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A comparison of two different doses of sildenafil in pulmonary arterial hypertension –a prospective randomized controlled study

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Abbreviations: PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; PAP, pulmonary artery pressure; MAP, mean arterial pressure; Hb, haemoglobin; PCV, packed cell volume; TLC, total leukocyte count; DLC, differential leukocyte count; ECG, electrocardiogram; Spo2, oxygen saturation; NIBP, non-invasive blood pressure; HR, heart rate; SBP, systolic blood pressures; DBP, diastolic blood pressures; RR, respiratory rate; IV, intravenous; MAP, mean arterial pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index

Introduction

Pulmonary arterial hypertension (PAH) is characterized by a progressive rise in pulmonary vascular resistance (PVR)[1–3] resulting from vascular remodeling; vasoconstriction; and cellular proliferation.[4] Sildenafil is a selective and potent inhibitor of PDE5 which specifically degrades cyclic guanosine monophosphate and is found in high concentrations in pulmonary arteries. Normally; endothelium-derived NO stimulates intracellular soluble guanylate cyclase resulting in increased levels of cGMP; which then acts to mediate smooth muscle relaxation. By inhibiting the degradation of cGMP it prolongs the actions of cGMP. It thus causes rapid and potent vasodilatation and a significant decrease in pulmonary artery pressure (PAP) and PVR with minimal or no effect on mean arterial pressure (MAP).[5] A group of pharmaceutical chemists working at Pfizer's Sandwich; Kent research facility in England synthesized sildenafil (compound UK-92;480). It was initially studied for use in hypertension and angina pectoris.[6] In the phase I a clinical trial it was found that it could induce marked penile erections and was marketed for erectile dysfunction.[7]

Aims and objectives

a. To compare two different doses of sildenafil in two group of patients with pulmonary arterial hypertension.

b. To study other side effects of it (if any).

Materials and methods

Sample size calculation

Sample size of forty patients was calculated considering previous study using EPI calculator@openepi.com taking the power of study as 80% and α-error as 5%.

Duration

Duration of the study was one year.

Study design

The study is an open label observer blind prospective randomised controlled study of forty cases. Cases were randomised into two groups by a set of computer generated numbers. Group 'A': These patients received an intravenous sildenafil 20mg starting if they had developing pulmonary hypertension pre-operatively. Group 'B': Here; the patients will receive an intravenous sildenafil 40mg starting if they had developing pulmonary hypertension pre-operatively. The observer taking the readings was blind about the drug given.

Inclusion criteria

i. Patients with documented pulmonary hypertension pre-operatively.

ii. Pati8ents with pulmonary artery pressure >24mmHg

Exclusion criteria

i. Patient's refusal

ii. Patients already on therapeutic endothelin receptor antagonists; phosphodiesterase type 5 inhibitors.

Procedure

The study was started after ethics committee approval. Preoperatively; the patients were kept nil by mouth for the last 10-12hours prior to surgery. On the day of surgery; patient's pre-operative investigations like haemoglobin (Hb); packed cell volume (PCV); total leukocyte count (TLC); differential leukocyte count (DLC) and platelet counts were checked for. Urine routine and microscopy were evaluated. For patients older than 40years; electrocardiogram (ECG) and blood sugar were also evaluated. Patients were examined thoroughly and allocated randomly into the two predetermined groups. A well informed written consent was taken. Preoperative vitals were recorded in the form of baseline pulse; ECG; oxygen saturation (SpO_2) and blood pressure. Venous cannulation was done. All patients

were premedicated with midazolam 0.03mg/kg IV; fentanyl 2mcg/kg IV; ondansetron 4mg IV 10minutes before induction.

Preparation of study medication and administration

a. Group 'A': Study medication was prepared in 50ml syringe; sildenafil 20mg was added to 50ml normal saline making a total volume of 50ml.

b. Group 'B': Study medication was prepared in 50ml syringe; sildenafil 40mg (10ml) added to 50ml normal saline making a total volume of 50ml.

c. Monitoring was done by cardio scope; SPO2; non-invasive blood pressure (NIBP). Heart rate (HR); systolic and diastolic blood pressures (SBP; DBP); respiratory rate (RR); SPO2 and pulmonary artery pressure were recorded preoperatively (baseline). Any expected and unexpected complications were looked for. Vitals were recorded before shifting the patient to the ward.

Observation and results

The mean age of patients in group A was 35.9±11.47years and in group B was 37.68±7.92years while the mean weight in group A and B was 60.64±3.901kg and 61.46±3.704kg respectively (Table 1). During pre-operative; intra-operative and post-operative periods; group A and B had similar oxygen saturation (SpO_2) throughout with no statistically significant difference between the two. Heart rate (HR) difference between the two groups during these periods was also found to be statistically insignificant (Table 2). Difference in PAP between the two groups during pre-operative and intra-operative periods was statistically insignificant but post-operatively; group A displayed a PAP of 30.45±5.65mmHg and for group B it was 30.62±6.74mmHg with a statistically significant difference (p-value<0.0001) (Table 3). Hypotension was observed in three (15%) patients from group A and two (10%) patients from group B. Two (10%) patients in group A had bradycardia. Group B did not suffer from bradycardia at any point of time (Figure 1).

Table 1 Demography

Demography	Group A	Group B
Age (years)	35.9±11.47	37.68±7.92
Weight (Kg)	60.64±3.901	61.46±3.704

Table 2 SpO_2 and HR in Group A and Group B

	Intervals	Group A	Group B	p-value
SpO_2 (%)	Pre-operative	99.1±0.008	99±0.09	0.54
	Intra-operative	98.8±0.05	99.1±0.05	0.061
	Post-operative	98.5±0.05	98.7±0.05	0.84
HR (bpm)	Pre-operative	78.68±9.861	80.88±6.997	0.201
	Intra-operative	87.52±10.62	90.6±9.26	0.12
	Post-operative	76.60±8.48	81.02±9.52	0.016

Table 3 Comparison of pulmonary artery pressure in Group A and Group B

PAP (mmHg)	Group A	Group B	p-value
Pre-operatively	45±9.24	45.98±9.29	0.914
Intra-operatively	35.32±9.23	35.02±9.0	0.638
Post-operatively	30.45±5.65	30.62±6.74	<0.0001*

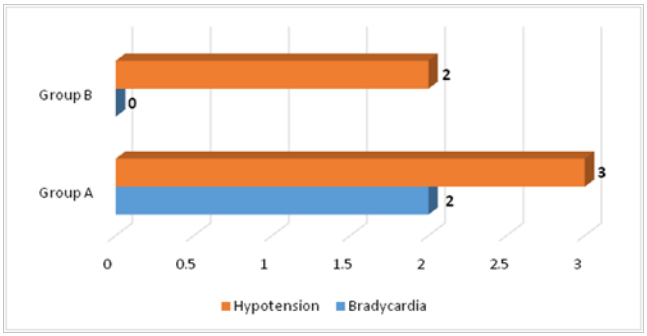

Figure 1 Adverse events.

Discussion

A randomized control trial was performed in 2002 by Ghofrani et al.,[1] to study the effect of sildenafil on lung fibrosis and pulmonary hypertension. They compared the vasodilatory effects of oral sildenafil and inhaled nitric oxide with epoprostenol in patients who developed pulmonary hypertension secondary to lung fibrosis. It was a randomized; open label study of sixteen patients who were analysed with the intention to treat. They found that sildenafil caused preferential pulmonary vasodilation with improved gas exchange in the studied subjects. The pulmonary vascular resistance was reduced in all the three groups (nitric oxide; epoprostenol and sildenafil) but the ratio of pulmonary to systemic vascular resistance decreased only in individuals who received nitric oxide and sildenafil. While epoprostenol increased ventilation-perfusion (V/Q) mismatch and decreased arterial oxygenation; nitric oxide and sildenafil maintained the V/Q matching. A raised arterial pressure of oxygen was observed with sildenafil. Bonnell et al.,[3] studied the effects of UK 343-644 (a potent sildenafil analogue developed by Pfizer) on acute pulmonary hypertension. They induced pulmonary hypertension by administering a continuous infusion of a thromboxane analogue U46619 in pigs. The study group then received 500mcg of UK 343-644 intravenously for two minutes. Haemodynamic data was observed over sixty minutes following administration of drug. The pulmonary artery pressure increased significantly in both groups after administering U46619 but in the study group it returned to baseline after infusing UK 343-644. There was no significant difference in cardiac output in the two groups. The depressed contractility of the right ventricle displayed by both groups showed no improvement on administration of UK 343-664. The study showed that UK 343-664 was effective for pulmonary vasodilation in thromboxane A2 mediated vasoconstriction.

The effect of sildenafil on post-operative pulmonary hypertension was studied by Trachte et al.,[8] They found that it was an effective agent for post-operative pulmonary hypertension and can also be used for weaning patients from inhaled and intravenous (IV) pulmonary vasodilators. A retrospective study was performed on eight patients who received sildenafil for persistent pulmonary hypertension that developed after cardiac surgery. Haemodynamic measurements were carried out prior to sildenafil administration and half an hour and one hour after sildenafil administration. The dose started depended on surgeon preference and ranged from 25mg to 50mg. A high degree of pulmonary selectivity was observed with pulmonary artery pressure decreasing by 9mmHg at the 30th and 60th minute after administration of sildenafil. The decrease in mean arterial pressure (MAP) and systemic vascular resistance index (SVRI) was not clinically significant. The pulmonary vascular resistance index

(PVRI) on the other hand was markedly decreased at the 30th and 60th minute after administration of sildenafil. Concomitant therapy for pulmonary vasodilation was weaned off while patients were still on sildenafil. In-hospital mortalities were absent in the eight patients of the study.

Low dose sildenafil when added to nitric oxide therapy was found to be a safe and effective therapy for pulmonary hypertension. It also prevents further pulmonary hypertensive crisis by noxious stimuli. Pulmonary tone was sustained during prolonged use of sildenafil with nitric oxide and it also facilitated weaning of nitric oxide.[5]

Children with pulmonary artery hypertension on oral sildenafil were found to have better haemodynamics and exercise capacity for up to twelve months. Fourteen children with a median age of 9.8years were administered oral sildenafil 0.25-1mg/kg four times a day. A six-minute walk test was done at sixth week and third; sixth and twelfth month. The distance travelled in six minutes increased at the sixth and twelfth month but a plateau was reached between the sixth and twelfth month.[9] In our study; both the groups showed intermittently improved values according to the dose that was administered. Group B (i.e. sildenafil 40mg) showed marginally better outcome as compared to that of group A (i.e. sildenafil 20mg). The improvements correlated with the post-operative step-down of intensive monitoring and care with better prognosis and rate of discharge.[10,11] Post-operative hourly PAP monitoring showed better outcome as demonstrated by their mean values taken over twenty-four hour period following surgery.[5,9,12] Complications such as bradycardia; hypotension; hypoxia as a natural outcome of right sided heart failure[12,13] were seen to be noticeably reduced during the study.

Conclusion

This study shows that both the doses of sildenafil i.e. 20mg and 40mg are efficacious in reducing pulmonary arterial hypertension. However; sildenafil 40mg is better in controlling pulmonary arterial hypertension. Recovery profile is better in patients with pulmonary arterial hypertension who were given sildenafil. There were no significant adverse events associated with the use of sildenafil hence; it can be used in patients with pulmonary arterial hypertension.

Acknowledgments

None.

Conflicts of interest

Authors declare there are no conflicts of interest.

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