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Effect of sildenafil in the management of preoperative pulmonary hypertension

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KEYWORDS

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Abstract *Background:* Pulmonary arterial hypertension (PAH) is a disabling chronic disorder of the pulmonary vasculature, which is characterized by increased pulmonary artery pressure (PAP) as a result of increased pulmonary vascular resistance (PVR). The most accepted hemodynamic definition of PH is a mean PAP >25 mmHg. It is accidentally discovered preoperatively through performing an echocardiogram in patients suspected of having PH, as these patients suffer from dyspnea which is the most frequently presenting symptom. Additional symptoms include fatigue, weakness, angina, syncope, and lower limb edema. The aim of the study was to evaluate the efficacy and safety of preoperative oral sildenafil administration in the management of pulmonary hypertensive patients scheduled for non-cardiac surgery.

Patients and methods: 30 Patients, (ASA II–III), suffering from pulmonary hypertension and scheduled for non-cardiac surgery were randomly assigned to one of two groups. Group I received 25 mg sildenafil twice daily for one week before surgery. Group II received placebo in the same way. PAP, LVEF and RVEF (through echocardiogram), heart rate, mean arterial blood pressure, SpO2 (oxygen saturation), functional class and 6-min walk distance were measured and recorded at baseline and one week after treatment in both groups.

Results: Sildenafil significantly reduced PAP and improved exercise tolerance, functional class, 6-min walk distance and SpO2 without significant alteration of heart rate and mean arterial blood pressure.

Conclusion: The study showed effective and safe administration of preoperative oral sildenafil in the management of pulmonary hypertensive patients scheduled for non-cardiac surgery.

1. Introduction

Pulmonary arterial hypertension (PAH) is a syndrome characterized by symptoms of dyspnea, fatigue, chest pain, and syncope. Underlying mechanisms are a progressive increase of pulmonary vascular resistance and a sustained elevation of pulmonary arterial pressure to more than 25 mmHg at rest.[1] It may lead to a decreased functional capacity, and right

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ventricular failure, and is often associated with early death.[2,3] PAH can be classified into five main categories according to the updated clinical classification of PAH.[1] Sildenafil is a selective inhibitor of type 5 phosphodiesterase (PDE), the predominant PDE isoform responsible for hydrolysis of intracellular cyclic guanosine monophosphate (cGMP), in the pulmonary vasculature.[4] Many studies were done on the effect of sildenafil on pulmonary hypertension, but no research has been done on its use in the preoperative management of patients with pulmonary hypertension. The aim of the study was to evaluate the efficacy and safety of sildenafil in the preoperative preparation of pulmonary hypertension patients scheduled for non-cardiac surgery.

2. Patients and methods

The protocol was approved by the faculty of medicine, Menoufiya university medical ethics committee and patients gave written informed consent. Thirty patients of both sex and aged 20–60 years admitted during 1 year period to Menoufiya University Hospitals with ASA physical status I–III and pulmonary hypertension scheduled for non-cardiac surgery, were allocated to one of two parallel groups (control, $n = 15$ and sildenafil, $n = 15$). Exclusion criteria included patients with class IV PAH, hemodynamic instability, patients taking nitrates and known allergy to the study drug.

The sildenafil group (group I) received 25 mg of oral sildenafil twice daily and the control group (group II) received placebo for 1 week during hospital admission. Before starting treatment baseline assessment of all patients was done including heart rate mean arterial blood pressure, SpO2, 6-minute walk distance, exercise tolerance (assessed through NYHA class)[5] and echocardiography to show PAP, LVED, EF. Also visual abnormalities (blurred vision or color vision abnormalities), liver enzymes and creatinine levels were recorded. These parameters were also measured and recorded one week after treatment. To determine the efficacy of sildenafil for the advanced treatment of PAH various endpoints have been investigated. Some were invasive and others were less invasive endpoints as the World Health Organization (WHO) functional class and the total distance walked in 6 min (6MWD) were also used to examine treatment efficacy.[6] The use of the World Health Organization modified functional classification (FC) scale allows for standardized grading.[7] The functional class ranges from class I representing PAH without limitation of physical activity to class IV meaning PAH with inability to carry out any physical activity without symptoms. The six-minute walking distance (6MWD) is an exercise test with outcome in meters. Benefit of the 6MWD is the simplicity, and the ease of its application.[8] The validity of the 6MWD is questionable in patients with an intellectual disability.[9,10]

Statistical analysis was performed using Student's *t*-test for quantitative data which are expressed as mean ± SD and chi-squared test for categorical data which are presented as number of patients (*n*). $P < 0.05$ was considered statistically significant.

3. Results

Thirty patients, presented with pulmonary hypertension, ASA physical status II–III and scheduled for non-cardiac surgery participated in the present study. They were classified into two equal groups (sildenafil, $n = 15$ and placebo, $n = 15$). The groups were comparable with respect to age, sex, weight and height (Table 1).

There was a non significant decrease in heart rate and mean arterial blood pressure in the sildenafil group more than the placebo group and between the basal measurement and after 1 week of treatment in the sildenafil group. In the sildenafil group, nine patients of NYHA class II–III showed improvement in functional class (from class III, 4 patients improved to class II and one improved to class I plus 4 improved from class II to class I). Overall 9/15 patients (60%) demonstrated improvement in overall health and well-being, with a significant difference ($P = 0.042$) after 1 week of treatment with sildenafil, while group II showed only improvement of 1 patient from NYHA class II to class I (1/15, 6.66%) (Table 2). Improvement was also noted in physical activity and patients reported that by the end of the study they were able to climb stairs and walk longer distances. This was approved by a significant increase in the 6-minute walk distance test (from 294.4 ± 12.36 to 305.73 ± 13.06 m, $P = 0.021$) between baseline and 1 week after treatment (Table 3) and a significant difference ($P < 0.001$) between the two groups (Table 5). Also, there was a significant decrease in mean PAP (from 49.47 ± 15.72 at baseline to 38.67 ± 10.81, $P = 0.037$) (Table 3) and between the two groups (from 48.93 ± 14.04 in the placebo group to 38.67 ± 10.81 in the sildenafil group, $P = 0.033$) (Tables 4 and 5) as detected through transthoracic echocardiography. There was a non significant improvement of right and left ventricular functions which could be detected by the improvement of FS and EF after sildenafil treatment in

Table 1 Baseline demographic data.

	Group I	Group II
Number	15	15
Age (years)	49.93 ± 10.12	49.6 ± 10.15
Sex (female/male)	3/12	4/11
Weight (kgs)	84.0 ± 7.12	82.93 ± 6.94
Height (cm)	172.6 ± 4.15	171 ± 4.33
NYHA class		
I	2	2
II	7	8
III	6	5

Group I: sildenafil, Group II: placebo, NYHA: New-york Heart Association, Data are expressed as number of patients and mean ± SD.

Table 2 NYHA class in 2 groups.

	Group I		Group II	
	Baseline	Week 1	Baseline	Week 1
I	2	7	2	3
II	7	7	8	7
III	6	1	5	5
P value	0.042*		0.875	

Group I: sildenafil, Group II: placebo. Data are presented as number of patients.
* $P < 0.05$ significant between two groups.

Table 3 Hemodynamic, 6-min walk spo_2 values before and after sildenafil administration (Group I).

	Base line	Week 1	*P* value
Heart rate	81.13 ± 6.8	77.53 ± 4.61	0.1
MAP	97.27 ± 7.31	91.8 ± 8.08	0.06
PAP	49.47 ± 15.72	38.67 ± 10.81*	0.037
EF	53.87 ± 4.49	54.4 ± 3.85	0.731
FS	29.53 ± 4.03	30.27 ± 3.53	0.597
6-min walk	294.4 ± 12.36	305.73 ± 13.06*	0.021
SpO_2	92.53 ± 1.6	94.2 ± 1.21*	0.003

Data are presented as mean ± SD.
* $P < 0.05$ significant between two groups.

Table 4 Hemodynamic, 6-min walk SpO_2 values before and after placebo administration (Group II).

	Base line	Week 1	*P* value
Heart rate	80.07 ± 5.99	79.6 ± 6.3	0.836
MAP	97.87 ± 9.04	96 ± 10.35	0.06
PAP	48.73 ± 15.94	48.93 ± 14.04	0.971
EF	51.8 ± 3.75	51.8 ± 3.65	1.00
FS	29.93 ± 3.92	30.0 ± 3.91	0.961
6-min walk	289 ± 10.44	289.6 ± 9.47	0.87
SpO_2	93.13 ± 1.41	93.27 ± 1.22	0.773

Data are presented as mean ± SD.

Table 5 One week characterstics of study subjects.

	Sildenafil	Placebo	*P* value
Heart rate	77.53 ± 4.61	79.6 ± 6.3	0.313
MAP	91.8 ± 8.08	96 ± 10.35	0.226
PAP	38.67 ± 10.81	48.93 ± 14.04*	0.033
EF	54.4 ± 3.85	51.8 ± 3.65	0.068
FS	30.27 ± 3.53	30.0 ± 3.91	0.844
6-min walk	305.73 ± 13.06	289.6 ± 9.47†	< 0.001
SpO2	94.2 ± 1.21	93.27 ± 1.22*	0.045

Data are presented as mean ± SD.
* $P < 0.05$ significant.
† $P < 0.001$ highly significant between two groups.

group I (Table 3) and between sildenafil and placebo groups (Tables 4 and 5). There was a significant increase in SpO2 (from 92.53 ± 1.6 at baseline to 94.2 ± 1.21, after sildinafil treatment $P = 0.003$) (Table 3) and in between the two groups (from 93.27 ± 1.22 in the placebo group to 94.2 ± 1.21 in the sildenafil group, $P = 0.045$) (Tables 4 and 5). There were no significant hemodynamic or other clinical and laboratory adverse effects between the two groups except for headache which increased significantly in the sildenafil group (Table 6).

Table 6 Clinical and laboratory adverse effects.

	Sildenafil	Placebo
Bleeding	0	0
Arrhythmia	1	1
Syncope	0	0
Headache	7*	1
Flushing	2	1
Visual dist.	0	0
↑liver enzyes	0	0
↑creatinine	0	0

Data are presented as number of patients.
* $P < 0.05$ significant between two groups.

4. Discussion

This study evaluated sildenafil as a preoperative treatment of PAH. Administration of oral sildenafil (25 mg twice daily) for 1 week was safe and led to improvement of functional class, exercise capacity and hemodynamics with no systemic side effects.

The present study showed a selective pulmonary vasodilation effect of sildenafil which was approved by the significant decrease of PAP, as sildenafil is a specific phosphodiestrase-5 inhibitor with acute and chronic hemodynamic effects in patients with pulmonary hypertension.[11,12] PDE-5 is an enzyme present in the lung and penile tissue which causes hydrolysis of c-GMP to inactive compounds.[13] Inhibition of PDE-5 by PDE-5 inhibitors as sildenafil increases c-GMP concentrations, which promotes vasodilatation.[14]

The study also showed a significant increase in exercise tolerance and 6-minute walk distance which occurred as a result of improvement of pulmonary hemodynamics and right ventricular function evidenced by an increase of RVEF.[15] Also increase cardic output is another cause reported by studies done by Gregory and others[16] who showed the improvement of exercise hemodynamics and oxygen uptake in patients with systolic heart failure after sildenafil treatment and Sastry and others[17] who studied the clinical efficacy of sildenafil in primary pulmonary hypertension. These observations are consistent with those of Sastry and colleagues,[17] Singh and colleagues[18] who found that sildenafil significantly improves the symptomatic status exercise capacity, NYHA class and hemodynamic parameters of patients with severe pulmonary artery hypertension, and Galie and colleagues[19] who reported improvement of exercise capacity, WHO functional class, and hemodynamics in patients with symptomatic pulmonary arterial hypertension. Furthermore, there was a significant increase in systemic oxygen saturations. A study done by Ghofrani and others[20] in patients with severe lung fibrosis and secondary pulmonary hypertension demonstrated that sildenafil acts as a selective pulmonary vasodilator and led to improved gas exchange by recruiting selectively well-ventilated areas of the lung. We did not specifically measure gas exchange in our patients. Hence, it remains unclear whether the increased oxygen saturations observed in the present study due to improved lung ventilation/perfusion matching, improved CO, and a reduction in right-to-left cardiac shunting either separately or in combination, these observations were matched with a study done by Mikhail and colleagues[21] who studied the acute and mid-term clinical and hemodynamic effects of sildenafil in pulmonary hypertension.

Adverse events as elevated liver enzymes, increased creatinine concentration, prolonged bleeding time and clinical side effects (visual disturbances, arrhythmia) did not differ between sildenafil and the placebo groups except for headache which occurred more in the sildenafil group 7/15 (46.7%) than in

the placebo group 1/15 (6.7%, $P = 0.039$). These observations documented the safe use of sildenafil in preoperative management as found by studies done by Michelakis and colleagues[15] and Gregory and others.[16]

In conclusion, the present study showed, one week of preoperative treatment with oral PDE-5 inhibitor sildenafil is a new and safe approach to achieve selective pulmonary vasodilatation in patients scheduled for non-cardiac surgery. As sildenafil in this study decreased PAP, improved exercise tolerance, functional class, 6-min walk distance, oxygen saturation and RVF with insignificant side effects.

Conflict of interest

None declared.

References

1. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix CP, Denton CP, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;**54**(Suppl. 1):S43–54.
2. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, et al. Eisenmenger syndrome. Factors relating to deterioration and death. *Eur Heart J* 1998;**19**(12):1845–55.
3. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med* 2004;**351**(16):1655–65.
4. Mark JS, Jeroen CV, Marielle GD, Berto J, Barbara JM. Adult patients with pulmonary arterial hypertension due to congenital heart disease: a review on advanced medical treatment with bosentan. *Ther Clin Risk Manag* 2010;**6**:359–66.
5. Stuart DR, Matthew AS, Jennifer LR, Myrvin HE, Stephen SG, Eileen MH, et al. New York heart association functional class predicts exercise parameters in the current era. *Am Heart J* 2009 October;**158**(Suppl. 4):S24–30.
6. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;**132**(8):919–23.
7. Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;**43**(12 Suppl. S):S40–7.
8. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000;**161**(2 Pt 1):487–92.
9. Vis JC, Thoonsen H, Duffels MG, de Bruin-Bon RA, Husiman AP, Van-Dijk AP, et al. Six-minute walk test in patients with Down syndrome: validity and reproducibility. *Arch Phys Med Rehabil* 2009;**90**(8):1423–7.
10. Duffels MG, Vis JC, Van Loon RL, Nieuwkerk PT, Van Dijk AP, Hoendermis ES, et al. Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without Down's syndrome. *Am J Cardiol* 2009;**103**(9):1309–15.
11. Bhatia S, Frantz RP, Severson CJ, Durst LA, McGoon MD. Immediate and long-term hemodynamic and clinical effects of sildenafil in patients with pulmonary arterial hypertension receiving vasodilator therapy. *Mayo Clin Proc* 2003;**78**:1207–13.
12. Michelakis E, Tymchak W, Noga M, Webster L, Wu Xc, Lien D, et al. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitricoxide. *Circulation* 2002;**105**:2398–403.
13. Corbin JD, Beasley A, Blount MA, Francis SH. High lung PDE5: a strong basis for treating pulmonary hypertension with PDE5 inhibitors. *Biochem Biophys Res Commun* 2005;**334**:930–8.
14. Joe R, Anderson, James J. Nawarskas: pharmacotherapeutic management of pulmonary arterial hypertension. *Cardiol Rev* 2010;**18**:148–62.
15. Michelakis ED, Tymchak W, Noga M, Weebster 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.
16. Gregory DL, Justine Lachmann, Janice Camuso, John JL, Jordan E, Maryann E, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. *Circulation* 2007;**115**:59–66.
17. Sastry BK, Narasimhan C, Reddy NK, Raju BS. Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, doubleblind, crossover study. *J Am Coll Cardiol* 2004;**43**:1149–53.
18. Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R. A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. *Am Heart J* 2006;**151**:851.
19. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil use in pulmonary arterial hypertension (SUPER) study group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006;**354**:2400–1.
20. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski N, Weissmann N, et al. Sildenafil for the treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet* 2002;**360**:895–900.
21. Mikhail GW, Prasad SK, Li W, Rogers P, Chester AH, Bayne S, et al. Clinical and haemodynamic effects of sildenafil in pulmonary hypertension: acute and mid-term effects. *Eur Heart J* 2004;**25**(5):431–6.