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

Authors
Vijay Shewale, Manish Jadhao, Vaibhav Shah, Chaitanya Raut, Prashant Mishra, Jayant Khandekar
Department of Cardiovascular and Thoracic Surgery, Lokmanya Tilak Municipal Medical College, Sion, Mumbai, India

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 sildenafil 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.
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 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 artery 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 colleagues⁸ 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 χ² 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       | 76.60+/−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+/−6.61         | 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 46.74+/−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.cm² m²) | C 1731.29+/−294.61   | 1720.78+/−280.85     | 1750.98+/−230.87     | 1727.46+/−203.93     | 1736.76+/−260.87     |
|                    | S 1646.67+/−249.89   | 1602.98+/−161.87     | 1698.12+/−154.87     | 1666.98+/−234.98     | 1732.56+/−253.472   |
| PVRI (dynes.sec.cm² m²) | C 503.78+/−181.12    | 552.87+/−158.98      | 541.57+/−172.57      | 580.56+/−151.56      | 509.98+/−165.78      |
|                    | S 223.45+/−64.56     | 205.897+/−65.56      | 201.67+/−58.98       | 182.67+/−50.99       | 192.67+/−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 and dipyridamole.

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

Vijay Shewale et al JMSCR Volume 08 Issue 04 April 2020
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., 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.

References
1. Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S):5S-12S.
2. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med. 1992;327:70-5.
3. Stewart DJ, Levy RD, Cernacek P, Langleben D. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med. 1991;114:464-9.
4. Ghofrani HA, Pepke-Zaba J, Barbera JA, Channick R, Keogh AM, Gomez-Sanchez MA, et al. Nitric oxide pathway and phosphodiesterase inhibitors in pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S):68S-72S.
5. Raja SG, Nayak SH. Sildenafil: emerging cardiovascular indications. Ann Thorac Surg. 2004;78:1496-506.
6. Matsumoto T, Kobayashi T, Kamata K. Phosphodiesterase in the vascular system. J Smooth Muscle Res. 2003;39:67-86.
7. Corbin JD, Francis SH. Pharmacology of phosphodiesterase-5 inhibitors. Int J Clin Pract. 2002;56:453-9.
8. Trachte AL, Labato EB, Urdaneta F, Hess PJ, Klodell CT, Martin TD, et al. Oral sildenafil reduces pulmonary hypertension after cardiac surgery. Ann Thorac Surg. 2005;79:194-7.
9. Ward C, Hancock BW. Extreme pulmonary hypertension caused by mitral valve disease: Natural history and results of surgery. Br Heart J 1975;37:74-8.

10. Malouf JF, Enriquez-Sarano M, Pellikka PA, Oh JK, Bailey KR, Chandrasekaran K, et al. Severe pulmonary hypertension in patients with severe aortic valve stenosis: Clinical profile and prognostic implications. J Am Coll Cardiol 2002;40:789-795.

11. Mangano DT. Biventricular function after myocardial revascularization in humans: deterioration and recovery patterns during the first 24 hours. Anesthesiology 1985;62:571-7.

12. Calvin JE Jr. Acute right heart failure: Pathophysiology, recognition, and pharmacological management. J Cardiothorac Vasc Anesth 1991;5:507-13.

13. Rabe KF, Tenor H, Dent G, Schudt C, Nakashima M, Magnussen H. Identification of PDE isozymes in human pulmonary artery and effect of selective PDE inhibitors. Am J Physiol 1994;266:536-43.

14. Giad A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med 1995;333:214-21.

15. Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, et al. Sildenafil: An orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. Int J Impot Res 1996;8:47-52.

16. Kloner RA, Zusman RM. Cardiovascular effects of sildenafil citrate and recommendations for its use. Am J Cardiol 1999;84:11N-7.

17. Sastry BK, Narasimhan C, Reddy NK, Raju BS. Clinical efficacy of sildenafil in primary pulmonary hypertension: A randomized, placebo-controlled, double-blind, crossover study. J Am Coll Cardiol 2004;43:1149-53.

18. Wilkens H, Guth A, König J, Forestier N, Cremers B, Hennen B, et al. Effects of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. Circulation 2001;104:1218-22.

19. Cubillos-Garzón LA, Casas JP, Morillo CA. Sildenafil in secondary pulmonary hypertension. Int J Cardiol 2003;89:101-2.

20. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: A randomized controlled trial. Lancet 2002;360:895-900.

21. Schermuly RT, Kreisselmeier KP, Ghofrani HA, Yilmaz H, Butrous G, Ernert L, et al. Chronic sildenafil treatment inhibits monocrotaline-induced pulmonary hypertension in rats. Am J Respir Crit Care Med 2004;169:39-45.