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Efficacy and safety of sildenafil treatment in pulmonary arterial hypertension: A systematic review

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Summary
Background: To evaluate the safety and efficacy of using sildenafil for ≥12 weeks to treat pulmonary arterial hypertension (PAH).
Methods: Randomized controlled trials (RCTs) of sildenafil therapy in patients with PAH published through May 2013 were identified by searching PubMed, the Cochrane Library, Embase, relevant websites, and reference lists of relevant studies. Two reviewers independently assessed the quality of the trials and extracted information.
Results: Meta-analysis was carried out with subsets of 4 trials involving 545 patients. Sildenafil therapy significantly reduced clinical worsening of PAH compared to placebo (RR 0.39, 95% CI 0.21–0.69) and improved the 6-min walk distance (MD 31.3 m, 95% CI 18.01–44.67), WHO functional class, hemodynamic variables and health-related quality of life (HRQoL). Sildenafil did not, however, improve all-cause mortality (RR 0.29, 95% CI 0.02–4.94) or Borg dyspnea score relative to placebo, nor did it significantly affect the incidence of serious adverse events. In fact, sildenafil was associated with higher total incidence of adverse events, but these additional events were mild to moderate in severity and were tolerable.
Conclusions: Sildenafil therapy lasting ≥12 weeks improves multiple clinical and hemodynamic outcomes in patients with PAH, but it appears to have no effect on mortality or serious adverse events. The long-term efficacy and safety of sildenafil therapy in PAH requires further study based on large and well-designed RCTs.

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Introduction

Pulmonary arterial hypertension (PAH), characterized by vascular proliferation and remodeling of small pulmonary vessels, leads to progressive increase in pulmonary vascular resistance (PVR) and, ultimately, to right ventricular failure and death [1]. Several factors contribute to PAH pathogenesis, and one of the signaling pathways participating in PAH pathogenesis is the nitric oxide (NO) pathway [2,3]. This pathway is targed by inhibitors of phosphodiesterase type 5 (PDE-5), an enzyme that degrades cyclic guanosine monophosphate (cGMP) and thereby causes vasoconstriction. PDE-5 inhibitors induce vasodilation by inhibiting the hydrolytic breakdown of cGMP [4].

The PDE-5 inhibitor sildenafil has been advocated as a first-line drug for treating PAH. It is a potent, orally active, and selective inhibitor that has been widely used in monotherapy and combination therapy for adults with PAH [5,6]. Several meta-analyses of drug therapies to treat PAH [7—10] have been carried out, and they suggest that sildenafil is safe and effective. However, these meta-analyses feature relatively small sample sizes, treatment durations of fewer than 12 weeks, and lack of blinding or randomization. Furthermore, they do not take into account two recently published randomized controlled trials (RCTs) of sildenafil therapy lasting 12 weeks [11,12]. In particular, we are unaware of meta-analyses of RCTs assessing the safety and efficacy of the drug when given to adults for periods of 12 weeks or more.

To address some of these gaps in previous meta-analyses, we systematically reviewed the literature on sildenafil safety and efficacy for treating PAH over periods of at least 12 weeks.

Materials and methods

Search strategy

We systematically searched for randomized controlled trials (RCTs) involving sildenafil published in English through May 2013 in PubMed, the Cochrane Library, and Embase databases, as well as in review articles and reference lists of relevant studies. We used the following search terms: "sildenafil" *and* "PAH" *or* "pulmonary arterial hypertension" *and* "randomized controlled". We also searched Clinicaltrials.gov to identify ongoing but still unpublished studies.

Study inclusion criteria

Studies were included if they satisfied all the following conditions: (1) the study is an RCT that compares PAH with placebo or other vasodilators (2) administered for $\geq$12 weeks to (3) adult patients who were (4) definitively diagnosed with group 1 PAH according to a standard clinical classification [13].

Efficacy and safety outcomes

Two investigators independently extracted the following data from included studies using a standardized form: first author, year of publication, study design, patient characteristics, interventions, and major outcomes, such as clinical worsening, all-cause mortality, 6-min walk distance (6MWD), WHO functional class (WHO FC), health-related quality of life (HRQoL) score, Borg dyspnea score, hemodynamic measures such as mean pulmonary arterial pressure (mPAP), PVR and cardiac index. Data on adverse events were also recorded to allow safety evaluation.

Quality assessment

Studies were assessed for quality of randomization, blinding, reporting of withdrawals, generation of random numbers and concealment of allocation according to the Cochrane systematic review software, RevMan 5.2.

Statistical analysis

Statistical analyses were performed using RevMan 5.2 software. The statistical heterogeneity of treatment effects between studies was tested using the chi-squared test, with a significance threshold of $P < 0.1$. Statistical heterogeneity was considered to be significant when $I^2 > 50\%$. Regardless of whether statistical heterogeneity was present, meta-analyses were performed using a random-effects model. We calculated risk ratios (RR) for dichotomous data and weighted mean differences (WMD) for continuous data; these estimates were reported together with 95% confidence intervals (CI). When studies failed to report the standard error of the mean (SEM) to allow calculation of effect size, it was estimated from published data [14]. If a study failed to report outcome values at the end of follow-up and the associated SEM, we calculated these values manually from figures if available.

Results

Study identification and inclusion

Our literature searches initially identified 941 articles, six of which satisfied the inclusion criteria [11,12,15—18]. We excluded the study by Wilkins et al. [17] because it involved only 26 patients, and we excluded the study by Iversen et al. [18] because most patients had Eisenmenger's syndrome. In the end, four multicenter, double-blind RCTs [11,12,15,16] were included in the meta-analysis (Fig. 1). The studies involved 545 patients, comprising 342 who received sildenafil and 203 who received placebo. Three of the four included trials [11,12,16] involved the same 278 patients, but they reported on different outcomes related to safety and efficacy, so duplicate counting of the same patients among the studies was not an issue.

Key characteristics of the four trials are shown in Tables 1 and 2. Of the 545 patients, 387 (71%) were diagnosed with idiopathic PAH, while the remainder was diagnosed with associated PAH; 500 of the 540 patients (92.6%) were in WHO FC II or III. (Data on WHO FC were missing for 5 patients.) One RCT investigated the effect of adding oral sildenafil to long-term intravenous epoprostenol therapy for patients with PAH over periods of 12—16 weeks [15]. The three other studies, involving the same 278 patients, examined the efficacy and safety of 12-week sildenafil monotherapy [11,12,16]. Primary endpoints were 6MWD [15,16], HRQoL [11], and ocular safety of sildenafil [12].