

Effects of Phosphodiesterase Type 5 (PDE-5) Inhibitors in the Management of Pulmonary Arterial Hypertension: A Systematic Review and Meta-analysis Pointing on Peak VO_2

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Abstract

Background: In settings where new drugs for pulmonary arterial hypertension (PAH) are not possible due to lack of availability and cost; PDE-5 inhibitors such as sildenafil is the drug of choice in the management of PAH. In this study we performed a meta-analysis to evaluate the effects of oral sildenafil in PAH, pointing on peak VO_2 improvement.

Methods: We retrieved randomized controlled trials (RCTs) of the effects of PDE-5 inhibitors, sildenafil in patients with PAH using PubMed, Medline, Embase, Cochrane Library, Google scholar and manual search from 2011 to 2016. Random controlled trials that compared oral sildenafil with placebo were selected. Data for populations, interventions, and outcomes were extracted independently by 2 investigators, and disagreements were resolved by consensus. Quality assessment was performed using the Cochrane risk-of-bias tool.

Results: Four randomized controlled clinical trials including a total of three hundred thirty six patients were identified in the primary analysis, with 51.5% patients in the PDE-5 inhibitors treatment group and 48.5% patients in the placebo group.

Two studies show reduction in statistical significance of mPAP (MD -4.15, 95% CI -17.28 to 8.98; $P < 0.00001$) and PVR (MD -51.27, 95% CI -127.63 to 25.10; $P < 0.00001$). Other three studies shown statistical significance in reduction of mPCWP (MD -2.70, 95% CI -7.14 to 1.75; $P < 0.0003$). Other two studies which accessed the quality of life show no much differences among the two groups (MD 1.18, 95% CI -4.92 to 7.27; $P < 0.00001$). However, all four trials, shown no statistical significant improvement in peak VO_2 , of patients allocated to PDE-5 inhibitors group, sildenafil compared to the placebo group with heterogeneity (MD 0.61, 95% CI -0.37 to 1.59, $P = 0.21$, $I^2 = 34\%$).

Conclusion: The results of present review suggest that treatment with PDE-5 inhibitors; sildenafil reduced mPAP, PVR and mPCWP but could not significantly improve the peak VO_2 .

Keywords: Pulmonary artery hypertension; Right cardiac catheterization; Pulmonary hypertension; Heart failure; Right ventricular hypertrophy; Right sided heart failure; Sildenafil

Introduction

Pulmonary arterial hypertension (PAH) is a continuous and multi-causal disorder of increased pulmonary vascular resistance (PVR) as a consequence of structural changes to pulmonary arterial bed with high morbidity and mortality [1,2]. PAH is defined as a mean pulmonary artery pressure (mPAP) of >25 mmHg at rest or 30 mmHg during exercise in the absence of pulmonary venous hypertension [3-6]. The composite pathogenesis of PAH involves dysfunction of three key mechanisms: the endothelin pathway, the prostacyclin pathway and the nitric oxide pathway. This dysfunction results in elevated pulmonary pressures, increased right ventricular (RV) afterload and RV failure, which is related with an even worse outcome [4,5]. Several studies of new current therapies for PAH consists mainly prostacyclins, endothelin receptor antagonists and phosphodiesterase type 5

inhibitors (PDE-5) [1-5]. In settings where new drugs for PAH is not possible due to lack of availability and cost; PDE-5 inhibitors such as Sildenafil is the drug of choice in the management of PAH. PDE-5 inhibitors are vasodilator that enhance and prolongs the action of cyclic guanosine monophosphate (cGMP), a primary mediator of vasodilation by selectively inhibiting the cGMP-specific PDE 5 isozyme. Inhibition of cGMP breakdown might be particularly effective in achieving pulmonary vasodilation, because cGMP formation and urinary excretion is increased in patients with Primary Pulmonary Hypertension (PPH) [6,7]. Pharmacologically-induced elevation of cGMP by PDE-5 inhibitors have been proved to prevent and reverse left ventricular (LV) hypertrophy in mice exposed to chronic pressure overload induced by transverse aortic constriction. In human PDE-5 has been proved to be abundant in the pulmonary circulation and helps in the inhibition of cell proliferation in pulmonary arteries [8]. Recent randomized controlled trials have demonstrated that the use of PDE-5 in patients with PAH improve exercise capacity, resting haemodynamics and quality of life [9-13]. Meta-analysis is a statistical method that combines the results of

several studies to produce a single estimate of a major effect with enhanced precision. The major advantage of meta-analysis is that it increases sample size, which possibly reduces the probability that random error will produce false-positive or false-negative associations [12]. One meta-analysis on additional use of a PDE-5 inhibitor in patients with PH secondary to chronic systolic heart failure analysed six studies which focused on Peak VO₂ and the results contradicts with one new RCT which examined the effects of sildenafil on invasive haemodynamic and exercise capacity in heart failure patients with preserved ejection fraction and PH [4,14]. Thus, a new meta-analysis is important since meta-analysis in 2014; meta-analysis in 2015 [1,2]. In the present study, we perform a new meta-analysis on PAH therapy with PDE-5I, sildenafil including data from one recently published RCT [4-10,13-27] pointing on peak VO₂ improvement.

Materials and Methods

Identification of articles

We conducted a systematically literature search for RCTs in PubMed, Medline, Embase and Google scholar (from 2011 to July 26, 2016). The searches were performed via combination of free-text terms and subjects terms related to PDE-5Is, HF and PH without additional restrictions. The following key words were employed: "Pulmonary artery hypertension" OR "Right Cardiac catheterization" OR "Pulmonary hypertension" OR "Heart failure" OR "Right Ventricular hypertrophy" OR "Right sided heart failure" AND "Sildenafil". In addition, an RCT filter was applied in PubMed and Embase. We also searched further reference lists from identified articles and relevant reviews by hand.

Inclusion and exclusion criteria

Studies involving the comparative evaluation of phosphodiesterase inhibitors group and placebo group for treatment of pulmonary arterial hypertension were included in this systematic review and meta-analysis. Two reviewers independently screened the article titles and abstracts to determine whether the articles were relevant to the systematic review and meta-analysis using broad inclusion criteria. Full texts of potentially eligible studies were then reviewed before final selection. Disagreements were resolved by consensus with a third reviewer. Studies meeting the following criteria were included: (i) randomized controlled trials; (ii) patients aged 18 years and above with symptomatic HF and PH; (iii) treated with oral sildenafil in comparison to placebo; (iv) peak VO₂ as endpoint and (v) intervention in each group had to last for at least 12 weeks and above. Exclusion criteria included severe non-cardiac limitation to exercise, significant left sided valve disease, studies with short duration.

Data extraction and quality assessment

The following data were extracted from each article: first author, year of publication, follow-up time, number of participants in each interventional group, demographic data, clinical characteristics, peak VO₂, PVR, VO₂ at AT, VE/VCO₂ slope, mPCWP, mPAP and QOL as endpoints (Table 1). The Cochrane risk-of-bias tool was used for quality assessment of the studies (Table 2) [20]. There were three possible judgments: low risk of bias, high risk and if insufficient details were available, the judgment was reported that the risk of bias was unclear.

Study, Year	Group	No of Patients	Age (y)	Peak VO ₂ (mL/min/kg)	NYHA I/II/III/IV (%)	Follow-up duration (weeks)	Outcome
Hoendermis ES [4]	Sildenafil	21	72 ± 12	11.7 ± 3.3	23/77/0	12	Change in peak VO ₂
	Placebo	22	76 ± 7	11.1 ± 2.5	19/81/0		
Redfield MM [13]	Sildenafil	113	68.75 ± 18.75	12.075 ± 1.4126	49/51/	12	Change in peak VO ₂
	Placebo	103	69.25 ± 18.76	12.075 ± 13.69	45/55/-		
Guazzi M [26]	Sildenafil	16	66.0 ± 8.0	9.6 ± 6.1	-/87/13	26 and 52	Peak VO ₂ , mPCWP, PAP, PVR, QOL
	Placebo	16	68.0 ± 6.0	10.4 ± 5.2	-/94/6		
Guazzi M [10]	Sildenafil	23	60 ± 4	12.9 ± 6.8	43/57/-	52	Peak VO ₂ , QOL
	Placebo	22	61 ± 4	12.7 ± 5.0	41/59/-		

Table 1: The baseline characteristics of four studies included in meta-analysis.

Author, publication year	Other bias	Selective reporting	Incomplete outcome data	Blinding outcome assessment	Blinding participants and personnel	Allocation concealment	Random sequence generator
Hoendermis ES [4]	L	L	L	L	L	L	L
Guazzi M [10]	L	U	L	U	L	L	L
Guazzi M [26]	L	U	L	U	L	L	L
Redfield MM [13]	L	L	U	L	L	L	L

L=Low risk, H=High risk, U=Unclear risk

Table 2: Risk of bias of included studies.

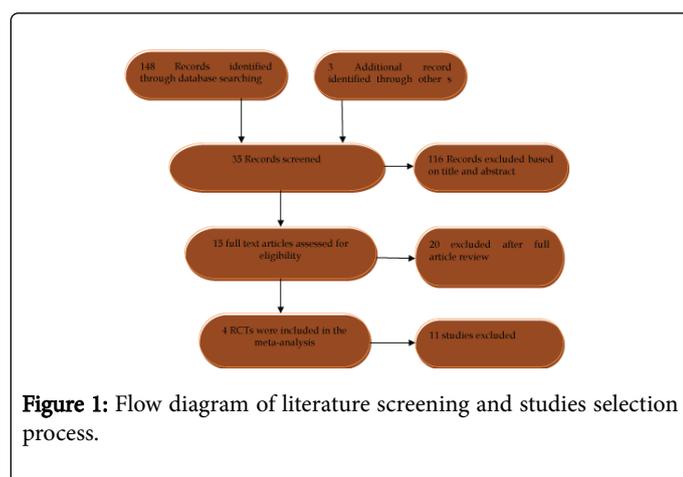
Data synthesis and statistical analysis

We carried our statistical analysis using the review manager software (RevMan 5.3). We calculated weighted mean differences (WMD) for continuous data, and corresponding 95% confidence intervals (CIs). We assessed within and between-study variation and heterogeneities using Cochran Q-statistics [21]. The heterogeneity test is used to assess the null hypothesis that all studies will be evaluating the same effect. When a significant Q-statistic ($p < 0.10$) indicates heterogeneity across studies, the random-effect model is used for the meta-analysis, and when it is not, the fixed-effect model is used. The fixed effect model assumes that all studies estimate the same underlying effect and considers only within-study variation. Statistical heterogeneity in each meta-analysis was assessed using the Tau², I² and Chi² statistics. We regarded heterogeneity as substantial if I² was greater than 30% and either the Tau² was greater than zero, or there was a low P value (less than 0.10) in the Chi² test for heterogeneity, where I² measures the degree of inconsistency between studies and determines whether the percentage total variation across studies is due to heterogeneity rather than to chance. I² range between 0% and 100%; I² values of 25%, 50%, or 75% are referred to as low, moderate, and high estimates respectively [12]. There were insufficient studies to carry out subgroup and sensitivity analyses.

Results

Studies selection

Following screening of titles and abstracts full text of fifteen studies were obtained and considered.



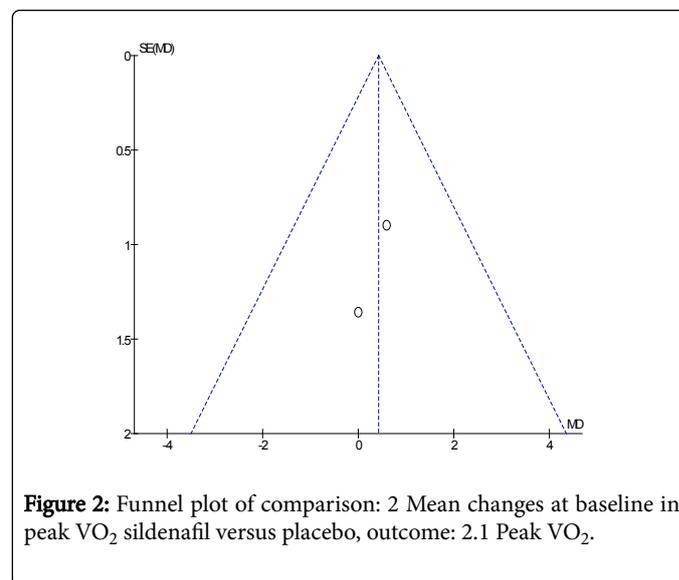
Thus, our final analysis included four studies which enrolled a total of three hundred thirty six patients and eleven studies were excluded. All included studies are small. The largest study recruited two hundred sixteen patients (Figure 1).

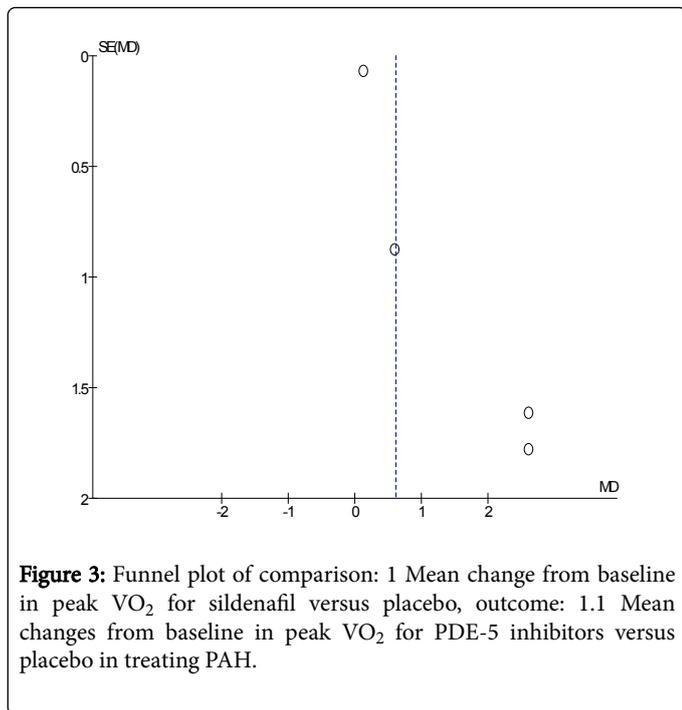
Baseline characteristics of included studies

The baseline characteristics of these trials are summarized in (Table 1). Our meta-analysis covered only one class of drug for PAH: PDE-5is; sildenafil. Patients were randomized into two groups, 51.5% patients in the PDE-5 inhibitors treatment group and 48.5% patients in the placebo group. Age (MSD) of the participants ranged between 60 ± 4 years and 76 ± 7 years. The mean follow-up duration ranged from 12 weeks to 24 weeks. To be noted, peak oxygen consumption was the primary end point in all 4 studies. We presented our results as weighted mean differences with 95% confidence intervals presented for the continuous outcomes. Data which had been presented in median and inter-quartiles; we requested original data from the authors and was not possible to get them therefore we estimated the mean and variance using simple formulas; using the values of the median (m), low and high end of the range (a and b respectively), and n (the sample size) [25].

Quality assessment

The quality of the 4 articles was assessed by the Cochrane handbook for systematic reviews of interventions for assessing the risk of bias for included studies [20]. There were three possible judgments: low risk of bias, high risk and if insufficient details were available, the judgment was reported that the risk of bias was unclear (Table 2). A low-level selection bias including publication bias was also evident from the visual examination of the funnel plot (Figures 2 and 3).





Effects of phosphodiesterase type 5 inhibitors, sildenafil on cardiopulmonary exercise testing pointing peak VO₂

Maximal cardiopulmonary exercise testing has been proven to be a beneficial non-invasive tool to assess physiological changes as linked with exercise. Peak VO₂ has been used as a marker for exercise capacity in a range of cardiopulmonary diseases since it is determined by the maximal cardiac output during exercise, the potential for O₂ extraction by the exercising muscle and the ventilator capacity. Peak VO₂ (also VO₂ max, maximal oxygen consumption, maximal oxygen uptake, peak oxygen uptake or maximal aerobic capacity) can be quantitated clinically by measurement of oxygen uptake (VO₂), carbon dioxide production (VCO₂), and minute ventilation. When Peak VO₂ is decreased in patients with pulmonary arterial hypertension, indicates an impaired cardiac reserve during exercise in this disease [23,24,27]. However, cardiopulmonary exercise testing could be performed in all patients with HF and PH in all 4 enrolled trials since all patients were stable during the trials. All four studies predominantly included NYHA class II or IV patients and results shown no statistical significant improvement in peak VO₂, of patients allocated to PDE-5 inhibitors group, sildenafil compared to the placebo group with heterogeneity (MD 0.61, 95% CI -0.37 to 1.59, P=0.21, I²=34%) (Figure 4). On the other hand, only two studies [10,26] assessed the exercise ventilation efficacy (ventilation to CO₂ production slope and the results favoured patients allocated to sildenafil group compared to the placebo group with heterogeneity (MD -0.74, 95% CI -4.97 to 3.48, P=0.73, I²=94%) (Figure 5).

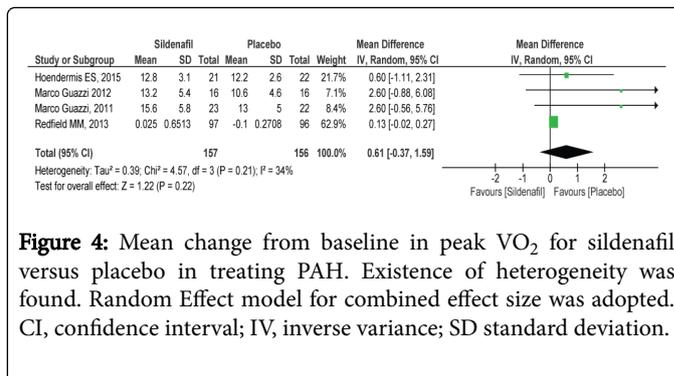


Figure 4: Mean change from baseline in peak VO₂ for sildenafil versus placebo in treating PAH. Existence of heterogeneity was found. Random Effect model for combined effect size was adopted. CI, confidence interval; IV, inverse variance; SD standard deviation.

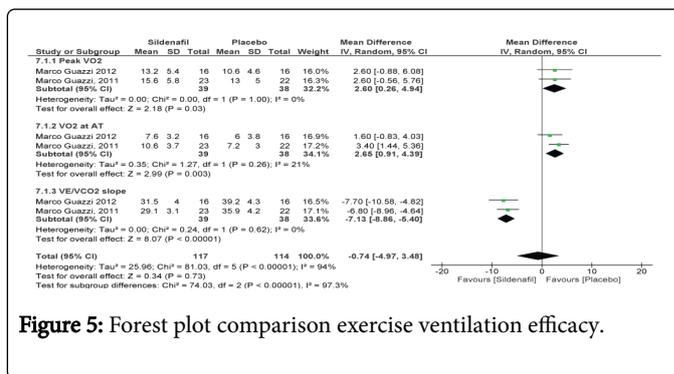


Figure 5: Forest plot comparison exercise ventilation efficacy.

Other pulmonary hemodynamic measurements

Two trials [4,26] shown that PDE-5 inhibitors, sildenafil led to statistically significance in reduction of mPAP (MD -4.15, 95% CI -17.28 to 8.98; P<0.00001) and PVR (MD -51.27, 95% CI -127.63 to 25.10; P<0.00001). Other three studies [4,10,26] show reduction in statistical significance of mPCWP (MD -2.70, 95% CI -7.14 to 1.75; P<0.0003). There was heterogeneity related to the mPAP, PVR and mPCWP measurements between the studies (mPAP, I²=95%, P<0.00001; I²=95%, P<0.00001; mPCWP, I²=91%, P=0.0001) (Figures 6A-6C).

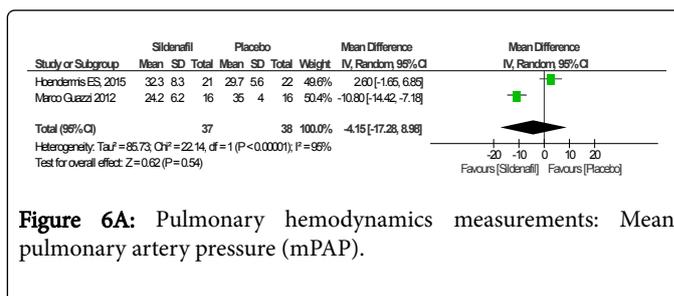


Figure 6A: Pulmonary hemodynamics measurements: Mean pulmonary artery pressure (mPAP).

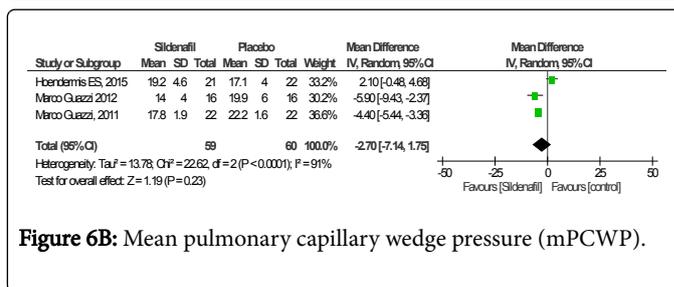


Figure 6B: Mean pulmonary capillary wedge pressure (mPCWP).

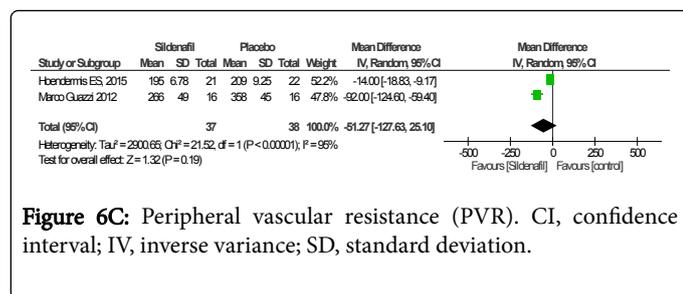


Figure 6C: Peripheral vascular resistance (PVR). CI, confidence interval; IV, inverse variance; SD, standard deviation.

Also two studies [10,26] accessed the quality of life (fatigue, breathlessness and Emotion Function) and shown no much difference among the two groups (MD 1.18, 95% CI -4.92 to 7.27; P < 0.00001) (Figure 7).

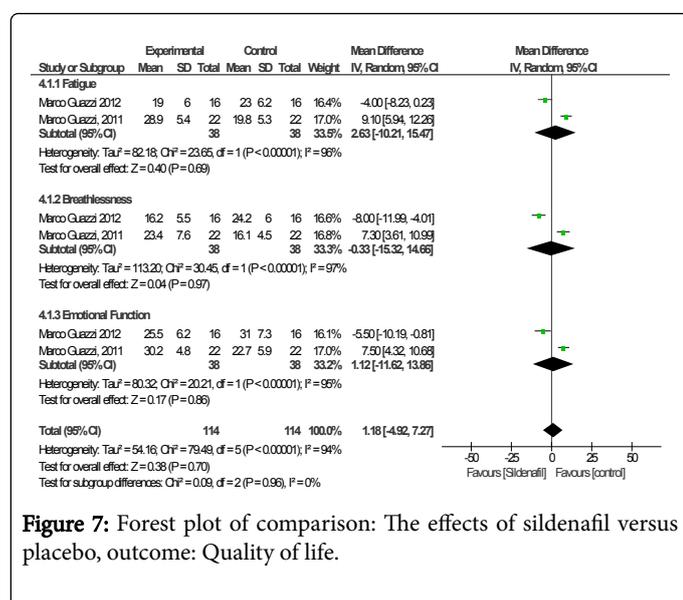


Figure 7: Forest plot of comparison: The effects of sildenafil versus placebo, outcome: Quality of life.

Discussion

The present study revealed that PDE-5 inhibitors therapy statistically significantly reduced the mean pulmonary arterial pressure, peripheral vascular resistance and mean pulmonary capillary wedge pressure. However, PDE-5 inhibitor, sildenafil could not significantly improve peak VO₂ in patients with PAH compared with the placebo group and also shown no much differences on the quality of life among the two groups which were assessed for.

Previous study shown the improvement of peak VO₂ with sildenafil for treating PAH but sildenafil was used as additional drug [14]. Recently a meta-analysis has demonstrated the efficacy and safety of PDE-5 inhibitors, sildenafil promoted a sustained beneficial effect on exercise tolerance and ventilation efficiency by increasing the peak VO₂ and decreasing the VE/VCO₂ slope, but it only enrolled large randomized controlled trials which may lead to potential publication bias [14]. Most previous meta-analysis generally calculated peak VO₂ without considering PDE-5 inhibitors as monotherapy. In present study, we found there was heterogeneity when we did our statistical analysis according to the single medication. Although PDE-5 inhibitors like Sildenafil is relatively more available and more affordable drug in developing countries for treating PAH, present meta-analysis PDE-5 inhibitor, Sildenafil did not improve peak VO₂

(MD 0.61, 95% CI -0.37 to 1.59, P=0.21, I²=34%). However, in the study He CJ et al. [1] evaluated the efficacy and safety of treating PAH with PDE-5 inhibitors, focusing on the improvement of 6 min walk distance (6MWD) and concluded that treatment with PDE-5 inhibitors improves the 6MWD, clinical symptoms, hemodynamic parameters, and a tendency of survival benefits. In patients treated with PDE-5 inhibitor monotherapy, the 6MWD significantly increased when compared to combination therapies.

This meta-analysis differs from the meta-analysis of additional use of a phosphodiesterase 5 inhibitor in patients with pulmonary hypertension secondary to chronic systolic heart failure by [1,14]. In the present study, we pointed on Sildenafil therapy only that included 4 RCTs, with 173 patients in the PDE-5 inhibitors treatment group and 163 patients in the placebo group, and the meta-analysis included more patients with HF and PH. However, the results of this meta-analysis regarding the effects of sildenafil for improvement of peak VO₂ in stable patients with PAH disagree with those of the previous study.

This study should be considered for limitations, first, because of the small sample size and limited number of RCTs included in the study. Second, the studies included in the meta-analysis were few to perform subgroup analysis and sensitivity analysis. Third, we pointed peak VO₂ as our focus and may be regarded as a weak endpoint for the most severe forms of pulmonary arterial hypertension patients.

Conclusion

In conclusion, this meta-analysis shown that sildenafil reduced mPAP, PVR and mPCWP but could not statistically improves the peak VO₂. We therefore recommend further long-term studies to adequately assess its effects on peak VO₂.

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Declarations of Interest

The authors declare no conflict of interest.

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