http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i4.51

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

Effect of preoperative oral sildenafil on intraoperative hemodynamics in patients with severe pulmonary artery hypertension undergoing mitral valve replacement

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Abstract
Aim: *Long standing severe mitral stenosis or mitral regurgitation is usually associated with pulmonary hypertension. Severe pulmonary hypertension is a risk factor for right ventricular dysfunction and is associated with morbidity and mortality in patients undergoing mitral valve surgery. Sildenafil is selective phosphodiesterase type 5 inhibitor which is increasingly used for pulmonary hypertension. But there is lack of evidence of its usefulness in pulmonary hypertension due to mitral valve disease. The study aims to assess the effectiveness of preoperative oral sildenafil on severe pulmonary hypertension and incidence of RV failure in patients undergoing mitral valve replacement surgery.*
Materials & Methods: *A total of 50 patients scheduled for mitral valve replacement with severe pulmonary hypertension (pulmonary artery pressure greater than 30 mm of hg) on preoperative transthoracic echo who got operated during January 2019 to march 2019 , were randomly treated with oral sildenafil 25 mg (N = 25) or placebo (N = 25) eight hourly for 48 hours before surgery. Hemodynamic variables were measured 5 minutes after induction of anaesthesia (T1-baseline), 30 minutes at weaning from cardiopulmonary bypass (CPB) (T2) and after 1,2, and 6 hours (T3, T4, T5, respectively) during the postoperative period.*
Result: *Patient characteristics and baseline hemodynamics were similar between groups. Systolic and mean pulmonary arterial pressures and pulmonary vascular resistance were significantly lower in the sildenafifil group at all times without any changes in mean systemic arterial pressure and systemic vascular resistance. Ventilation time and postoperative recovery room stay were significantly lower in sildenafil group.*
Conclusion: *Sildenafil has significant vasodilatory effect on pulmonary vessels as compared with placebo in mitral valve replacement patients with severe pulmonary hypertension. It also reduces ventilation time and intensive care unit (ICU) stay time as compared with placebo. It is concluded that sildenafil is effective in reducing pulmonary hypertension when administered preoperatively in patients with severe pulmonary hypertension undergoing mitral valve replacement surgery.*
Keywords: *Sildenafil, Pulmonary Hypertension, Mitral Valve Replacement, Pulmonary Hemodynamics.*

Introduction

Pulmonary arterial hypertension (PAH) is characterized by increase in pulmonary vascular resistance leading to right ventricular (RV) failure.[1] Pathologic processes behind the complex vascular changes associated with PAH include

vasoconstrictor-vasodilator imbalance, thrombosis, misguided angiogenesis, and inflammation.[2 ¯3] Among the vasodilators, nitric oxide plays a critical role in pulmonary vasomotor regulation, which is mainly mediated by the guanylate cyclase– cyclic guanylate monophosphate (cGMP) pathway.[4]

Phosphodiesterase type 5 (PDE5) is an enzyme with predominant presence in the vascular smooth muscles, where it catabolizes cGMP. PDE5 inhibitors prevent cGMP degradation and thus potentiate the vasodilatory effect of the nitric oxide– cGMP pathway.Since the introduction of the selective PDE5 inhibitor sildenafil citrate, there has been growing evidence of its efficacy in treatment of both primary and secondary PAH.[5 ¯7]

PAH with subsequent RV failure remains a major problem during the perioperative period for surgical correction of long-standing valvular heart disease. There is still a lack of evidence, however, regarding the intraoperative pulmonary vasodilatory effects of sildenafil in anesthetized cardiac surgical patients. We therefore evaluated the effect of oral sildenafil on hemodynamics in patients with concomitant PAH undergoing valvular heart surgery in a controlled, prospective, randomized trial.

Materials and Methods

After institutional ethical committee approval and informed consent were taken, A total of 50 patients scheduled for mitral valve replacement with severe pulmonary hypertension (pulmonary artery pressure greater than 30 mm of hg) on preoperative transthoracic echo were enrolled who got operated during January 2019 to march 2019. Patients were randomly allocated to either sildenafil (available in routine hospital supply) or control (multivitamin tablet) group with a computerized randomization table. Patients with coronary artery disease, other valve lesion, EF < 45%, previous cardiac surgery, lung ,hepatic or renal disease were excluded. Patients taking nitrates were also excluded.

All cardiovascular medications except digoxin and diuretics were continued until the day of surgery. Patients in group S (sildenafil, in routine hospital supply) and group C (control group) were administered oral sildenafil 25 mg three times a day in 48 h preoperative period and placebo in the same fashion, respectively. Nursing staff who were administering the drugs to the patients were blinded during the study. All the patients were administered tablet alprazolam 0.25 mg and tablet pantoprazole 40 mg the night before surgery.

On the day of surgery after arrival to operation room, patients received 4-5 l of oxygen with mask. ECG (electrocardiogram), NIBP (non invasive blood pressure) and pulse oxymetry attached. After infiltration of local anesthesia (2% lidocaine), a peripheral venous cannula (16 or 18 G) and 20 G arterial cannula in the radial artery of nondominant hand were inserted. Anesthesia was induced with injection midazolam (0.1 mg/kg), fentanyl (7-10 µg/kg), and injection vecuronium (0.08-0.12 mg/kg) and maintained with intermittent bolus doses of fentanyl (2 µg/kg) and vecuronium (0.04 mg/kg) with sevoflurane (1-2%). After induction of anesthesia, the lungs were ventilated with tidal volume of 8 ml/kg at a rate of 12 breaths/min in 50% oxygen- air mixture. Positive end- expiratory pressure was not applied. After that, ventilatory parameters were adjusted to maintain PaO2 between 150-250 mmHg, PaCO2 between 33-38 mmHg, and pH 7.35-7.45.

After induction of anesthesia and under all aseptic and antiseptic precautions, pulmonary artery catheter (PAC) was inserted in the right internal jugular vein to monitor pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP) and cardiac indices (CIs), SVRI (systemic vascular resistance index), and PVRI (pulmonary vascular resistance index). A temperature probe was inserted into nasopharynx for monitoring of body temperature.

Routine mitral valve replacement with median sternotomy and cardiopulmonary bypass (CPB). During weaning from CPB, GTN and Milrinone (0.30 to 0.75 mics) was administered in all

patients after achieving body temperature greater than 36°C and normalizing acid-base and electrolyte balance. After 10 min of weaning from CPB, inotropes were titrated according to MAP (mean arterial pressure) and SPAP (systolic pulmonary artery pressure). The number of patients requiring inotropes was recorded.

Hemodynamic variables were measured 5 min after induction of anesthesia (T1), 20 min after weaning from CPB (T2), 1, 2, and 6 h after transferring the patient to postoperative recovery period (T3, T4, T5). Heart rate (HR), MAP, systolic pulmonary arterial pressure (SPAP), mean pulmonary artery pressure (MPAP), PCWP, cardiac index (CI), systolic vascular resistance index (SVRI), and PVRI were measured at each interval. Statistical analyses were performed with SPSS 12.0 (SPSS Inc, Chicago, Ill). All data are expressed as mean _ SD or number of patients. Because there was no controlled study comparing the effect of oral single dose of sildenafil in cardiac surgical patients, sample-size calculation was based on a study by Trachte and colleagues[8] with the following assumptions: clinical significance α at .05 with a independent *t*-test and power to expect a significant result at .9, the mean difference between groups at 10 mm Hg with SD at 9 mm Hg of the mean value of MPAP. This generated an estimate of 25 patients per group. Data were compared between the groups with χ^2 test, Fisher exact test, or independent *t*-test as appropriate. Changes between time points within the groups were compared with repeated measurements of analysis of variance with post hoc comparison by Dunnett test.

Results

A total of 50 patients were included in the study, 25 patients in each group. Demographic characteristics were similar in both groups. Other parameters like preoperative pulmonary artery systolic pressure (PASP), CPB time, and cross- clamp time were similar in both groups ($P = 0.836$, $P = 0.768$, $P = 0.852$, respectively) [Table 1]. Hemodynamic parameters, i. e. HR, MAP, and PCWP were similar in both groups after induction, after weaning from CPB, and in the postoperative period [Table 2]. SPAP and MPAP were significantly lower ($P < 0.0001$) during T1-T5 times in sildenafil group as compared with the control group [Table 2].

On comparison of CI and SVRI there was no statistical significance between the two groups. PVRI was significantly lower in sildenafil group after induction, after weaning from

CPB, and in the postoperative period [Table 2]. During the period of weaning from CPB, the number of patients who required milrinone infusion was lower in S group ($P < 0.01$), whereas the number of patients requiring adrenaline+/- noradrenaline infusion was not significantly different between the two groups ($P < 0.43$; Table 3].

Postoperative parameters like ventilation time and postoperative ICU (intensive care unit) stay time was significantly lower in sildenafil group ($P = 0.009$) as compared with control group [Table 3]. During study, there was one mortality due to low output noted in control group on second postoperative day.

Table 1 showing characteristics of patients with mitral valve disease and severe pulmonary hypertension (data are mean+/- SD or actual number as appropriate)

Characteristics	S group	C group	P value
Age(years)	28.5+/-5.67	29.9+/-7.25	0.765
Sex (M/F)	11/14	12/13	0.345
BSA (m2)	1.49+/-0.18	1.50+/-0.23	0.232
A fib	12	10	
MS	16	18	
MR	4	3	
MS+MR	5	2	
PASP(mm of hg) preoperative	45+/-13.47	42.56+/-16.23	0.836
CPB (min)	68.67+/-10.87	65.87+/-12.34	0.768
Cross clamp time(min)	47.76+/-8.54	46.76+/-7.65	0.852

Table 2 showing hemodynamic parameters during surgery in both group (data are mean+/- SD or actual number as appropriate)

Parameter		T1	T2	T3	T4	T5
HR (beats/min)	C	84.23+/-14.56	84.80+/-7.27	86.50+/-9.75	87.7+/-8.04	89.85+/-8.91
	S	85.65+/-13.45	85.57+/-11.01	85.10+/-8.95	88.10+/-10.47	89.50+/-8.77
MAP (mm of hg)	C	74.70+/-6.89	72.10+/-3.68	76.40+/-5.84	77.30+/-5.25	78.70+/-6.74
	S	72.45+/-7.50	74.60+/-5.80	72.90+/-6.57	76.05+/-5.63	79.15+/-6.98
SPAP (mm of hg)	C	69.90+/-8.04	63.40+/-7.04	61.75+/-6.41	58.30+/-6.48	58.85+/-6.56
	S	53.20+/-6.89	49.70+/-6.78	49.20+/-5.10	46.65+/-4.90	44.30+/-4.67
MPAP (mm of hg)	C	46.7+/-6.9	42.85+/-5.58	41.40+/-5.79	38.75+/-5.68	38.50+/-5.50
	S	30.95+/-4.88	28.55+/-4.68	27.80+/-4.78	25.75+/-3.99	24.70+/-3.62
PCWP (mm of hg)	C	22.25+/-2.19	19.95+/-2.62	18.35+/-2.22	17.23+/-2.11	16,20+/-2.55
	S	20.60+/-1.83	19.35+/-2.55	18.75+/-2.51	17.30+/-2.65	15.85+/-2.66
CI (l/min/m2)	C	3.35+/-0.44	3.34+/-0.39	3.38+/-0.36	3.39+/-0.34	3.44+/-0.36
	S	3.33+/-0.37	3.31+/-0.36	3.40+/-0.31	3.41+/-0.20	3.41+/-0.34
SVRI (dynes.sec.cm^5 m^2)	C	1731.29+/-294.61	1720.78+/-280.85	1750.98+/-230.87	1727.465+/-203.93	1736.765+/-260.876
	S	1646.67+/-249.89	1602.98+/-161.87	1698.12+/-154.87	1666.987+/-234.98	1732.567+/-253.472
PVRI (dynes.sec.cm^5 m^2)	C	503.78+/-181.12	552.87+/-158.98	541.577+/-172.577	580.5677+/-151.567	509.98+/-165.78
	S	223.45+/-64.56	205.897+/-65.56	201.67+/-58.98	182.67+/-50.99	192.677+/-49.672

Table 3 showing perioperative parameters in both group (data are mean+/- SD or actual number as appropriate)

Parameters	C group	S group	P value
Milrinone requirement	14	5	
Adrenaline +/- noradrenaline requirement	6	4	
Ventilation time (min)	370+/-33	310.87+/-46	0.001
Post op recovery room stay	92.32+/-22	65.1+/-14	0.0001
mortality	1	0	

Discussion

In this prospective double- blind randomized controlled study, oral sildenafil 25 mg three times over 48h before surgery produced significant pulmonary vasodilatation without any significant systemic effects. Sildenafil has a favourable effect like lowering pulmonary vascular resistance after induction of anaesthesia that extended into postoperative period. SPAP, MPAP, and PVRI were significantly lower in sildenafil group (P < 0.0001) as compared with controlled group during the intraoperative period as well as in postoperative period.

Cardiac surgery in patients with valvular heart disease with severe PAH is often complicated with RV failure with an adverse consequence on its prognosis.[9 – 10] Right ventricle is susceptible to ischemic injury, as CPB exacerbates PAH,[11] This necessitates perioperative strategy to manage PAH and RV dysfunction. This goal should be achieved without compromising systemic blood pressure and coronary perfusion.[12] The final messenger for vascular smooth muscle relaxation, cGMP, is metabolized by PDE5.[13] Among the various phosphodiesterase, PDE5 is the predominant type in the normal pulmonary vasculature that may be upregulated after CPB.[14] The inhibition of PDE5 is therefore a logical step to increase the bioavailability of cGMP and support endogenous vasodilation in patient with PAH. PDE5 is selectively inhibited by sildenafil, vardenafil, and tadalafil and less selectively by zaprinast anddipyridamole.

Oral sildenafil is widely used in treatment of patients with erectile dysfunction and shows an excellent cardiovascular safety profile. It is emerging as an effective and safe pulmonary vasodilator in primary pulmonary hypertension as well as secondary pulmonary hypertension.PDE5 is abundant in lung tissue; hence sildenafil selectively inhibits it and preferentially dilates pulmonary vascular beds. Oral sildenafil selectively reduced pulmonary hypertension without any adverse systemic effects.[15 – 21]

In the present study, 25 mg of oral sildenafil was administered three times a day for 48 h with the last dose administered 3 h prior to surgery. Wilkens *et al*.,[18] demonstrated that the maximal hemodynamic effects of sildenafil on pulmonary circulation could be achieved with a dose as low as 25 mg. We used three doses over 48 h to reduce pulmonary hypertension and improve RV function prior to surgery. Sildenafil has a half- life of about 4 h; it is rapidly absorbed via the stomach and its plasma levels peaks within 30-120 min after ingestion. Considering these facts, the last dose of sildenafil was administered 3 h prior to surgery.

In this study, SPAP, MPAP, and PVRI were significantly lower ($P < 0.0001$) after induction of anaesthesia, after weaning from CPB, and in immediate postoperative period in sildenafil group as compared with control group. But MAP, PCWP and CI, and SVRI were no significantly differing between two groups. During weaning from CPB, we started GTN infusion and milrinone infusion in all patients. Inotropes, milronone infusion (0.25 – 0.75 µg/kg/min) continued when MAP was lower than 60 mmHg and also adrenaline+/- noradrenaline infusion (0.05-0.1 µg/kg/min) was added whenever required. In sildenafil group, six (30%) patients required milrinone infusion, of these two (33.3%) patients required noradrenaline infusion. In the control group, 14 patients required milrinone infusion and of these five patients required noradrenaline infusion. Sildenafil group had fewer requirements of inotropes than control group. Ventilation time and postoperative recovery room times were significantly lower ($P = 0.001$) in sildenafil group as compared with control group. Mortality occurred on the second postoperative day due to low output.

Conclusion

Preoperative oral sildenafil decreases pulmonary artery pressure in severe pulmonary hypertension secondary to mitral valve disease undergoing mitral valve replacement. Because of the predominant selective activity of sildenafil in management of pulmonary hypertension and improvement of RV function without compromising the systemic blood pressure, the use of this drug in cardiac surgical patients should be considered. Elaborate studies of oral sildenafil in secondary PAH in larger populations will help validate the results of this study.

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