L-Ornithine-L-aspartate in the management of hepatic encephalopathy: a meta-analysis

Jiang Q, Jiang X H, Zheng M H, Chen Y P

CRD summary
The authors concluded that L-ornithine-L-aspartate can improve overt grade I or II hepatic encephalopathy, but not subclinical hepatic encephalopathy. The authors' conclusions appear to be reliable, but given the small sample size and the risk of publication bias, they should be interpreted with caution.

Authors' objectives
To evaluate the effectiveness and safety of L-ornithine-L-aspartate (LOLA) in the management of hepatic encephalopathy (HE).

Searching
Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Science Citation Index and the Chinese Biomedical Disc Database were searched up to February 2008. Search terms were reported. Internet pages were searched using the Google search engine. The bibliographies of retrieved articles and relevant reviews were also searched. No limitations were placed on the language and the publication status of the articles, but articles published in only abstract form were excluded.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion if they compared LOLA with any control therapy, in the treatment of cirrhotic patients aged over 18 years with chronic persistent HE and hyperammonaemia. Eligibility was irrespective of aetiological or precipitating factors. Trials were eligible if they reported the number of patients with improvements in HE. Studies of patients with major psychiatric illness, chronic renal and/or respiratory insufficiency, tumours or intercurrent infections and pregnant or lactating women were excluded. As were those with patients who took other concurrent anti-HE medication.

Included RCTs were of LOLA administered orally in doses of 3g or 6g three times a day or intravenous infusions of 20g over four hours, compared with placebo or lactulose in patients with chronic subclinical, grade I or grade II HE. The duration of the included studies was one or two weeks. The outcomes were mental state, number connecting test time, asterixis, postprandial or fasting ammonia, electrocardiography, portal-systemic encephalopathy index, liver blood tests, bowel movements, quality of life and adverse events.

Two reviewers independently selected the studies for the review, with disagreements resolved through discussion.

Assessment of study quality
The methodological quality of the included studies was assessed using the Jadad scale, a three item checklist assessing randomisation, blinding and withdrawals, with a maximum score of 5. Two reviewers independently assessed the methodological quality of the included studies, with disagreements resolved through discussion.

Data extraction
The number of patients showing clinical efficacy were extracted for the control and intervention groups in each study and used to calculate relative risks with corresponding 95% confidence interval (CIs). Clinical efficacy was defined as the disappearance of the HE clinical syndrome, passing to a lower stage of disease or decreasing grade of HE mental state or portal-systemic encephalopathy index. For continuous data, the mean and standard deviation were extracted for each group.

Two reviewers independently extracted the data, with disagreements resolved through discussion.

Methods of synthesis
For dichotomous data, pooled relative risks with corresponding 95% CIs were calculated using a fixed-effects model.
For continuous data, weighted mean differences were calculated. Heterogeneity was assessed using the Q statistic. In the case of significant heterogeneity, a random-effects model was used. Subgroup analyses were performed for patients with grade I or II HE and those with subclinical HE.

Results of the review
Three RCTs were included in the review (n=212). Two studies scored 5 on the Jadad scale and one scored 3. The sample sizes of the included studies ranged from 20 to 126.

LOLA was associated with a significant improvement in chronic HE compared with placebo (relative risk 1.89, 95% CI: 1.32 to 2.71, p=0.0005; two RCTs, n=192). The RCT comparing LOLA with lactulose showed no significant difference between the two groups (one study, n=20). LOLA was associated with significant improvements in HE in patients with grade I or II HE compared with placebo (relative risk 1.87, 95% CI: 1.30 to 2.68, p=0.0007; two studies, n=136). There was no difference between LOLA and placebo in patients with subclinical HE.

There was evidence of significant statistical heterogeneity for the meta-analysis of patients with subclinical HE, but not for any other analyses. The authors reported that blood ammonia concentration dropped in both intervention and placebo groups during the course of treatment; these dropped to a greater extent and more quickly in patients treated with LOLA. No statistical data were reported for these outcomes. One study reported adverse events (upper gastrointestinal and central nervous system symptoms) in three patients.

Authors’ conclusions
LOLA could improve overt grade I or II HE, but not subclinical HE.

CRD commentary
The review addressed a clear question and the inclusion criteria were well-defined for participants, study design and intervention. The inclusion criteria for outcomes were broad. Several relevant databases were searched for articles in any language, thereby minimising the risk of language bias. Although the search was not restricted by publication status, specific attempts do not appear to have been made to identify unpublished data and so the risk of publication bias cannot be ruled out. Appropriate steps were taken to minimise the risk of reviewer error and bias. A suitable validity assessment was carried out and the quality of the included studies was high, but the sample sizes were small. Appropriate methods were used to pool the results and statistical heterogeneity was investigated. Further analyses were carried out to investigate the effects of a number of important variables.

The authors conclusions appear to be reliable, but given the small sample size and the risk of publication bias, they should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that more research was needed into the efficacy of LOLA in the treatment of HE, with larger samples of patients.

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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.