The Egyptian Cardiothoracic Surgeon

Vol. 2, No. 4, 148 - 154

Original Article

Evaluation of the preoperative administration of sildenafil on operative and early postoperative outcome after mitral valve replacement in patients with pulmonary hypertension

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Abstract

Background: Mitral valve diseases are commonly associated with pulmonary hypertension. The aim of this study was to evaluate the effect of preoperative administration of sildenafil on the outcome after mitral valve replacement in patients with pulmonary hypertension.

Methods: This prospective randomized study was carried out on 67 patients who had a mitral valve replacement and associated high systolic pulmonary artery pressure more than 50 mmHg. Patients were randomized into three groups: group A (n= 20) received preoperative sildenafil for one week, group B (n=22) received sildenafil for one month, and group C (n= 25) did not receive sildenafil. All patients had transthoracic echocardiography preoperatively, one week and one month postoperatively.

Results: There was no difference in preoperative and operative variables among groups. Dobutamine support was required in 15 patients (60%) in group C vs. 6 patients (30%) in group A and 5 patients (22.5%) in group B (p= 0.012). Duration of mechanical ventilation was significantly longer in group C (389.2 ± 48.79 minutes) compared to group A and B (295.5 ± 17.01 and 281.4 ± 39.44 minutes, respectively, p<0.001). ICU stay was longer in group C (61.72 ± 13.69 hours) compared to groups A and B (53.55 ± 14.49 and 45.64 ± 13.43 hours, respectively, p=0001). The hospital stay was longer in group C (8.0 ± 1.80 days) compared to group A and B (6.05 ± 0.94 and 6.27 ± 1.24 days, respectively; p< 0.001). The transthoracic echocardiographic study one month after the operation showed that pulmonary artery systolic pressure significantly lower in groups A and B (28.30 ± 3.3 and 28.2 ± 4.98 mmHg, respectively) compared to group C (43.12 ± 4.99 mmHg) (p <0.001). There was no statistically significant difference between groups A and B regarding PASP after five days (p= 0.287) or one month (p= 0.939).

Conclusion: We found that preoperative administration of oral sildenafil in patients with pulmonary hypertension undergoing mitral valve replacement may reduce pulmonary hypertension postoperatively. We could not find a difference in the administration of sildenafil for either one week or one month preoperatively.

KEYWORDS

Mitral valve; Pulmonary hypertension; Sildenafil; Mitral valve replacement

Article History

Submitted: 2 May 2020

Revised: 14 May 2020

Accepted: 3 June 2020

Published: 1 Oct 2020

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Introduction

Mitral valve disease is commonly associated with pulmonary hypertension, which can lead to right ventricular failure and increase mortality. Pulmonary hypertension is defined as an increase of the mean pulmonary artery pressure more than 25 mmHg at rest as assessed by right heart catheterization [1].

Sildenafil is a selective pharmacological inhibitor of isoform 5 phosphodiesterase enzyme [2], which increases cyclic guanosine monophosphate (cGMP) levels and has shown to be effective for primary pulmonary hypertension [2, 3]. Sildenafil was also used to manage secondary pulmonary hypertension in the perioperative period in patients undergoing cardiac surgeries. [4]

There are few studies on the use of sildenafil in the preoperative management of pulmonary hypertension associated with mitral valve disease [5]. The aim of this study was to evaluate the effect of preoperative administration of sildenafil on the outcome after mitral valve replacement in patients with pulmonary hypertension.

Patients and Methods:

Study design and patients:

This prospective randomized study was conducted between March 2017 and October 2019 at Menoufia University Hospitals. A total of 67 patients who were scheduled for elective mitral valve replacement surgery with pulmonary hypertension (pulmonary artery systolic pressure ≥50mmHg) were included in the study. We obtained written informed consent from all patients before the enrollment in the trial, and the Ethical Committee has approved the study.

Patients were divided into three groups; group A (n= 20) included patients who received oral sildenafil 20 mg three times a day for one week preoperatively, group B (n= 22) included patients who received oral sildenafil 20 mg three times a day for one month preoperatively, and group C (n= 25) included patients who did not receive sildenafil. Patients with coronary artery disease, double-valve disease, emergency cases, redo cases, congestive heart failure, renal or hepatic dysfunction, and chronic obstructive airway disease were excluded from the study.

Data collection:

Each patient was subjected to full history taking, thorough clinical examination, preoperative laboratory and radiological investigations, and full transthoracic echocardiographic assessment including measurement of the left ventricular end-diastolic diameter (LVEDD), the left ventricular end-systolic diameter (LVESD), the left atrium size, the ejection fraction, the mitral valve area, the Wilkins score, and the pulmonary artery systolic pressure. A transesophageal echocardiogram was done after induction of anesthesia and before skin incision.

Surgical technique:

All patients had a standard median sternotomy incision. After induction of anesthesia and before skin incision, pulmonary artery systolic pressure (PASP) was measured by transesophageal ECHO. Cardiopulmonary bypass was instituted through aorto-bicaval cannulation.

Table 1: Pre-operative Data

Variable		Group A (*n* = 20)	Group B (*n* = 22)	Group C (*n* = 25)	*p* value
Male sex (Number (%))		8 (40)	11 (50)	12 (48)	0.722
Age (Mean ± SD) years		52.2 ± 8.5	51.7 ± 9.3	54.5 ± 9.3	0.526
Systemic hypertension (Number (%))		6 (30)	8 (36.3)	9 (36)	0.611
Diabetes Mellitus (Number (%))		5 (25)	4 (18)	6 (24)	0.626
Atrial fibrillation (Number (%))		4 (20)	3 (13.6)	6 (24%)	0.683
Dyspnea (Number (%))	**NYHA II**	11 (55.0)	11 (50)	14 (56)	0.910
	NYHA III	9 (45.0)	11 (50)	11 (44)	

SD: standard deviation, NYHA: New York Heart Association

Table 2: Preoperative echocardiographic data

Variable		Group A (*n* = 20)	Group B (*n* = 22)	Group C (*n* = 25)	*p* value
EF (Mean ± SD) %		63.05 ± 6.47	64.27 ± 6.47	62.48 ± 6.90	0.647
MVA (cm^2) (Mean ± SD)		1.30 ± 0.52	1.16 ± 0.41	1.06 ± 0.28	0.481
Wilkins score (Mean ± SD)		10.45 ± 1.10	9.77 ± 1.02	10.36 ± 1.32	0.121
LVESD (cm) (Mean ± SD)		3.90 ± 0.62	3.64 ± 0.60	3.98 ± 0.27	0.187
LA diameter (cm) (Mean ± SD)		4.99 ± 0.93	5.25 ± 1.14	5.10 ± 0.89	0.638
LVEDD (cm) (Mean ± SD)		5.3 ± 0.2	5.2 ±.2	5.12 ±.3	0.891
Mitral valve disease (Number (%))	Mitral stenosis	11 (55)	10 (45.5)	12 (48)	0.927
	Mitral regurgitation	6 (30)	6 (27.3)	7 (28)	
	Double mitral	3 (15)	6 (27.3)	6 (24)	
Mitral etiology (Number (%))	Rheumatic	18 (9)	19 (86.4)	21 (84)	0.906
	Degenerative	2 (20)	3 (13.6)	4 (16)	
PASP (Mean ± SD) mmHg		61.25 ± 6.46	61.86 ± 7.25	62.20 ± 6.25	0.289

SD: standard deviation, EF: ejection fraction, MVA: mitral valve area, LVESD: left ventricular end-systolic diameter, LA: left atrial, LVEDD: left ventricular end-diastolic diameter, PASP: pulmonary artery systolic pressure

Aorta was cross-clamped and cardiac arrest induced by infusion of cold potassium cardioplegic solution into the aortic root. The left atrium was approached though the interatrial groove. We used mechanical valves in all cases for the replacement of the mitral valve [6,7].

Twenty minutes post cardiopulmonary bypass, PASP was measured by transesophageal ECHO. Inotropes were titrated and recorded according to patient hemodynamics.

Patients were transferred intubated to the ICU with care focused on control of patients' hemodynamics. Transthoracic echocardiogram was performed before discharge on postoperative day 5-7 and was repeated in the outpatient clinic one month after the surgery.

Statistical analysis:

All preoperative, operative, postoperative, and outpatient follow-up data were collected. Quantitative variables were expressed as mean ± standard deviation, whereas qualitative data were expressed as number (n) and percentage. Statistical significance was tested using IBM SPSS statistics software package (version 19; SPSS Inc., Chicago, Illinois, USA). The significance of quantitative variables was tested using analysis of variance test (ANOVA), while Chi-square or Fisher exact test was used for qualitative data. We considered probability values less than 0.05 as statistically significant.

Results

We noticed no statistically significant difference between the three groups regarding; demographic data, patients' preoperative comorbidities, preoperative NYHA class, or preoperative echocardiographic data (Table 1 and Table 2).

PASP post cardiopulmonary bypass was statistically significantly lower in groups A and B than in group C (p <0.001) (Table 3).

Table 3: Intra-operative transesophageal echocardiographic data post cardiopulmonary bypass weaning

Variable	Group A (*n* = 20)	Group B (*n* = 22)	Group C (*n* = 25)	*p* value
EF (Mean ± SD) %	62.25 ± 6.97	63.23 ± 6.84	63.12 ± 6.90	0.882
PASP (Mean ± SD) mmHg	35.60 ± 4.12	32.00 ± 5.35	50.0 ± 6.01	<0.001

SD: standard deviation, EF: ejection fraction, PASP: pulmonary artery systolic pressure

Table 4: Operative data

Intraoperative data	Group A (*n* = 20) (Mean ± SD)	Group B (*n* = 22) (Mean ± SD)	Group C (*n* = 25) (Mean ± SD)	*p*-value
Aortic cross clamp time (minutes)	44.45 ± 3.86	41.95 ± 3.72	45.40 ± 13.67	0.227
Total bypass time (minutes)	63.05 ± 3.15	62.09 ± 3.05	67.52 ± 17.82	0.559
Total operative time (minutes)	108.4 ± 14.04	107.5 ± 7.52	109.1 ± 11.09	0.794

SD: standard deviation

Mean pulmonary artery systolic pressure was reduced in group A from 61.25 ± 6.46 mmHg preoperatively to 35.60 ± 4.12 mmHg post cardiopulmonary bypass (CPB) weaning and in group B from 61.86 ± 7.25 mmHg preoperatively to 32.00 ± 5.35 mmHg post CPB weaning (Table 2 and Table 3).

Regarding operative data, there was no statistically significant difference between the three groups regarding; the aortic cross-clamp time (p= 0.227), the total cardiopulmonary bypass time (p = 0.559), or the total operative time (p= 0.794) (Table 4). The duration of mechanical ventilation, intensive care unit (ICU) stay, and total hospital stay were all statistically significantly higher in group C than both groups A and B; however, there was no statistically significant difference between groups A and B regarding these durations (p= 0.137, 0.075 and 0.519, respectively) (Table 5). Postoperative complications and postoperative mortality showed no statistically significant difference between the three groups (Table 5).

There was no statistically significant difference between the three groups regarding the number of patients who received norepinephrine, dose, or duration of treatment (Table 6). However, the number of patients needed treatment with dobutamine was higher in group C than both groups A and B, and the difference was statistically significant, although there was no statistically significant difference between the treated patients in the three groups regarding the dose or duration of treatment (Table 6). The number of cases needed postoperative treatment with glyceryl trinitrate, and milrinone was statistically significantly higher in group C than both groups A and B (p <0.001 and 0.019, respectively) (Table 6).

The transthoracic echocardiographic study 5 days and one month after the operation showed that pulmonary artery systolic pressure (PASP) was significantly lower in groups A and B than in group C and this difference was highly statistically significant (p-value <0.001) (Table 7 and Table 8). However, there was no statistically significant difference between groups A and B regarding PASP after five days (p= 0.287) or one month (p= 0.939) (Table 7 and Table 8). There was no statistically significant difference between the three groups regarding; ejection fraction (EF), mitral valve (MV) pressure gradient, left ventricular end-systolic diameter (LVESD), left atrial (LA) diameter or left ventricular end-diastolic diameter (LVEDD); either in 5-7 days or one-month postoperative echocardiographic study (Table 7 and Table 8).

Table 5: Postoperative data

Variables	Group A (*n* = 20)	Group B (*n* = 22)	Group C (*n* = 25)	*p* value
Ventilation time (minutes) (Mean ± SD)	295.5 ± 17.01	281.4 ± 39.44	389.2 ± 48.79	<0.001
ICU stay (hours) (Mean ± SD)	53.55 ± 14.49	45.64 ± 13.43	61.72 ± 13.69	0.001
Hospital stay (days) (Mean ± SD)	6.05 ± 0.94	6.27 ± 1.24	8.0 ± 1.80	<0.001
Re-exploration (Number (%))	1 (5%)	1 (4.5%)	1 (4%)	>0.99
Sternal wound infection (Number (%))	2 (10%).	2 (9.1%)	3 (12%)	0.899
New atrial fibrillation (Number (%))	8 (40%)	6 (27.2 %)	8 (32%)	0.785
Mortality (Number (%))	0	0	1 (4%)	0.921

SD: standard deviation, ICU: intensive care unit

Table 6: postoperative inotropic support and vasodilators use

Postoperative drugs		Group A (*n* = 20)	Group B (*n* = 22)	Group C (*n* = 25)	*p* value
Norepinephrine	Number (%)	2 (10.0)	2 (9.1)	6 (24)	0.362
	Duration (Mean ± SD) hours	5.0 ± 1.41	5.0 ± 0.0	5.67 ± 0.61	0.385
	Dose (Mean ± SD) mg/ml	0.07 ± 0.02	0.05 ± 0.01	0.07 ± 0.02	0.310
Dobutamine	Number (%)	6 (30)	5 (22.5)	15 (60)	0.012
	Duration (Mean ± SD) hours	5.60 ± 0.89	5.10 ± 0.89	5.43 ± 0.90	0.691
	Dose (Mean ± SD) mg/ml	7.40 ± 1.82	5.40 ± 1.52	7.07 ± 2.15	0.161
Glyceryl Trinitrate (Number (%))		3 (15)	4 (18.2)	16 (64)	<0.001
Milrinone (Number (%))		3 (15)	2 (9.1)	11 (44)	0.019

SD: standard deviation

Concerning mortality, 1 (5%) patient in Group C had passed away intraoperatively because of vasoplegia as a result of hypersensitivity from transfusion of fresh frozen plasma. There was no significant statistical difference between the three groups (p= 0.921).

Discussion

We performed this study to evaluate the effect of preoperative administration of sildenafil on operative and early postoperative outcome after mitral valve replacement in patients with pulmonary hypertension. Pulmonary hypertension affects almost all patients with severe symptomatic mitral valve disease [8]. Mitral valve diseases increase left atrial pressure, which leads to an initially passive and potentially reversible increase in pulmonary artery pressure. Vascular injury then triggers a cascade of venous and small artery remodeling, which result in non-reversible arterial pulmonary hypertension, and eventually, right ventricular dysfunction [9]. In our study, the mean age in group A was 52.2 ± 8.5 years, in group B was 51.7 ± 9.3 years, and in group C was 54.5 ± 9.3 years. There was no statistically significant difference between the three groups regarding age (p= 0.526). There was no statistically significant difference between the three groups regarding the preoperative echocardiographic data.

We performed intraoperative transesophageal echocardiography immediately post cardiopulmonary bypass (CPB) weaning for all patients included in our study. The mean PASP for group A was 35.60 ± 4.12 mmHg, for group B was 32.00 ± 5.35 mmHg and was 50.0 ± 6.01 mmHg in group C. The difference was statistically significant between group C and the two other groups (p <0.001). However, there was no statistically significant difference between group A and B regarding PASP.

Table 7: Echocardiographic data 5-7 days postoperative

Variable	Group A (*n* = 20)	Group B (*n* = 22)	Group C (*n* = 25)	*p* value
EF (Mean ± SD) %	62.25 ± 6.97	63.23 ± 6.84	63.12 ± 6.90	0.882
MV pressure gradient (Mean ± SD) mmHg	4.60 ± 0.50	4.59 ± 0.50	4.56 ± 0.51	0.960
LVESD (cm) (Mean ± SD)	3.88 ± 0.62	3.64 ± 0.60	3.88 ± 0.37	0.189
LA diameter (cm) (Mean ± SD)	4.89 ± 0.91	5.16 ± 1.08	5.05 ± 0.86	0.638
LVEDD (cm) (Mean ± SD)	5.2 ± 0.2	5.0 ±.2	5.12 ±.3	0.860
PASP (Mean ± SD) mmHg	31.04 ± 3.9	29.69 ± 4.2	46.4 ± 5.6	<0.001

SD: standard deviation, EF: ejection fraction, MV: mitral valve, LVESD: left ventricular end-systolic diameter, LA: left atrial, LVEDD: left ventricular end-diastolic diameter, PASP: pulmonary artery systolic pressure

Table 8: Echocardiographic data one month postoperative

Variable	Group A (*n* = 20)	Group B (*n* = 22)	Group C (*n* = 25)	*p* value
EF (Mean ± SD)	61.90 ± 5.96	61.95 ± 5.74	61.60 ± 6.36	0.977
MV pressure gradient (Mean ± SD) mmHg	4.60 ± 0.50	4.59 ± 0.50	4.56 ± 0.51	0.960
LVESD (cm) (Mean ± SD)	3.99 ± 0.52	3.54 ± 0.60	3.98 ± 0.37	0.199
LA diameter (cm) (Mean ± SD)	4.9 ± 0.91	5.26 ± 1.08	5.15 ± 0.86	0.648
LVEDD (cm) (Mean ± SD)	5.26 ± 0.30	5.1±.31	5.0± 0.34	0.972
PASP (Mean ± SD) mmHg	28.30 ± 3.3	28.2 ± 4.98	43.12 ± 4.99	<0.001

SD: standard deviation, EF: ejection fraction, MV: mitral valve, LVESD: left ventricular end-systolic diameter, LA: left atrial, LVEDD: left ventricular end-diastolic diameter, PASP: pulmonary artery systolic pressure

Our results agree with the results of Gandhi and colleagues [10] who studied 40 patients scheduled for a mitral valve replacement with severe pulmonary hypertension and were randomly treated with oral sildenafil 25 mg (n = 20) or placebo (n = 20) for 24 hours before surgery. They found that systolic and mean pulmonary artery pressures were significantly lower ($p < 0.0001$) in the sildenafil group than the placebo group at all times.

In our study, we demonstrated that preoperative sildenafil administration significantly decreased the pulmonary artery systolic pressure (PASP) during the perioperative period, and this decrease in PASP continued to the postoperative period up to one month after surgery for patients who received sildenafil. This reduction could be explained by the relaxant effect of sildenafil on the pulmonary arterial wall.

Regarding operative data, there was no statistically significant difference between the three groups regarding the bypass time, the aortic cross-clamp time, and the total operative duration. The postoperative recovery was significantly shorter in the two groups who received sildenafil than the control group (group C), with shorter mechanical ventilation time ($p < 0.001$), ICU stay ($p = 0.001$), and hospital stay ($p < 0.001$). Gandhi and associates [10] found that postoperative parameters like ventilation time and postoperative ICU stay time were significantly lower in the sildenafil group ($p= 0.011$) as compared with the control group [10].

In our study, the number of patients who needed treatment with dobutamine, glyceryl trinitrate, and milrinone was statistically significantly higher in group C than both groups A and B. However; there was no statistically significant difference between the three groups regarding the number of patients who received norepinephrine. This was similar to the results found by Gandhi and coworkers [10]. Shim and associates found that the numbers of patients requiring norepinephrine and milrinone were similar between the groups [4].

The transthoracic echocardiographic study five days and one month after the operation showed that pulmonary artery systolic pressure (PASP) was statistically significantly lower in groups A and B than in group C. However, there was no statistically significant difference between groups A and B regarding PASP in either echocardiographic data.

There are few studies about the effect of sildenafil on postoperative PASP with no echocardiographic studies were done beyond the early postoperative period.

As there was no statistically significant difference between the echocardiographic findings, operative or postoperative outcome for patients who received sildenafil for one week preoperatively (group A) and patient who received sildenafil for one month preoperatively (group B); giving sildenafil for those patients for more than one week preoperatively is not needed.

We had only one case of mortality in group C who died intraoperatively most likely due to severe reaction to fresh frozen plasma transfusion. However, there was no statistically significant difference between the three groups regarding postoperative complications and postoperative mortality.

Study limitations

The study is limited by the number of patients, and it is a single-center experience, and generalization of the results may not be possible.

Conclusion

We found that the preoperative administration of oral sildenafil in patients undergoing mitral valve replacement with pulmonary hypertension may reduce pulmonary hypertension postoperatively. We could not find a difference in the administration of sildenafil for either one week or one month preoperatively.

Conflict of interest: Authors declare no conflict of interest.

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