Review Article

Effectiveness of Sildenafil in Pulmonary Hypertension Secondary to Valvular Heart Disease: A Systematic Review and Meta-Analysis

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Abstract

Sildenafil is commonly used as off-label medication in Pulmonary Hypertension (PH) secondary to Valvular Heart Disease (VHD). Previously, published systematic review reported the efficacy of sildenafil for PH with VHD specifically in preoperative condition. We conducted this systematic review and meta-analysis to summarize the potential benefits of sildenafil at different treatment phases, namely acute or chronic. Articles available up to June 2020 were identified using Web of Science, Ovid & Medline, EBSCOHOST, the Cochrane Library, PubMed and Google scholar. Quality assessment and data analysis were conducted using Review Manager (RevMan) version 5.4 and Black and Downs' Checklist. A total of nine studies (n = 614 patients) were eligible for analysis. Sildenafil improved systolic pulmonary arterial pressure (sPAP) (MD -5.89 mmHg ± 17.07), mean Pulmonary Arterial Pressure (mPAP) (MD -4.62 mmHg ± 12.24) and Pulmonary Vascular Resistance Index (PVRI) (MD -60.11 dynes.sec.cm^{5}m^2 ± 500.85) during acute and chronic phase in three studies. Data showed no changes in systemic hemodynamic during acute phase but improved in CO and Cl readings during chronic phase. Sildenafil reduced mechanical ventilation time and post-operative recovery room stay during acute and chronic phases. Patients required inotrope support were similar between placebo and sildenafil groups during acute phase (RR, 0.51%; 95% Cl, 0.21-1.27); *P = 0.15:* no heterogeneity). Sildenafil has little or no effect on pulmonary and systemic hemodynamic, perioperative monitoring, 6MWT and composite clinical score whether it is given as preoperative or postoperative during acute or chronic treatment phase.

Keywords: Sildenafil, sPAP, Pulmonary hypertension, Valvular heart disease

Introduction

Pulmonary Hypertension (PH), a potentially lethal condition with a prevalence of approximately 1% worldwide, is most commonly associated with Left Heart Disease (PH-LHD) [1-3]. Valve malfunction and diastolic dysfunction emerged as the prominent causes [4]. World Health Organization (WHO) classified PH-LHD as Group 2 PH which represents PH secondary to Left Ventricular (LV) systolic dysfunction (Heart Failure with reduced Ejection Fraction – HFrEF), LV diastolic dysfunction (Heart Failure with preserved Ejection Fraction – HFpEF), or Valvular Heart Disease (VHD) [5]. PH in VHD is described as an enhancement in mean Pulmonary Arterial Pressure (mPAP) ≥ 25 mmHg at rest as evaluated by right heart catheterization and a combination of precapillary-postcapillary PH [6, 7]. In VHD, persistent PH causes pulmonary vascular remodeling and reduced vascular compliance [8]. Thus, controlling VHD progression is critical, and early interventions such as valve replacement or repair help in slowing down the worsening of PH [8]. Despite important improvements in the timing of valve interventions, long-standing PH after surgery is common [9]. Thus, medical intervention is required specifically in asymptomatic patients with severe VHD or in symptomatic patients with moderate VHD [10].

The treatment options for PH secondary to VHD include Phosphodiesterase-5 inhibitors (PDE5i) such as sildenafil [6, 11].

Sildenafil relaxes the pulmonary vascular smooth muscles, and thus lowers pulmonary artery hypertension and pulmonary vascular resistance in patients with different types

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of PH [12, 13]. The off-label use of sildenafil in treating persistent PH after the correction of VHD has received considerable critical attention [14]. To date, limited investigations and guidelines are available to recommend the usefulness of sildenafil for group 2 PH-LHD. Based on the guidelines of 2015 European Society of Cardiology (ESC) and European Respiratory Society (ERS), there is no novel evidence to support the use of pulmonary artery hypertension therapies in PH-LHD [6]. This is partly because of the lack of researches that stratify patients with PH and target this estate [6]. The 2017 American Heart Association (AHA)/American College of Cardiology (ACC) Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease did not provide any recommendation on slowing down the progression of valve diseases, but only focused on medical therapy for concomitant hypertension [15]. In the United States, the use of PDE5i for group 2 and 3 PH showed an increasing trend despite guidelines recommending against this low value practice [16].

Several systematic and meta-analysis studies have been conducted to determine the effectiveness of sildenafil in various populations [17-20]. A recent review only evaluated the effects of preoperative sildenafil in PH patients undergoing mitral valve surgery [18] and did not compare the effects of sildenafil when given postoperatively and long term for PH secondary to VHD. The current review, therefore, aimed to establish a summary of all potential benefits of sildenafil in terms of hemodynamic parameters and patient-centered outcomes as acute and chronic treatment for PH secondary to VHD. Thus, the results of this review will inform debates about the efficacy or potential benefits of sildenafil in PH with VHD.

Materials and Methods

Search Strategies and Study Identification

A systematic study and meta-analysis of published literature was done following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21]. Studies were identified from inception (1946) to June 2020 through a comprehensive literature search on Web of Science, Medline (Ovid), EBSCOhost, the Cochrane Library, and PubMed, as well as Google Scholar as an additional source for published and unpublished studies. Reference lists of all selected studies were further scrutinized for any additional Randomized Controlled Trials (RCTs). Missing outcome data were traced by contacting the authors of the study. Search keywords were chosen appropriate to the Population, Intervention, Comparator and Outcome (PICO) model **(Table 1)**. The population was set at PH with VHD. The intervention was sildenafil treatment. The comparison was with placebo, other medication or without other intervention. The outcome was determined by hemodynamic parameters or clinical performance. Thus, the search keywords used were 'pulmonary hypertension', 'valvular heart disease', 'left-sided valve disease', 'sildenafil', 'phosphodiesterase-5', '6-Minute Walk Test (6MWT)', 'systolic Pulmonary Artery Pressure (sPAP)', 'mean Pulmonary Artery Pressure (mPAP)', 'pulmonary hemodynamic', 'systemic hemodynamic', 'WHO functional class', 'adverse events' and 'Cardiac Output (CO)'. Boolean operators such as 'AND' and 'OR' were used to increase sensitivity and specificity of the search when needed.

Selection of Studies

We included double-blinded RCTs, non-RCTs, and retrospective or prospective studies in which sildenafil was compared to a placebo. Only studies available in English were selected. Any non-English manuscripts, conference abstracts, case reports, and animal studies were excluded from this systematic review. Two reviewers (FAG and ADY) performed the screening of titles and abstracts based on the criteria presented in **Table 1**. All disagreements were resolved by negotiating with a third author (MMB).

Table 1: Study Inclusion and Exclusion Criteria

Component	Description
Population	Adult patient with confirmed diagnosis of PH secondary to VHD (mPAP ≥25mmHg at rest, sPAP ≥45mmHg, combined pre- and postcapillary PH mPCWP >15 mm Hg, PVR >3 WU) who undergo left-sided valve surgery (surgical or percutaneous replacement, repair or dilatation)
Intervention	Administration of Sildenafil in PH secondary to VHD either preoperative or post-operative of valve surgery
Comparator	Placebo or any other intervention
Outcomes measures	Improvements in hemodynamic parameters: • Pulmonary hemodynamic parameters such as change in mean systolic Pulmonary Artery Pressure (sPAP), mean Pulmonary Artery Pressure (mPAP) and Pulmonary Vascular Resistance Index (PVRI) • Systemic hemodynamic parameters such as Cardiac Index (CI), Systemic Vascular Resistance (SVR) • Other parameters such as 6MWT and composite clinical score
Exclusion criteria	• Patients did not represent the majority of the study population, studies that did not focus on sildenafil, and those that included Sildenafil administration to patients with inoperable valves • Conference abstracts, editorials, reviews, animal studies, case reports, and letters
Types of studies	• Randomized and Non-Randomized controlled trial studies • Retrospective cohort study • Prospective cohort study

Data Extraction

Extracted data included study design, treatment doses, duration of sildenafil administration, outcome measures, and results. For the purpose of this study, the articles were sub-grouped into acute or chronic treatment. Acute treatment was defined as preoperative or post-operative sildenafil that was

stopped within 48 hours of first administration. Preoperative data was extracted at two different time points: between the preoperative and intraoperative period and between the intraoperative and post-operative period. Chronic treatment was defined as preoperative or post-operative sildenafil that was continued until the next follow-up clinic, which may be prolonged to two months or more. Chronic treatment was divided into two different data analyses, based on whether sildenafil was initiated preoperatively or postoperatively.

Risk of Bias Assessment

The bias risk in RCTs was evaluated by domains proposed by the Cochrane Handbook of Systematic Reviews [22], particularly emphasizing on allocation concealment, sequence generation, outcome assessment, blinding, and selective reporting. The bias risk for each field was rated as low, unclear, or high risk. The total bias risk was labelled as high if minimally one field was at high risk of bias. The bias risk of non-RCT researches was assessed using the Black and Downs checklist.

Data Synthesis and Analysis

A meta-analysis was conducted to summarize two or more studies with similar outcome measures. The model of inverse variance random-effects for continuous results was utilized to form Mean Differences (MD) and 95% Confidence Intervals (CIs) for Forest plots. All results are indicated as the mean ± SD unless the contrary mentioned. Heterogeneity was assessed through the Chi-square and I2 test. The Mantel-Haenzel random-effects model was utilized for dichotomous outcomes, to form risk ratios and 95% CIs for Forest plots. All statistical analyses were done by Review Manager (RevMan) version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Results and Discussion

Research Characteristics

The electronic search yielded a total of 6,074 articles **(Figure 1)**. Out of these, 1,982 articles were duplicated and excluded. Title and abstract screening excluded 3,869 articles due to inappropriate nature of the literature, such as reviews, editorial, conference abstracts, animal studies, molecular studies, and case reports. Full text assessment excluded 10 articles due to population conflicts and case reports. In total, nine eligible studies (eight RCTs and one non-RCT) involving 614 patients were included and considered for meta-analysis. Studies conducted at acute phase represented by four RCTs for preoperative administration of sildenafil and two RCTs involved post-operative administration. Chronic sildenafil treatment was employed in three studies (two RCTs and one non-RCT). The characteristics of all studies are presented in **Table 2**.

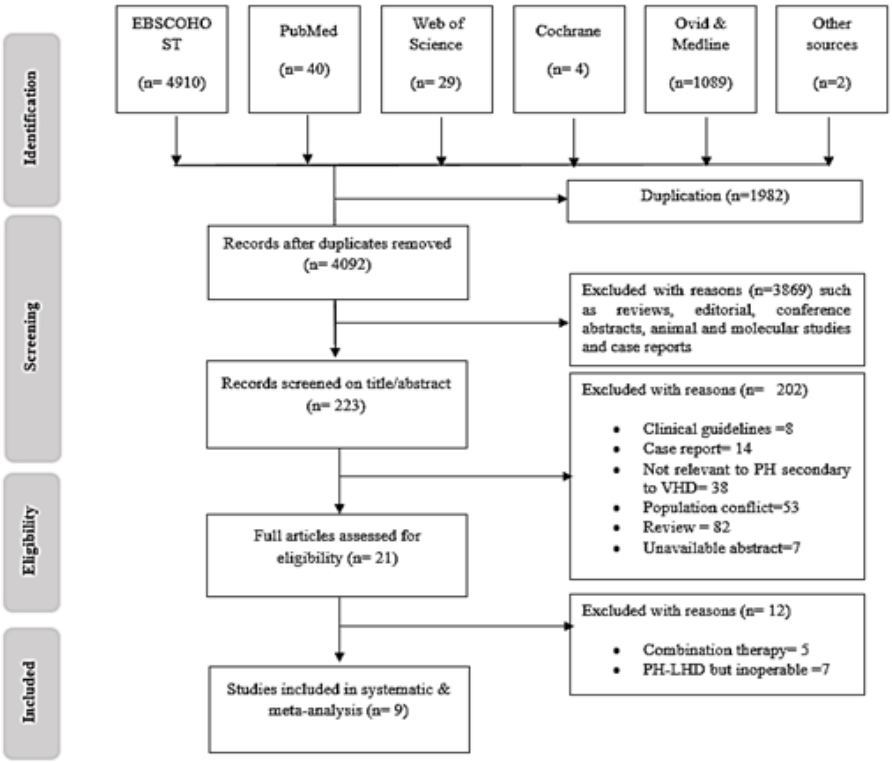


Figure 1. Search Flow Diagram for Systematic and Meta-analysis according to PRISMA Statement

Risk of Bias within the Studies

All eight RCTs were considered to have a low overall risk of bias. Six of the RCTs met all of specified criteria **(Figure 2)**, while those by Ayyad (2012) and Shewale *et al.* (2020) [23, 24] did not report random sequence generation, allocation concealment, or blinding of personnel and outcome assessment. The non-RCT study [25] was considered as fair quality of evidence due to internal validity-confounding (selection bias).

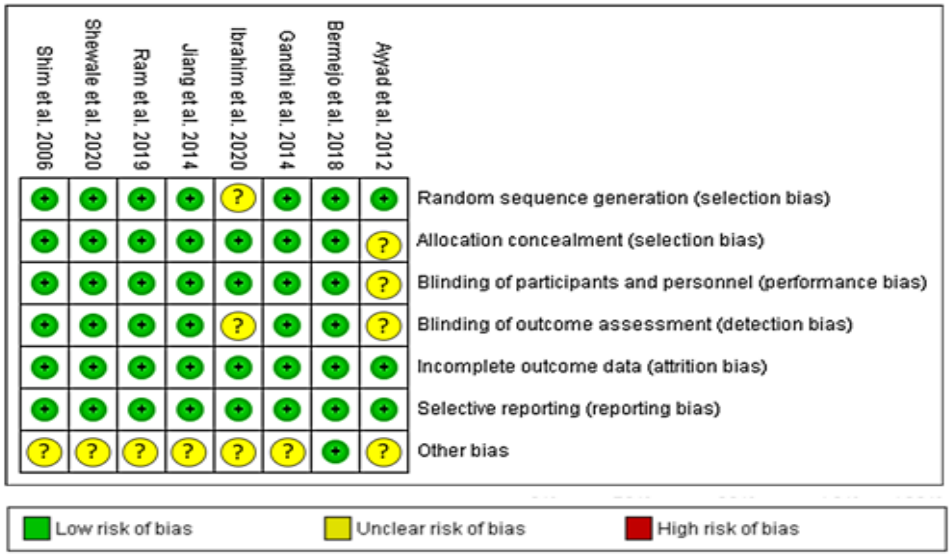


Figure 2. Risk of Bias Summary of RCTs Studies

Table 2. Baseline Characteristic of Included Studies

Study	Study Design	Treatment and Comparator, daily doses	Duration of sildenafil administration		Outcome Measures	Results
			Pre operative	Post-operative		
Shim *et al.* 2006 [26]	RCT	50 mg oral sildenafil 10 minutes before induction, n = 26 Placebo, n = 27	10 minutes before induction	NA	Hemodynamic parameters measured at T0, Baseline, T30 and T60	At T30, sPAP, mPAP, and PVRI: sildenafil < placebo (sig). sPAP and mPAP decreased according to baseline values in sildenafil group. At T60, hemodynamic variables: sildenafil vs placebo (nonsig). CVP increased relative to baseline in sildenafil group (sig).
Ayyad et al. 2012 [23]	RCT	25-50mg oral sildenafil, n=30 Placebo, n=30	Sildenafil was given 60 minutes before induction of anaesthesia	NA	Systematic blood pressure; preoperative echocardiography; sPAP and CVP (taken as preoperative, intraoperative, and post-operative)	Mean sPAP: at preop = 75.3 mmHg; intraop = 39.4 mmHg postop = 35.1 mmHg, sPAP reduced from 75.3mmHg to 35.1 mmHg (sig).
Gandhi et al 2014 [27]	RCT	25mg sildenafil q8h, n = 20 Placebo, n=20	24 hrs	NA	Hemodynamic & Post-operative parameters	After induction & weaning from CPB; HR, MAP, and PCWP: sildenafil = placebo (nonsig); PVRI: sildenafil < placebo (sig). Post-operative period; sPAP and mPAP at T1-T5: sildenafil << placebo (sig); CI and SVRI: sildenafil vs placebo (nonsig); PVRI: sildenafil < placebo (sig).

Shewale et al. 2020 [24]	RCT	25mg q8h, n = 25 Placebo, n=25	48hrs	NA	Hemodynamic & Post-operative parameters	Preoperative; sPAP, CPB time & cross-clamp time: sildenafil vs placebo (nonsig). Post-operative; HR, MAP & PCWP: sildenafil vs placebo (nonsig). SPAP and MPAP at T1-T5: sildenafil < placebo (sig). CI and SVRI: sildenafil vs placebo (nonsig). PVRI: sildenafil < placebo (sig). Required milrinone infusion: sildenafil < placebo (sig). Two patients requiring adrenaline+/- noradrenaline infusion: sildenafil vs placebo (nonsig). Ventilation & post-operative ICU stay time: sildenafil < placebo (sig).
Ibrahim et al. 2020 [28]	RCT	Sildenafil (Group A) 20mg q8h (n=20) (Group B) 20mg q8h (n=22) Placebo (Group C) (n=25)	Group A 1 week Group B 1 month	NA	Hemodynamic parameter such PASP, EF Post-operative parameters such as ventilation time, and post-operative ICU stay time, inotropes requirement and mortality.	PASP post cardiopulmonary bypass (P<0.001); Group A and B < Group C (sig) Mean PASP was reduced from preoperative to post CPB weaning in group A (61.25 ± 6.46 mmHg to 35.60 ± 4.12 mmHg and in group B (61.86 ± 7.25 mmHg to 32.00 ± 5.35 mmHg); Group A = group B (nonsig) Aortic cross-clamp time (P= 0.227), the total cardiopulmonary bypass time (P = 0.559), or the total operative time (P = 0.794); Group A=B=C (nonsig).
Chapman et al. 2009 [25]	Non-RCT	50mg q8h	NA	2-12 months	Mean PA pressure, CO, PVR and six-minute walk test.	PVR improved from initial to 2–12 months (P =0.048) and to long term (P =0.041). CO improved from initial to 2–12 months (P =0.019). No improvement in PA pressure or six-minute walk distance.
Jiang et al 2014 [29]	RCT	0.5 mg/kg q8h sildenafil citrate in 30ml normal saline (n=45) 30 ml pure normal saline solution as placebo (n=45)	NA	4 hours	Hemodynamic parameters: CVP, PAP, PCWP and right ventricular pressure (RVP) Prognostic markers: Post-operative mechanical ventilation time, ICU-monitoring time and hospitalization period.	sPAP, mPAP, PVR, PVRI were lower than the baseline (*P < 0.001) at every point of time. sildenafil < placebo (sig). Decreased of the ratio between sPAP and Arterial Blood Systolic Pressure (ABPs) lasted for four hours (0.36 ± 0.124 h, baseline 0.40 ± 0.11, *P < 0.001), sildenafil < placebo (sig) Mechanical ventilation time (18.6 ± 9.5 vs 24.8 ± 15.2 h, *P < 0.05); sildenafil < placebo (sig). ICU-monitoring time (30.8 ± 10.4 vs 37.5 ± 13.6 h, P < 0.05); sildenafil < placebo (sig). Hospitalization period (12.9 ± 4.3 vs 15.2 ± 6.1d, *P < 0.05); sildenafil < placebo (sig).
Bermejo et al 2018 [14]	RCT	20 mg q8h for 2 weeks then titrated to 40mg q8h (n=104) Placebo (n=96)	NA	6 months	Primary outcomes: based on the composite clinical score at 6 months. (i) Worsened, (ii) Improved, (iii) Unchanged (otherwise) Secondary Outcome: (i) death or HF admission (ii) no. of HF admissions	Improved: sildenafil < placebo Worsen: sildenafil > placebo; sig (OR 0.39; 95% CI = 0.22–0.67) Unchanged: sildenafil < placebo 5 deaths during the study, sildenafil > placebo (log-rank P=0.72) (nonsig.) 3 cardiac deaths were because of HF (log-rank test P=0.63 for sildenafil vs. placebo) (non-sig.) The Kaplan–Meier estimates for survival without admission due to HF were 0.76 for sildenafil and 0.86 for placebo groups, respectively (risk ratio 2.0, 95% CI=1.0–4.0 (sig.)

					(iii) Other (BNP, 6MWT & imaging)	No difference between sildenafil and placebo group in 6MWT, BNP, and Doppler-derived systolic pulmonary pressure.
Ram. et al 2019 [30]	RCT	25mg q8h (n=25) Placebo (n=25)	NA	36 hours	Primary: mPAP at 36 hours	Decrease in mPAP from 32 ± 7 mmHg at baseline to 26 ± 3 mmHg after 36 hours: sildenafil < placebo No changes were observed in placebo (*P <0.001) (sig.)
					Secondary: systemic blood pressure; CVP; systemic vascular resistance; Cl; and parameters obtained from the blood gas evaluation (e. g, pH, partial pressure of carbon dioxide, partial pressure of oxygen, lactate) at different time points in both groups (every 6 hours for 36 hours).	SBP at 36 hrs (79 ±16 vs 80 ± 12, P =0.903); sildenafil < placebo (non-sig.) CVP at 36 hours (15 ±7 vs 17 ± 4, P =0.669); sildenafil < placebo (non-sig.) SVR (1 021 ±260 vs 974 ±256, *P =0.03); (sig.) Cl (3.03 ±0.61vs 3.39 ±1.04, P =0.058); (non-sig.) PaCo2 (mmHg, 40 ±4 vs 38 ±5, P =0.06) (non-sig.) pH (7.41 ±0.03 vs 7.41 ±0.05, P =0.811) (non-sig.)

Abbreviations: S = sildenafil; P = placebo; NA = not available; sPAP = systolic Pulmonary Arterial Pressure; mPAP = mean Pulmonary Arterial Pressure; PVRI = Pulmonary Vascular Resistance Index; SVRI = Systemic Vascular Resistance Index, T0 = time before induction; T30 = 30 minutes after 50mg oral sildenafil or placebo; T60 = 60 minutes after 50mg oral sildenafil or placebo; RVESVI = right ventricular end systolic volume index; RVEDVI = right ventricular end diastolic volume index; Cl = cardiac index; CVP = Central Venous Pressure; CPB = cardiopulmonary bypass; PCWP = Pulmonary Capillary Wedges Pressure; MAP = Mean system in Arterial Pressure; PASP = Pulmonary Artery Systolic Pressure; EF = Ejection Fraction; PA = Pulmonary Artery; sig. = Statistically Significant; non-sig. = Statistically Non-significant.

Pulmonary Hemodynamic Parameters

Effects of Acute Preoperative Sildenafil Treatment

Meta-analysis on studies by Ayyad *et al.* (2012) and Shim *et al.* (2006) [23, 26] showed a non-significant reduction in sPAP between the preoperative and intraoperative periods by 9.23 mmHg **(Figure 3a)**; (95% CI: -26.56 to 8.10 mmHg; P = 0.30; I2 = 0.8) after preoperative administration of 25 – 50 mg sildenafil. Both studies demonstrated significant improvements in other parameters, such as mPAP and Pulmonary Vascular Resistance Index (PVRI). However, the studies by Gandhi *et al.* (2014) and Shewale *et al.* (2020) [24, 27] did not show a significant reduction in sPAP between the intraoperative and postoperative periods, and favored the placebo group (3.72 mmHg; 95% CI: -0.43 to 7.86 mmHg; P = 0.08) after acute treatment with 25 mg sildenafil three times daily. Both studies showed similar findings in mPAP **(Figure 3b)**; (2.15 mmHg; 95% CI: -1.35 to 6.4 mmHg; P = 0.23; I2 = 0) and favored the placebo group. No significant reduction in PVRI was reported at 30.46 dynes.sec.cm5m2 **(Figure 3c)**; (95% CI: 111.98 to 51.06 dynes.sec.cm5m2; P = 0.46, I2 = 0) following acute sildenafil treatment (intraoperative vs. post-operative).

Effects of Acute Post-operative Sildenafil Treatment

Only one study reported a reduction in sPAP (MD -5.89 mmHg ± 17.07), mPAP (MD -4.62 mmHg ± 12.24), and PVRI (MD -60.11 dynes.sec.cm5m2 ± 500.85) following acute postoperative sildenafil treatment compared to placebo [17]. Ram *et al.* (2019) reported a mean sPAP of 66 mmHg in the sildenafil group, which was comparable to that of the placebo group, but reported a significant reduction in mPAP from 32 ± 7 mmHg at baseline to 26 ± 3 mmHg after 36 hours of sildenafil compared to placebo (P < 0.001). However, PVR and pulmonary arterial wedge pressure were not reported in the study [27].

Effects of Chronic Sildenafil Treatment

The study by Ibrahim *et al.* (2020) involved three different groups (Group A received sildenafil for a week, group B received sildenafil for a month, and group C received a placebo), with treatment of all groups initiated preoperatively [28]. A significant reduction was observed in sPAP following Cardiopulmonary Bypass (CPB) and was lower in groups A and B than in group C (P < 0.001). Two other studies (Bermejo *et al.* 2018; Chapman *et al.* 2009) [14, 25] reported comparable hemodynamic parameters with long-term post-operative sildenafil therapy (40–50 mg three times daily). Sildenafil improved mPAP and PVR in four patients who received sildenafil between 2 – 12 months [25]. Bermejo *et al.* (2018), however, showed that the use of sildenafil (oral 40 mg three times daily) for 6 months resulted in no changes in sPAP compared to the placebo group, with a mean difference of -1 mmHg (SD 24.08).

Systemic Hemodynamic Parameters

Effects of Acute Preoperative Sildenafil Treatment

No significant reduction in SVRI **(Figure 4a)** with low heterogeneity (I^2 = 0%) was demonstrated in two studies [26, 27]. Both studies reported no alterations in heart rate or mean

arterial pressure after induction, after CPB weaning, and during the post-operative period. Nevertheless, the study by Shim *et al.* (2006) demonstrated a reduction in both parameters. In addition, central venous pressure in the sildenafil group was significantly enhanced according to baseline.

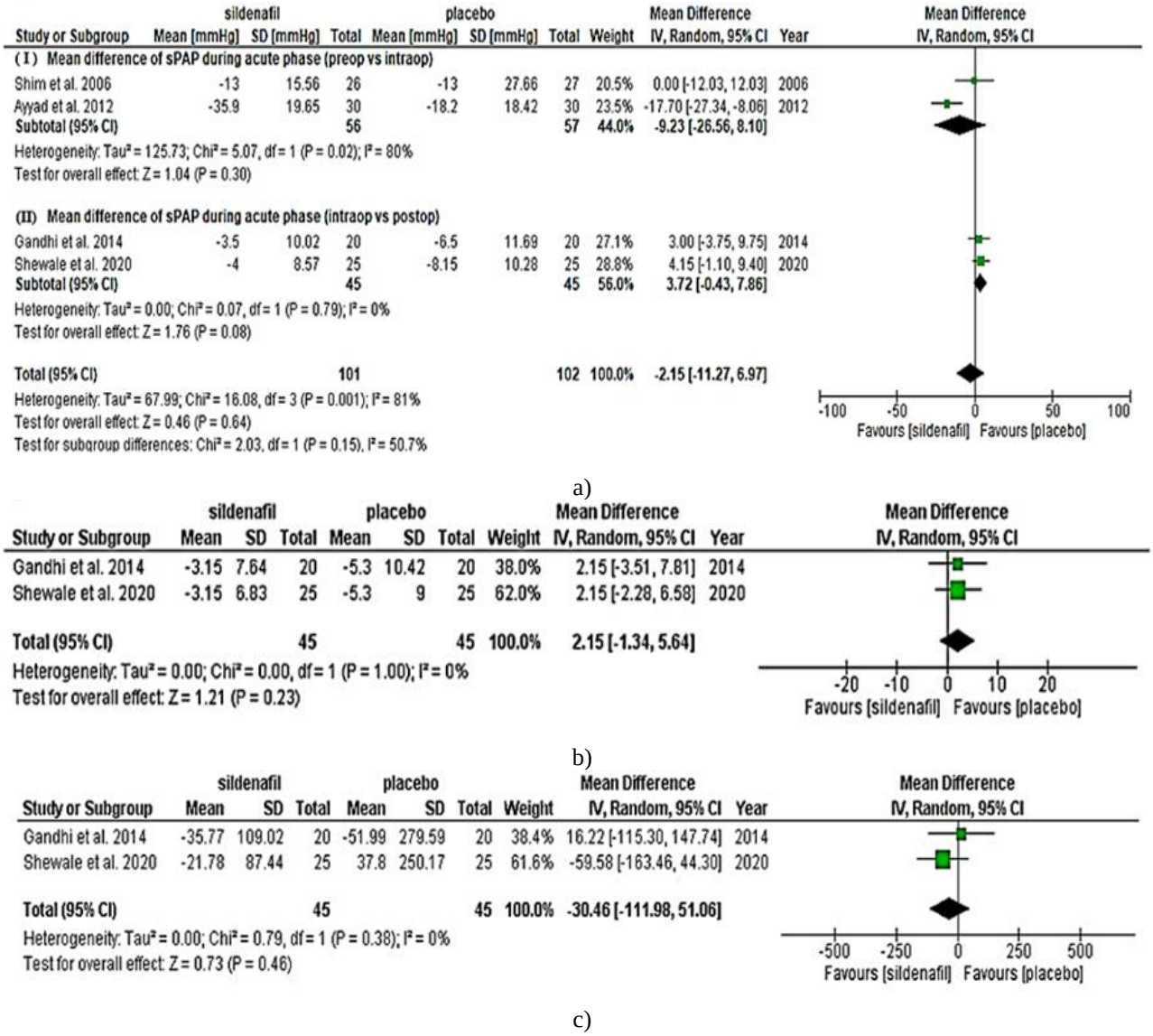
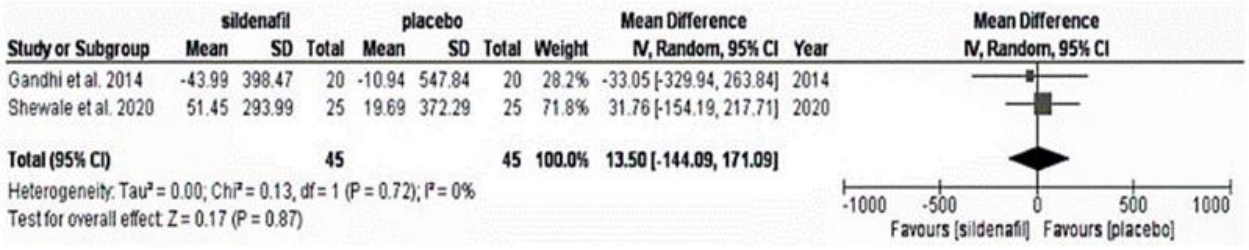


Figure 3. Forest plot showing mean difference of pulmonary hemodynamic parameters during acute phase. a) systolic pulmonary arterial pressure (sPAP; mmHg), b) Pulmonary vascular resistance index (dynes.sec.cm^{5}m^2), and c) Mean pulmonary arterial pressure (mPAP; mmHg).

Effects of Acute Post-operative Sildenafil Treatment

Jiang *et al.* (2014) and Ram *et al.* (2019) showed no changes in cardiac index (CI); **(Figure 5a)** and systemic vascular resistance (SVR); **(Figure 5b)** following post-operative administration of sildenafil compared to placebo, and their data showed low to moderate heterogeneity (I^2 = 0 and I^2 = 68%, respectively) (26,27). Sildenafil was given through either a nasogastric tube (27) or intravenous injection (26) at specific doses (0.5 mg/kg q8h or 20 mg q8h for 4 – 36 hours). Both studies also demonstrated that sildenafil was able to maintain CO and CI during the post-operative period.



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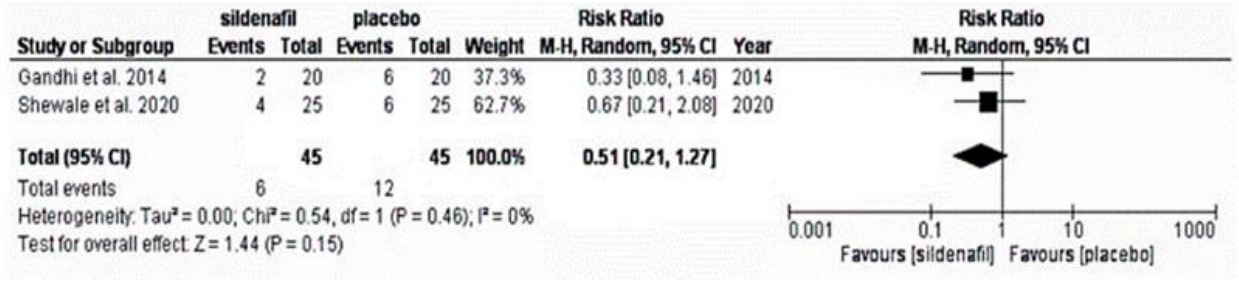
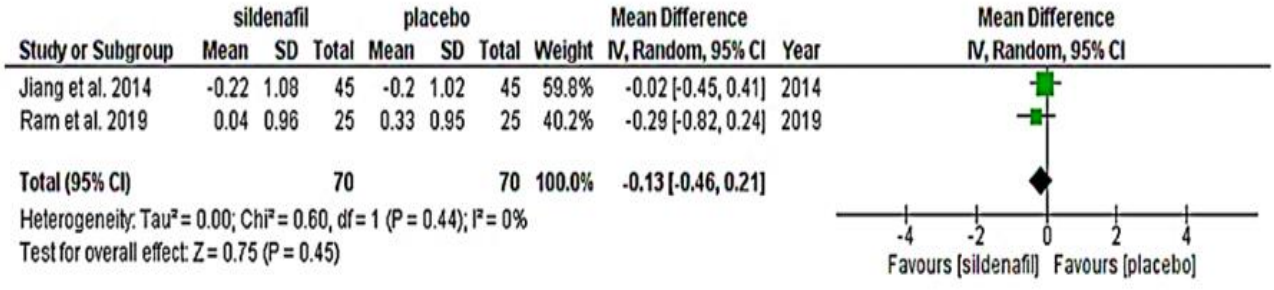
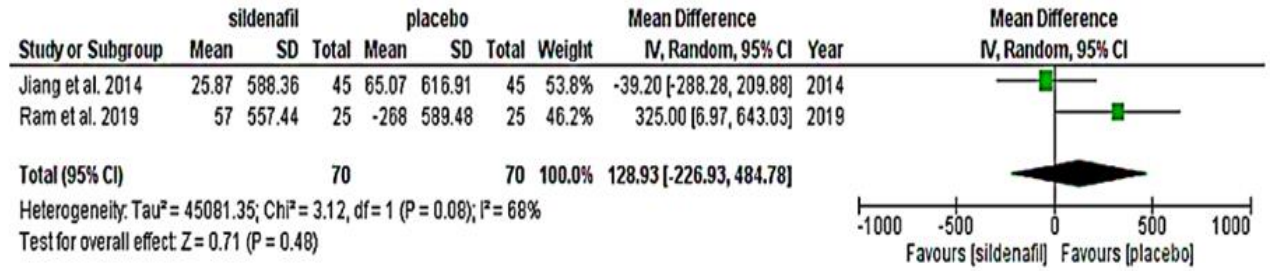


b)

Figure 4. Forest plot showing mean difference of systemic vascular resistance index (dynes.sec.cm^{5}m^2, a) and the pooled risk ratio of inotrope requirement. b) during acute phase (intraoperative *versus* post-operative)



a)



b)

Figure 5. Forest plot showing mean difference of systemic hemodynamic parameters during acute phase (post-operative). a) Cardiac index (Cl – L/min/m^2) and b) Systemic vascular resistance (SVR- dynes.sec.cm^5)

Effects of Chronic Sildenafil Treatment

Chapman *et al.* (2009) demonstrated that CO was improved from the initiation up to 12 months (P = 0.019) in sildenafil group compared to placebo [25]. However, Bermejo *et al.* (2018) showed a significant effect of treatment on Cl in the control group, rather than in the treatment group [14].

Other Parameters

Perioperative Monitoring Parameters

Gandhi *et al.* (2014) and Shewale *et al.* (2020) reported that more patients in the placebo group than in the sildenafil group required inotrope support after CPB weaning, with a relative risk of 0.51 (95% Cl; 0.21-0.74, P = 0.15; I^2 = 0) **(Figure 4b)**. Similarly, both studies demonstrated a significant reduction in mechanical ventilation time and post-operative recovery room stay time (P = 0.001). Jiang *et al.* (2014) reported that acute sildenafil treatment significantly improved and

shortened mechanical ventilation period (18.6 ± 9.5 hours vs 24.8 ±15.2 hours, $P < 0.05$), ICU monitoring period (30.8 ± 10.4 hours vs 37.5 ± 13.6 hours, $P < 0.05$), and period of hospital stay (12.9 ± 4.3 day vs 15.2 ± 6.1 day, $P < 0.05$) in comparison to the control group. Ram *et al.* (2019) reported that patients who received sildenafil were associated with shorter median mechanical lung ventilation time (16 vs. 19 hours, $P = 0.431$), intensive care unit stay (74 vs. 91 hours, $P= 0.410$), and total hospitalization stay (7 vs. 11 days, $P = 0.009$) compared to placebo. Comparable findings were also demonstrated in the study by Ibrahim *et al.* (2020).

Six-minute Walk Test (6MWT)

Bermejo *et al.* (2018) and Chapman *et al.* (2009) showed no significant improvement in 6MWT compared to baseline with chronic sildenafil use [14, 25].

Composite Clinical Scores

Composite clinical scores consisted of three key elements, including major clinical events, the World Health Organization (WHO) functional class, and global patient self-assessment. The scores were subcategorized into three levels, namely improved, worsened, or remained unchanged. Bermejo *et al.* (2018) reported that the scores of 34% of patients (n = 33) worsened, those of 28% (n = 27) improved, while those of 38% (n = 37) remained unchanged with chronic sildenafil treatment [14].

This meta-analysis and systematic review aimed to quantify the potential benefits of sildenafil and its effects on hemodynamic parameters and overall outcomes in patients with PH secondary to VHD. The evidence from nine studies suggest that sildenafil has little or no effects on PH in VHD. Despite the small evidence size, there were novel findings and similar themes among studies that warrant further considerations. Sildenafil may have little or no effects on pulmonary hemodynamic parameters, specifically sPAP, mPAP, and PVRI following both acute and chronic treatment. The meta-analysis of eight RCTs [14, 23, 24, 26-30] suggested no significant association between pulmonary hemodynamic parameters and sildenafil doses with either acute or chronic administration. Our findings also showed that sPAP remained unchanged (24,25) when oral sildenafil was given at 25 mg three times daily over 24 – 48 hours before surgery (intraoperative and post-operative) before surgery (intraoperative and post-operative) and at 40 mg three times daily over 6 months in the study by Bermejo *et al.* (2018) [14].

Nevertheless, Ayyad *et al.* (2012) and Shim *et al.* (2006) showed that a single dose of sildenafil created considerable pulmonary vasodilation without eliciting systemic impacts 30 minutes after administration [23, 26]. Acute administration of a single oral dose of sildenafil caused a significant decrease in mPAP and PVR with minimal or no effects on MAP, but a trend towards improvement in CO could be observed [31]. These findings were consistent with the fact that sildenafil is quickly absorbed via the stomach, and its plasma contents peak within 30 – 120 min after ingestion [32]. Such characteristic thereby produces significant pulmonary vasodilator effects with short onset sildenafil can increase intracellular cyclic adenosine monophosphate levels, which produces inotropic effects [33]. Limited studies have focused on the optimum timing of sildenafil treatment commencement and dosing regimen, but it is reasonable to titrate oral sildenafil up to 75 mg daily or to an equivalent dose of other PDE5i based on the seen hemodynamic reaction and tolerability [34].

Systemic parameters, particularly SVR, SVRI, Cl, and CO, remained unchanged following both acute and chronic sildenafil treatment. Based on the evidence, sildenafil may possess short term effects on SVR. Sildenafil may also be able to prevent further reduction in CO and Cl compared to placebo [29]. Sildenafil also did not significantly change the heart rate, systolic blood pressure, or diastolic blood pressure of patients with secondary PH [35]. Sildenafil showed a decrease in LV filling pressure and increased the stroke volume in severe aortic valve stenosis [36]. This study illustrated the safety and tolerability of the PDE5i and gave insight into the circulatory hemodynamics of patients, who often have inappropriate elevations in SVR after aortic valve stenosis repair [37].

Acute sildenafil treatment showed no significant short-term benefits in reducing ventilation time or intensive care unit length of stay as shown in five studies [24, 26, 28-30]. Acute sildenafil administration showed potential effects on inotrope requirement; such observation may be explained by the mechanism of sildenafil action, through its effects on pulmonary cyclic guanosine monophosphate which enhance the vasodilatory effect. Furthermore, sildenafil can produce early beneficial effects at 6 weeks, which can persist for 6 months [31]. No changes in 6 MWT results were reported [14, 24] with chronic sildenafil treatment. The 6MWT is commonly used as a clinical assessment for exercise capacity in patients with cardiopulmonary or neuromuscular diseases [38]; it is also a key method to validate the effectiveness of treatment [39]. Few clinical experiments have recommended that sildenafil can better the hemodynamic profile, overall exercise performance [40], and life quality [41] of patients with chronic PH-LHD of non-valvular etiology.

The SIOVAC trial (Sildenafil Improving Outcomes in patients with Valvular heart disease and persistent pulmonary hypertension) investigated the safety and effectiveness of long term (6 months) off-label sildenafil use in the treatment of patients with persistent PH [14]. Contradictions in composite clinical scores were reported in the study, whereby more patients who received chronic sildenafil treatment were associated with worsened clinical conditions [14]. Though the mechanisms attributable to the worse results observed in the research are speculative, a chronic enhancement in pulmonary capillary pressure is the highest possible

explanation. The combination of advanced age, common atrial fibrillation, and long-standing atrial overload may reduce atrial compliance in patients with PH secondary to VHD [42]. Given the sparsity of available published articles on this topic, studies included in this review are limited. There are possible differences in data extraction and reporting of results based on our operational definition. Nevertheless, several steps have been taken to reduce biases such as standardizing the operational definitions based on treatment duration (acute vs. chronic) and reported outcomes (short- vs. long-term).

Conclusion

As a conclusion, findings of this research suggest that sildenafil in the management of PH secondary to VHD has little or no positive effects on pulmonary and systematic hemodynamic parameters, perioperative monitoring parameters, 6MWT results, and composite clinical scores. The use of sildenafil is considered non-specific and controversial for the treatment of PH secondary to VHD. The role of PDE5i remains unclear and warrants further investigations, especially in the clinical management of PH in VHD.

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References

1. Fernández AI, Yotti R, González-Mansilla A, Mombiela T, Gutiérrez-Ibanes E, Del Villar CP, et al. The biological bases of group 2 pulmonary hypertension. Int J Mol Sci. 2019;20(23):1-19.
2. Almuqati AL, Alluqmani MS, Balhareth SH, Alosaimi MA, Alosaimi MM, Alzughaibi AM, et al. Evaluation of role of family physicians in management and diagnosis of hypertension in primary health care centers: a simple literature review. Int J Pharm Res Allied Sci. 2020;9(1):105-9
3. Mohamed AM, Badr NM, Hagag AA, Mohamed YM. Intra versus extra-thoracic oscillations in chronic obstructive pulmonary disease (a randomized clinical trial). J Adv Pharm Edu Res. 2019;9(3):85-90.
4. Weitsman T, Weisz G, Farkash R, Klutstein M, Butnaru A, Rosenmann D, et al. Pulmonary hypertension with left heart disease: prevalence, temporal shifts in etiologies and outcome. Am J Med. 2017;130(11):1272-9.
5. Fang JC, Demarco T, Givertz MM, Borlaug BA, Lewis GD, Rame JE, et al. World health organization pulmonary hypertension group 2: pulmonary hypertension due to left heart disease in the adult - a summary statement from the pulmonary hypertension council of the international society for heart and lung transplantation. J Heart Lung Transplant. 2012;31(9):913-33.
6. Nazzareno G, Marc H, Jean LV, Simon G, Irene L, Adam T. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2015;46: 903-75.
7. Al-Omary MS, Sugito S, Boyle AJ, Sverdlov AL, Collins, NJ. Pulmonary hypertension due to left heart disease. Hypertension 2020;75(6): 1397-408
8. Kaple RK, Horn EM. Pulmonary hypertension due to valvular heart disease: aortic and mitral. Adv Pulm Hypertens. 2015;14(2):95-101.
9. Li M, Dumesnil JG, Mathieu P, Pibarot P. Impact of valve prosthesis-patient mismatch on pulmonary arterial pressure after mitral valve replacement. J Am Coll Cardiol. 2005;45:1034-40.
10. Martinez C, Tsugu T, Sugimoto T, Lancellotti P. Pulmonary hypertension with valvular heart disease: when to treat the valve disease and when to treat the pulmonary hypertension. Curr Cardiol Rep. 2019;21(151):1-7.
11. Vachiéry JL, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, et al. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol. 2013;62(25):D100-D8.
12. Ghoreishi M, Evans CF, Defilippi CR, Hobbs, G, Young CA, Griffith BP et al. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: Implications for timing of surgery. J Thorac Cardiovasc Surg. 2011;142(6):1439-52.
13. Michelakis E, Tymchak W, Lien D, Webster L, Hashimoto K, Archer S. Oral sildenafil is and effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: Comparison with inhaled nitric oxide. Circulation. 2002;105(2):2398-403.
14. Bermejo J, Yotti R, García-Orta R, Sánchez-Fernández PL, Castaño M, Segovia-Cubero J, et al. Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: A multicenter, double-blind, randomized clinical trial. Eur Heart J. 2018;39(15):1255-64.
15. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA. et al. AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2017;70(2):252-89.
16. Gillmeyer KR, Rinne ST, Glickman ME, Lee KM, Shao Q, Qian SX. et al. Factors associated with potentially inappropriate phosphodiesterase-5 inhibitor use for pulmonary hypertension in the united states, 2006 to 2015. Circ Cardiovasc Qual Outcomes. 2020;13(5):216-27.
17. Jiang R, Wang L, Zhu CT, Yuan P, Pudasaini B, Zhao QH, et al. Comparative effectiveness of sildenafil for pulmonary hypertension due to left heart disease with HFrEF. Hypertens Res. 2015;38(12):829-39.
18. Villanueva DLE, Agustin RD, Llanes EJ. Pre-Operative sildenafil for patients with pulmonary hypertension undergoing mitral valve surgery: a systematic review and meta analysis. Cardiol Res. 2019;10(6):369-77.
19. Cao JY, Wales KM, Cordina R, Lau EMT, Celermajer DS. Pulmonary vasodilator therapies are of no benefit in pulmonary hypertension due to left heart disease: A meta-analysis. Int J Cardiol. 2018;273:213-20.
20. De Vecchis R, Cesaro A, Ariano C, Giasi A, Cioppa C. Phosphodiesterase-5 inhibitors improve clinical outcomes, exercise capacity and pulmonary hemodynamics in patients with heart failure with reduced left ventricular ejection fraction: a meta-analysis. Orig Artic J Clin Med Res. 2017;9(6):488-98.
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg. 2010;8(5):336-41.
22. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. cochrane handbook for systematic reviews of interventions. England: Wiley Blackwell; 2019. 187p.
23. Ayyad M, Abdel-Geleel A. Effect of immediate preoperative oral sildenafil administration for pulmonary hypertension undergoing valve replacement. J Eqyptian Soc Cardio-Thoracic Surg. 2012;20:113-7.
24. Shewale V, Jadhao M, Shah V, Raut C, Mishra P, Khandekar J. Effect of preoperative oral sildenafil on intraoperative hemodynamics in patients with severe pulmonary artery hypertension undergoing mitral valve replacement. J Med Sci Clin Res. 2020;8(4):279-84.
25. Chapman TH, Wilde M, Sheth A, Madden BP. Sildenafil therapy in secondary pulmonary hypertension: Is there benefit in prolonged use? Vascul Pharmacol. 2009;51(2-3):90-5.
26. Shim JK, Choi YS, Oh YJ, Kim DH, Hong YW, Kwak YL. Effect of oral sildenafil citrate on intraoperative hemodynamics in patients with pulmonary hypertension undergoing valvular heart surgery. J Thorac Cardiovasc Surg. 2006;132 (6):1420-5.
27. Gandhi H, Shah B, Patel R, Toshani R, Pujara J, Kothari J, et al. Effect of preoperative oral sildenafil on severe pulmonary artery hypertension

in patients undergoing mitral valve replacement. Indian J Pharmacol. 2014;46(3):281-5.
28. Ibrahim IM, Dokhan AL, Elsebaey RS, Abdellatif MG. Evaluation of the preoperative administration of sildenafil on operative and early postoperative outcome after mitral valve replacement in patients with pulmonary hypertension. Egypt Cardiothorac Surg. 2020;2(4):148-54.
29. Jiang G, Li B, Zhang G, Xu E, Liu Y, Xu Z. Effects of sildenafil on prognosis in patients with pulmonary hypertension after left-sided valvular surgery. Heart Lung Circ. 2014;23(7):680-5.
30. Ram E, Sternik L, Klempfner R, Eldar M, Goldenberg I, Peled Y, et al. Sildenafil for pulmonary hypertension in the early postoperative period after mitral valve surgery. J Cardiothorac Vasc Anesth. 2019;33(6):1648-56.
31. Barnett CF, Machado RF. Sildenafil in the treatment of pulmonary hypertension. Vasc Health Risk Manag. 2006;2(4):411-22.
32. Pfizer Inc. [Internet]. Revatio® (sildenafil). Medical information. Updated 2021 [cited 20 June 2021]. Available from: https://www.pfizermedicalinformation.com/en-us/revatio
33. Kaufmann J, Kung E. Factors affecting cardiovascular physiology in cardiothoracic surgery: implications for lumped-parameter modeling. Front Surg. 2019;6(62):1-7.
34. Papathanasiou M, Ruhparwar A, Kamler M, Rassaf T, Luedike P. Off-label use of pulmonary vasodilators after left ventricular assist device implantation: Calling in the evidence. Pharmacol Ther. 2020;214:107619.
35. Salem M, Diab A, Ateya A, Sanad O. Short term effects of sildenafil citrate therapy in secondary pulmonary hypertension. Egypt Hear J. 2014;66(1):49-53.
36. Lindman BR, Zajarias A, Madrazo JA, Shah J, Gage BF, Novak E, et al. Effects of phosphodiesterase type 5 inhibition on systemic and pulmonary hemodynamics and ventricular function in patients with severe symptomatic aortic stenosis. Circulation. 2012;125(19):2353-62.
37. Rassa A, Zahr F. Hypertension and aortic stenosis: A review. Curr Hypertens Rev. 2018;14(1):6-14.
38. Halliday SJ, Wang L, Yu C, Vickers BP, Newman JH, Fremont RD, et al. Six-minute walk distance in healthy young adults. Respir Med. 2020;165:105933.
39. Hao Y, Zhu Y, Mao Y, Xu J, He X, Huang S, et al. Efficacy and safety of Sildenafil treatment in pulmonary hypertension caused by chronic obstructive pulmonary disease: A meta-analysis. Life Sci. 2020;257:118001.
40. Cooper TJ, Guazzi M, Al-Mohammad A, Amir O, Bengal T, Cleland JG. et al. Sildenafil in heart failure (SilHF). an investigator-initiated multinational randomized controlled clinical trial: rationale and design. J Hear Fail. 2013;15(1):119-22.
41. Guazzi M, Vicenzi M, Arena R. Phosphodiesterase 5 inhibition with sildenafil reverses exercise oscillatory breathing in chronic heart failure: A long-term cardiopulmonary exercise testing placebo-controlled study. Eur J Heart Fail. 2012;14(1):82-90.
42. Magne J, Pibarot P, Sengupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary hypertension in valvular disease: comprehensive review on pathophysiology to therapy from the HAVEC group. JACC Cardiovasc Imaging. 2015;8(1):83-99.