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[Intervention Review]

Ascorbic acid for the treatment of Charcot-Marie-Tooth disease

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ABSTRACT

Background

Charcot-Marie-Tooth disease (CMT) comprises a large group of different forms of hereditary motor and sensory neuropathy. The molecular basis of several CMT subtypes has been clarified during the last 20 years. Since slowly progressive muscle weakness and sensory disturbances are the main features of these syndromes, treatments aim to improve motor impairment and sensory disturbances to improve abilities. Pharmacological treatment trials in CMT are rare. This review was derived from a Cochrane review, Treatment for Charcot Marie Tooth disease, which will be updated via this review and a forthcoming title, Treatments other than ascorbic acid for Charcot-Marie-Tooth disease.

Objectives

To assess the effects of ascorbic acid (vitamin C) treatment for CMT.

Search methods

On 21 September 2015, we searched the Cochrane Neuromuscular Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and LILACS for randomised controlled trials (RCTs) of treatment for CMT. We also checked clinical trials registries for ongoing studies.

Selection criteria

We included RCTs and quasi-RCTs of any ascorbic acid treatment for people with CMT. Where a study aimed to evaluate the treatment of general neuromuscular symptoms of people with peripheral neuropathy including CMT, we included the study if we were able to identify the effect of treatment in the CMT group. We did not include observational studies or case reports of ascorbic acid treatment in people with CMT.

Data collection and analysis

Two review authors (BG and JB) independently extracted the data and assessed study quality.



Main results

Six RCTs compared the effect of oral ascorbic acid (1 to 4 grams) and placebo treatment in CMT1A. In five trials involving adults with CMT1A, a total of 622 participants received ascorbic acid or placebo. Trials were largely at low risk of bias. There is high-quality evidence that ascorbic acid does not improve the course of CMT1A in adults as measured by the CMT neuropathy score (0 to 36 scale) at 12 months (mean difference (MD) -0.37; 95% confidence intervals (CI) -0.83 to 0.09; five studies; N = 533), or at 24 months (MD -0.21; 95% CI -0.81 to 0.39; three studies; N = 388). Ascorbic acid treatment showed a positive effect on the nine-hole peg test versus placebo (MD -1.16 seconds; 95% CI -1.96 to -0.37), but the clinical significance of this result is probably small. Meta-analyses of other secondary outcome parameters showed no relevant benefit of ascorbic acid. In one trial, 80 children with CMT1A received ascorbic acid or placebo. The trial showed no clinical benefit of ascorbic acid treatment. Adverse effects did not differ in their nature or abundance between ascorbic acid and placebo.

Authors' conclusions

High-quality evidence indicates that ascorbic acid does not improve the course of CMT1A in adults in terms of the outcome parameters used. According to low-quality evidence, ascorbic acid does not improve the course of CMT1A in children. However, CMT1A is slowly progressive and the outcome parameters show only small change over time. Longer study durations should be considered, and outcome parameters more sensitive to change over time should be designed and validated for future studies.

PLAIN LANGUAGE SUMMARY

Vitamin C for Charcot-Marie-Tooth (CMT) disease (hereditary motor and sensory neuropathy)

Review question

What are the benefits or harms of vitamin C (ascorbic acid) in the treatment of Charcot-Marie-Tooth (CMT) disease?

Background

CMT disease represents a broad spectrum of inherited peripheral neuropathies (conditions in which the nerves outside the brain and spinal cord are damaged), which in general progress slowly, and cause muscle wasting and loss of sensation. Muscle wasting and loss of sensation are caused by destruction of nerve fibres that go to the muscles or skin. Vitamin C has been proposed as a treatment for CMT, because vitamin C is necessary for myelination (development of the myelin, or insulation around the nerve fibres) in laboratory cultures of nerve cells and the peripheral nerves of mice.

Study characteristics

We searched the medical literature for trials of vitamin C in CMT disease and found six trials - five in adults and one in children - on the treatment of CMT type 1A (CMT1A) with vitamin C. All compared vitamin C doses of 1 to 4 grams per day with a placebo (a dummy or sugar pill disguised as vitamin C), and lasted for 12 or 24 months. The trials in adults included a total of 622 people. The other trial included 80 children. The main measure of the effects of vitamin C in this review was change in impairment. We also collected information on disability, nerve conduction studies, sensation, muscle strength, quality of life and harmful effects of vitamin C.

Key results and quality of the evidence

We found that ascorbic acid treatment did not improve impairment from CMT1A in adults as measured by the CMT neuropathy score (CMTNS). In children, the CMTNS was not reported, as it is a measure developed for adults with CMT. The measures used for children in this study did not show benefit from vitamin C. The studies were largely at low risk of bias, meaning they were well designed and the results were not easily influenced by chance. Adverse events were similar in nature and number in vitamin C and placebo groups.

There is high-quality evidence for adults and low-quality evidence for children that vitamin C does not improve the course of CMT1A. However, CMT progresses slowly, so the study durations of 12 or 24 months may not have been long enough to detect effects of treatment. Further research with longer study duration and more sensitive outcome parameters should be done, although any large effect in adults or children is unlikely.