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Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials

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Review published: 2005.

CRD summary

This review assessed the effectiveness of vitamin B12 for the treatment of diabetic neuropathy. The authors concluded that vitamin B12 treatment appears to improve symptomatic relief more than electrophysiologic results. This conclusion should be viewed as tentative given the poor quality of the evidence reviewed.

Authors' objectives

To assess the effectiveness of vitamin B12 supplements for the treatment of diabetic neuropathy.

Searching

MEDLINE and the Cochrane Controlled Trials Register were searched from June 1954 to July 2004. No language restrictions were applied and the search terms were reported. In addition, the references of retrieved studies and related publications were checked. Studies that were reported as abstracts or conference presentations were excluded.

Study selection

Study designs of evaluations included in the review

Randomised controlled trials (RCTs) were eligible for inclusion. Uncontrolled trials and observational studies were excluded.

Specific interventions included in the review

Studies that assessed any type of vitamin B12 therapy, including coenzyme forms of vitamin B12 (methylcobalamin, cyanocobalamin, hydroxycobalamin), in either oral or injection form were eligible for inclusion. Studies involving combination therapy were also included if vitamin B12 or its coenzyme form was one of the treatment agents. The specific interventions assessed were vitamin B complex (B1, B6 and B12) as a combination agent, and methylcobalamin as a single agent. The duration of treatment ranged from 4 to 16 weeks.

Participants included in the review

Studies of participants with diabetic neuropathy were included. Diabetic neuropathy was defined as peripheral large- or small-fibre neuropathy resulting in autonomic or somatic sensory symptoms. Studies focusing on only a specific population, such as patients with uraemia, and studies in patients with other medical conditions were excluded. The primary studies were conducted in patients with type 1 and type 2 diabetes mellitus. In the included studies, the mean age of the patients was 50 to 60 years and the mean duration of diabetes mellitus, where reported, was 9 to 12 years.

Outcomes assessed in the review

Studies that reported clinical scores of somatic and autonomic symptoms or signs, vibrometer-detected thresholds of vibration perception, or electrophysiological measures such as nerve conduction velocities (NCVs) and somatosensory evoked potentials, were eligible for inclusion. The included studies used different methods to measure pain and somatosensory symptoms.

How were decisions on the relevance of primary studies made?

Two reviewers independently assessed studies for inclusion, with any disagreements being resolved by consensus.

Assessment of study quality

The validity of the primary studies was assessed and scored according to the Jadad criteria, which address methods of randomisation, blinding, and the reporting of withdrawals and drop-outs. The maximum possible score was 5 points. One reviewer assessed the quality of the primary studies, with a second reviewer checking for accuracy. Any disagreements were resolved by consensus.

Data extraction

One reviewer extracted the data, with a second reviewer checking for accuracy. The P-value for the differences in outcome measure scores between the treatment groups were extracted for each trial.

Methods of synthesis

How were the studies combined?

The studies were grouped according to the intervention and outcome measure and combined in a narrative.

How were differences between studies investigated?

Differences between the studies in terms of the participants and interventions were discussed in the text.

Results of the review

Seven controlled trials (n=336) were included.

Only 2 studies were judged to be of fairly good quality (Jadad score 3 out of 5). The other 5 studies were of a poor quality (Jadad score less than or equal to 2 out of 5). None of the studies involved an intention-to-treat analysis.

Pain or somatosensory symptoms (6 studies): all studies showed a statistically significant benefit compared with baseline or placebo.

Vibration perception threshold (4 studies): 3 studies showed a beneficial outcome with vitamin B12 compared with control or baseline, and one showed no improvement with methylcobalamin.

Autonomic symptoms (3 studies): all 3 studies found improvements with methylcobalamin.

Electrophysiological measures (5 studies): in one trial that used a neuromotor assessment process to measure the current perception threshold, a beneficial treatment effect for vitamin B complex was observed. Of the 4 trials that included NCV testing, the only trial of vitamin B combination therapy and 2 of the 3 trials of methylcobalamin showed beneficial outcomes compared with placebo. The other study of methylcobalamin found no change.

Methylcobalamin versus conventional vitamin B12 (1 study): the study found that the outcomes were better with methylcobalamin than with conventional vitamin B12 in terms of autonomic symptoms, somatosensory symptoms and electrophysiological results.

Authors' conclusions

Among patients with diabetic neuropathy, treatment with both combination agents (vitamin B complex with cyanocobalamin) and pure methylcobalamin appeared to improve symptomatic relief more than electrophysiologic results.

CRD commentary

The review question was clearly defined in terms of the interventions, participants, outcomes and study designs. Only two databases were searched for relevant studies, and no efforts were made to identify unpublished studies. This means that some potentially relevant studies might have been missed. Efforts were made to minimise reviewer bias and errors in the study inclusion, data extraction and quality assessment processes. Validity was assessed using established criteria, but there was no assessment of the validity of methods used to assess the outcomes.

Adequate details of the studies were presented in tabular format. The narrative synthesis of the studies was appropriate given the differences between them. However, the authors classified some studies as showing positive results when there was an improvement from baseline, rather than an improvement in comparison with the control treatment; this can exaggerate the strength of the evidence. Some differences between the studies were discussed with respect to differences in the interventions and outcomes assessed. The authors appropriately highlighted the poor quality of the evidence base and the need for further research. Given the limited evidence from generally poor-quality, small studies, the authors' conclusions should be viewed as tentative until they are confirmed by further high-quality RCTs.

Implications of the review for practice and research

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

Research: The authors stated that more high-quality, double-blind RCTs are needed to confirm the clinical effectiveness of vitamin B12 and its active coenzyme. They also stated that future subgroup analyses of diabetic participants, with or without B12 deficiency, in clinical trials of vitamin therapy are important.

Bibliographic details

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Record Status

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.

CRD has determined that this article meets the [DARE scientific quality criteria](#) for a systematic review.

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