NIHR Health Technology Assessment programme funded project

NHS National Institute for Health Research

A systematic review and meta analysis of the clinical effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for symptom management of intermittent claudication.

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OBJECTIVES

Assess clinical effectiveness of cilostazol, naftidrofuryl oxalate, pentoxifylline or inositol nicotinate for symptom management of intermittent claudication.

PICO

Population People with IC due to PAD whose symptoms continue despite a period of conservative management.

Intervention Cilostazol, naftidrofuryl oxalate, pentoxifylline or inositol nicotinate.

Comparators Placebo, or intervention drugs compared with each other.

Outcomes Maximal walking distance (MWD), pain-free walking distance (PFWD), adverse events, cardiovascular events, mortality, and health-related quality of life (HRQoL).

SEARCH: April-June 2010

1867 unique titles retrieved

•Databases were searched from inception.

•MEDLINE, EMBASE, Cochrane Library, CINAHL, Web of Science, Conference Proceedings, BIOSIS, National Research Register, and MetaRegister of Clinical Trials.

STUDY SELECTION

•Pre-specified inclusion/exclusion criteria according to PICO.

•One reviewer screened titles, abstracts and full text.

24 RCTs included

Cilostazol 200mg vs placebo: 11 trials
Naftidrofuryl oxalate 600mg vs placebo: 4 trials
Naftidrofuryl oxalate 300mg vs placebo: 1 trial
Pentoxifylline 1200mg vs placebo: 9 trials
Inositol nicotinate 4g vs placebo: 3 trials
Cilostazol 200mg vs pentoxifylline 1200mg: 3 trials
Cilostazol 200mg (with/without supervised exercise) vs usual care (with/without supervised exercise): 1 trial

DATA EXTRACTION & QUALITY ASSESSMENT

•One reviewer extracted using a tailored form, a second checked.

•Risk of bias criteria from the NHS Centre for Reviews and Dissemination Report No.4[1]

•Elements of study design specifically relevant to studies of PAD: criteria adapted from European Medicines Agency research recommendations.[2]

RESULTS

•Not all studies reported all outcomes

•Follow up times varied; most only had follow-up periods up to 24 weeks.

•Some studies expressed data in incompatible ways

•Some studies did not use appropriate methods to measure walking distances e.g. used patient report instead of treadmill tests

CONCLUSIONS

Network meta analysis suggests that naftidrofuryl oxalate is the most effective treatment for increasing MWD and PFWD in PAD at 24 weeks.

IMPLICATIONS

Naftidrofuryl oxalate and cilostazol appear to be effective treatments for the symptomatic relief of PAD.

OTHER OUTCOMES

Mortality: no significant differences in mortality rates between treatment groups. None directly attributed to intervention drugs. However, follow-up times were short and few deaths occurred.

Cardiovascular events: no significant differences between treatment groups within trials.

HRQoL: no one measure used to assess all four treatments. Very limited data which shows some improvements in some domains for cilostazol and naftidrofuryl oxalate, but suggests no improvements for pentoxifylline.

Adverse events: some trials had unclear AE definitions or only reported AEs which lead to discontinuation, precluding meta-analysis. Naftidrofuryl oxalate, pentoxifylline and inositol nicotinate trials reported no significant differences vs pacebo. Some evidence of increased headaches, diarrhoea, and palpitations with cilostazol vs placebo.

NETWORK META ANALYSIS MWD & PFWD

Not all trials were included due to incompatibility of study characteristics and availability of data. In most trials, the comparator was placebo. No studies of inositol nicotinate were includable. Estimation was performed using Markov chain Monte Carlo. See full report for details.[3]

Figure 1. Network of evidence used in network meta analysis

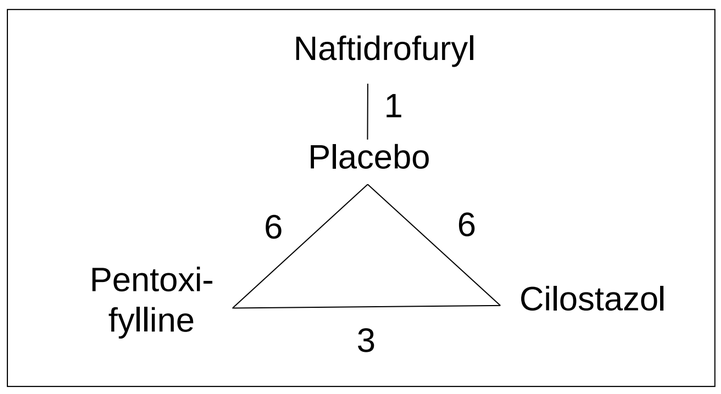

Table1. Means and 95% credible intervals for the ratio of the mean change from baseline MWD and PFWD compared to placebo

Treatment	MWD Mean, 95% Credible Interval	PFWD Mean, 95% Credible Interval
Cilostazol	1.245, (1.114, 1.400)	1.133, (1.024, 1.258)
Naftidrofuryl oxalate	1.601, (1.199, 2.142)	1.491, (1.225, 1.810)
Pentoxifylline	1.106, (0.985, 1.242)	1.090, (0.980, 1.216)

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(1) http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf
(2) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003341.pdf
(3) Full report available at http://www.hta.ac.uk/project/2246.asp

This work was funded by the UK National co-ordinating Centre for Health Technology Assessment (NCCHTA). The views and opinions expressed are those of the authors and do not necessarily reflect those of the UK Department of Health. Project Number 09/92/01.