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# [Intervention Review]

# L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis

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# ABSTRACT

### Background

Hepatic encephalopathy is a common complication of cirrhosis and has high associated morbidity and mortality. The condition is classified as *overt* if it is clinically apparent or *minimal* if only evident though psychometric testing. The exact pathogenesis of this syndrome is unknown although ammonia is thought to play a key role. L-ornithine L-aspartate has ammonia-lowering properties and may, therefore, benefit people with cirrhosis and hepatic encephalopathy.

# Objectives

To evaluate the beneficial and harmful effects of L-ornithine L-aspartate versus placebo, no intervention, or other active interventions in people with cirrhosis and hepatic encephalopathy.

### Search methods

We undertook electronic searches of The Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, LILACS and Science Citation Index Expanded to December 2017 and manual searches of meetings and conference proceedings; checks of bibliographies; and corresponded with investigators and pharmaceutical companies.

## **Selection criteria**

We included randomised clinical trials, irrespective of publication status, language, or blinding. We included participants with cirrhosis who had minimal or overt hepatic encephalopathy or who were at risk for developing hepatic encephalopathy. We compared: L-ornithine L-aspartate versus placebo or no intervention; and L-ornithine L-aspartate versus other active agents such as non-absorbable disaccharides, antibiotics, probiotics, or branched-chain amino acids.

### Data collection and analysis

Two review authors, working independently, retrieved data from published reports and correspondence with investigators and pharmaceutical companies. The primary outcomes were mortality, hepatic encephalopathy, and serious adverse events. We undertook meta-analyses and presented the results as risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI). We assessed bias control using the Cochrane Hepato-Biliary Group domains; we evaluated the risk of publication bias and other small trial effects in

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regression analyses; conducted subgroup and sensitivity analyses; and performed Trial Sequential Analyses. We determined the quality of the evidence using GRADE.

## **Main results**

We identified 36 randomised clinical trials, involving at least 2377 registered participants, which fulfilled our inclusion criteria including 10 unpublished randomised clinical trials. However, we were only able to access outcome data from 29 trials involving 1891 participants. Five of the included trials assessed prevention, while 31 trials assessed treatment. Five trials were at low risk of bias in the overall assessment of mortality; one trial was at low risk of bias in the assessment of the remaining outcomes.

L-ornithine L-aspartate had a beneficial effect on mortality compared with placebo or no intervention when including all trials (RR 0.42, 95% CI 0.24 to 0.72; I<sup>2</sup> = 0%; 19 trials; 1489 participants; very low quality evidence), but not when the analysis was restricted to the trials at low risk of bias (RR 0.47, 95% CI 0.06 to 3.58; 4 trials; 244 participants). It had a beneficial effect on hepatic encephalopathy compared with placebo or no intervention when including all trials (RR 0.70, 95% CI 0.59 to 0.83; 22 trials; 1375 participants; I<sup>2</sup> = 62%; very low quality evidence), but not in the one trial at low risk of bias (RR 0.96, 95% CI 0.85 to 1.07; 63 participants). The analysis of serious adverse events showed a potential benefit of L-ornithine L-aspartate when including all randomised clinical trials (RR 0.63, 95% CI 0.45 to 0.90; 1 trial; 1489 participants; I<sup>2</sup> = 0%; very low guality evidence), but not in the one trial at low risk of bias for this outcome (RR 0.83, 95% CI 0.15 to 4.65; 63 participants). The Trial Sequential Analyses of mortality, hepatic encephalopathy, and serious adverse events found insufficient evidence to support or refute beneficial effects. Subgroup analyses showed no difference in outcomes in the trials evaluating evaluating the prevention or treatment of either overt or minimal hepatic encephalopathy or trials evaluating oral versus intravenous administration We were unable to undertake a meta-analysis of the three trials involving 288 participants evaluating health-related quality of life. Overall, we found no difference between L-ornithine L-aspartate and placebo or no intervention in non-serious adverse events (RR 1.15, 95% CI 0.75 to 1.77; 14 trials; 1076 participants; I<sup>2</sup> = 40%). In comparison with lactulose, L-ornithine L-aspartate had no effect on mortality (RR 0.68, 95% CI 0.11 to 4.17; 4 trials; 175 participants; I<sup>2</sup> = 0%); hepatic encephalopathy (RR 1.13, 95% CI 0.81 to 1.57); serious adverse events (RR 0.69, 95% CI 0.22 to 2.11); or non-serious adverse events (RR 0.05, 95% CI 0.01 to 0.18). In comparison with probiotics, L-ornithine Laspartate had no effect on mortality (RR 1.01, 95% CI 0.11 to 9.51); serious adverse events (RR 1.07, 95% CI 0.23 to 4.88); or changes in blood ammonia concentrations from baseline (RR -2.30 95% CI -6.08 to 1.48), but it had a possible beneficial effect on hepatic encephalopathy (RR 0.71, 95% CI 0.56 to 0.90). Finally, in comparison with rifaximin, L-ornithine L-aspartate had no effect on mortality (RR 0.33, 95% CI 0.04 to 3.03; 2 trials; 105 participants); hepatic encephalopathy (RR 1.06, 95% CI 0.57 to 1.96); serious adverse events (RR 0.32, 95% CI 0.01 to 7.42), or non-serious adverse events (RR 0.32, 95% CI 0.01 to 7.42).

## Authors' conclusions

The results of this review suggest a possible beneficial effect of L-ornithine L-aspartate on mortality, hepatic encephalopathy, and serious adverse events in comparisons with placebo or no-intervention, but, because the quality of the evidence is very low, we are very uncertain about these findings. There was very low quality evidence of a possible beneficial effect of L-ornithine L-aspartate on hepatic encephalopathy, when compared with probiotics, but no other benefits were demonstrated in comparison with other active agents. Additional access to data from completed, but unpublished trials, and new randomised placebo-controlled, double-blind clinical trials are needed.

# PLAIN LANGUAGE SUMMARY

# L-ornithine L-aspartate for people with chronic liver disease and hepatic encephalopathy (poor brain functioning)

### Background

Cirrhosis is a chronic disorder of the liver. People with this condition commonly develop hepatic encephalopathy, a complication that results in poor brain functioning. Some people with cirrhosis develop obvious clinical features of disturbed brain functioning, such as difficulties with speech, balance and daily functioning; they are said to have *overt* hepatic encephalopathy; the changes may be short-lived, may recur, or may persist for long periods. Other people with cirrhosis may show no obvious clinical changes but some aspects of their brain function, such as attention and the ability to perform complex tasks are found to be impaired when tested; they are said to have minimal hepatic encephalopathy. The reason why people develop hepatic encephalopathy is complex, but the accumulation in the blood of toxins from the gut, particularly of a compound called ammonia, plays a key role. L-ornithine L-aspartate lowers blood ammonia levels and so may have beneficial effects in people with hepatic encephalopathy or help stop them developing it.

# **Review question**

We investigated the use of L-ornithine L-aspartate given either by mouth (oral) or into a vein in an fluid drip (intravenous) for the prevention and treatment of hepatic encephalopathy by reviewing clinical trials in which people with cirrhosis were randomly allocated to treatment with L-ornithine L-aspartate, to an inactive dummy (called placebo), to no treatment, or to another medicine for this condition such as lactulose, probiotics and rifaximin. We included participants with cirrhosis who had overt or minimal hepatic encephalopathy or who were at risk for developing this complication.

## Search date

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## December 2017.

# Study funding sources

Six of the 36 randomised clinical trials we included received no funding or any other support from pharmaceutical companies. Seventeen trials received financial support from pharmaceutical companies and a further three received L-ornithine L-aspartate or inactive placebo free of charge; there was no information on funding in the remaining 10 trials.

# Study characteristics

We included 33 randomised clinical trials comparing L-ornithine L-aspartate with inactive placebo or no intervention and six randomised clinical trials comparing L-ornithine L-aspartate with other anti-encephalopathy treatments; some trials included more than one comparison. Five of the included trials tested L-ornithine L-aspartate for the prevention of hepatic encephalopathy while 30 trials tested its use as treatment for people with acute, chronic, or minimal hepatic encephalopathy. The length of treatment varied from three to 35 days in the trials testing the intravenous preparation (average eight days) and from seven to 180 days in those testing the oral preparation (average 30 days).

# **Key results**

Our analyses showed L-ornithine L-aspartate might reduce deaths, improve hepatic encephalopathy, and prevent serious side effects compared with placebo or no treatment, but that it had no additional beneficial effects when compared with other medicines used to prevent and treat this condition.

## Quality of the evidence

The evidence we found was very weak, and so we are not confident that L-ornithine L-aspartate is of use for preventing or treating hepatic encephalopathy in people with cirrhosis. Many studies were unpublished and so had not been carefully vetted, and many of the published trials received support from the pharmaceutical industry which introduces an element of bias. Accordingly, more information is needed before the value of L-ornithine L-aspartate for preventing and treating hepatic encephalopathy can be determined.