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REVIEW ARTICLES

What do we currently know about treatment of AIDS-related myelopathy?

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Abstract

Objective: To evaluate the effectiveness and safety of various interventions for treating AIDS-associated myelopathy. *Methods:* This is a systematic review of randomised controlled trials. Predefined criteria were used to select randomised controlled trials comparing use of any intervention aimed at treating AIDS-associated myelopathy with placebo or another intervention in any language. Two assessors independently reviewed each trial, and disagreements were resolved by consensus. *Results:* One trial with 58 participants met the inclusion criteria that compared L-methionine with placebo. No difference was detected for clinical improvement -mean central conduction time (weighted mean difference (WMD) -2.4; -5.78 to 0.98), strength (WMD 1.8; -10.77 to 14.37), spasticity (WMD 0.7; -3.97 to 5.37), or urinary function (WMD -0.2; -1.59 to 1.19), after 12 weeks of treatment, and there was no difference detected in adverse events. One death was reported in the L-methionine group (relative risk (RR) 3.0; 95% CI 0.13 to 70.64)
Conclusion: We found no evidence of benefit of L-methionine for AIDS-related myelopathy after 12 weeks of treatment. There is insufficient reliable research on AIDS related myelopathy. A well designed, adequately powered randomised controlled trial and validated scale is needed.

INTRODUCTION

Vacuolar myelopathy (VM) is the most common cause of spinal cord disease in patients with AIDS, with prevalence between 22% and 55% in autopsy series.[1-3] The primary clinical features of VM are slowly progressive, usually painless; and include weakness in the lower extremities, gait ataxia, sensory abnormalities in the legs, urinary frequency, sphincter dysfunction, and impotence in men.[1] The clinical diagnosis of AIDS-associated myelopathy is primarily one of exclusion and often remains unrecognized during life.[4] We evaluated the evidence from available randomised controlled trials in order to evaluate the effectiveness and safety of intervention for treating AIDS associated myelopathy.

METHODS

The following databases were searched: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PSYCHLIT, Allied and Complementary Medicine Database (AMED), and the Cochrane Controlled Trials Register (CCTR). Reference lists for all primary and other pertinent articles identified were searched. The time period searched was from 1980 to July 2007. No language restrictions were placed on the search. Key words used include: vacoular myelopathy, myelopathy, acquired immunodeficiency syndrome, human immunodeficiency virus, and a sensitive filter was added to identify all possible reports of relevant randomised trials.

Trials investigating the effects of intervention on AIDS-related myelopathy were included if they were randomised, placebo controlled, double blind, parallel, or crossover studies. The two authors of this article independently assessed the titles and abstracts of all reports of studies identified by the search; and methodological quality of each trial in terms of generation of allocation sequence, allocation concealment, blinding, and inclusion of all randomized participants in the analysis. Trials were also graded using the Jadad scale.[5] This validated score lies in the range 0-5. Studies are scored according to the presence of three key methodological features of randomization, blinding and accountability of all patients, including withdrawals.

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RESULTS

Description of studies

We found six studies through searching the electronic databases and cross-checking the references. Only one randomised controlled trial[6] met our inclusion criteria. This trial evaluated 56 patients with established diagnosis of HIV infection by Western blot and a clinical diagnosis of progressive AIDS-associated myelopathy at the Albert Einstein College of Medicine, Beth Israel Medical Center, Mount Sinai School of Medicine, and Baylor University Medical Center in USA. After informed consent, they were randomized to receive L-methionine (28 participants) or placebo (28 participants) for a period of 12 weeks.

Methodological quality

The included trial[6] was of moderate methodological quality (Jadad score of 3). The trial was randomised and double-blind. A matching placebo was used in conjunction with the study drug. The trialists did not report method of allocation sequence generation. There was no clear evidence of allocation concealment. Sample size calculations and blinding method were not provided. The participants lost to follow up were 18%, 11%, and 14% among the treatment group, control group, and overall respectively.

Excluded study

Five non-randomised open label studies identified by the search strategy were excluded after reading the full text. Two were pilot study of methionine for the treatment of AIDS-associated myelopathy[7,8] and the other three explored the treatment with zidovudine.[9-11]

Efficacy

There was no significant improvement in mean central conduction time (weighted mean difference (WMD) -2.4; -5.78 to 0.98). Also, there was no significant effect of treatment on strength (WMD 1.8; -10.77 to 14.37), spasticity (WMD 0.7; -3.97 to 5.37), or urinary function (WMD -0.2; -1.59 to 1.19).

Safety and tolerability

L-methionine was well tolerated; the analysis of tolerability (relative risk (RR) 0.92; 95% CI 0.74 to 1.14) showed no significant differences between intervention and control groups in most trials. Various adverse effects were recorded, none of the events showed statistical difference between the intervention and control groups (Figure 1). One death was reported in the L-methionine group (RR 3.0; 95% CI 0.13 to 70.64).

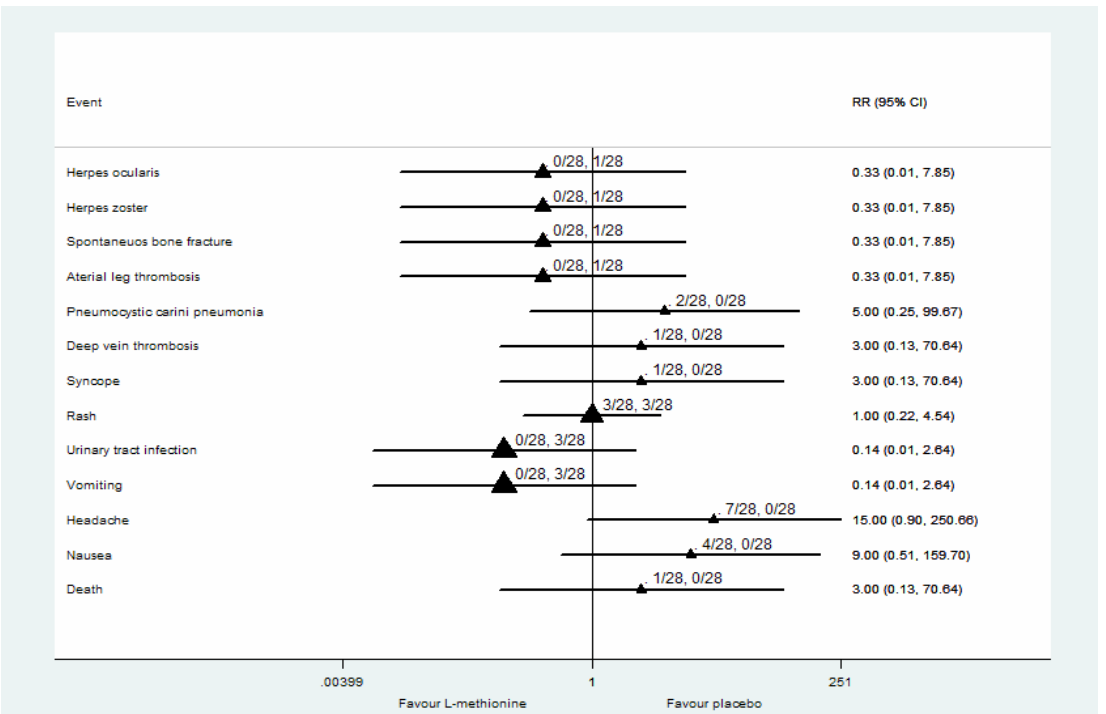

Figure 1: Reported adverse events

DISCUSSION

We believe this is the first systematic review to investigate, identify and describe all randomised controlled trials for the treatment of AIDS related myelopathy. The one included trial[6] found no significant difference between methionine and placebo. We also found insufficient evidence from one open trial[7] about effects of methionine for AIDS related myelopathy. Two open trials[9,10] found no evidence of improvement with zidovudine.

The small size of this trial[6] makes it lack statistical power and hence it difficult to draw a reliable conclusion. There was no indication that power calculations were used to determine the number of patients needed for an expected effect size which in essence renders the studies inappropriate. In addition, our findings echo McArthur's[12] general observation that a priority for future research is to improve diagnostic imaging techniques so that AIDS associated myelopathy can be distinguished from other myelopathies, and to allow for early identification of neurological diseases. There is also a need for a well validated scale for AIDS-associated myelopathy.

After more than two decades of innovation in the management of AIDS to improve the quality of treatment management for AIDS patients, only one small randomized phase II trial has been conducted to investigate the efficacy and safety of interventions for treating AIDS-associated myelopathy. This lack of trials shows a gap between clinical medicine and clinical investigation. We remain uncertain about the ideal drug and dose needed to treat AIDS-associated myelopathy with minimal adverse events. The research community must respond. Better evidence is required.

This systematic review has identified the need for well-designed, adequately powered randomised controlled trials to assess the benefits and harms of interventions for treating AIDS associated myelopathy. The trials regarding this issue should be structured and reported according to the CONSORT statement (www.consort-statement.org) to improve the quality of reporting of efficacy and to get better reports of harms in clinical research.[13]

In conclusion, we found insufficient evidence from one small randomised controlled trial about the clinical effects of methionine versus placebo after 12 weeks of treatment. The small number of participants and the lack of validated scale impede definitive conclusions. Current clinical practice in treatment of AIDS associated myelopathy is based on case series and case reports. This is a weak evidence base.

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