L-ornithine-l-aspartate for hepatic encephalopathy in patients with cirrhosis: a meta-analysis of randomized controlled trials
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CRD summary
The authors concluded that CL-ornithine-CL-aspartate was more effective than placebo/no intervention in improving hepatic encephalopathy and reducing serum ammonia in patients with cirrhosis and did not increase adverse events. The evidence base was small and heterogeneous and no significant differences were found compared to other treatments. The authors conclusions and recommendations should be considered tentative.

Authors' objectives
To assess the safety and efficacy of CL-ornithine-CL-aspartate for the treatment of hepatic encephalopathy in patients with liver disease.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to June 2012 for articles published in English. Search terms were reported. Reference lists of all identified articles were searched manually and the World Health Organisation website was searched for unpublished or ongoing trials.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared the safety and efficacy of CL-ornithine-CL-aspartate with a control for the treatment of hepatic encephalopathy in patients with liver disease (cirrhosis). Control could be placebo, no intervention or other treatments (such as lactulose, probiotics). The primary outcome of interest was improvement of hepatic encephalopathy (as defined in the review). Other outcomes included reduction of serum ammonia, mortality, incidence of adverse events and tolerance ratio. Abstracts without full text were excluded from the review. Trials in patients with acute liver disease were excluded.

The mean age of patients in the included studies ranged from 41 to 64 years. Various criteria were used to diagnose minimal and overt hepatic encephalopathy; 46% of patients had minimal hepatic encephalopathy and 56% had overt hepatic encephalopathy. More than half of the studies included patients with hyperammonaemia. The etiology of cirrhosis was viral-induced or alcohol-induced. Where reported, between 6% and 87% of patients in the control group and 8% to 78% of patients in the intervention group had Child-Pugh score C. CL-ornithine-CL-aspartate was administered orally (3g to 6g three times a day for 14 days or three months) or by infusion (20g once a day for three to eight days). Trial duration ranged from three days to three months. Control groups received lactulose, probiotics, placebo or no intervention.

Two reviewers screened studies for inclusion; discrepancies were resolved by consensus.

Assessment of study quality
Trial risk of bias was assessed according to Cochrane criteria. Each criterion was rated as high, low or unclear risk of bias. Trials were assessed as having low risk of bias if at least four of five criteria were considered to a low risk of bias overall.

Two reviewers independently assessed trial risk of bias. Disagreements were resolved through discussions.

Data extraction
Continuous outcome data were extracted to calculate mean differences with 95% confidence intervals. Dichotomous outcome data were extracted to calculate risk ratios and 95% confidence intervals.

Two reviewers extracted data; any disagreements were resolved by consensus among all reviewers.

Methods of synthesis
A fixed-effect model (or random-effects model where there was evidence of statistical heterogeneity) was used to pool mean differences (MD), risk ratios (RR) and their 95% confidence intervals (CIs). Trials that reported no events in either treatment group were not pooled in meta-analysis.

Statistical heterogeneity was assessed using the $X^2$ test and $I^2$ statistic. Subgroup analyses were undertaken for trial risk of bias, publication data (before 2000 versus after 2000) and treatment duration/method (>10 days/oral versus <10 days/infusion). Sensitivity analysis was performed, excluding an open label trial.

**Results of the review**

Eight RCTs (646 patients, range 20 to 160) were included in the review. Four trials were at low risk of bias. Three trials were at high risk of bias due to blinding issues or use of per-protocol analysis due to incomplete outcome data. One trial had unclear risk of bias.

**Hepatic encephalopathy:** Hepatic encephalopathy was statistically significantly reduced in patients with both minimal and overt hepatic encephalopathy who received CL-ornithine-CL-aspartate compared to placebo/no intervention (RR 1.49, 95% CI 1.10 to 2.01; five RCTs). There was evidence of significant heterogeneity ($I^2=76\%$).

Similar findings in favour of CL-ornithine-CL-aspartate were reported in subgroup analyses including only overt or minimal hepatic encephalopathy patients. Subgroup analyses in trials at low risk of bias resulted in no statistically significant differences for any patient group compared to control. Results on other subgroup and sensitivity analyses were reported in the review.

**Serum ammonia:** CL-ornithine-CL-aspartate compared to placebo/no intervention statistically significantly lowered post-treatment fasting ammonia levels (MD -18.26, 95% CI -26.96 to -9.56; four RCTs), increased the change in fasting serum ammonia (MD 9.84, 95% CI 6.44 to 13.24; four RCTs) and increased the post-treatment value of postprandial serum ammonia (MD -20.54, 95% CI -28.71 to -12.36). None of the pooled analyses for serum ammonia found evidence of heterogeneity.

**Other outcomes:** There were no statistically significant differences in mortality, adverse events or tolerance rates between patients who received CL-ornithine-CL-aspartate and patients who received placebo/no intervention.

Comparisons between CL-ornithine-CL-aspartate and lactulose revealed significantly increased abdominal pain and flatulence with lactulose. No other statistically significant differences between CL-ornithine-CL-aspartate and other treatments were found for any of the outcomes measured.

**Authors' conclusions**

CL-ornithine-CL-aspartate was more effective than placebo/no intervention in the improvement of hepatic encephalopathy and reduction of serum ammonia in patients with cirrhosis. CL-ornithine-CL-aspartate did not increase the incidence of adverse events or decrease tolerance levels but cannot improve patient survival.

**CRD commentary**

The review question and supporting inclusion criteria were clearly defined. There was a satisfactory search of the literature and this included attempts to locate unpublished data. Language bias could not be ruled out as the search was restricted by language. Trial risk of bias was assessed using appropriate criteria; half of the studies were at low risk of bias and half had some risk of bias. Each stage of the review process was performed in duplicate which reduced potential for reviewer error and bias.

Patient and study details were reported in the review. These highlighted differences between the trials, including methods to diagnose minimal hepatic encephalopathy and treatments administered to control groups. Data were combined in meta-analyses. The authors went some way to explore reasons for statistical heterogeneity. Trial sample sizes were small and only small numbers of trials were included in most meta-analyses. Some benefits were only small and confidence intervals were wide for some outcomes, which reduced the robustness of the findings.

The evidence base was small and heterogeneous and no significant differences were reported between CL-ornithine-CL-aspartate and other treatments so it was unclear how appropriate the authors' recommendations for practice are and the findings should be considered tentative.
Implications of the review for practice and research

Practice: The authors stated that there was a role for CL-ornithine-CL-aspartate in treating hepatic encephalopathy and they suggested use of CL-ornithine-CL-aspartate to manage patients with both overt and minimal hepatic encephalopathy, particularly patients with hyperammonaemia.

Research: The authors stated that further research was needed to evaluate the safety, efficacy and cost-effectiveness of CL-ornithine-CL-aspartate and other effective treatments.

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