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Intravenous naftidrofuryl for critical limb ischaemia (Review)

Smith FB, Bradbury A, Fowkes G

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[Intervention Review]

Intravenous naftidrofuryl for critical limb ischaemia

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ABSTRACT

Background

Peripheral arterial disease affects five per cent of men and women by late middle age. Approximately 25% of those affected will develop critical limb ischaemia (rest pain, ulceration and gangrene) within five years. Naftidrofuryl is a vasoactive drug which may be beneficial in the treatment of critical limb ischaemia.

Objectives

To determine whether naftidrofuryl, when administered intravenously, is effective in alleviating symptoms and reducing progression of disease in patients with critical limb ischaemia.

Search methods

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched May 2012) and CENTRAL (2012, Issue 4). We searched the reference lists of articles. We also contacted pharmaceutical companies for any unpublished trials.

Selection criteria

All randomised controlled trials of critical limb ischaemia in which participants were randomly allocated to intravenous naftidrofuryl or control (either pharmacological, inert placebo or conservative therapy) were included. People with intermittent claudication were not included.

Data collection and analysis

Sixteen trials were identified, but eight were excluded because of poor methodology. The eight included trials involved a total of 269 participants from five different countries. The following outcomes were reported: pain reduction, rest pain/necrosis, progression of disease in terms of incidence of surgical reconstruction/amputation, mortality and side effects. On extraction of the data, odds ratios and mean differences were estimated where appropriate.

Main results

Treatment with naftidrofuryl tended to show reduction of pain evaluated by both analogue score and analgesic consumption, but the effect was statistically non-significant (mean difference (MD): 0.42; 95% confidence interval (CI)1.19 to 0.35). Similarly, improvement in rest pain or skin necrosis occurred, but these effects were also non-significant. The effect on mean ankle systolic pressure was inconclusive.

Authors' conclusions

Based on the results of these trials, it cannot be confirmed that intravenous naftidrofuryl is effective in the treatment of people with critical limb ischaemia. However, these results were based on trials of generally low methodological quality which had only a small number of participants, the duration of treatment was extremely short, and the methods varied between the trials. The wide range of endpoints effectively precluded any meaningful pooling of the results. Intravenous naftidrofuryl was withdrawn as a treatment for severe peripheral arterial disease in 1995 because of reported side effects.

PLAIN LANGUAGE SUMMARY

Intravenous naftidrofuryl for treating critical limb ischaemia

Peripheral arterial disease is relatively common, particularly in late middle age. Blockages in the leg arteries can reduce blood flow in the legs enough to cause cramping leg pain that limits walking (termed intermittent claudication). They can become severe and cause critical limb ischaemia, pain at rest, leg ulceration and gangrene that requires amputation. When a patient with critical limb ischaemia is being assessed for vascular surgery or if they are unsuitable or refuse surgery, they are treated conservatively as with bed rest. Drug therapy may be used to relieve symptoms and reduce progression of disease. Vasodilator drugs such as prostaglandins increase local blood flow to the leg but may not improve blockages (stenoses). Naftidrofuryl is also vasoactive and blocks serotonin. It has been used intravenously in severe critical limb ischaemia for rapid effect.

The review authors identified eight controlled trials that randomly allocated a total of 269 participants from five different countries to receive intravenous naftidrofuryl, other treatments, and placebo alone or with another treatment. There was no clear indication that short-term intravenous naftidrofuryl significantly improves either symptoms of ischaemic rest pain or skin necrosis. Treatment with naftidrofuryl tended to reduce pain, measured using a scale or with analgesic consumption, and improve rest pain and skin necrosis but the effects were not clear (statistically significant). The trials were generally of low methodological quality, included small numbers of predominantly elderly participants with varying levels of severity of critical limb ischaemia and used different measures of effect. The duration of treatment was short, from three to 42 days, most often seven days. Other treatments were haemodilution, anti-coagulant medication, prostaglandins, bed rest and reflex heating, and gingko biloba. Side effects included mild blood clotting (thrombophlebitis) at the injection site and in one trial two participants experienced renal insufficiency. Intravenous naftidrofuryl was withdrawn as a treatment for severe peripheral arterial disease in 1995 because of reported side effects.

BACKGROUND

Description of the condition

Peripheral arterial disease is a relatively common condition and by late middle age about five per cent of men and women demonstrate symptoms of intermittent claudication. Approximately 25% of all claudicants referred to a peripheral vascular clinic progress to critical limb ischaemia (rest pain, ulceration and gangrene) within five years. Many of these people undergo major surgery and the amputation rate can be as high as five per cent (Leng 1993).

Description of the intervention

Conservative treatment, such as bed rest or exercise programmes, is initially used to treat the acute ischaemic symptoms in people who are either being assessed for revascularization, or are considered unsuitable for surgery. When standard therapy has been unsuccessful, or is not possible, drug therapy is an alternative option which may be considered. However, vasodilator drugs, such as prostanoids which increase local blood flow to the ischaemic limb, do not appear to improve haemodynamically significant stenoses.

How the intervention might work

The vasoactive drug, naftidrofuryl, can be administered either intravenously or orally. It is a serotonergic receptor antagonist which may be beneficial in the treatment of severe lower limb disease. Intravenous treatment has been preferred initially in severe critical limb ischaemia because of the more rapid conversion to active metabolites, and has been used at a higher dosage than the oral form. This drug increases oxidative metabolism and reduces lactic acidosis in ischaemic cells.

Why it is important to do this review

A meta-analysis of clinical trials of the effect of oral naftidrofuryl on intermittent claudication found that walking distance was significantly improved in people treated with naftidrofuryl (Lehert 1990). Fewer trials have been conducted on more severe peripheral arterial disease, although naftidrofuryl has been widely prescribed in Europe for the treatment of critical limb ischaemia and was initially considered to have only minor side effects. This systematic review assessed the therapeutic effects of intravenous naftidrofuryl on critical limb ischaemia.

OBJECTIVES

To determine whether intravenous naftidrofuryl is effective in terms of alleviating symptoms and reducing progression of disease in people with critical limb ischaemia.

METHODS

Criteria for considering studies for this review

Types of studies

The studies in this review include only those in which people with critical limb ischaemia (rest pain, ulceration or gangrene) were stated to be randomly allocated to either intravenous naftidrofuryl or control (either pharmacological, inert placebo or conservative therapy).

Types of participants

The participants were males and females of any age who had a diagnosis of critical limb ischaemia and who had been admitted to hospital for treatment. Participants were either unsuitable for reconstructive arterial surgery or were undergoing assessment for surgery or angioplasty. People with symptoms of intermittent claudication were not eligible for inclusion.

Types of interventions

Participants were randomly allocated to intravenous infusion of naftidrofuryl or control. Control interventions included conventional conservative therapy, e.g. bed rest, or other pharmacological therapy, or administration of an inert placebo such as isotonic saline.

Types of outcome measures

Primary outcomes

1. All cause mortality.
2. Reduction in pain assessed by analgesic requirements or pain analogue scales.
3. Progression of disease in terms of incidence of surgical reconstruction or amputation.

Secondary outcomes

1. Mean ankle systolic pressure.
2. Drug side effects.

Search methods for identification of studies

Electronic searches

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched May 2012) and the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 4, part of *The Cochrane Library*, www.thecochranelibrary.com. See Appendix 1 for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.thecochranelibrary.com).

Searching other resources

Additional articles were identified by reviewing the references of papers resulting from the initial search. We also contacted all the major pharmaceutical companies that manufacture naftidrofuryl for any unpublished trials.

Data collection and analysis

Selection of trials

Selection of trials was carried out by FBS and their eligibility for inclusion in the review was assessed independently by two of the review authors (FBS and FGRF). For studies in which eligibility was uncertain, a third review author (AWB) carried out a further independent assessment so that a consensus was reached. We

obtained additional information, if required, from the principal investigators of all trials that appeared to meet the inclusion criteria.

Methodological quality

Information on the method of randomisation, blinding and whether an intention-to-treat analysis was performed, was extracted by FBS. Any doubts on the accuracy of information was discussed with a second author (FGRF). The quality of each trial was measured using the five point Jadad scale (Jadad 1996) to assess concealment of allocation, blinding and withdrawals.

Data extraction

Discrete and continuous data concerning outcome measures, extracted by FBS, were recorded on forms developed by the PVD Group.

Statistical analysis

Heterogeneity between trials was assessed subjectively by examining differences in patient populations, interventions and outcome assessments.

The first draft of the review was produced by the first author (FBS) and detailed comments and amendments were made by AWB and FGRF.

RESULTS

Description of studies

Sixteen trials examining the effect of intravenous naftidrofuryl on critical limb ischaemia were identified. Eight studies were not included in the review because they did not fulfil the inclusion criteria, or were of poor quality (*see* Characteristics of excluded studies). The eight included trials were relatively small and involved a total of 269 participants. Three trials were conducted in the UK, three in Germany and one each in France and Austria. There does not appear to be any other trials in progress.

The severity of critical limb ischaemia varied. Four of the trials used participants with rest pain and/or necrosis (Bohme 1994; Heiss 1985; Karnik 1986; Testart 1994), whereas the remainder used participants with rest pain only (Meehan 1982a; Negus 1987; Raftery 1982). In four trials, unsuitability for reconstructive surgery was used as an inclusion criterion. The majority of trials excluded people with other medical conditions. Most trials were conducted on predominantly elderly people of both sexes. In two of the trials, the sex of the people was not stated (Bohme 1994; Heiss 1985).

A combination of naftidrofuryl and other therapy, including haemodilution (Heiss 1985), bed rest and reflex heating (Meehan 1982a) and anti-coagulant medication (Testart 1994), rather than treatment with naftidrofuryl alone was used in some of the trials. The dosage and duration of treatment also varied between the studies. The most commonly used dosage was 800 mg intravenous (i.v.) naftidrofuryl daily, but other trials used 600 mg (Karnik 1986) or 400 mg (Horsch 1998; Meehan 1982a; Raftery 1982). Duration of treatment varied between three and 42 days, but seven days was the most frequent length of treatment.

Three trials compared naftidrofuryl with prostaglandins (Bohme 1994; Karnik 1986; Negus 1987), and four trials against placebo/conservative therapy. In the placebo-controlled trials, three trials used placebo i.v. fluids, either alone (Raftery 1982), with haemodilution (Heiss 1985), or with anti-coagulant medication (Testart 1994). In the Meehan trial, the control group received bed rest and reflex heating. The Horsch trial (Horsch 1998) compared naftidrofuryl with gingko biloba.

Evaluation of pain, either subjectively or objectively using either analogue scales or analgesic consumption was reported in all the trials, as was the reporting of side effects from naftidrofuryl. State/healing of skin necrosis was reported in two studies (Bohme 1994; Heiss 1985). Transcutaneous oxygen pressure was reported in two trials (Bohme 1994; Horsch 1998). There was one report of all-cause mortality (Horsch 1998) and two reports of amputation as a non-fatal outcome (Heiss 1985; Horsch 1998).

Risk of bias in included studies

Eight trials met our inclusion criteria. The methods used in these trials are described in detail in the 'Included Studies Table'. In general, the quality of the included trials was only just adequate. In five trials, the method of treatment allocation was described as 'random', but no further information was available (Heiss 1985; Horsch 1998; Karnik 1986; Meehan 1982a; Raftery 1982). Three trials were randomised by a randomisation list (Bohme 1994); by random numbers (Negus 1987); or by a random numbers table (Testart 1994). Double blinding occurred in four trials (Horsch 1998; Negus 1987; Raftery 1982; Testart 1994). The Meehan trial (Meehan 1982a) was blinded only in respect to outcome. It was unclear whether blinding was used in two trials (Bohme 1994; Karnik 1986). Losses to follow up occurred in most studies, particularly in the Heiss 1985 trial, in which 11 participants out of 40 were lost to follow up.

Effects of interventions

All cause mortality

There was one report of all-cause mortality (Horsch 1998). One patient in the naftidrofuryl group died from bronchopneumonia, which was unrelated to treatment.

Pain evaluation by analogue score

Three trials which evaluated ischaemic pain by an analogue scale (Horsch 1998; Meehan 1982a; Testart 1994) found that pain decreased in those treated by naftidrofuryl compared to the control groups. Although the age of participants and the duration of the Meehan and Testart trials were similar, the dosage of intravenous naftidrofuryl used was twice as high in the Testart trial (800 mg) than in the Meehan trial (400 mg). In the Horsch trial, the dosage was 400 mg daily but duration was 21 days. These data were unable to be analysed in a meta-analysis because no standard deviations were reported (Horsch 1998).

Pain evaluation by analgesic consumption

Three trials evaluated pain using scores based on the amount and type of analgesia required to alleviate pain (Horsch 1998; Testart 1994; Raftery 1982). In two trials (Testart 1994; Raftery 1982), analgesic requirements were lower in the naftidrofuryl treated groups compared with the control groups after seven or eight days respectively, but the difference was statistically non-significant (mean difference (MD) -0.42; (95% confidence interval (CI) -1.19 to 0.35). In the Horsch trial, the number of participants who reduced their analgesic intake was higher in the control group compared with the naftidrofuryl group. The Horsch data were unable to be

included in the meta-analysis since actual values were given rather than mean values and standard deviations.

Rest pain/skin necrosis

Assessment of rest pain, and state of skin necrosis recorded photographically were reported in three trials (Bohme 1994; Heiss 1985; Horsch 1998). Rest pain was evaluated by five grades of severity according to Peitgen (Peitgen 1985) in the Heiss trial, and by changes in clinical symptoms in the Bohme trial. The trial conducted by Bohme used the prostaglandin, alprostadil, as control. In addition to naftidrofuryl or placebo, haemodilution (Rheomacrodex) was used as therapy in both groups in the Heiss trial.

In total, 83.3% of the treated subjects improved compared with 70.6% of the controls. However, improvement in symptoms using naftidrofuryl was not statistically significant in either trial.

In the Horsch trial, rest pain was measured using a visual analogue scale. There was no statistically significant difference in rest pain between the two groups. With regard to skin necrosis, there was a greater reduction in maximal length and width of necrosis in the naftidrofuryl group compared with the gingko biloba group (Horsch 1998).

Incident reconstructive surgery/amputation

It was stated that in four of the trials (Bohme 1994; Heiss 1985; Negus 1987; Raftery 1982) participants were either unsuitable for reconstructive surgery, or had refused surgery. In the remainder, the incidence of reconstructive surgery was not reported. In one trial (Horsch 1998), one patient in the naftidrofuryl group dropped out following femoral amputation.

Only one study examined incidence of amputation after treatment with naftidrofuryl (Heiss 1985). This study found that the incidence of amputation within 45 days after hospitalisation was 7.5%, which increased to 21% after a follow-up period of a maximum of two years. It was noted that only one of the nine participants who eventually underwent amputation had been treated by naftidrofuryl.

Mean ankle systolic pressure

Mean ankle systolic pressures were measured before and after treatment in two trials. In the Bohme trial (Bohme 1994), ankle pressure in the naftidrofuryl group rose significantly to 40 mm Hg (standard deviation (SD) 20) during treatment from the initial level of 17 mm Hg (SD 19), $P < 0.05$, whereas the ankle systolic pressures of the group allocated to alprostadil dropped slightly from 43 mm Hg (SD 41) to 39 mm Hg (SD 41). There were no significant differences in ankle systolic pressure levels after treatment between the naftidrofuryl and control groups MD 1.00 (95% CI -30.2 to 32.2). However, the mean ankle pressure was much lower in the naftidrofuryl group than in the alprostadil group before treatment commenced. In the Karnik trial (Karnik 1986), ankle systolic pressures were slightly higher in the prostacyclin group compared to those treated by naftidrofuryl. After one week of treatment, there were no significant changes in either group.

Side effects

In the Bohme trial (Bohme 1994), one patient in each of the treatment groups suffered dizziness during infusion of the drugs.

Systemic side effects were reported in 35% of participants receiving naftidrofuryl/rheomacrodex therapy at a dosage of 800 mg daily, and in 32% of participants randomised to placebo/rheomacrodex in the Heiss study (Heiss 1985). These included renal insufficiency, nausea/vomiting, pruritus (itching), pulmonary congestion, somnolence (drowsiness), dyspnoea and depression. Seven participants in the naftidrofuryl group also developed thrombophlebitis at the injection site.

Minor side effects were recorded in three participants who received naftidrofuryl in the Karnik trial (Karnik 1986). These consisted of flushing (two participants) and pain in the extremities (one patient).

Nine cases of thrombophlebitis were noted out of a total of 323 infusions in the Meehan trial (Meehan 1982a).

A minor infection and a thrombosis occurred at the cannulation site of two participants (Negus 1987).

Side effects were not reported in the Raftery trial (Raftery 1982).

No specific side effects were mentioned in the Testart study (Testart 1994), but the participants were observed as showing 'good overall tolerance' of naftidrofuryl.

In the Horsch trial (Horsch 1998), one patient dropped out of the study because of a skin reaction to naftidrofuryl. Intravenous gingko biloba was well tolerated by all participants in that group.

DISCUSSION

The trials included in this review involved a small number of participants and there was substantial variation in both treatment dosage of naftidrofuryl and in outcome measures. The duration of intravenous treatment was also very short. There was no clear indication that short-term intravenous naftidrofuryl significantly improved either symptoms of ischaemic rest pain or skin necrosis. Although participants had reduced pain after treatment in comparison with controls, this was also statistically non-significant.

Similarly, there was little clinical benefit from treatment by naftidrofuryl on ankle systolic pressures which if increased would indicate an improvement in circulation. This lack of effect may be due to the small numbers of participants, and the short duration of treatment.

Side effects were generally local and mild. However, in the trial conducted by Heiss (Heiss 1985), two participants were withdrawn from treatment using naftidrofuryl because of renal insufficiency.

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of these trials, there is no clear indication of clinical benefit from using intravenous naftidrofuryl in the treatment of critical limb ischaemia. Following a review by the UK and other European regulatory authorities, naftidrofuryl in the form of 200 mg/10 ml ampoules was withdrawn in 1995 as an intravenous treatment for severe peripheral arterial disease. This was because the risks of cardiac and neurological side effects were found to outweigh the possible benefit of intravenous naftidrofuryl in peripheral arterial disease.

Implications for research

Although intravenous naftidrofuryl has been withdrawn as a treatment for severe peripheral arterial disease, oral treatment with this drug is permitted. In many of the trials included in this review assessing intravenous naftidrofuryl, oral naftidrofuryl was continued after the intravenous phase was completed. A systematic review of oral naftidrofuryl in the treatment of critical limb ischaemia is required.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bohme 1994

Methods	Study design: Randomised controlled trial. Method of randomisation: Randomisation list, unclear if any blinding. Exclusions post-randomisation: Not stated. Losses to follow up: 3 lost to assessment of rest pain follow up.
Participants	Country: Germany. Participants: 30 randomised. Age: median 77 years in naftidrofuryl group; 70 years in alprostadil group. Sex: Not stated. Inclusion criteria: Stage III and IV Fontaine PAD lasting more than 4 weeks. Stage III patients underwent neurological examination prior to randomisation, vascular surgery, catheter techniques, fibrinolysis not possible. Exclusion criteria: decompensated heart failure, poorly controlled hypertension (systolic more than 200 mmHg), unstable heart disease, renal failure (creatinine more than 21.2 mg/ 100 ml).
Interventions	Treatment: 400 mg intravenous naftidrofuryl twice daily. Control: 40 g intravenous alprostadil twice daily. Duration: 21 days.
Outcomes	State/healing of necrosis recorded by photograph at 7, 14 and 21 days, pain assessment, doppler pressures, transcutaneous oxygen pressures, side effects.
Notes	Wash-out phase of 2 to 4 days preceding treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Heiss 1985

Methods	Study design: Randomised, double blind controlled trial. Method of randomisation: Not stated. Exclusions post-randomisation: Not stated. Losses to follow up: 4 lost in infusion phase, 7 in oral phase.
Participants	Country: Germany. Participants: 40 randomised. Age: mean 73.9 years in haemodilution/naftidrofuryl group; 70.3 years in haemodilution/placebo group. Sex: Not stated. Inclusion criteria: Stage IV Fontaine PAD, no indication for surgery or had refused surgery. Exclusion criteria: acute arterial occlusion, MI within previous 6 months, cardiac insufficiency at rest, renal insufficiency (creatinine more than 1.5 mg/ 100 ml), defibrinating, anti-aggregatory or anti-coagulant medication, non-digitalis induced conduction disorder, vascular surgery or sympathectomy within previous 6 months.
Interventions	Treatment: 800 mg intravenous naftidrofuryl + hypervolaemic haemodilution (Rheomacrodex) therapy, then 600 mg naftidrofuryl orally. Control: intravenous placebo + Rheomacrodex. Duration: 42 days
Outcomes	State/healing of necrosis recorded by photograph at 7, 14, 21 days, analgesic consumption, pain evaluation, doppler ultrasound, oscillography, ECG, side effects.
Notes	Wash-out phase of 2 to 4 days preceding treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Horsch 1998

Methods	Study design: Stated as randomised, double blind. Method of randomisation: Not stated. Exclusions post randomisation: Not stated. Losses to follow up: 6.
Participants	Country: Germany. Participants: 40 randomised. Age: median 77.7 years in naftidrofuryl group; 70.0 years in gingko biloba group.

Horsch 1998 *(Continued)*

	Sex: male and female. Inclusion criteria: Stage III and IV Fontaine angiographically verified PAD. Exclusion criteria: ulcers exposing bones and sinew, indication for surgery, fibrinolysis or sympathectomy, myocardial infarction during previous 6 months, heart disease NYHA III or IV, severe high blood pressure (diastolic pressure more than 120 mmHg); severe kidney insufficiency (creatinine more than 2.0 mg/ 100 ml); severe liver function problems (transaminase increase more than 3 times normal), respiratory insufficiency, impairment through orthopaedic diseases (e.g.. arthritis); venous insufficiency at Grade II (Basler classification); poorly controlled diabetes mellitus; anaemia (haemoglobin less than 10 g/100 ml); expected poor compliance. Medications with similar indications to the test substances were also excluded. Only essential medication was allowed. Treatment with nitrates and calcium antagonists were permitted as long as they were taken right from the start of the study.
Interventions	Treatment: 400 mg intravenous naftidrofuryl. Control: 200 mg Ginko Special Extract EGb 761. Duration: 21 days.
Outcomes	Night pain assessment using analogue scores, transcutaneous oxygen pressures, amount and size of ulcers and necrosis, analgesic use, side effects, all cause mortality.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Karnik 1986

Methods	Study design: Randomised cross-over study. Method of randomisation: Not stated. Blinding unclear. Exclusions post randomisation: Not stated. Losses to follow up: one.
Participants	Country: Austria. Participants: 20 randomised. Age: Mean 74 years naftidrofuryl group, 67 years prostacyclin group. Sex: male and female. Inclusion criteria: Stage III and IV Fontaine PAD of at least 4 weeks duration. Exclusion criteria: stenoses/occlusion of iliac arteries.
Interventions	Treatment: 600 mg intravenous naftidrofuryl. Control: 5 ng/kg/min intravenous prostacyclin.

Karnik 1986 *(Continued)*

	Duration: 7 days naftidrofuryl, 5 days prostacyclin.
Outcomes	Pain + trophic evaluation, resting calf blood flow, venous plethysmography, reactive hyperaemia test, doppler systolic blood pressure, side effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Meehan 1982a

Methods	Study design: Stated as randomised. Method of randomisation: Not stated, single blind. Exclusions post randomisation: Not stated. Losses to follow up: 3.
Participants	Country: Scotland. Participants: 40 randomised. Age: mean 73 years naftidrofuryl group, 67 years conservative treatment group. Sex: male and female. Inclusion criteria: rest pain due to PAD and assessed for vascular reconstruction. Exclusion criteria: diabetes, previous reconstructive surgery, sympathectomy.
Interventions	Treatment: 400 mg intravenous naftidrofuryl daily + 600 mg oral naftidrofuryl daily + bed rest + reflex heating. Control: Bed rest + reflex heating. Duration: 7 days.
Outcomes	Changes in rest pain symptoms, mental state and well-being assessment by analogue scales, side effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Negus 1987

Methods	Study design: Randomised controlled trial. Method of randomisation: random numbers, double blind. Exclusions post randomisation: Not stated. Losses to follow up: 3.
Participants	Country: England. Participants: 32 randomised. Age: mean 70 years naftidrofuryl group, 68 years prostacyclin group. Sex: male and female. Inclusion criteria: Ischaemic rest pain requiring analgesics, unsuitable for reconstructive surgery. Exclusion criteria: Not stated.
Interventions	Treatment: 0.02 mg/kg/min naftidrofuryl by arterial catheter. Control: 8 ng/kg/min prostacyclin by arterial catheter. Duration: 3 days.
Outcomes	Estimation of skin perfusion (histamine flare), relief of rest pain, analgesic consumption, amputation rate, ABPI, side effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Raftery 1982

Methods	Study design: Stated as randomised. Method of randomisation: Not stated, double blind. Exclusions post randomisation: Not stated. Losses to follow up: None.
Participants	Country: England. Participants: 30 randomised. Age: mean 66 years naftidrofuryl group, 64 years placebo group; sex: male and female. Inclusion criteria: rest pain associated with PAD, patients unsuitable for reconstructive surgery. Exclusion criteria: diabetes mellitus, congestive cardiac failure, collagen disease, previous medication with naftidrofuryl, gangrene more than 1 digit, ischaemic ulceration.
Interventions	Treatment: 400 mg intravenous naftidrofuryl daily + 100 mg naftidrofuryl orally daily. Patients who showed improvement after 7 days were given 200 mg orally for maximum 3 months.

Raftery 1982 *(Continued)*

	Control: identical placebo. Duration: 7 days.
Outcomes	Analgesic consumption, improvement after 7 days.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Testart 1994

Methods	Study design: Randomised controlled trial. Method of randomisation: Four-factor random number table, double blind. Exclusions post randomisation: Not stated. Losses to follow up: 3.
Participants	Country: France. Participants: 37 randomised. Age: mean 69.8 years. Sex: male and female. Inclusion criteria: permanent ischaemia associated with PAD with or without trophic disorders. Exclusion criteria: Not stated.
Interventions	Treatment: 800 mg intravenous naftidrofuryl daily + anticoagulant therapy (heparin or vitamin K antagonists). Control: identical intravenous placebo + anticoagulant therapy. Duration: 8 days.
Outcomes	Assessment of pain using analogue scales, consumption of analgesics, clinical evaluation, side effects.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

ECG: electromyocardiograph
MI: myocardial infarction
NYHA: New York heart association

PAD: peripheral arterial disease

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bianchi 1974	This trial was not restricted to patients with critical limb ischaemia and included some patients with intermittent claudication It was also not stated if the study was randomised.
Fellmann 1989	This study was probably not a randomised trial. In addition, the group of 30 patients treated with naftidrofuryl included 11 patients with intermittent claudication. There was no separate analysis on patients with symptoms of critical limb ischaemia.
Greenhalgh 1981	This study of 21 patients was not a randomised controlled trial. The placebo was given first and then naftidrofuryl was subsequently administered over an eight day period.
Horsch 1988	This trial simply compares two dose regimes of naftidrofuryl with no control group.
Meehan 1982b	Although this appeared to be an adequately designed randomised controlled trial of naftidrofuryl versus conservative therapy, measurement of tissue pH was the only outcome reported. This was considered to have little relevance in the assessment of the clinical efficacy of naftidrofuryl in the treatment of critical limb ischaemia. This study was not therefore included in the review.
Mustapha 1984	This study was conducted on 20 patients with ischaemia of the lower limb and a group of healthy volunteers. There was, however, no randomisation of treatment in patients with PAD and for this reason the study was considered unsuitable for inclusion into the review.
Taggart 1989	Twenty patients were randomised to either naftidrofuryl or saline. Each group, however, was not confined to those with rest pain but included seven patients with intermittent claudication, which made the trial unsuitable for inclusion in the review.
Wong 1980	This was not a randomised controlled trial. The study consisted of treatment with naftidrofuryl, analgesia and bed rest. There was no control group and all patients received the same treatment.

PAD: peripheral arterial disease

DATA AND ANALYSES

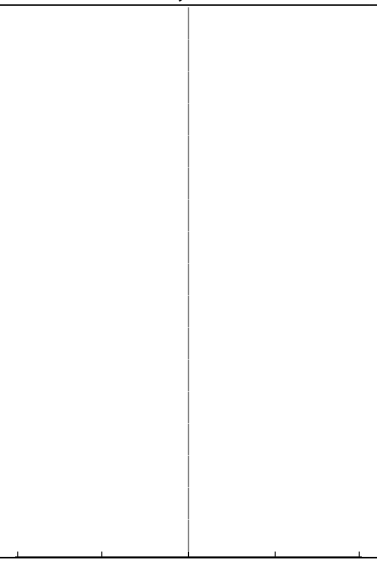
Comparison 1. Naftidrofuryl versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain evaluation by analogue scale	3	114	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Naftidrofuryl versus gingko	1	40	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Naftidrofuryl versus placebo	2	74	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Pain evaluation by analgesic consumption	3	107	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-1.19, 0.35]
2.1 Naftidrofuryl versus gingko	1	40	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Naftidrofuryl versus placebo	2	67	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-1.19, 0.35]
3 Mean ankle systolic pressure	2	33	Mean Difference (IV, Fixed, 95% CI)	1.0 [-30.20, 32.20]

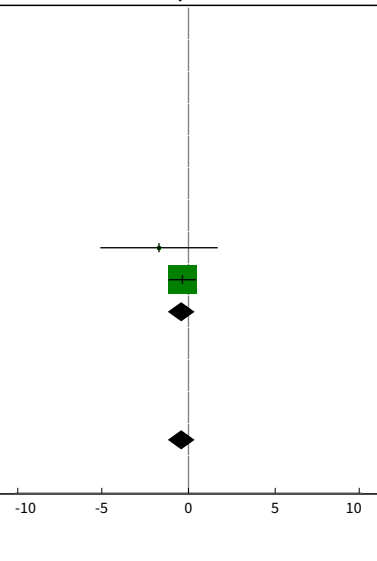
Analysis 1.1. Comparison 1 Naftidrofuryl versus control, Outcome 1 Pain evaluation by analogue scale.

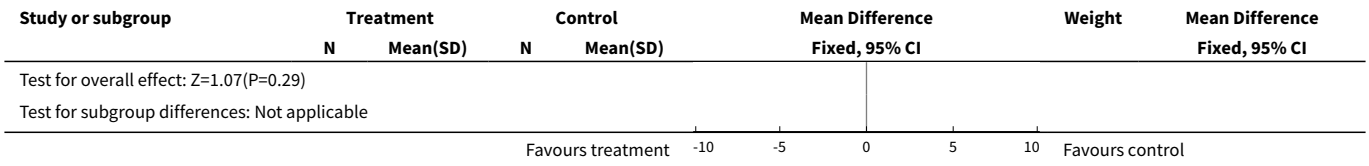
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 Naftidrofuryl versus gingko							
Horsch 1998	20	2.7 (0)	20	3.2 (0)			Not estimable
Subtotal ***	**20**		**20**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.1.2 Naftidrofuryl versus placebo							
Meehan 1982a	22	39 (0)	15	67 (0)			Not estimable
Testart 1994	20	18 (0)	17	28 (0)			Not estimable
Subtotal ***	**42**		**32**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**62**		**52**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



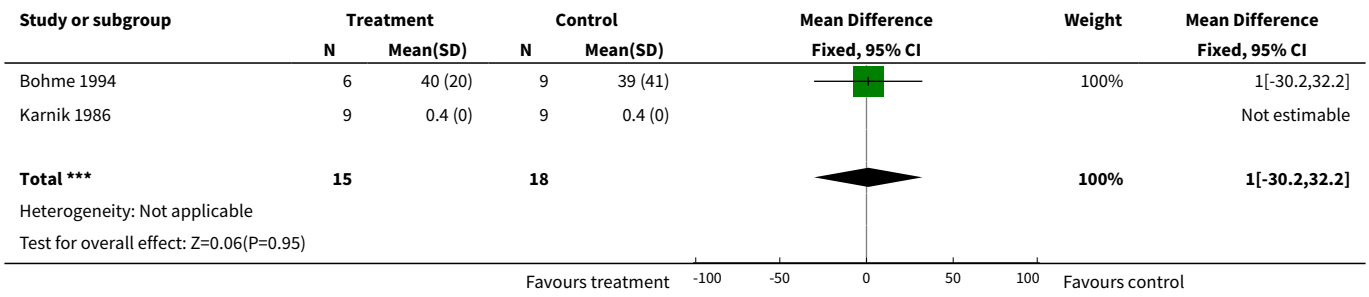
Analysis 1.2. Comparison 1 Naftidrofuryl versus control, Outcome 2 Pain evaluation by analgesic consumption.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 Naftidrofuryl versus gingko							
Horsch 1998	20	9 (0)	20	14 (0)			Not estimable
Subtotal ***	**20**		**20**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.2.2 Naftidrofuryl versus placebo							
Raftery 1982	16	3.7 (4.1)	14	5.4 (5.2)		5.23%	-1.7[-5.08,1.68]
Testart 1994	20	0.4 (1)	17	0.8 (1.4)		94.77%	-0.35[-1.14,0.44]
Subtotal ***	**36**		**31**			**100%**	**-0.42[-1.19,0.35]**
Heterogeneity: Tau^2=0; Chi^2=0.58, df=1(P=0.45); I^2=0%							
Test for overall effect: Z=1.07(P=0.29)							
Total ***	**56**		**51**			**100%**	**-0.42[-1.19,0.35]**
Heterogeneity: Tau^2=0; Chi^2=0.58, df=1(P=0.45); I^2=0%							





Analysis 1.3. Comparison 1 Naftidrofuryl versus control, Outcome 3 Mean ankle systolic pressure.



APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor Arteriosclerosis, this term only	893
#2	MeSH descriptor Arteriolosclerosis, this term only	0
#3	MeSH descriptor Arteriosclerosis Obliterans, this term only	70
#4	MeSH descriptor Atherosclerosis, this term only	370
#5	MeSH descriptor Arterial Occlusive Diseases, this term only	750
#6	MeSH descriptor Intermittent Claudication, this term only	700
#7	MeSH descriptor Ischemia, this term only	740
#8	MeSH descriptor Peripheral Vascular Diseases explode all trees	2125
#9	MeSH descriptor Vascular Diseases, this term only	376
#10	(atherosclero* or arteriosclero* or PVD or PAOD or PAD)	16465
#11	(arter*) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	4829
#12	(vascular) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	1326
#13	(vein*) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	703

(Continued)

#14	(veno*) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	972
#15	(peripher*) near (*occlus* or steno* or obstuct* or lesio* or block* or obliter*)	1340
#16	peripheral near3 dis*	3124
#17	arteriopathic	6
#18	(claudic* or hinken*)	1416
#19	(isch* or CLI)	16556
#20	dysvascular*	15
#21	leg near4 (obstruct* or occlus* or steno* or block* or obliter*)	180
#22	limb near4 (obstruct* or occlus* or steno* or block* or obliter*)	229
#23	(lower near3 extrem*) near4 (obstruct* or occlus* or steno* or block* or obliter*)	133
#24	(aort* or iliac or femoral or popliteal or femoropop* or fempop* or crural) near3 (obstruct* or occlus*)	319
#25	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24)	38109
#26	MeSH descriptor Nafronyl, this term only	98
#27	MeSH descriptor Furans, this term only	191
#28	(naftidrofur* or nafronyl* or naftifurin or naftirofuryl or naphthydrofur* or naphthohydrofur*)	242
#29	(praxilene or dusodril or LS 121 or LS121 or artocoron or EU 1806 or EU1806 or gevatran or iridus or sodipryl or di-actane or vascuprax)	500
#30	artocoron or azunaftil or esedril or luctor or naftodril or naftiratiopharm or stimlor or vasolate	3
#31	(#26 OR #27 OR #28 OR #29 OR #30)	849
#32	(#25 AND #31)	112

WHAT'S NEW

Date	Event	Description
19 June 2012	Review declared as stable	This Cochrane Review is no longer being updated because intravenous naftidrofuryl was withdrawn from the market as a treatment for severe peripheral arterial disease in 1995. Intravenous naftidrofuryl was withdrawn because of reported side effects.

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 2, 2000

Date	Event	Description
4 May 2012	New citation required but conclusions have not changed	Searches re-run, no new trials found. Minor copy edits made. The review was assessed as up to date. Conclusions not changed.
4 May 2012	New search has been performed	Searches re-run, no new trials found. The review was assessed as up to date.
3 September 2010	New search has been performed	Searches re-run. No new trials found. The review was assessed as up to date.
30 July 2008	New search has been performed	Searches re-run. No new trials found. The review was assessed as up to date.
30 May 2008	Amended	Converted to new review format.
5 January 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Felicity Smith: Identified potentially relevant trials, assessed their eligibility for inclusion in the review, assessed quality of trials, extracted data, and wrote the text of the review.

Gerry Fowkes: Assessed trial eligibility for inclusion in the review and addressed questions concerning accuracy of information available in trial papers.

Andrew Bradbury: Read and provided comments on the review and acted as arbiter in cases where study eligibility was uncertain.

The Peripheral Vascular Diseases Review Group assisted with developing the search strategy and running the searches for trials for this review.

DECLARATIONS OF INTEREST

Felicity Smith: Supplementary financial support was provided by Merck (Lipha Pharmaceuticals) for the original review. The review was conducted independently without input from Merck other than the provision of references and protocols. Subsequent updates were completed without financial support.
Gerry Fowkes: None known
Andrew Bradbury: None known

SOURCES OF SUPPORT

Internal sources

- University of Edinburgh, UK.

External sources

- Chief Scientist Office, Government Health Directorates, The Scottish Government, UK.

  The PVD Group editorial base is supported by the Chief Scientist Office.
- Merck (Lipha Pharmaceuticals), Middlesex, UK.

Supplementary financial support was provided by Merck (Lipha Pharmaceuticals) for the original review. The review was conducted independently without input from Merck other than the provision of references and protocols. Subsequent updates were completed without financial support.

INDEX TERMS

Medical Subject Headings (MeSH)

Amputation, Surgical [statistics & numerical data]; Extremities [*blood supply]; Infusions, Intravenous; Ischemia [*drug therapy]; Nafronyl [administration & dosage] [*therapeutic use]; Pain [drug therapy]; Pain Measurement [drug effects]; Peripheral Vascular Diseases [*drug therapy]; Randomized Controlled Trials as Topic; Vasodilator Agents [administration & dosage] [*therapeutic use]

MeSH check words

Female; Humans; Male