Acknowledgments

The authors gratefully acknowledge the help given by Dr. V. Laxmi Narayana in conducting the study, Dr. I. S. Anand for his suggestions in preparing the manuscript, and Dr. B. Anand for his help in statistical analysis.

**Reprint requests and correspondence:** Dr. B. K. S. Sastry, Cardiologist, CARE Hospital, Exhibition Road, Nampally, Hyderabad. AP, India 500 001. E-mail: bkssastry@hotmail.com.

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