Chelation therapy for intermittent claudication and coronary heart disease

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Authors' objectives
To address the question, what is the effectiveness and cost of ethylene diamine tetra-acetic acid (EDTA) chelation therapy for the treatment of patients with intermittent claudication (IC) or coronary heart disease (CHD).

Searching
MEDLINE (from 1966 to July 2001) and EMBASE (from 1980 to July 2001) were searched for studies in any language. For RCTs, the search strategy of the NHS Centre for Reviews and Dissemination (see Other Publications of Related Interest no. 1) was used, along with the following index and textwords: exp 'chelation therapy', 'EDTA', 'ethylenediamine tetraacetic acid', exp 'chelating agents', exp 'editic acid'. Cohort studies were sought by searching for 'cohort studies' and exp 'case control studies'. Additional searches were conducted during April 2001. The sources searched were CINAHL, Grateful Med, the Cochrane Library, CHID Online, the NCCAM website (the National Center for Complementary and Alternative Medicine), ISI Web of Science (via MIMAS) and BioMedNet. Internet search engines (Google, Dogpile) were also utilised.

The reference lists of review articles, meta-analyses and RCTs were searched. In addition, handsearches of specialised and general journals (JAMA, New England Journal of Medicine, BMJ, Lancet, Circulation, Atherosclerosis, and Annals of Internal Medicine) were conducted for the period September 2000 to July 2001. Practitioners of chelation therapy and colleagues were consulted. Economic analysis papers were also sought. Full details of the search were provided in the report.

Study selection
Study designs of evaluations included in the review
The inclusion criteria stated randomised controlled studies; other studies were acceptable if they involved more than 100 people. Only RCTs were identified.

Specific interventions included in the review
The inclusion criteria stated that chelation therapy had to involve repeated intravenous administration of EDTA solutions containing at least 1 g EDTA per infusion, and at least 10 infusions in total. For randomised controlled trials (RCTs), the comparators were placebos or other interventions that were not chelation therapy; for case-control studies, the comparators were matched untreated controls. Studies involving chelation therapy with agents other than EDTA were excluded.

In the IC studies, the treatment consisted of an infusion of EDTA with heparin in Ringers solution, sodium chloride or magnesium chloride. The control groups also received the additional treatments. Where specified, the treatments comprised 10 to 20 infusions over 31 days to 10 weeks. Full details of the regimens were provided in the report. In the CHD studies, the treatment consisted of EDTA in solution with other agents (further details provided) for 20 to 33 treatments. The control groups were given the same treatment, but without EDTA or isotonic saline solution. All participants also received oral multivitamins.

Participants included in the review
Participants with atherosclerosis causing peripheral arterial disease with IC, or CHD were included. Participants with atherosclerotic cerebral disease were excluded. In the included IC studies, the mean ages were between 47 and 67 years, and both men and women were included. The patients had IC and pain-free walking distances of 50 to 200 m (where given). In the included CHD studies, the participants were men and women aged 21 years or older, to 64 years. The patients had angina of effort, proven ischaemic heart disease and stable angina or angiographically confirmed CHD. Candidates for revascularisation, or those who had been treated previously with chelation therapy, were excluded.

Outcomes assessed in the review
The inclusion criteria stated a measure of effectiveness, determined using an exercise test. Studies were excluded if no objective measure of outcome was reported.

The primary outcome in the included IC studies was walking distance, as tested by Master's two-step test, a bicycle exercise test, and pain-free and maximal walking distances on a treadmill. Measurements of the differences between baseline and various time points were used, as well as comparisons of distances between treatment and placebo groups. The follow-up time was up to 6 months. Summary walking distances were calculated, together with 95% confidence intervals (CIs), for the treatment and control groups in the individual trials. The secondary outcome measures in the studies included blood-pressure measurements, subjective evaluation of patients, other physiological measures, quality of life and patient assessment of treatment.

The primary outcomes in the included CHD studies were comparisons of exercise stress testing and 'ischaemic score', in some cases, compared with baseline measures (more details in report) or measures of 'work' (increase in time of work duration). The follow-up times were 3 to 12 months. Summary 'time to ischemia' or 'work' and 95% CIs were calculated for the treatment and control groups in each study. The secondary outcomes included well-being, side-effects, laboratory measures and clinical events.

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

Assessment of study quality
The studies were assessed using a number of criteria: the methods of randomisation and concealment of allocation; comparison of the baseline characteristics of the groups; whether the groups were treated similarly except for the randomisation intervention; the extent of crossover; losses to follow-up; intention-to-treat analysis; blinding of assessment; and whether the conclusions matched the results. In addition, RCTs were scored on a scale based on the scale of Jadad et al.(see Other Publications of Related Interest no. 2). The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
Two reviewers independently extracted the data from all the included studies into predefined tables. There was one discrepancy, which was resolved by discussion.

Methods of synthesis
How were the studies combined?
The results of the studies were tabulated and combined in a narrative discussion.

How were differences between studies investigated?
The authors used tables and a narrative discussion to describe the differences between the studies.

Results of the review
Five RCTs were included: 3 on IC (201 participants) and 2 on CHD (100 participants).

For IC, all 3 RCTs were underpowered and one was very small (n=10). This small RCT showed a statistically-significant difference in favour of chelation therapy for the primary outcome measure, whereas the other 2 RCTs showed no significant difference. Small effect sizes in favour of chelation therapy were observed in some secondary outcome measures. A further study could be justified, as some of the secondary outcomes in one study were in favour of chelation therapy. Adverse events and side-effects were observed, but neither of the 2 larger studies reported a significant difference between the treatment and control groups. For CHD neither of the 2 RCTs included showed a statistically-significant difference in the primary outcome measures.
Cost information
The authors also attempted an economic analysis. Only one potentially useful economic study was found, but the authors were unable to obtain this (see Other Publications of Related Interest no. 3). They estimated the possible costs of an infusion course together with initial medical assessment (in the context of the NHS) depending on the number of treatments needed: between £1,330 and £1,535 for 10 infusions, between £2,410 and £2,615 for 20 infusions, and between £4,570 and £4,775 for 40 infusions.

Authors' conclusions
Currently, there is little objective evidence that chelation therapy is effective for CHD or IC. Conversely, there is little evidence that chelation therapy does harm.

CRD commentary
This was a detailed and thorough review with clear aims. The search strategy was good. The criteria for the quality assessment were well described, as were details of the included studies. Much additional information was provided in the appendices, and the authors also reviewed the quality of published systematic reviews on chelation therapy. A narrative synthesis seems to have been appropriate. The authors’ conclusions are supported by the evidence presented.

Implications of the review for practice and research
Practice: The authors state that the recommendation for the use of chelation therapy for IC and CHD is not supported (by the evidence).

Research: The authors state that in order to establish the true level of the effectiveness of chelation therapy, large numbers of patients would need to be enrolled in an RCT. However, they comment that this is very unlikely to be carried out.

Bibliographic details

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Other publications of related interest

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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.