Introduction: Ammonia plays a key role in the pathogenesis of hepatic encephalopathy (HE). L-ornithine L-aspartate (LOLA) has documented ammonia-lowering properties. The aim of this study was to undertake a systematic review with meta-analysis of randomised controlled trials (RCTs) comparing LOLA versus placebo/no intervention or other active interventions to assess its efficacy and safety in the prevention and treatment of HE in patients with cirrhosis.

Methods: Extensive electronic and manual searches of the literature were performed; further information/data clarification was obtained from trialists and pharmaceutical companies; on-going trials were identified in ClinicalTrials.gov and similar trial registries. Meta-analyses were conducted and results presented as relative risks (RR) with 95% confidence intervals (CI). Regression analyses of funnel-plot asymmetry and fil-and-trim analyses were conducted to evaluate the risk of publication bias and other small study effects. Subgroup and trial sequential analyses were performed to evaluate sources of heterogeneity and the influence of random and systematic errors. Results: Twenty-six RCTs with 1783 patients fulfilled inclusion criteria; however, outcome data were only available from 20 RCTs with 1376 patients. Twenty-three RCTs compared LOLA versus placebo/no intervention. Four RCTs included active control groups (lactulose, probiotics, and/or rifaximin). Fifteen RCTs evaluated intravenous LOLA. Random effects meta-analysis, including all RCTs, showed LOLA was associated with reduced mortality compared with placebo/no intervention (RR 0.42, 95% CI 0.22 to 0.84) but data were only available for 65% of eligible participants. LOLA was not associated with reduced mortality when the five RCTs with a low risk of bias were analysed independently (RR 0.47, 95% CI 0.06 to 3.58; participants=244). Subgroup analyses showed a beneficial effect of LOLA on mortality in patients with acute HE (RR 0.45, 95% CI 0.21 to 0.96; participants=404), but not in patients with chronic or minimal HE or in RCTs evaluating HE prevention. Trial sequential analysis showed that there was insufficient information to draw conclusions and that the effect of LOLA may reflect random/systematic errors. Regression analyses showed no publication bias or other small study effects.

Analysis of 16 RCTs with 1023 participants showed a beneficial effect of LOLA on HE (RR 0.60, 95% CI 0.44 to 0.82); but data were only available for 59% of eligible participants. Subgroup analyses showed benefit in patients with acute or chronic HE, but not in RCTs evaluating minimal HE or HE prevention. LOLA did not increase the risk of adverse events. None of the
analyses comparing LOLA versus active interventions found benefit or harm. Conclusion: Although there was low quality evidence that LOLA has beneficial effects in patients with cirrhosis and overt HE, the release of data from already completed studies or from new RCTs are needed to fairly evaluate the beneficial and harmful effects of this agent.

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