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Early outcome of the effect of phosphodiesterase-5 inhibitor on pulmonary hypertension in patients undergoing mitral valve surgery

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***Abstract*---Background:** The most frequent reason for pulmonary hypertension is left-sided cardiac disease. In certain cases, pulmonary arterial vasoconstriction & vascular remodeling may result in a superimposed active component that raises pulmonary arterial pressure even further. When PHTN is present, individuals with left-sided cardiac disease have a poorer prognosis. According to recent research, sildenafil, a phosphodiesterase-5 inhibitor, is a useful medication for treating pulmonary hypertension in patients with left-sided heart disease. **Objective:** To investigate how sildenafil works for pulmonary hypertension in patients with mitral valve disease. **Patients and Methods:** This study was conducted between 2015 & 2019 at Cairo University's Kasr El Aini Faculty of Medicine's Department of Cardiothoracic Surgery with local ethical committee permission. One hundred adults studied cases with mitral valve lesions & PHTN who had undergone mitral valve surgery were enrolled. Two groups of fifty studied cases each were assigned, & their preoperative risk factors were appropriately matched. studied cases in Group A (no=50) & pulmonary artery pressure (50-80mmHg) received sildenafil citrate. Clinical evaluation & TEE were used to measure hemodynamics (ABP, HR, CVP, & PASP in mmHg), mitral valve functions, & LV performance (LVEF%) before surgery, throughout the

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intensive care unit & hospital stay, & six months after the procedure. **Result:** In our research, the mean post-six-month pulmonary hypertension was 28.28±5.0mmHg in group A and 46.40±4.8 mmHg in group B. The P value was 0.02 to indicate a significant statistical difference. **Conclusion:** Use of Sildenafil helped in improving the prognosis and reduced pulmonary artery pressure.

***Keywords*---**Phosphodiesterase-5 inhibitor, Pulmonary hypertension, Mitral valve surgery.

Introduction

The most frequent reason for pulmonary hypertension is left-sided cardiac disease. In certain cases, pulmonary arterial vasoconstriction & vascular remodeling may result in a superimposed active component that raises pulmonary arterial pressure even further. When PHTN is present, individuals with left-sided cardiac disease have a poorer prognosis. According to recent research, sildenafil, a phosphodiesterase-5 inhibitor, is a useful medication for treating pulmonary hypertension in patients with left-sided heart disease. PHTN treatment in LHD. For studied cases with end-stage heart failure, unloading the left ventricle with circulatory assistance may also reverse severe PHTN. Permitting heart transplant candidates (Badesch et al. 2010). This study aimed to investigate how sildenafil works for pulmonary hypertension in patients with mitral valve disease.

Patients and Methods

Pre-operative assessment: History (general and local) Examination, echocardiography, & coronary angiography in studied cases with risk factors & renal function. Post-operative assessment: inotropic support, mortality morbid post-operative ICU stay, stroke, pulmonary artery pressure immediately post-operative, and pulmonary artery pressure follow six months. Group B had a pulmonary artery pressure of more than 80mmHg, while Group A had a pressure between 50 & 80mmHg.Clinical evaluation & TEE were used to measure hemodynamics (ABP, HR, CVP, & PASP in mmHg), mitral valve functions, & LV performance (LVEF%) before surgery, throughout the intensive care unit & hospital stay, & six months after surgery. Management of Anaesthesia Temperature, ECG, peripheral oxygen saturation, end-tidal carbon dioxide tension, noninvasive & invasive arterial blood pressure, central venous pressure, & hourly urine output were all recorded for each studied case. & a triple lumen 7 Fr central venous catheter (Arrow International Inc. PA, USA) was placed.

Fentanyl (10µg/kg) & midazolam (0.1mg/kg) were used to induce anesthesia. To simplify endotracheal intubation, 0.15mg/kg of pancuronium was given. This was repeated intraoperatively as needed to keep muscles relaxed. A nasogastric tube was placed following induction. All echocardiographic measurements were performed using a 7.5-MHz multi-plane TEE probe & system (Vivid 3, GE Medical Systems, Milwaukee, Wis). Following the standards set forth by the American

Society of Echocardiography/Society of Cardiovascular Anaesthesiologists, every patient had a comprehensive transesophageal echocardiography examination.

After aortic cross-clamping, cardiac standstill during CPB was achieved with antegrade hyperkalemic cold oxygenated blood cardioplegic solution via aortic root. Moderate hypothermia was maintained around nasopharyngeal temperature of 28°C in all cases. After normothermia was achieved, mechanical ventilation was reinstituted, & studied cases were weaned from CPB. Weaning from CPB was attempted after adequate rewarming till systemic body temperature > 35 °C after correction of any electrolyte or acid-base disturbance. Inotropic support was started in case of evident systolic dysfunction of LV or RV as evident by TEE.

Intraoperative measurement (by TEE):
From the transgastric mid-papillary short-axis view, the probe was rotated to the right to visualise the RV transgastric inflow image.

Mitral valve function:

In the mid-esophageal 4 chamber view, 0 degrees plane using continuous wave Doppler to obtain the pressure gradient across the valve. Right & left ventricular functions are calculated by obtaining LVEDD, LVESD, and LVEF% "Fractional Area of Contraction"
FAC = EDA-ESA / EDA"
Normal limits are between 60-75 %, and dysfunction Limits are 50's-40's.
IV. Postoperative follow-up:

(1) Immediate postoperative in the OR:

- Inotropic support is needed for weaning off-CPB.
- Pulmonary artery pressure measurements by TEE.

(2) During ICU stay:

- Haemodynamics of the patients (blood pressure, heart rate, rhythm, central venous pressure, & peripheral temperature.
- Weaning from ventilator support.
- Weaning from inotropic support.

(3) During hospital stay after discharge from ICU:

- Morbidity and Mortality.
- Period of hospital stay.

(4) Before hospital discharge TTE was done to assess:

- Function of the Mitral Valve after repair or replacement.
- Function of the tricuspid valve (if repair was done).
- Pulmonary Artery Pressure(s).
- Left & right ventricular diameters and functions.

(5) 6 months after hospital discharge TTE was done to assess:

- Function of the Mitral Valve after repair or replacement.
- Function of the tricuspid valve (if repair was done).
- Pulmonary Artery Pressure(s).
- Left & right ventricular diameters and functions.

Statistic method:

SPSS version 20.0 computer program was used for data analysis. Results are expressed are mean and standard deviation. Comparison between the mean values of the different variables was performed using (the Man-Whitney test) and (the Wilcoxon signed test).

Results

Preoperative data:

Demographic data: The demographic data of both groups showed statistically insignificant differences regarding DM, HTN, as well as clinical diagnosis for Diabetes mellitus group A had 8 (16%) patients, and group B had 6 patients (12%). As for Systemic Hypertension group A, there were 15 (30%) patients and in group B there were 18 patients (36%). As for Ex-Cigarette smoking group A were 27 (54%) patients and in group B were 29 patients (58%).

-In group A there was 24 with Mitral stenosis (48%), 10 with Mitral regurgitation (20%),15 patients (thirty percent) of the studied cases with mild tricuspid regurgitation and15 patients (30%) with moderate, and 20 patients (40%) with severe tricuspid regurgitation. But in group B there was25 patients with Mitral stenosis (50%), 8 with mitral regurgitation (16%), and 25 patients (50%) in the form of severe tricuspid regurgitation.

- In our study according to the inotropes 52 patients (86%) needed inotropes in the form of dubtamine and milrinone.
- In our study, 40 patients (40%) had hepatic dysfunction.
- In our study group Perioperative Demographic and Echocardiographic Data showed statistical insignificance:

Table (1): Perioperative demographic and echocardiographic data

Group		Age	EF	Left atrium	Preoperative PHTN	Operative time	Bypass time	Ischemic time
Group A	Mean	45.31	61.17	5.96	60.69	128.97	68.28	52.59
	N	30	30	30	30	30	30	30
	Deviation	10.492	7.788	1.127	7.714	17.028	17.075	16.617
	Median	42.00	60.00	5.90	60.00	125.00	65.00	50.00
	Minimum	30	49	4	50	110	45	30
	Maximum	73	75	11	80	200	140	120
Group B	Mean	41.83	57.83	7.70	90.00	147.83	95.67	73.33
	N	30	30	30	30	30	30	30
	Deviation	8.392	6.988	1.092	7.922	27.439	39.255	30.691
	Median	40.00	56.00	7.70	90.00	135.00	75.00	57.50
	Minimum	29	45	4	80	110	45	30
	Maximum	60	72	11	100	195	170	140
Total	Mean	43.54	59.47	6.85	75.59	138.56	82.20	63.14
	N	60	60	60	60	60	60	60
	Deviation	9.562	7.519	1.406	16.689	24.636	33.196	26.715
	Median	42.00	59.00	6.80	80.00	130.00	70.00	55.00
	Minimum	30	45	4	50	110	45	30
	Maximum	73	75	11	100	200	170	140

Table (2): Op. PHTN, ICU stay, post-operative PHTN Data and Hospital stay

Group		OP_PHTN	ICU stay	POST_PHTN	LATE_PHTN	Hospital stay
GA	Mean	33.90	4.59	33.00	28.28	7.07
	N	30	30	30	30	30
	Deviation	6.161	1.427	4.551	5.014	1.361
	Median	33.00	5.00	32.00	30.00	7.00
	Minimum	30	2	25	20	6
	Maximum	50	10	45	40	11
GB	Mean	54.00	6.13	47.80	46.40	7.30
	N	30	30	30	30	30
	Deviation	7.292	1.776	5.910	4.804	1.022
	Median	55.00	6.00	48.00	46.50	7.00
	Minimum	40	2	35	35	6
	Maximum	70	9	60	55	11
Total	Mean	44.12	5.37	40.53	37.49	7.19
	N	60	60	60	60	60
	Deviation	12.151	1.780	9.119	10.353	1.196
	Median	45.00	5.00	40.00	40.00	7.00
	Minimum	30	2	25	20	6
	Maximum	70	10	60	55	11

- In our research, in group A the mean age was 45.31±10.4 years while in group B it was 41.88±8 years which showed an insignificant statistical difference as the P value was 0.22. In our studies, in group A the mean EF was 61.17±7.7% while in group B it was 57.83±6.9%, which explained a significant statistical difference as the P value was 0.13.
- In our research in group A the mean left atrium size was 5.96±1.1cn while in group B it was 7.70±1.0cm which explained a significant statistical difference as the P value is0.03. In our research in group A the mean pre-operative pulmonary hypertension was 60.65±90.00mmHg while in group B was7.7±7mmHg which showed a statistically insignificant difference as the P value was 0.02.
-In our research in group A the mean operative time was 128.97±17.02 minutes while in group B it was 147.83±27.43minute which explained a significant statistical difference as the P value was 0.005. In our research, in group A the mean bypass time was 68.28±17.07 minutes while in group B it was 95.67±9.25minute which appeared a significant statistical difference as the P value was 0.008.
-In our research in group A the mean ischemic time was 52.59±16.6 minutes while in group B was73.33±30.6minute which exposed a significant statistical difference as the P value was 0.001In our research in group A the mean intra-operative pulmonary hyphenation was 33.90±6.5mmHg while in group B was 54.00±7.2 mmHg which shows a significant statistical difference as P value was 0.01.
-In our research in group A the mean ICU stay was 4.5±1.4day while in group B was6.13±1.7day which presented a significant statistical difference as the P value was 0.02.

-In our research in group A the mean hospital stay was 7.07±1.3day while in group B was7.30±1.0 day which explained an insignificant statistical difference as the P value was 0.07.
-In our research in group A the mean post-operative pulmonary hypertension was 33.00 ±4.5mmHg while in group B it was 47.30± 5.9 mmHg which explained the insignificant statistical difference as the P value was 0.02.
-The mean post-6-month pulmonary hypertension in group A of our research was 28.28±5.0 mmHg, but the mean in group B was 46.40±4.8 mmHg. This difference was statistically significant, as indicated by the P value of 0.02.

Postoperative Outcome:

Mortality: Eight patients died (total mortality of 8%).
1. In group A, two patients died (4 %). On the 1st. the patient died due to uncontrollable post-operative medical bleeding after a long bypass time (CPB three hours). The second patient was a diabetic who died of a severe chest infection.
2. In group B, two patients died (4 %). The first patient had hepatitis Virus-C positive and died of progressive hepatic insufficiency then failure on the 11th. Post-operative day. The second patient was a diabetic who died due to severe deep wound infection with mediastinitis.

Morbidity: It occurred in 18 patients (18 %):
-In group A one patient needed high inotropic support, one patient needed prolonged mechanical ventilation, and one patient had sildenafil-related side effect in the form of blurring vision.
In group B three patients needed high inotropic support, four patients needed prolonged mechanical ventilation, and one patient had sildenafil-related side effects in the form of headache

Discussion

Surgery for mitral valve repair or replacement in the presence of PHTN (PAP ≥ 70mmHg) is a serious management challenge. The magnitude of this problem is further accentuated in developing communities like Egypt where RHD is highly prevalent. Moreover, a higher percentage of those mitral valve disease patients do present late with PHTN, hence jeopardizing the surgical results and endangering the patient's own life. Several methods were proposed in an attempt to control PHTN before mitral valve surgeries to minimize or prevent side effects and complications (Ghofrani et al., 2002). Individuals who have chronic mitral valve disease are susceptible to pulmonary hypertension (Trachte et al, 2005). During heart surgery, pulmonary hypertension is a significant risk factor for the development of acute right-sided heart failure (Lepore et al., 2001). Right ventricular failure is linked to higher rates of morbidity & death even with prompt & appropriate treatment (Ghofrani et al., 2002). Several strategies are needed to address RV failure effectively. The primary objective is to use a vasodilating substance to reduce RV afterload (Weimann et al., 2000).

Using beta agonists (like isoproterenol) or phosphodiesterase type III inhibitors (like milrinone) to increase vascular smooth muscle cyclic adenosine

monophosphate levels is the goal of strategies to lower pulmonary vascular tone. Alternatively, nitroso vasodilators (sodium nitroprusside, nitroglycerin, and inhaled nitric oxide) that raise cyclic guanine monophosphate also decrease pulmonary vascular tone (Shim et al. 2006).

Verbal By selectively inhibiting phosphodiesterase type 5, of which the lung has an abundant supply, sildenafil, a strong & selective vasodilator, prolongs the effects of cyclic guanosine monophosphate. It has been demonstrated to be just as successful in treating pulmonary fibrosis & primary pulmonary hypertension as inhaled NO. Nevertheless, sildenafil does not result in rebound pulmonary hypertension & does not require an inhaled delivery mechanism (Zwissler, 2000).
Aaron and colleagues' study in 2005, assessed the effect of administrating 25-50mg of sildenafil preoperatively in studied cases with pulmonary hypertension undergoing cardiac surgery for mitral valve disease, in eight patients. It demonstrated that the mean pulmonary artery pressure decreased by twenty percent & twenty-two percent at thirty & sixty minutes following the initial dose of sildenafil, respectively ($p < 0.05$). At thirty & sixty minutes, the pulmonary vascular resistance index dropped by forty-nine percent & forty-four percent, respectively ($p < 0.05$). Systemic vascular resistance, mean arterial pressure, and cardiac index were not clinically significantly impacted by sildenafil. Sildenafil was given in subsequent doses at regular intervals, which made it possible to successfully wean concurrent pulmonary vasodilators. Despite that study did observe a statistically significant decrease in MAP it showed also an initial statistically significant decrease in SVRI (Aaron et al., 2005).

The decrease in MAP and SVRI was probably due to preoperative use of other pulmonary vasodilators as Calcium channel blockers, GTN and Milirinone in order to control pulmonary hypertension prior to surgery also it may be due to the method of induction of anesthesia. The sample number should also be taken into consideration as it was conducted on eight patients only (Aaron et al., 2005).
Shim et al. Study in 2006, assessed the impact of administrating 50mg of sildenafil preoperatively in studied cases with pulmonary hypertension undergoing cardiac surgery for mitral valve disease, it was conducted on 53 patients. At thirty minutes following treatment, it revealed that the sildenafil group had considerably lower systolic & mean pulmonary arterial pressures as well as pulmonary vascular resistance but mean systemic arterial pressure & systemic vascular resistance were same. Additionally, the study found that sildenafil significantly reduced HR. Additionally, the study found that the control group's RVEDVI & RVESVI significantly increased, whilst the sildenafil group did not. Even though there was no change in RVEF, this suggested that sildenafil might contribute to better RV performance (Shim et al. 2006).

Ghofrani et al. (2002), further discovered a dose-dependent correlation between alterations in the pulmonary vascular resistance index, PAP, and cardiac index. Additionally, they noted that the acute administration of a single oral dose of sildenafil resulted in an increase, or a trend towards improvement, in cardiac output & a substantial reduction in MPAP & PVR with little to no impact on mean arterial pressure. The impact lasts up to four hours & peaks at sixty minutes.

Stiebellehner et al. (2012) reported the management of severe persistent primary PHTN following surgical closure of ASD by adding chronic oral sildenafil in studied cases with already on stable doses of IV prostacyclin. The addition of 75 to 200mg/d of sildenafil in divided doses over five months decreased the dyspnea, & MPAP by 14-41 % & improved 6-minute walking distance by 35 to 105 meters, Dose-limiting adverse effects consisted of headache & nausea, likely because of systemic vasodilation & mild hypotension (Mehta, 2003).

Based primarily upon the outcomes of the SUPER-1 study (2003), sildenafil was approved for treatment of PAH in both USA & Europe at 20mg three times per day dose. Throughout the pivotal trial period, there were dose-dependent alterations in hemodynamic measures, especially MPAP, but no variations in 6MWD among the 3 dosages (Michelakis et al., 2003).

In pilot research done by Michelakis et al. (2003), they applied regimen of 50 mg orally TDS for 3 months. In a study by Bhatia et al. (2007), they gave 25 mg TDS (max 100mg) for only 24-48 hours. In randomized double-blinded cross-over research by Bharani et al. (2007) they used 25 mg TDS only for 2 weeks postoperatively; while Kothari et al. (2002) used a median dose of 87.5mg/day (for < 30kgm) and 150mg/day (for > 30 Kgm) for 7.3 ± 2.4months (range 3-14months).

An Egyptian clinical study made by Ghanem et al. (2009), mentioned giving 50 mg via the nasogastric tube just after induction of anaesthesia. A last study by Trachte et al. (2010) used 25-50 mg BID (combined with other pulmonary vasodilators) for mean of 60 days postoperatively. Sildenafil's safety has already been proven, at least for normal dosages (50–100 mg) given sporadically to treat erectile dysfunction. Adverse effects as systemic hypotension may occur especially with larger doses as by then its vasodilatory effects may not be pulmonary vascular specific (Mehta, 2003).

Based on the previous expert opinions & background knowledge on using different perioperative doses of sildenafil citrate, and keeping in mind the drug's reported side effects that we noticed during our first case trial, we reached the protocol that we used in our study. It started by giving oral Sildenafil (50 mg tabs) two times per day for 10 days before surgery; followed by a single 50 mg tablet 10 minutes just before anaesthesia induction & continued twice daily for one week after surgery.

Our baseline value was that recorded 10 days preoperatively after starting oral sildenafil. Owing to its liability for rapid absorption. Bharani et al. (2007) confirmed the presence of the drug's effect within 10-15 minutes following its administration. Another recent study stated that the pulmonary vasodilatory effect of oral sildenafil starts after 12-15minutes with a mean time to peak concentration is 50-55 minutes. Most of the studies reported time to maximal pulmonary vasodilatory effect of 30- 60 minutes (Ghoreishi et al., 2011).

Despite using a protocol that combines preoperative to intraoperative and postoperative doses of Sildenafil, the general impression of the results (decreased pulmonary pressure values with stable or no changes in systemic blood pressure values) was like other studies using only a single intraoperative dose of Sildenafil

like (Wheeler et al., 2002; Madden et al., 2005; Trachte et al., 2005 and Shim et al., 2006) as follows:

Wheeler et al. (2002), reported a case report study demonstrating effects 30 minutes after 100 mg of sildenafil orally, Intra-operatively via a NGT in PHTN patients undergoing cardiac transplantation. The initial PASP of 54/22 mmHg & MPAP of 36mmHg and PVR of 278 dynes. sec.cm–5, significantly decreased to 38/19mmHg, with a mean of 32mm Hg & a PVR of 154 dynes.sec.cm–5.

Madden et al. (2002), assessed administering 50mg of sildenafil intra-operatively in 2 patients with PHTN undergoing cardiac surgery for mitral valve disease. They detected a significant decrease in PASP MPAP and PVR that occurred 1 hour after administration of sildenafil in one patient and after 30 minutes in the other.

Trachte et al., (2005), administered 25-50mg of sildenafil preoperatively to 8 patients with PHTN undergoing cardiac surgery for mitral valve disease. Initially, MPAP was reduced by 20% & 22% after 30 & 60minutes respectively ($p<0.05$). PVRI decreased by 49% & 44% after 30 & 60minutes respectively ($p < 0.05$). Sildenafil had no clinically significant effects on cardiac index, mean ABP values, or SVRI.

In the current study, statistical significance was detected between the two study groups regarding the surgical data and operative times. Moreover, there was less need for high inotropic support and multiple DC shocks during intraoperative weaning off-CPB in group A as well as inotropic support and mechanical ventilator assistance during ICU stay.

This favorable response was attributed to the improvement in LV & RV parameters (diastolic/systolic dimensions) and contractility index (ejection fraction %) due to the use of sildenafil in studied cases. Similar findings were reported in 2 series describing the perioperative use of sildenafil for worsening PHTN in studied cases requiring multiple vasopressors & inotropic support. Fung et al. (2005) stated that compared to their vasopressor group; sildenafil reduced the MPAP from 58 to 29mmHg & the PCWP from 32 to 18mmHg after coronary bypass & mitral annuloplasty, improving systemic blood pressure without the need for vasopressor support. Madden & Crerar-Gilbert (2005), reported that sildenafil was given intra-operatively throughout an aortic valve replacement for an MPAP of 90mmHg accompanied by no systemic hypotension; compared to the control group in which epinephrine & milrinone were needed to decrease MPAP to 50mmHg.

In the present study, the mean systemic pressure values measured in group A (SAP, DAP, MAP) showed a reduction (with statistical significance) versus group B at almost all study times. Using TEE, the RV & LV ejection fraction was found to increase (with statistical significance). This could be explained by the better RV kinematics (due to afterload reduction through pulmonary vasodilatation) that led to a similar improvement in their LV equivalents.

Consistent with the previous statement in our results, Groeneweg et al. (2008) reported the absence of changes in systemic ABP in a study on 24 patients

receiving tadalafil 20mg for 12 weeks as initial systolic blood pressure was 142 (± eighteen) mmHg & at the end of the research, it was 140 (± nineteen) mmHg. Kloner et al. (2003) & Kloner (2004) after assessment of a database of 4,000 patients who received 10 mg of sildenafil concluded that it only resulted in small changes in blood pressure, which are not believed to be clinically relevant; Shim et al. (2006) demonstrated that use of single dose of sildenafil in patients undergoing valve surgery with PHTN didn't have any deleterious effects on HR, CVP or systemic ABP values (SBP, DBP, or MABP).

In the current study, there was mortality in both groups. The causes of mortality were attributed to general medical causes not related to the drug and conform well with mortality rates reported in the literature concerning open-heart valve surgery. Morbidity occurred in 4 patients (13 %); versus 7 (23 %) in group B. In group A patients only one patient needed high inotropic support (vs. 3 patients in group B); while another patient needed prolonged mechanical ventilation longer than 48 hours vs. 4 patients in group B (high statistical significance).

In the current work, sildenafil-related side effects occurred in 2 patients only (6 %) in the form of blurring of vision in a single case; and flushing with headache in another single case. They were controlled both safely and effectively by other non-specific supportive medications. Those undesired side effects were mentioned in the drug's pamphlet as minor allergic symptoms that should not occur repeatedly. Other series also reported the occurrence of side effects (Kloner 2004; Madden & Crerar-Gilbert 2005; Groeneweg et al., 2008 and Ramani & Park, 2010).

Kothari et al. (2002), reported outcomes of a 14-patient prospective research on a median dose of 87.5mg/day (<30Kg) & 150mg/d (>30Kg). These patients were found to have significant improvement in NYHA Class, RVSP, at three months and improvement in 6MWT at 6 months PO.

Michelakis et al. (2003), conducted a pilot study involving 5 patients taking Sildenafil 50mg POQ 8 hourly for 3 months. They found significant improvement in NYHA-FC; 6 MWT together with a significant decrease in mean PAP, PVRI & RV mass.

Bhatia et al. (2003) reported results of 13-patient retrospective study that were given 25 mg sildenafil Q 8 hours (max of 100 mg Q 8 hours) for 24-48 hours. They noticed that cardiac output has increased significantly while PASP, MPAP, PVRI, MAP decreased significantly.

Bharani et al. (2003) published their results of using sildenafil in a 10-patient randomized double-blind cross-over study. Their patients who took 25mg PO/ every 8 hours for 2 weeks, showed significant improvement in 6MWT; NYHA class symptoms; reduction in modified Borg dyspnea score & reduction in dolloer-estimated PASP. Despite different recommendations, a generally accepted standardization of cardiopulmonary exercise testing concerning data acquisition & analysis in PAH is lacking.
The primary causes of this disparity were found to be a lack of standardization & a lack of proficiency in conducting cardiopulmonary exercise testing; the 6MWT is still the only exercise endpoint approved by the Food & Drug Administration

& the European Agency for the Evaluation of Medicinal Products for research assessing treatment effects in PAH (Ross et al, 2003).
Therefore, we cannot strongly support our result, but we recommend giving patients with moderate to severe PHTN oral sildenafil.

Conclusion

Preoperative Oral Sildenafil appears to produce a significant pulmonary vasodilatory effect. This was demonstrated by the significant decrease in systolic pulmonary artery pressure, which means pulmonary pressure, & pulmonary vascular resistance in anesthetized cardiac surgical studied cases with mitral valve disease & pulmonary hypertension. These changes were not associated with significant changes in mean systemic arterial pressure systemic vascular resistance or cardiac output. This study couldn't observe any favorable effect of sildenafil on RV performance.

Due to the favorable and selective activity of sildenafil on the pulmonary vasculature shown in this study, the use of oral sildenafil to control pulmonary hypertension in the perioperative period in cardiac surgical studied cases must be considered & is advisable.

Limitation of the research: The main limitations of our research are short follow-up and small sample size.

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