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 -6.62 mmHg ± 12.24) and Pulmonary Vascular Resistance Index (PVRI) (MD -60.11 dynes.sec.cm⁻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 CI 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% CI, 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 studies, which 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 >5 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 subgrouped 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.

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**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).

![Risk of Bias Summary of RCTs Studies](image)

Table 2. Baseline Characteristic of Included Studies

| Study          | Study Design | Treatment and Comparator, daily doses | Duration of sildenafil administration | Outcome Measures | Results                                                                 |
|---------------|--------------|----------------------------------------|----------------------------------------|------------------|------------------------------------------------------------------------|
| 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). |
| 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

Ibrahim et al. 2020 [28] RCT Sildenafil (Group A) 20mg q8h (n=20) Group A 1 week Sildenafil parameter such as PASP, EF

Placebo (Group C) (n=25)

Chapman et al. 2009 [25] Non-RCT 50mg q8h NA 2-12 months Mean PA pressure, CO, PVR and six-minute walk test.

Jiang et al 2014 [29] RCT 0.5 mg/kg q8h sildenafil citrate in 30ml normal saline (n=45) NA 4 hours Hemodynamic parameters: CVP, PAP, PCWP and right ventricular pressure (RVP)

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 Secondary Outcome: (i) death or HF admission (ii) no. of HF admissions

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).

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).

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).
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.)
**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. postoperative).

**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 postoperative 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 (I² = 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.

![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).](image)

**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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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 CI 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% CI: 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 vasodilatation 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].

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-valvar 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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None.

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