Prostanoids in the treatment of intermittent claudication: a meta-analysis

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Authors' objectives
The authors assessed the effects of prostanoids in the treatment of patients with intermittent claudication.

Searching
MEDLINE and EMBASE were searched using the search strategy described by the Cochrane Peripheral Vascular Diseases Group. Relevant journals were handsearched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Non-randomised controlled studies and studies in which treatment allocation was unclear were excluded. Studies that did not report standard deviations were not included in the meta-analysis, although they were included in evaluations of side-effects and long-term effects. One RCT with a very short follow-up (less than 2 weeks) was excluded from the follow-up analysis.

Specific interventions included in the review
Studies that compared prostanoids with placebo or any alternative treatment were eligible for inclusion. In the included studies, the drugs were given by intra-arterial, intravenous and oral routes. The included studies compared the following treatments: prostaglandin E1 (PGE1) with placebo, L-arginine, laevadosin, naftidofuryl or pentoxifylline; iloprost with placebo or hydroxyethyl starch; beraprost sodium with placebo; taprostene with placebo; and prostacyclin (PGI2) with placebo.

Participants included in the review
Studies of patients with intermittent claudication were eligible for inclusion.

Outcomes assessed in the review
Studies that assessed objective and subjective outcomes, side-effects and the effect of long-term treatment were included. The review assessed the following outcomes: objective measures of the pain-free walking distance (PFWD) and maximal walking distance (MWD) by treadmill test; ankle-brachial pressure index (ABI); venous-occlusion plethysmography; haematological parameters; vascular surgery; amputation; mortality; cardiovascular events; drug side-effects; and quality of life. Studies used different quality of life and walking impairment questionnaires. The outcomes were also assessed at follow-up. Follow-up ranged, where stated, from 2 to 52 weeks.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using the 5-point Jadad scale, which considers randomisation, blinding and withdrawals. It was unclear whether validity was assessed by the same methods used to extract the data.

Data extraction
All reviewers independently extracted data and resolved any disagreements through discussion. Information tabulated in the review included intervention details, number of patients in each treatment group, and duration of follow-up (where reported). The authors of the publications were contacted for additional details.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the treatments being compared. The data were pooled wherever possible. The pooled weighted mean difference and 95% confidence interval (CI) between treatments were estimated using a random-effects model for walking distance and ABI. The proportion of patients with at least one adverse effect was estimated for PGI2 and its analogues and for PGE1.

How were differences between studies investigated?
Heterogeneity was apparently assessed, but it was not stated whether this was clinical or statistical heterogeneity. In addition, no details of the methods used were reported. Studies comparing intravenous prostanoids with placebo were subsequently analysed separately. For two analyses (PGE1 and analogues versus placebo and any intravenous prostanoid versus placebo) the influence of one study was assessed by repeating the meta-analysis after omitting this study.

Results of the review
Nineteen RCTs (n=1,528) were included.

The quality scores ranged from 1 to 4 out of a possible 5 points.

PGE1 versus placebo (6 RCTs, 433 patients): PGE1 administered by any route significantly improved the PFWD and MWD compared with placebo. The mean improvements in PFWD and MWD were 65% (95% CI: 37, 93, P<0.0001) and 59% (95% CI: 30, 88, P<0.0001), respectively.

PGE1 versus pentoxifylline (3 RCTs): only one RCT (29 patients) could be assessed. It found that PGE1 significantly improved PFWD and MWD compared with placebo. The mean increases in PFWD and MWD were 499% (95% CI: 18, 980, P=0.04) and 252% (P=0.07), respectively. A second RCT (158 patients) found no significant difference between treatments for ABI (P=0.8).

PGE1 versus L-arginine (1 RCT, 26 patients): the RCT found that L-arginine significantly improved PFWD (increase 51%, 95% CI: 8, 93, P=0.02), but found no significant difference for MWD (P=0.07) or ABI (P=0.4).

Beraprost sodium versus placebo (2 RCTs): only one RCT (80 patients) could be assessed. It found no significant difference between treatments for PFWD (P=0.12) or MWD (P=0.08).

PGI2, iloprost and taprostene versus placebo (4 RCTs): PGI2 and its analogues significantly improved PFWD (P=0.0002) and MWD (P<0.00001). After omitting one small RCT (15 patients) that strongly favoured prostanoids the difference was no longer statistically significant: PFWD (P=0.5) and MWD (P=0.3). One RCT (23 patients) found no significant difference between intravenous iloprost and hydroxylethyl starch for PFWD (P=0.3), MWD (P=0.90), ABI (P=0.8), calf blood-flow at rest (P=0.3) or after ischaemia induced by a tourniquet (P=1).

Any intravenous prostanoid versus placebo (8 RCTs): prostaglandins significantly improved PFWD and MWD. The improvements in PFWD (557 patients) and MWD (519 patients) were 28% (95% CI: 7, 49, P=0.008) and 30% (95% CI: 11, 50, P=0.002), retrospectively. After omitting one small RCT (15 patients), the difference was still statistically significant: PFWD (P=0.5) and MWD (P=0.3). The improvements in PFWD and MWD were 31% (95% CI: 6, 56, P=0.02) and 33% (95% CI: 6, 56, P=0.02), respectively.

Follow-up (6 RCTs; 5 RCTs included in analysis): the studies found that improvement was maintained at the follow-up assessment.

Quality of life (3 RCTs): studies reported that prostanoids significantly improved some domains.

Routine laboratory test: studies found no significant change in values.

Side-effects (18 RCTs): studies reported at last one adverse effect in 133 of 336 patients (39.6%) given PGI2 or its analogues compared with 54 of 392 patients (13.7%) given PGE1. The adverse effects included facial flushing (74 with PGI2 and 12 with PGE1), reaction at injection site (21 with PGI2 and 36 with PGE1), headache (50 with PGI2 and 1 with PGE1) and gastrointestinal effects (10 with PGI2 and 66 with PGE1).
No deaths or amputations were reported.

During 12 months' follow-up there was one stroke with PGE1, and two amputations and two bypass operations with pentoxifylline.

**Authors' conclusions**

PGE1 significantly improves walking distance in patients with intermittent claudication.

**CRD commentary**

The review question was clear in terms of the study design, intervention, participants and outcomes. Two databases and relevant journals were searched, but no details of the dates searched, journals searched, or any language restrictions were given. No attempt was made to locate unpublished studies, thus raising the possibility of publication bias. The methods used to select the studies were not described. Hence, efforts made to reduce errors and bias cannot be judged for this item. All of the reviewers independently extracted data, which reduces the potential for bias and errors. Validity was assessed using validated criteria, but it was unclear whether all the reviewers also assessed validity.

Some information on the included studies was tabulated. However, there was no information on the duration of treatment or patient characteristics, so it was unclear which patients the review referred to. The studies were appropriately grouped according to the drugs compared. The review states that a random-effects model was used because heterogeneity was found, but no further details were given. The influence of some studies on some pooled analyses was assessed by repeating the analysis after omitting each study in turn, but it was unclear how a particular analysis and studies were selected for this exploration. Some results were based on results from a small number of patients. The evidence presented appears to support the authors' conclusions.

**Implications of the review for practice and research**

Practice: The authors stated that PGE1 can be used for patients with stage 11b peripheral arterial disease and should be considered for patients with limited capacity for training.

Research: The authors stated that adequately powered RCTs should be used to compare the effect of recommended (by manufacturers) PGE1 regimens with placebo or walking exercise on walking distance, using standardised treadmill tests. In addition, they stated that amputations and vascular surgery, adverse effects of drugs, quality of life and cost-effectiveness should also be assessed.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.