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Prostanoids in patients with peripheral arterial disease
A meta-analysis of placebo-controlled randomized clinical trials

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ABSTRACT

Aims: Prostanoids are indicated in the treatment of peripheral arterial disease (PAD). Available trials suggest that these compounds could reduce the symptoms of intermittent claudication, even though the quality of studies is poor. The present meta-analysis is aimed at verifying the effects of prostanoids on amputation rate and ulcer healing in patients with lower limb PAD.

Materials and methods: The review protocol was published on http://www.crd.york.ac.uk/prospero (CRD42015020258). A comprehensive search for published and unpublished trials comparing iloprost, alprostadil, prostaglandin-E1, epoprostenol, or taprostene with placebo/no therapy on amputation rate in patients with PAD and ulcer healing rate in patients with concomitant foot ulcers. Mantel–Haenzel odds ratio (MH-OR) was calculated with random effect models for the chosen endpoints.

Results: A total of 18 trials, enrolling 3,077 and 2,763 patients in the prostanoid and comparator groups, respectively were included in the analysis. Only 11 and 10 of those trials reported data on total and major amputations, respectively. Prostanoids were associated with a significantly lower risk of major (MH-OR [95% confidence interval] was 0.77 [0.63; 0.93], $p = 0.007$), but not total, amputations. Healing rate (available only in 7 trials) was not significantly augmented by prostanoid treatment.

Conclusions: Available data are not sufficient to support an extensive use of prostanoids in patients with critical limb ischemia, as an adjunct to revascularization or as an alternative to major amputation in cases which cannot undergo revascularization.

1. Introduction

Prostanoids are indicated in the treatment of peripheral arterial disease (PAD). Available clinical trials suggest that these compounds could reduce the symptoms of intermittent claudication, even though the quality of studies is poor (Robertson & Andras, 2013). In addition, prostanoids have been proposed as adjunct to endovascular revascularization and/or surgery in patients with severe PAD, or as a treatment for limb salvage in those patients in whom revascularization is not possible. For this latter use, a Cochrane systematic review of randomized clinical trials, while underlining the low quality of many studies, highlighted a small but significant effect on ulcer healing, whereas amputation rate was not modified (Ruffolo, Romano, & Ciapponi, 2010). The Cochrane review attempted a retrieval of completed but unpublished trials through direct contact with pharmaceutical companies and experts in the field, without searching public registers of clinical trials. In addition, the review also included trials comparing prostanoids with other active treatments, which could have attenuated the observed benefit.

Aim of the present meta-analysis is the assessment of the effects of prostanoids on amputation rate and ulcer healing in patients with lower limb arterial disease.

2. Materials and methods

The review protocol was published on http://www.crd.york.ac.uk/prospero (CRD42015020258).

2.1. Data sources and searches

A Medline/Embase search for iloprost, alprostadil, prostaglandin E1, epoprostenol, or taprostene was performed, collecting all

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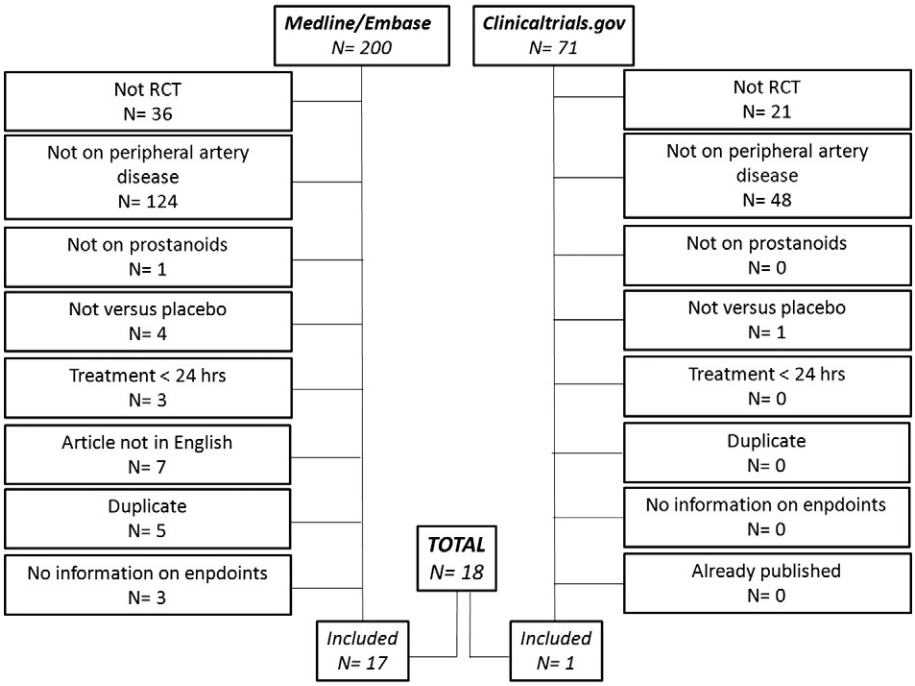

Fig. 1. Funnel plot of standard error by MH log OR.

randomized clinical trials on humans up to March 10th, 2015. The identification of relevant abstracts, the selection of studies based on the criteria described below, and the subsequent data extraction were performed independently by two of the authors (V.V., M.M.), and conflicts resolved by the third investigator (E.M.). Completed but still unpublished trials were identified through a search of www.clinicaltrials.gov website, using the same keywords.

2.2. Study selection

A meta-analysis was performed including all randomized clinical trials with a duration of treatment of at least 24 hours, with a follow-up of at least 4 weeks, enrolling patients with PAD of any severity.

2.3. Data extraction and quality assessment

Results of unpublished trials were retrieved, if available, on www.clinicaltrials.gov. The quality of trials was assessed using some of the parameters proposed by Jadad et al. (1996). The score was not used as a criterion for the selection of trials, whereas some items were used only for descriptive purposes.

2.4. Data synthesis and analysis

The principal outcome of this analysis was the effect of prostanoids, compared either with placebo or no therapy, on total and major amputation rate in patients with PAD. In trials enrolling

Table 1
Quality description of the included trials.

First author (reference)	Procedures description				
	Randomization	Allocation	Blinding	Drop-outs	Intention-to-treat
De Donato (de Donato et al., 2006)	A	NA	NA	A	YES
Belch (Belch et al., 2010)	A	A	A	A	YES
Gruss (Gruss, 1997)	A	NA	NA	NA	YES
Dormandy (Dormandy et al., 1994)	A	NA	OL	A	YES
Nehler (Nehler et al., 2007)	A	A	A	A	YES
Brass (Brass, Anthony, Dormandy, Hiatt, & Jiao, 2006)	A	NA	A	NA	YES
Oral Iloprost (a) (The Oral Iloprost in severe Leg Ischaemia Study Group, 2000)	A	NA	A	NA	YES
Oral Iloprost (b) (The Oral Iloprost in severe Leg Ischaemia Study Group, 2000)	A	NA	A	NA	YES
ICAI group (The ICAI Study Group. Prostanoids for chronic critical leg ischemia, 1999)	A	A	OL	A	YES
Belch (Belch et al., 1983)	A	A	NA	NA	YES
Rhodes (Rhodes & Heard, 1983)	A	NA	A	A	YES
Norgren (Norgren et al., 1990)	A	NA	A	NA	NO
Ciprostene Study Group (The Ciprostene Study Group, 1991)	A	A	A	A	YES
U.K. Study Group (U.K. Severe Limb Ischaemia Study Group, 1991)	A	A	A	A	YES
Balzer (Balzer et al., 1991)	NA	NA	A	NA	NO
Guilmot (Guilmot & Diot, 1991)	NA	NA	A	NA	NO
Telles (Telles et al., 1984)	NA	NA	A	A	NO
NCT00596752 (Anonymous)	A	NA	A	NA	YES