L-Ornithine L-Aspartate is Effective and Safe for the Treatment of Hepatic Encephalopathy in Cirrhosis

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Lactulose and to a lesser extent lactitol are considered standard treatments that are aimed at reducing the amount of ammonia absorbed into the blood stream.¹ Lactulose is metabolized by bacteria in the colon to acetic and lactic acids, which reduce colonic pH, decrease survival of urease-producing bacteria in the gut, and facilitate conversion of NH_3 to NH_4^+ . The cathartic effect of lactulose also increases fecal nitrogen waste. Despite the lack of evidence for the use of lactulose on patients with acute hepatic encephalopathy (HE), a recent meta-analysis showed that nonabsorbable disaccharides have beneficial effects in the treatment and prevention of HE.² Furthermore, other benefits include reduction in serious liver-related morbidities and all-cause mortality.³ Studies comparing lactulose to control are lacking and, therefore, no comparative studies exist to strongly validate the use of lactulose for the treatment of hyperammonemia.⁴ In addition, one study showed that nearly 50% of HE recurrence was related to either no adherence or inappropriate dosing.⁵ There is, however, a danger for overuse of lactulose leading to complications, such as dehydration, aspiration, hyponatremia, and perianal skin irritation. This can lead to difficulties during liver transplantation and can cause malnutrition in patients or even precipitate HE.⁵ Rifaximin is the most commonly used antibiotic for the treatment of HE and has also been used in a number of trials.⁶ A meta-analysis by Wu et al⁷ has shown that rifaximin is as effective and potentially better than non-absorbable disaccharides at treating HE. A double-blind, randomized study with 120 patients revealed a significant decrease in overt HE when both treatments, lactulose and rifaximin, were used in combination rather than when lactulose treatment was used alone. The length of hospital stay was also significantly decreased.⁸ The data clearly demonstrate that patients tolerate rifaximin better and that best results are achieved when it is coupled with lactulose. Despite this, further research is required to support the use of rifaximin alone because limitations such as the lack of comparison to placebo represent the current studies.⁹ L-ornithine L-aspartate (LOLA), the salt of the natural amino acids ornithine and aspartate, acts through the mechanism of substrate activation to detoxify ammonia. LOLA is a substrate for the urea cycle and can increase urea production in periportal hepatocytes. LOLA also activates glutamine pro-

duction by activating glutamine synthetase in perivenous hepatocytes and skeletal muscles. Evidence suggests that LOLA has direct hepatoprotective properties in chronic liver disease.¹⁰ Such evidence includes reports of attenuation of increased liver enzymes and bilirubin as well as improvements in prothrombin times, Child-Pugh, and model of end-stage liver disease (MELD) scores in patients with cirrhosis of liver and HE. These improvements in markers of improved liver function occur in parallel with the reduction in circulating ammonia and improvements in HE.¹¹ Hepatoprotective properties of LOLA occur in patients with cirrhosis and overt HE, covert HE, or HE resulting from post-transjugular intrahepatic portal-systemic shunt. Several mechanisms have been proposed to account for hepatoprotection due to LOLA. Metabolic changes mediated directly via L-ornithine and/or L-aspartate and related metabolites (glutamate, glutamine, glutathione) as well as increased synthesis of nitric oxide (NO) via the increased production of arginine are considered to play a role. Antioxidant actions may occur because of increased synthesis of glutathione from glutamate and reduced tissue concentrations of potentially harmful reactive species. In addition, improvement of hepatic microcirculation via NO could also contribute to the hepatoprotective properties of LOLA. These findings strongly suggest that the ammonia-lowering properties of LOLA in patients with cirrhosis could result not only from the ability of the constituent amino acids L-ornithine and L-aspartate to stimulate ammonia incorporation into urea and glutamine in residual hepatocytes of the damaged liver. LOLA may also directly limit hepatocyte damage and necrosis.¹⁰

The current systematic review and meta-analysis by Butterworth and Canbay¹² quantitatively analyzed the efficacy of LOLA in patients with cirrhosis and HE. The primary outcome measure was defined as improvement in mental state of patients with cirrhosis and at least one episode of overt HE or minimal HE. Mental state improvement was determined by improvement of overt HE grade using West Haven criteria or improvement of minimal HE assessed by number connection tests NCT-A, NCT-B, or psychometric HE score.¹³

A second primary outcome measure was defined as the reduction of hyperammonemia based on measurement of blood ammonia using standard biochemical laboratory testing or commercially available ammonia test kits. Electronic searches of the databases identified 43 trials with a further 16 from manual searches. Study quality and risk of bias were assessed using the Jadad Composite Scale together with the Cochrane Scoring Tool. The overall trial quality was

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considered to be high for trials with a Jadad score 3 or above in addition to low risk of bias by the Cochrane tool.

Ten randomized controlled trials (RCTs) (884 patients) studies were included that compared LOLA to placebo or no intervention control as part of RCTs with adequate description of patient characteristics, patient numbers, trial design, blinding of personnel, patients and investigators, dropouts, dose and route of administration of test substances, and control in sufficient detail to assess trial quality and risk of biases. The primary subgroup analyses were carried out relating to intravenous versus oral formulations of LOLA as well as the type of HE (overt HE, minimal HE).

Comparison with placebo/no intervention controls revealed that LOLA was significantly more effective for improvement of the mental state in all types of HE (risk ratio [RR] 1.36 [95% confidence interval {CI}, 1.10–1.69], $P = 0.005$), overt HE (RR 1.19 [95% CI, 1.01–1.39], test for overall effect: $Z = 2.14$, $P = 0.03$), minimal HE (RR 2.15 95% CI, [1.48–3.14], $P < 0.0001$), and for lowering of blood ammonia (MD = -17.50 mmol/l, 95% CI: -27.73 to -7.26 , test for overall effect: $Z = 3.35$, $P = 0.0008$). Improvement of mental state was greater in 8 trials with low risk of bias. Oral LOLA appeared particularly effective for the treatment of minimal HE. The authors concluded that LOLA appears to improve mental state and lower ammonia in patients with overt HE or minimal HE.

The first limitations of the current review is that 4 trials included in this systematic review, that is, trials by Kircheis et al,¹⁴ Stauch et al¹⁵ Chen et al,¹⁶ and Ahmad et al¹⁷ were performed before 2009. The rest of the 6 trials^{18–23} were performed later. Hence, the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines²⁴ could not be applied to this systematic review and meta-analysis.

As most RCTs included in the current systematic review and meta-analysis were conducted on patients with minimal HE and overt HE before the Spectrum of Neurocognitive Impairment in Cirrhosis classification,²⁵ new studies are needed on LOLA in covert and overt HE to be in consonance with the current literature.

We had performed a large prospective, double-blind, placebo-controlled trial that was conducted at 2 major tertiary care centers in India. In this study, 193 patients were randomized to receive LOLA or placebo. The standard medical treatment given to both groups included lactulose and prophylactic ceftriaxone. The grade of HE was significantly lower over days 1–4 in the LOLA group. However, on day 5 of therapy, there was no significant difference between the 2 groups. This was possibly because of the effects of LOLA peaking by the fourth day of therapy. Patients receiving intravenous infusion of LOLA had a significantly shorter recovery time and a significantly shorter length of hospital stay. The hospital stay was, however, longer than the time taken to recover from overt HE because there were other complications of cirrhosis such as gastrointestinal bleeding

and septicemia, which also required treatment. The levels of ammonia at day 5 were also significantly lower in the LOLA group. The side effect profile in the LOLA and placebo groups were similar. There was, however, no impact of LOLA on mortality. The mortality rate at 1-month follow-up was 19.3% in the LOLA group and 18.3% in the control group. The MELD score was 21 in both groups, which explains an equivalent mortality in both groups of patients. A post hoc exploratory subgroup analysis demonstrated that LOLA was found more effective in lower (particularly grade II) than higher overt HE grades (III/IV) in comparison with placebo. However, this result has to be interpreted cautiously as the type 1 error rate of observing a false-negative result is increased due to multiple testing. Four prior meta-analyses have also evaluated the effectiveness of LOLA on HE. The first meta-analysis, by Jiang et al²⁶ including 212 patients from three randomized controlled trials, concluded that LOLA benefited patients with overt HE (grade 1 or 2), whereas the data did not support the use of LOLA for patients with subclinical HE. Another meta-analysis by Bai et al²⁷ included 8 randomized controlled trials with 646 patients and compared LOLA with placebo/no-intervention control. LOLA was significantly more effective in the improvement of HE in the whole group. A recent meta-analysis by Zhu et al²⁸ concluded that LOLA treatment shows a trend in superiority for clinical efficacy among standard interventions for overt HE. A Cochrane systematic review and meta-analysis²⁹ extracted data on HE from 22 trials involving 1375 participants. The random effects meta-analysis suggested a beneficial effect favoring LOLA when including all trials, but the between-trial heterogeneity was substantial (RR 0.70, 95% CI, 0.59–0.83; $I^2 = 62\%$); there was no beneficial effect on the one trial at low risk of bias (RR 0.96, 95% CI, 0.85–1.07; 63 participants). Regression analysis and visual inspection of a funnel plot showed no evidence of small study effects ($P = 0.23$). The trial sequential analysis (relative RR, 17%; assumed control risk, 40%; alpha, 3%; and power, 90%; diversity, 50%) ignored trials in interim analyses and found that the Z-curve crossed the monitoring boundary when including all trials, regardless of bias control (trial sequential analysis (TSA)-adjusted RR 0.75; 95% CI, 0.35–1.42). Subgroup analyses found no difference in the effect of LOLA on HE in trials evaluating acute HE, chronic HE, minimal HE, or the prevention of HE (test for subgroup differences: $\chi^2 = 7.15$, $P = 0.07$, $I^2 = 58\%$).

There was no subgroup difference in the effect on HE between trials evaluating LOLA given intravenously or orally (test for subgroup differences $\chi^2 = 0.26$, $P = 0.61$, $I^2 = 0\%$). The author's conclusions were that there is a possible beneficial effect of LOLA on mortality, HE, and serious adverse events in comparisons with placebo or no intervention. However, as the quality of the evidence is very low, the authors were very uncertain about these findings. There was very low-quality evidence of a possible beneficial effect of LOLA on HE, when compared with

probiotics, but no other benefits were demonstrated in comparison with other active agents.

Thus, the current review and meta-analysis is one of the largest and most comprehensive on the efficacy of LOLA in HE. LOLA is effective for the treatment of both covert HE and bouts of overt HE in patients with cirrhosis (including higher grades of HE). However, larger trials of LOLA, involving more patients with higher grades of HE, are needed. LOLA can be used as a stand-alone treatment for covert HE. In bouts of overt HE, the addition of parenteral LOLA to lactulose is associated with a significantly shorter recovery time and a shorter length of hospital stay. Unlike lactulose and rifaximin, LOLA has been compared with placebo in high-quality trials and found to be effective. Future studies are required to define the efficacy of LOLA as a stand-alone treatment for bouts of covert HE. Finally, the side effect profile of LOLA is much better than lactulose.³⁰

CONFLICTS OF INTEREST

All authors have none to declare.

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