ORIGINAL RESEARCH PAPER

Anaesthesiology

EFFECT OF SILDENAFIL ON INTRAOPERATIVE HEMODYNAMICS IN PATIENTS WITH PULMONARY HYPERTENSION UNDERGOING VALVULAR HEART SURGERY

KEY WORDS: Sildenafil; Severe pulmonary hypertension; Valvular heart surgery; Systolic Pulmonary artery pressure ;Mean Pulmonary artery pressure.

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ABSTRACT

Aim: Pulmonary hypertension still remains a major obstacle during the perioperative period in patients undergoing surgical correction for long-standing valvular heart disease. Sildenafil citrate is a selective phosphodiesterase type 5 inhibitor which is being increasingly used in the treatment of pulmonary hypertension. But there is lack of evidence, regarding its pulmonary vasodilatory effect in anesthetized cardiac surgical patients. We therefore evaluated the effects of sildenafil on hemodynamics in patients with concomitant pulmonary hypertension undergoing valvular heart surgery in a controlled, prospective, randomized, double blind trial. **Methods:** Patients scheduled for valvular heart surgery with systolic RV pressure of more than 50 mm of Hg as measured by preoperative transthoracic echocardiography were included in the study. After induction of anesthesia a pulmonary artery catheter (swan ganz , Edwards life sciences) was inserted through the right internal jugular vein. Patients with mean pulmonary artery pressure (MPAP) of more than 30 mm of Hg were included in the study. 60 patients were selected out of which 53 patients met this criteria. Sildenafil group (n=26) and control group (n=27) Hemodynamic variables were measured at 5 minutes after induction of anaesthesia (baseline) and at 30 and 60 minutes after medication. **Results:** Patient characteristics and baseline hemodynamics were similar between groups. Systolic and mean pulmonary arterial pressures and pulmonary vascular resistance were significantly lower in the sildenafil group at 30 minutes after medication, without any changes in mean systemic arterial pressure and systemic vascular resistance. **Conclusions:** Administration of pre-operative sildenafil to patients with pulmonary hypertension undergoing valvular heart surgery decreases Intra-operative and post-operative systolic pulmonary arterial pressure without significantly affecting other systemic hemodynamic parameters.

INTRODUCTION:

The joint task force for diagnosis and treatment of pulmonary hypertension of European society of cardiologist (ERS) 2015 defines pulmonary hypertension as an increase in mean pulmonary arterial pressure (mPAP) as > 25 mm Hg at rest as assessed by right heart catheterization. (1) ERS classifies pulmonary hypertension (PH) into five groups depending on the etiology. The most common cause of PH is group 2 which is due to left heart disease and in this group valvular heart disease is the leading cause of pulmonary hypertension. (2)

Patients with severe symptomatic valvular heart disease invariably have pulmonary hypertension. PAH is characterized by progressive increase in pulmonary vascular resistance leading to right ventricular failure and death. (3) Pathological changes associated with PAH involves a complex valvular changes like an imbalance between vasodilators and vasoconstrictors, thrombosis, unguided angiogenesis and inflammation. (4)

Patients with valvular heart disease with severe PAH undergoing cardiac surgery usually are associated with right ventricular failure and further deterioration of right ventricular function with exacerbation of PAH occurs during cardiopulmonary bypass (5). This necessitates a perioperative strategy to manage PAH and right ventricular dysfunction without compromising systemic blood pressure and coronary perfusion (6)

Phosphodiesterase type 5 (PDE 5) is an enzyme which is predominantly present in the vascular smooth muscles where it catabolizes Cyclic Guanosine Monophosphate (CGMP). Here comes the important role of PDE 5 inhibitors which prevents degradation of CGMP and thus potentiates the vasodilatory effect of nitric oxide CGMP pathway. (7) Sildenafil is a selective PDE 5 inhibitor which is available in oral, inhaled and intravenous form, the biggest advantage of sildenafil when compared to other PDE 5 inhibitor is its relatively higher selectivity for pulmonary vasculature and a longer half life. (8)

PAH with subsequent right ventricular failure still remains a major problem during the perioperative period in patients with long standing valvular heart disease. Therefore, the aim of the present study was to determine the effects of pre-operative administration of oral sildenafil on the intraoperative parameters of patients with pulmonary hypertension undergoing valvular heart surgery.

MATERIALS AND METHOD

This study was carried out at a tertiary care hospital in the southern india after approval from the ethical committee and written informed consent from the patients. 60 patients scheduled for valvular heart surgery with systolic RV pressure of more than 50 mm of Hg as measured by preoperative transthoracic echocardiography were included in the study. These patients were randomly allocated to either sildenafil group (group A) or placebo group (group B) with a computerized randomization table.

Exclusion criterias included patients with preexisting lung parenchymal disease, coronary artery occlusive disease, hepatic/renal disease and tricuspid regurgitation of atleast 2.

On the day of surgery, after arrival of patient to operation theatre, all standard monitors were attached and patients were induced with injection fentanyl 2mcg/kg , Inj. Etomidate 0.2 mg/kg and intubation was facilitated with Inj. Rocuronium

0.9-1mg/kg and anesthesia was maintained with air, oxygen and sevoflurane (1-2%). After induction of anesthetics the lungs were ventilated with a tidal volume of 8ml/kg at a rate of 10 breaths/minute in 60% oxygen and air and positive end expiratory pressure was not applied. The respiratory rate was adjusted to maintain a $PaCO_2$ between 33 to 38 mm of Hg and pH around 7.4 throughout the study period.

Once the patients were induced a pulmonary artery catheter (swan ganz , Edwards life sciences) was inserted through the right internal jugular vein. Patients with mean pulmonary artery pressure (MPAP) of more than 30 mm of Hg were included in the study. 60 patients were selected out of which 53 patients met these criteria.Sildenafil group (n=26) and control group (n=27)

This study was planned to be terminated if systolic arterial pressure decreased more than 20% of post induction value after medication, necessitating vasoactive drug administration. Hemodynamic variables were measured before induction of anesthesia(T0) ,5 minutes after induction of anesthesia(baseline), and at 30 and 60 minutes after medication (T30 and T60, respectively).

Hemodynamic measurements included mean arterial pressure, systolic pulmonary arterial pressure (SPAP), mPAP, Central venous pressure, cardiac index, RV end-diastolic volume index (RVEDVI), and RV end-systolic volume index (RVESVI). Corresponding systemic vascular resistance (SVRI) and pulmonary vascular resistance index (PVRI) were calculated.

During the period of weaning from cardiopulmonary bypass(CPB), numbers of patients requiring norepinephrine 0.03-0.3 mcg/kg/min or milrinone 0.3-0.7 mcg/kg/min were recorded.

Statistical analysis was performed with SPSS 12.0 (SPSS Inc, Chicago,III). All data are expressed as mean +/- SD. Data were compared between the groups with Chi-square 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:

Patient characteristics and hemodynamic variables measured at T_0 were similar between the groups (Table 1, 2 and 3). There was no significant difference in baseline hemodynamic variables between the groups. SPAP, MPAP, PVRI, MAP and SVRI after anesthesia (baseline values) were significantly decreased in both groups relative to values at T_0. (Pre induction value,Table 2)

At $T_{30,}$ SPAP, MPAP and PVRI were significantly lower in the sildenafil group than in the control group (table 2). SPAP and MPAP at T_{30} were significantly decreased relative to baseline values only in the sildenafil group (Table 2)

At $T_{60,}$ hemodynamic variables were similar between the groups. SPAP, MPAP and PVRI were lower in the sildenafil group but without statistical difference (p = 0.07, p = 0.087, p = 0.09 respectively Table 2)

Table 1: Patient characteristics

Characteristics	Control (n=26)	Sildenafil (n=27)	P value
Age (Y, mean ± SD)	63 ± 12	67 ± 13	0.3
Sex (Male/Female)	16 : 11	16 : 10	0.87
BSA (m^2)	1.7 ± 0.2	1.7 ± 0.2	0.42
Disease (no.)			
MS	11	12	
MR	10	11	
MS+MR	4	2	
AS+AR	9	7	
Procedure (no.)			
MVR	19	19	
AVR	3	2	
DVR	4	6	

MS: Mitral stenosis, MR: Mitral regurgitation AS: Aortic stenosis, AR: Aortic regurgitation MVR: Mitral valve replacement AVR: Aortic valve replacement DVR: Double valve replacement

Table 2: Changes in pulmonary and systemic arterial pressure and Vascular resistance.

Group	T_0	Baseline	T_{30}	T_{60}	P value	
					Baseline	Control
SPAP(mmHg)	60 ± 21	42 ± 13	43 ± 13	47 ± 18	0.02	0.02
Control	53 ± 11	40 ± 11	35 ± 8	40 ± 11		
Sildenafil						
MPAP(mmHg)	40 ± 13	28 ± 9	28 ± 8	32 ± 12	0.03	0.04
Control	35 ± 8	27 ± 6	24 ± 6	27 ± 7		
Sildenafil						
SVRI (dynes.sec. $cm^{-5}.m^2$)	2281 ± 624	1862 ± 565	1811 ± 482	2096 ± 706	0.021	
Control	2261 ± 839	1799 ± 493	1821 ± 613	1991 ± 783		
Sildenafil						
PVRI (dynes.sec. $cm^{-5}.m^2$)	390 ± 193	257 ± 130	284 ± 139	339 ± 163	0.02	0.04
Control	349 ± 138	228 ± 123	211 ± 114	267 ± 142		
Sildenafil						
MAP(mmHg)						
Control	94 ± 15	76 ± 12	73 ± 11	75 ± 13		
Sildenafil	92 ± 16	76 ± 12	72 ± 12	72 ± 12		

Values are expressed as mean ± SD. T0, before induction of anaesthesia;

Baseline, 5 minutes after induction of anaesthesia; T30, 30 minutes after 50 mg oral sildenafil or placebo; T60, 60 minutes after 50 mg oral sildenafil or placebo; SPAP, systolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure;

PVRI, pulmonary vascular resistance index; MAP, mean systemic arterial pressure; SVRI, systemic vascular resistance index.

Table 3: Changes in hemodynamic variables

Group	T_0	Baseline	T_{30}	T_{60}	Pvs baseline
HR (bpm)					
Control	83 ± 14	73 ± 20	71 ± 16	68 ± 13	
Sildenafil	85 ± 21	75 ± 21	72 ± 17	71 ± 14	
CVP	6 ± 2	8 ± 2	8 ± 2	9 ± 2	
Control	6 ± 3	7 ± 2	7 ± 2	9 ± 3	0.002
Sildenafil					
PCWP	29 ± 10	23 ± 8	22 ± 7	25 ± 9	
Control	25 ± 7	22 ± 6	21 ± 5	22 ± 5	
Sildenafil					

CI (L/min/m^2)	3.1 ± 0.8	3.1 ± 1.1	2.9 ± 0.7	2.6 ± 0.6	0.01
Control	3.2 ± 0.8	3.1 ± 0.7	2.9 ± 0.6	2.6 ± 0.6	0.003
Sildenafil					
RVEF (%)	22 ± 8	24 ± 9	23 ± 9	23 ± 8	
Control	26 ± 8	25 ± 9	25 ± 8	26 ± 8	
Sildenafil					
RVESVI(%)	127 ± 38	132 ± 63	144 ± 71	139 ± 50	0.031
Control	120 ± 43	141 ± 75	132 ± 67	123 ± 44	
Sildenafil					
RVEDVI(ml /m^2)	177 ± 45	165 ± 48	177 ± 56	191 ± 59	0.048
Control	168 ± 46	187 ± 70	191 ± 78	184 ± 63	
Sildenafil					

HR, heart rate; CVP, central venous pressure; PCWP, Pulmonary capillary wedge pressure; CI, cardiac index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end systolic volume index;

RVEDVI, right ventricular end diastolic volume index.

PVRI, RVEDVI, RVESVI and SVRI at T60 were significantly increased relative to baseline values only in the control group (Table 2 and 3). Cardiac index was significantly decreased in both groups and CVP in the sildenafil group was significantly increased relative to baseline (Table 3).

DISCUSSION

Patients with Valvular heart disease and significant pulmonary hypertension are usually associated with an adverse outcome further the right ventricle is susceptible to ischemic injury, as cardiopulmonary bypass exacerbates PH (5). This necessitates perioperative strategy to manage PH and RV dysfunction, without compromising systemic blood pressure as well as coronary perfusion (9) research in recent years has therefore been directed toward selective pulmonary vasodilators.

Our study was a controlled, prospective, randomized, double-blind study, where a single dose of oral sildenafil was given immediately before induction of anaesthesia which produced significant pulmonary vasodilatation without eliciting systemic effects 30 minutes after medication. At 60 minutes after medication, sildenafil prevented the increase in PVRI that occurred in the control group, although significant differences in MPAP and PVRI between the groups could not be observed. The final messenger for vascular smooth muscle relaxation, c-GMP, and is metabolized by PDE5.(10)Among the various phosphodiesterases, PDE5 is the predominant type in the normal pulmonary vasculature that may be up regulated after CPB.(11) The inhibition of PDE5 is therefore a logical step to increase the bioavailability of cGMP and support endogenous vasodilatation in patient with PH. PDE5 is selectively inhibited by sildenafil, vardenafil, and tadalafil and less selectively by zaprinast and dipyridamole.

Sildenafil is a potent and selective inhibitor of cGMP-specific PDE5. Its potent and relatively selective pulmonary vasodilatory effects have been demonstrated in animal models, (12) in children and in adults with PAH (13-15). In addition, its beneficial effects with regard to myocardial preconditioning and remodelling further advocate its potential use in cardiac surgical patients. (16) There has been little experience with the use of oral sildenafil in adult cardiac surgical patients with PAH, mostly limited to the postoperative period. Although pulmonary vasodilatory effects of oral sildenafil have been reported after 12 to 15 minutes, mean time to peak concentration is 0.8 to 0.9 h with most of the studies reporting time to maximal pulmonary vasodilatory effect of 30 to 60 minutes (17). In accordance with this value, the baseline hemodynamic values were similar between the groups in this study.

As with previous reports, we could observe significant decreases in pulmonary arterial pressure and PVRI without any changes in mean arterial pressure and SVRI, which Supports sildenafil's predominantly selective activity on pulmonary vasculature. Sildenafil also had clinically insignificant effects on cardiac index, heart rate, and other hemodynamic variables measured in this study. We could not observe any statistically significant subsequent improvement in RV ejection fraction or reduction in RVEDVI and RVESVI in the sildenafil group, even at T30 when maximal pulmonary vasodilatation had occurred. The findings that RVESVI and RVEDVI were significantly increased in theControl group at T60 relative to baseline values and that RVESVI showed a trend toward decrease in the sildenafil group; however, indicate that there may have been potential improvement in RV performance. Sildenafil has an elimination half-life of 3.7 hours(16) and a pulmonary vasodilatory effect lasting for at least 3 hours without affecting systemic arterial pressure has been reported. In this study, significant intergroup differences in pulmonary arterial pressure could not be observed after 60 minutes of medication.

The finding that PVRI and RVEDVI and RVESVI were significantly increased relative to baseline values only in the control group, however, indicates that there may have been some beneficial effect of sildenafil at this time point. Possible explanations are that adverse effects of continued mechanical ventilation on PVRI attenuated the vasodilatory effect of sildenafil. Reduced absorption of sildenafil as a result of general anaesthesia also may have affected the results. Even though 50 mg oral sildenafil has been proved to be sufficient to produce significant pulmonary vasodilatation, (18) studies with oral sildenafil in anesthetized animals have reported reduced plasma concentration rather than delayed absorption(19,20) which could not be verified in this study and is a limitation of this study. Further investigations regarding pharmacokinetics of oral sildenafil in anesthetized patients are therefore necessary to clarify optimal dosing and dosing interval.

CONCLUSION:

Our study has demonstrated that pre-operative administration of sildenafil reduces intra-operative sPAP, reduces need for post-operative inotropic support, and reduces post-operative ventilation time among patients with PH undergoing valvular heart surgery.

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