Studies on the effectiveness and safety of cilostazol, beraprost sodium, prostaglandin E1 for the treatment of intermittent claudication
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CRD summary
This review assessed cilostazol, beraprost sodium and prostaglandin E1 (PGE1) for treating intermittent claudication to improve walking distance. The authors concluded that cilostazol and PGE1 are effective, but further studies of beraprost sodium are needed. A narrow literature search limits the reliability of these conclusions.

Authors' objectives
To assess the effectiveness of cilostazol, beraprost sodium and prostaglandin E1 (PGE1) in improving walking distance in patients with intermittent claudication.

Searching
MEDLINE was searched for papers published in English or Japanese between January 1966 and May 2001; the search terms were reported. The reference lists of retrieved papers were checked for further studies, while experts in the field and relevant pharmaceutical companies were contacted for unpublished and ongoing trials.

Study selection
Study designs of evaluations included in the review
Double-blind, placebo-controlled, randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of cilostazol, beraprost sodium or PGE1 were eligible for inclusion. The included studies of cilostazol used a daily oral dose of 200 mg for between 6 and 24 weeks; studies of beraprost used a daily oral dose of 120 micrograms for either 12 weeks or 6 months; studies of PGE1 used a daily intravenous dose of 60 micrograms (either every day, 2 days per week or 5 days per week) for between 4 and 12 weeks.

Participants included in the review
Studies of adults with arteriosclerosis obliterans and a main complaint of intermittent claudication (stage II according to the Fontaine classification) were eligible for inclusion.

Outcomes assessed in the review
Studies reporting the maximum walking distance (MWD) or pain-free walking distance (PFWD), as evaluated using a treadmill test, were eligible for inclusion. Adverse event outcomes were also included in the review.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion.

Assessment of study quality
The studies were assessed using a scoring system developed by Chalmers. The scoring system considered the following factors within 30 items: study hypothesis, participant selection, participant characteristics, sample size, randomisation and blinding, outcome definition and measurement, and statistical methods. The scoring for each item allowed a maximum total score of 100. The studies were classed as high quality (more than 70 points), moderate quality (40 to 69 points), or low quality (less than 40 points). Three reviewers independently assessed study quality, with any differences resolved by consensus.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The mean value and standard deviation were extracted for MWD and PFWD at baseline, and for changes immediately following the treatment period, at 4 weeks after the commencement of treatment, and at the end of the maximum follow-up period after treatment. The number of participants experiencing adverse events was also extracted for each study and used to calculate the odds ratio (OR) with 95% confidence intervals (CIs).

Methods of synthesis
How were the studies combined?
Studies rated as moderate or high quality were combined using meta-analysis, employing a fixed-effect model with studies weighted by sample size, to derive pooled effect sizes and 95% CIs for each drug and outcome. For MWD and PFWD, the weighted mean difference (WMD) was calculated using the general variance method; for adverse events, the pooled OR was estimated using the Mantel-Haenszel method. If statistical heterogeneity was detected, the pooled estimate was calculated using a random-effects model (DerSimonian and Laird) instead.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic with a P-value of less than 0.05 judged to be statistically significant.

Results of the review
The review included 11 RCTs (n=2,131).

All 11 studies were rated as being of moderate quality, with scores ranging from 54 to 66.

Cilostazol (6 RCTs, 1,352 participants).
Effectiveness: at the end of the treatment period (ranging from 12 to 24 weeks), cilostazol had a significantly greater effect than placebo on both the MWD (WMD +52.19 m, 95% CI: 32.08, 72.31; 5 RCTs) and PFWD (WMD +39.75 m, 95% CI: 23.39, 56.10; 3 RCTs). Similar smaller, but still statistically significant, effects were seen 4 weeks into treatment (3 RCTs). Only one RCT reported follow-up after the end of treatment. This trial found no significant effect of cilastazol over placebo 6 weeks after active treatment ceased.

Adverse events: the drop-out rate was significantly higher in the cilostazol group than in the placebo group (OR 1.98, 95% CI: 1.27, 3.07; 5 RCTs). The death rates were similar in the cilostazol and placebo groups (5 RCTs; 0.7% in each group), and there was no significant difference between the groups in the rate of serious adverse events (4 RCTs). Adverse effects that were more common in those taking cilostazol included headache, dizziness, palpitation, diarrhoea and abnormal stool.

Beraprost (2 RCTs, 505 participants).
Effectiveness: one RCT reported changes in MWD and PFWD after 12 weeks; these were not statistically significantly greater in the beraprost group than in the placebo group.

Adverse events: beraprost was associated with significantly more headaches (2 RCTs), flushes (1 RCT) and vasodilation (1 RCT).

PGE1 (3 RCTs, 274 participants).
Effectiveness: at the end of the treatment period (4 weeks in 2 RCTs, 8 weeks in the other), PGE1 had a significantly greater effect than placebo on both the MWD (WMD +100.27 m, 95% CI: 15.76, 184.78; 3 RCTs) and PFWD (WMD +55.73 m, 95% CI: 21.54, 89.92; 3 RCTs). The results were similar when the analysis was at 4 weeks. Two RCTs reported follow-up after the end of treatment (one after 12 weeks and the other after 8 weeks), but found no benefit of PGE1 over placebo for either MWD or PFWD.
Adverse events: no serious adverse events were reported (3 RCTs). There were no significant differences between PGE1 and placebo for reddening of infusion vein (1 RCT), hypotension (1 RCT), or diarrhoea or nausea (1 RCT).

Cost information
The drug cost (in Japanese yen, Y) per metre increase of PFWD was calculated to be Y 1,124 for cilostazol, Y 750 for beraprost and Y 8,036 for PGE1.

Authors' conclusions
Cilostazol and PGE1 can be considered effective for the treatment of intermittent claudication. Further studies are needed to clarify the efficacy of beraprost sodium.

CRD commentary
The review question and inclusion criteria were clearly defined. The search used only one electronic database and, although other methods were used to locate published and unpublished studies, some relevant literature might have been missed (as the authors acknowledged). The inclusion of only papers in Japanese and English also raises the possibility of language bias. More than one reviewer performed the study section and quality assessment, which should have minimised the introduction of errors and bias during these processes. Study quality was formally evaluated, and the fact that the studies had to meet a certain level of quality to be included in the analysis should enhance the reliability of the results of the review.

The decision to pool studies using a meta-analysis might not have been appropriate for the PGE1 studies, as the use of the random-effects model meant that statistical heterogeneity was detected. Furthermore, the authors stated that the studies, in general, were also clinically heterogeneous in terms of the treatment period, disease status of participants and treadmill conditions; this makes direct comparisons questionable. The conclusions of the review follow from the results presented. However, the narrow literature search and small number of heterogeneous studies analysed, particularly for PGE1, limits the reliability of the conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research is needed to clarify the efficacy of beraprost sodium and to assess limaprost alfadex (an oral formulation of PGE1).

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