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ORIGINAL ARTICLE

Optimal Duration of Oral Sildenafil for Perioperative Management of Severe Pulmonary Hypertension in Mitral Valve Replacement

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ABSTRACT

Background: Rheumatic heart disease (RHD) involves the mitral valve in 50–60% of cases. Long-term mitral valve pathologies cause multiple sequelae in the form of atrial fibrillation, pulmonary hypertension, and heart failure. Sildenafil has been used as a therapy for the control of pulmonary hypertension, with emphasis on the perioperative period.

Aim: To investigate the influence of oral administration of sildenafil at different durations on intraoperative and postoperative pulmonary hypertension and to compare these effects with preoperative pulmonary pressures.

Methods: This comparative cross-sectional study was conducted at Department of Cardiac Surgery, King Edward Medical University/ Mayo Hospital Lahore between July 2024 and January 2025. Patients were divided into 2 groups. Patients enrolled in the short course of sildenafil were administered oral Sildenafil 50mg/5ml, 3 times a day for 2 days before surgery. And in the long course, the same regimen was given for 7 days.

Results: A Mann-Whitney U test showed that there was no significant difference in the preoperative mean pulmonary artery pressures between the groups receiving the short and long course of oral sildenafil (p-value 0.890). The reduction in mean pulmonary artery pressures from preoperative to postoperative was analyzed to be 16.46 ± 4.13 for the short course whereas it was 24.83 ± 5.04 for the long course and the difference between these two results was found to be statistically significant ($p< 0.05$, $p< 0.001$).

Conclusion: Sildenafil has been shown to be effective in the perioperative management of pulmonary hypertension in mitral valve surgery with longer duration of sildenafil administration leading to greater reduction in pressures.

Keywords: Rheumatic Heart Disease, Pulmonary Hypertension, Mitral Valve Surgery, Sildenafil, Perioperative Care.

INTRODUCTION

Rheumatic Heart Disease (RHD) has an estimated prevalence of 2% worldwide and 7.5% in Pakistan[1]. The mitral valve is the most commonly affected valve in 50–60% of all cases of RHD with sequelae of long-standing mitral pathology, including atrial fibrillation, pulmonary hypertension, and heart failure[2]. Pulmonary hypertension is a hemodynamic condition defined, according to the 6th World Symposium on Pulmonary Hypertension (WSPH), as mean pulmonary artery pressure (mean PAP) above 20 mmHg at rest[3].

Pulmonary Hypertension is present in 30 to 40% of patients with mitral stenosis (MS) and in between 15% and 32% of patients with severe mitral regurgitation undergoing valve replacement or valvuloplasty[4]. Operative

mortality and long-term survival are related to levels of preoperative systolic pulmonary artery pressure (systolic PAP) with severe pulmonary hypertension (systolic PAP ≥60mmHg) having an operative mortality of 12% compared with 2% in patients with systolic PAP < 40 mmHg[5].

All forms of Pulmonary Hypertension result in reduced Nitric Oxide (NO) bioavailability and increased expression of Phosphodiesterase-5 (PDE-5) in endothelial smooth muscle(6). The PDE-5 inhibitor sildenafil acts to prevent the breakdown of cyclic guanine monophosphate (cGMP) and therefore increases the level of NO availability resulting in vasodilation and reduced pulmonary artery pressure[7].

Trials have been conducted to study the efficacy of sildenafil in managing pulmonary hypertension in patients undergoing mitral valve replacement (MVR)[8].

The purpose of this study is to determine how the duration of sildenafil administered orally affects pulmonary hypertension during and after surgery and how this effect compares to preoperative values. The studywill enhanceour understanding concerning sildenafil utilisation in patients with RHD having pulmonary hypertension. The results will contribute to devising protocols for perioperative management of patients with mitral valve disease and pulmonary hypertension.

MATERIAL AND METHOD

Study design

The study was conducted in Department of Cardiac Surgery, King Edward Medical University with cross sectional design, from July 2024 and January 2025. Patients were enrolled for study after approval from the Institutional Review Board (IRB 177/RC/KEMU 2025) from the institute. After informed consent, 25 patients voluntarily agreed to participate in the study.

Inclusion and exclusion criteria

We included patients with age ≥ 18 years, symptomatic mitral stenosis with or without regurgitation with mean PAP>40 mm Hg on transthoracic echocardiography scheduled for MVR. Patients were excluded if they were undergoing any other concomitant procedure (e.g. Aortic Valve Replacement, Coronary Artery Bypass Graft), if they required preoperative inotropic support for hemodynamic instability (defined as Systolic Blood Pressure < 80mmHg) or if nitrate administration was used preoperatively. Moreover, patients having Bronchial asthma, pulmonary thromboembolic disease, renal dysfunction, hepatic dysfunction, coagulopathy, and/or thrombocytopenia were also excluded. Patients were randomly assigned to receive either the long course or a short course of sildenafil. The minimum calculated sample size was 10 in each treatment group determined using G*Power version 3.1.9.7 for a two-tailed t-test with an effect size (d) of 1.5, alpha error probability of 0.05 and a power (1-β) of 0.8.

Intervention

Patients were divided into 2 groups. 13 patients received the Short Course of Oral Sildenafil and 12 received the Long Course of Oral Sildenafil. Patients enrolled in the Short course of sildenafil were administered oral Sildenafil 50mg/5ml,(Silagro, Nabi Qasim Pharmaceuticals, Pakistan), 3 times a day for 2 days before surgery. In the Long course, the same regimen was given for 7 days. Before starting either regimen, a preoperative TTE was performed by a single operator. Ejection Fraction was recorded as a percentage (%). The systolic PAP was derived from the peak velocity of tricuspid regurgitation continuous wave doppler jet. The mean PAP was derived from the systolic PAP with this formula Mean PAP = 0.61 * (Systolic PAP) + 2.

Tablet Alprazolam 0.5 mg given the previous night of surgery as premedication. Induction was done with midazolam 0.05mg/kg, nalbuphine 0.1mg, propofol 1mg/kg, and atracurium was given to facilitate the endotracheal intubation. Immediately after induction a central venous catheter was inserted for monitoring and administration of medication. Lungs were ventilated with a mixture of oxygen and air to maintain normocapnia and anesthesia was maintained with isoflurane.

Intraoperatively, after opening the pericardium and before going on bypass, the pulmonary artery pressures (systolic, diastolic and mean) were measured by a manometer. The total duration of Cardiopulmonary Bypass and Cross-Clamp time for each patient was noted in minutes. All MVR were performed via a median sternotomy before weaning off from cardiopulmonary bypass, milrinone 0.05ug/kg/min started which continued for 24 hours. On shifting to the ICU, 50mg/5ml per Nasogastric tube was administered and continued3 times a day, being changed to per oral after extubation. The postoperative TTE was performed 5 days after surgery and the mean PAP was recorded.

Statistical analysis

Normally distributed data are presented as mean ± standard deviation with categorical variables given as frequencies and percentages. Continuous variables, specifically the Mean Pulmonary Artery Pressure (PAP), were tested with the *t* test for normal distribution and Mann Whitney for non-normal distributed variables.Statistical analyses were conducted using IBM SPSS (version 27)

RESULTS

The mean age of the patients enrolled in the study was 47.52 ± 13.02 years with a preoperative mean ejection fraction of 53% and intraoperative data showing a mean bypass time of 107.84 minutes and cross clamp time of 82.60 minutes (Table 1).

Table 1. Baseline Characteristics of the Study Population

Parameter	Mean	SD	Range
Age (Years)	47.52	13.02	19-65
Weight (Kilograms)	71.56	5.99	57-82
Ejection Fraction (%)	53	7.22	40-60
Cross Clamp Time (minutes)	82.60	6.96	73-95
Cardiopulmonary Bypass Time (Minutes)	107.84	7.93	95-121

Table 2. Perioperative Mean PAP for Short Course of Sildenafil

Preop Mean PAP (mmHg)	Intraop Mean PAP (mmHg)	Postop Mean PAP (mmHg)
50	45	30
40	36	25
45	40	30
50	45	40
45	40	25
40	38	20
42	40	20
45	45	25
50	45	35
45	42	35
52	50	40
40	38	25
45	40	25

Table 2 shows the cumulative data of each individual patient with regards to their preoperative, intraoperative and postoperative mean PAP in the Short Course of Sildenafil with the same quantitative parameters being shown in Table 3 for the Long Course of Sildenafil.

Table 3. Perioperative Mean PAP for Long Course of Sildenafil

Preop Mean PAP (mmHg)	Intraop Mean PAP (mmHg)	Postop Mean PAP (mmHg)
53	45	30
54	48	25
55	48	25
55	47	25
45	40	25
40	38	25
42	35	20
50	42	20
44	40	20
45	40	20
40	35	20
55	45	25

A Mann-Whitney U test showed that there was no significant difference in the preoperative mean PAP between the groups receiving the short and long course of oral sildenafil (p=0.890). An Independent-Samples T-test showed no significant difference in the intraoperative mean PAP between the 2 groups (p=0.968) but a significant difference in the postoperative mean PAP between the cohorts of Short and Long Course of sildenafil (p=0.018) (Table 4).

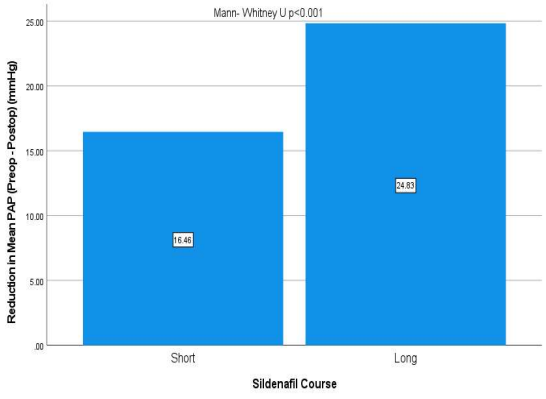
Table 4. Comparison of Mean PAP between Short and Long Course of Sildenafil

Mean PAP (mmHg)	Short Course	Long Course	p- value
Preoperative	45.31 ±4.15	48.17 ±6.10	0.890
Intraoperative	41.85 ±3.91	41.92 ± 4.68	0.968
Postoperative	28.85 ± 6.81	23.33 ±3.26	0.018

The reduction in mean PAP from preoperative to intraoperative was analyzed to be 3.46±1.71 for the short course ($p<0.05$) whereas it was 6.25±2.18 for the long course and the difference between these two results was found to be statistically significant (p= 0.003) (Figure 1).

Figure 1: Comparison between Short and Long Course of Sildenafil on the Intraoperative PAP

Figure 2: Comparison between Short and Long Course of Sildenafil on Postoperative PAP



The reduction in mean PAP from preoperative to postoperative was analyzed to be 16.46±4.13 for the short course ($p<0.05$) whereas it was 24.83±5.04 for the long course and the difference between these two results was found to be statistically significant ($p< 0.001$).

DISCUSSION

This study evaluated the impact of varying durations of sildenafil administration on meanPAP in patients undergoing mitral valve replacement (MVR). The findings indicate that a longer duration of sildenafil therapy leads to a statistically significant reduction in mean PAP compared to a shorter course.

Currently, there are no standardized guidelines for the perioperative management of pulmonary hypertension in patients undergoing MVR[4]. The management strategies are often based on institutional protocols and clinician experience

Several studies have demonstrated the benefits of preoperative sildenafil administration. Gandhi et al. reported that systolic PAP and mean PAP were significantly lower ($P<0.0001$) in the sildenafil group compared with placebo at all intraoperative and postoperative measuring intervals[9]. Similarly, Khilji et al. conducted a study at the Faisalabad Institute of Cardiology, where preoperative administration of sildenafil (25 mg thrice daily) for two days resulted in a marked difference in the postoperative tricuspid valve pressure gradient (TVPG) of the study group (32.5 4±9.038) compared with the placebo group (43.08±14.608) which was highly statistically significant (p-value <.0001)[10]. Mitra et al. administered oral sildenafil (25mg thrice daily) for two weeks before surgery in a subgroup of seven patients and observed a significant reduction in pulmonary artery systolic pressure (PASP) compared to the placebo subgroup[11].

These studies together highlight the advantages of preoperative sildenafil for reduction of elevating pulmonary artery pressures and good perioperative outcomes in patients undergoing MVR. Nonetheless, differences between study designs, populations and sildenafil dosages in the treatment regimens indicate the necessity of conducting more extensive studies to develop therapeutic guidelines[12].

Similarly, in the Sildenafil for Improving Outcomes after Valvular Correction (SIOVAC) trial, a multicenter, double-blind, randomized trial, the efficacy of sildenafil for chonic pulmonary hypertension (PH) after successful valvular surgery was studied. The trial showed a worse effect on clinical outcomes, including a higher rate of admission to the hospital for heart failure, of sildenafil compared with placebo. These findings should advice for precaution, when planning to apply sildenafil in the postoperative treatment of pulmonary hypertension in these patients[13].

According to the results of many studies the preoperative assay of sildenafil is helpful in the management of PH for patients receiving mitral valve surgery. In view of the high prevalence of pulmonary hypertension in the Pakistani RHD population, the use of sildenafil should be considered as a component of perioperative management 30 especially in patients with moderate and severe pulmonary hypertension[14-18]. Individual Treatment Strategies Because sildenafil responses are heterogeneous, treatment duration and dose ought to be individualized based on patient factors, such as the severity of PH, comorbidities, and other risk factors. More clinical trials, based on Pakistani population, will be helpful in determining the exact dose and optimal duration of sildenafil. It is important to sensitize healthcare providers in Pakistan on the usefulness of sildenafil in perioperative management of pulmonary hypertension in patients with mitral valve disease. Training and educational programs should be conducted to help providers in appropriately managing this set of patients[18-20].

Following operation, the patient needs to be closely monitored for the possibility of persistent pulmonary hypertension. Despite the favorable outcomes seen with sildenafil in the perioperative period, it is important to be cautious in considering its application in the postoperative phase, as data from studies such as the SIOVAC trial indicates that the advantages may not be universally applicable across all patients. Continue to monitor to determine if more drugs are needed. Securing healthcare and medical care in Pakistan, especially in rural or remote areas, is often difficult to come by, while specialized treatments can be scarce. Healthcare infrastructure should be improved, and access to high quality cardiovascular care with essential medications, such as sildenafil, needs to be enhanced, especially in the public hospitals/clinics.

The small sample size of our series did not allow us to perform multivariable regression analysis in order to evaluate the influence of the duration of sildenafil treatment upon other relevant post-operative outcomes, such as mechanical ventilation time, and ICU stay.

CONCLUSIONS

Sildenafil has demonstrated good effectiveness for intraoperative and postoperative treatment of pulmonary hypertension in mitral valve surgery. This effect is greater when sildenafil is given over longer periods and greater reductions in mean PAP are achieved. Perioperative

management of pulmonary vascular remodeling in PAH is of paramount importance. Sildenafil treatment should be included in perioperative regimen for better management and recovery.

DECLARATION

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Authors contribution

Each author of this article fulfilled following Criteria of Authorship:

1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.

All authors agree to be responsible for all aspects of their research work.

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Data availability

The data that support the fndings of this study are available from the corresponding author, upon reasonable request.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of King Edward Medical University, Lahore.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Competing Interests

The authors declare that the research was conducted in the absence of any commercial or fnancial relationships that could be construed as a potential confict of interest.

Conflict of Interest

The authors declared no conflict of interest.

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