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A systematic review and meta-analysis of alpha-lipoic acid in the treatment of diabetic peripheral neuropathy

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Review published: 2012.

CRD summary

The authors concluded that intravenous alpha lipoic acid (300 to 600mg per day, for two to four weeks) was safe and could significantly improve nerve conduction velocity and positive neuropathic symptoms, for patients with diabetic peripheral neuropathy, but the evidence was mainly of poor quality. The conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives

To evaluate the effectiveness and safety of 300 to 600mg of alpha lipoic acid, given intravenously, for diabetic peripheral neuropathy.

Searching

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and CBM were searched for studies published between 1966 and December 2011. There were no language limitations, and search terms were reported.

Study selection

Randomised controlled trials (RCTs) that assessed the effects of intravenous alpha lipoic acid, 300 to 600mg per day, for patients with diabetic peripheral neuropathy, were eligible for inclusion. The primary outcomes were efficacy (defined as improvement in symptoms, tendon reflex, and nerve conduction velocities) and various measures of nerve conduction velocity. Secondary outcomes were adverse events.

About half of the included trials assessed the combination of alpha lipoic acid and methylcobalamin versus methylcobalamin alone. The other half assessed combinations of alpha lipoic acid with prostaglandin E1, ginkgo biloba leaf extract injection, vitamin B1, ligustrazine, or cilostazol, versus the same intervention without alpha lipoic acid. The mean age of the patient groups ranged from 43.9 to 66 years. The daily dose of alpha lipoic acid was 600mg in most trials; one trial used 450mg and one used 300mg. Trials lasted from 14 to 28 days.

The authors did not state how many reviewers assessed studies for inclusion.

Assessment of study quality

Two reviewers independently assessed trial quality, using a modified Jadad scale, for the adequacy of allocation concealment, randomisation, blinding, handling of withdrawals, and intention-to-treat analysis. Disagreements were resolved by discussion.

Data extraction

Two reviewers independently abstracted the baseline characteristics of the patients, the doses of alpha lipoic acid, and the data needed to calculate odds ratios and mean differences, with 95% confidence intervals.

Methods of synthesis

Pooled odds ratios (for binary outcomes) or weighted mean differences (for continuous outcomes), with 95% confidence intervals, were calculated using fixed-effect meta-analysis, if there was no evidence of statistical heterogeneity, or random-effects meta-analysis, if evidence was found. Statistical heterogeneity was assessed using I^2 and X^2 .

Sensitivity analyses were used to explore the effects of changing the meta-analysis approach (fixed-effect versus random-effects) and excluding trials with extreme results. Publication bias was assessed in a funnel plot.

Results of the review

Fifteen RCTs were included, with 1,058 patients (range 38 to 96). Overall the quality of the trials was poor; most had small samples and did not report their methods of randomisation.

Compared with control, alpha lipoic acid was associated with a significant improvement in efficacy (OR 4.03, 95% CI 2.73 to 5.94; $I^2=0$; nine RCTs), and nerve conduction velocity outcomes. The most common side-effects, for alpha lipoic acid, were stomach upset (three cases) and minor stretching (one case).

The main effect sizes did not change in the sensitivity analyses. No evidence of publication bias was found.

Authors' conclusions

Intravenous alpha lipoic acid (300 to 600mg per day, for two to four weeks) was safe and could significantly improve nerve conduction velocity and positive neuropathic symptoms, for patients with diabetic peripheral neuropathy, but the evidence was mainly of poor quality.

CRD commentary

The review addressed a clear question; the eligible study designs, interventions, and outcome measures were specified. Four major databases were searched, without any language limitations, minimising language bias. Little effort was made to search for grey literature; some relevant trials could

have been missed. Trial quality was assessed by two people minimising reviewer error and bias, but it was unclear whether similar processes were used for study selection and data extraction. Quality was assessed using appropriate criteria and the overall quality of the trials was poor; the results for each criterion were not reported. Statistical heterogeneity was assessed and the data were combined using appropriate meta-analysis.

The authors' conclusions reflect the evidence presented. The limited trial quality has to be balanced against the size and consistency of the observed effects; the conclusion that alpha lipoic acid could improve the symptoms of neuropathy is likely to be reliable.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further randomised, double-blind, placebo-controlled trials, assessing the effects of alpha lipoic acid on objective improvement, in nerve conduction velocities, in patients with diabetic peripheral neuropathy, were needed.

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Record Status

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CRD has determined that this article meets the DARE scientific quality criteria for a systematic review.

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