Meta-analysis of randomized controlled trials on treatment of pulmonary arterial hypertension


CRD summary
This review concluded that inhaled iloprost and oral bosentan and sildenafil were effective and safe in treating pulmonary arterial hypertension. The authors’ conclusions reflected the evidence presented, but potential for publication bias and a lack of reporting of some review methods made the reliability of the conclusions uncertain.

Authors’ objectives
To evaluate the efficacy and safety of treating pulmonary arterial hypertension with inhaled iloprost, oral bosentan and sildenafil.

Searching
Published trials were identified through a search of BIOSIS Previews, EMBASE, MEDLINE and the CNKI to August 2009. Dissertations and conference proceedings were handsearched. Search terms were reported.

Study selection
Randomised controlled trials of inhaled iloprost, oral bosentan and sildenafil compared with placebo in patients diagnosed with pulmonary arterial hypertension were eligible for inclusion. Diagnosis of pulmonary arterial hypertension diagnosis was required to be made under one of five categories: idiopathic pulmonary arterial hypertension; familial pulmonary arterial hypertension; associated with pulmonary arterial hypertension; (associated with significant venous or capillary involvement, pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis; and persistent pulmonary hypertension of the newborn.

Interventions in the included studies were bosentan, sildenafil and iloprost. Some patients in the included studies were simultaneously treated with other medications. Most participants were considered to have idiopathic pulmonary arterial hypertension or aetiology associated with pulmonary arterial hypertension. Outcomes included clinical worsening, functional class, six-minute walk test, haemodynamic parameters and safety. Follow-up ranged from eight to 26 weeks.

Two reviewers selected studies for inclusion.

Assessment of study quality
Study quality was assessed by two reviewers who used the Juni scale of randomisation, allocation concealment, blinding and withdrawals. Studies were assigned grades from A (all four evaluation criteria met) to C (several criteria not satisfied).

Data extraction
Data for dichotomous and continuous outcomes were extracted.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Data were used to calculate the pooled odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous outcomes and weighted mean differences (WMDs) and 95% CIs for continuous outcomes. A fixed-effect meta-analysis was used where there was no evidence of statistical heterogeneity. A random-effects model was used where statistically significant heterogeneity was observed. The Q test and I² statistic were used to assess heterogeneity. Publication bias was assessed using funnel plots.

Results of the review
Eleven trials (n=1,391) were included in the review. Overall study quality was good: six trials scored A, four trials scored B and one trial scored C.

**Clinical worsening:** Medication significantly reduced clinical worsening compared with placebo (OR 0.33, 95% CI 0.22 to 0.49; 11 trials). In subgroup analyses, reduction in clinical worsening remained significant for patients treated with bosentan (OR 0.26, 95% CI 0.13 to 0.50; five trials) and sildenafil (OR 0.34, 95% CI 0.18 to 0.64; three trials), but not for iloprost (three trials). There was no evidence of statistical heterogeneity.

**Functional class:** Medication significantly improved functional class compared with placebo (OR 2.81, 95% CI 1.95 to 4.03; eight trials). Improvement in functional class was significant for bosentan, sildenafil and iloprost.

**Six-minute walk test:** Medication significantly improved the six-minute walk test compared with placebo by an average of 31.13m in the bosentan group, 36.53m in the sildenafil group and 31.46m in the iloprost group (11 trials).

**Haemodynamic parameters:** Medication significantly improved all haemodynamic parameters compared to placebo. Pulmonary arterial systolic pressure was reduced by an average of 4.64mmHg (95% CI -6.02 to -3.26; five trials). Mean pulmonary arterial pressure was reduced by an average of 4.05mmHg (95% CI -4.54 to -3.56; four trials). Pulmonary vascular resistance was reduced by an average of 246.09 dyns/cm² (95% CI -319.13 to -173.04; seven trials). The cardiac index was increased by an average of 0.40L/min/m² (95% CI 0.08 to 0.98; three trials). Cardiac output was increased by an average of 0.53L/min (95% CI 0.11 to 0.69; four trials). There was evidence of statistical heterogeneity for analyses of pulmonary vascular resistance, cardiac index and cardiac output.

**Safety:** There was no significant difference in the number of serious adverse events between participants who received one of the three study medications and those who received placebo (OR 1.09, 95% CI 0.69 to 1.71; 11 trials). The incidence of serious adverse events was lowest in patients who received bosentan and highest in patients who received iloprost ($\chi^2=57.134$, $p<0.0001$). There was no evidence of statistical heterogeneity for this analysis.

An asymmetric funnel plot indicated possible publication bias.

**Authors’ conclusions**
Inhaled iloprost and oral bosentan and sildenafil were effective and safe in treating pulmonary arterial hypertension

**CRD commentary**
This review addressed a clear question supported by appropriate inclusion criteria. Outcomes were not explicitly defined. Some relevant databases were searched. Attempts were made to identify unpublished data. Search terms were reported. It was unclear whether language limitations were applied. Publication bias was assessed in the report and some evidence of it was found. Suitable methods to minimise risk of reviewer error and bias were reported for study selection; the methods of data extraction were not reported. Study validity was assessed, although only a summary grade was reported. Results were pooled using meta-analysis. Heterogeneity was assessed, but not explored.

The authors’ conclusions reflected the evidence presented, but potential for publication bias and a lack of reporting for some of the review methods made the reliability of the conclusions uncertain.

**Implications of the review for practice and research**
**Practice:** The authors stated that inhaled iloprost and oral bosentan and sildenafil were effective and safe in treating pulmonary arterial hypertension.

**Research:** The authors stated that further randomised controlled trials on combination therapy, new pulmonary arterial hypertension medications and evaluation of the long term efficacy of medication for pulmonary arterial hypertension were needed.

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