

Critical analysis of studies evaluating the efficacy of infusion of L-ornithine L-aspartate in clinical hepatic encephalopathy in patients with liver failure

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ABSTRACT

Introduction. Hepatic encephalopathy (HE) refers to a complex neuropsychiatric syndrome that is progressive but potentially reversible and may have a significant impact on quality of life, as it is characterized by alterations in cognitive function, behavior and personality as well as transient neurological symptoms and electroencephalographic abnormalities. **Objective.** The aim of this study was to evaluate scientific evidence for the effectiveness and safety of LOLA infusions for treatment of clinical hepatic encephalopathy in patients with chronic liver disease. **Material and methods.** We included all randomized, controlled, double-blind, and humans' studies that were published in indexed journals. **Results.** Were identified 48 references (17 using PubMed, 12 using Medline and 19 using the Cochrane database). Of these, six were selected as having met the inclusion criteria. A total of 623 patients were randomized in these publications. **Conclusion.** The available scientific evidence supports the adoption of LOLA infusion as a treatment for clinical encephalopathy in patients with liver failure, because it has been shown to improve neuropsychiatric status and decrease serum levels of ammonia with a low incidence of adverse effects (less than 5%).

Key words. Hepatic encephalopathy. LOLA infusion. Chronic liver disease.

INTRODUCTION

Hepatic encephalopathy (HE) or portosystemic encephalopathy (PSE) refers to a complex neuropsychiatric syndrome that is progressive but potentially reversible and presents as a complication of acute or chronic liver failure.¹ HE may have a significant impact on quality of life, as it is characterized by alterations in cognitive function, behavior and personality as well as transient neurological symptoms and electroencephalographic abnormalities.²

The association between HE and ammonia has been known for many years, as Eck described neuropsychiatric abnormalities after feeding dogs with portacaval shunts. Blood ammonia concentrations are consistently elevated in liver failure³⁻⁴ and am-

monia concentration in the brain can reach millimolar levels. Positron emission tomography (PET) with ¹³NH₃ revealed an increase in the percentage of cerebral metabolism of ammonia and an increase in the permeability of the blood brain barrier in patients with chronic liver disease.⁴ In acute liver failure, arterial ammonia concentrations are correlated with the degree of brain herniation,³ which is caused by elevated intracranial pressure. Ammonia concentration in the low millimolar range (which are observed in the cerebral circulation in liver failure), exert adverse effects on brain function via direct and indirect mechanisms. The ammonium ion (NH₄⁺) exerts direct effects on inhibitory and excitatory neurotransmitters via different mechanisms. For example, millimolar concentrations of ammonia alter postsynaptic inhibition by inactivating chlorine (Cl⁻) ejection from neurons, destroying the concentration gradient of this ion across the neuronal membrane,⁵ and abolishing inhibitory postsynaptic potential. NH₄⁺ also affects excitatory neurotransmitters by interfering with the action of glutamate, the major excitatory neurotransmitter in the mammalian brain, which binds to postsynaptic recep-

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tors.⁵ Ammonia can also inhibit the supply of energy to the brain by affecting the activity of α -ketoglutarate dehydrogenase and thus the activity of the tricarboxylic acid cycle.⁶

There is evidence to suggest that hyperammonemia in liver failure is the result of alteration in the movement of ammonia between organs. The enterocytes of the intestine express glutaminase, which converts glutamine to glutamate and ammonia. In liver failure, the intestinal contribution to hyperammonemia is predominantly the result of a reduction in ammonia detoxification by the liver together with the action of short intra and extrahepatic caval circuits.⁷

Ammonia is detoxified in the liver at two distinct but metabolically related sites. The synthesis of urea from ammonia via the urea cycle takes place in periportal hepatocytes, whereas perivenous hepatocytes produce ammonia from glutamine via the action of the enzyme glutamine synthetase. The simultaneous effects of these two systems and that of periportal glutaminase result in an intercellular glutamine cycle in the liver.⁸ Cirrhotic patients develop portosystemic intra- and extrahepatic short circuit, which can constitute more than 50% of portal blood flow.⁷ In these patients, loss of hepatocytes and impaired liver function decreases the ability to produce glutamine and urea and, therefore, the ability to detoxify ammonia.

L-ornithine L-aspartate (LOLA) is a substrate for the metabolism and conversion of ammonia to urea and glutamine. Its effects are mediated as follows:

- L-ornithine, an intermediate of the urea cycle, promotes urea synthesis.
- LOLA promotes glutamine synthesis in skeletal muscle, which is used as a substrate for glutamate production by glutamine synthetase. Both L-ornithine and L-aspartate are substrates for transamination reactions that result in the production of glutamate.⁹⁻¹¹

Experimental studies with animals show that LOLA is effective in lowering blood ammonia concentration and preventing of cerebral edema in acute liver failure; studies with humans in which LOLA was compared with disaccharides or a placebo, show that it is an effective treatment for hepatic encephalopathy.

OBJECTIVE

The aim of this study was to evaluate scientific evidence for the effectiveness and safety of

LOLA infusions for treatment of clinical hepatic encephalopathy in patients with chronic liver disease.

MATERIAL AND METHODS

Criteria for inclusion of studies in this review were as follows.

- **Study type.** We included all randomized, controlled, double-blind, and human studies that were published in indexed journals.
- **Type of participants.** Patients with cirrhosis or liver failure with hyperammonemia and hepatic encephalopathy, of either sex and any age and ethnicity were included.
- **Type of intervention.** We considered experimental interventions involving intravenous administration of LOLA and control and placebo groups.
- **Search methodology to identify studies.** A search of the MEDLINE, Cochrane and PubMed databases was conducted using the key words: "L-ornithine-L-aspartate" or "ornithine-aspartate" to identify relevant studies published between 1980 and 2010. Papers published in English or Spanish were included. We excluded abstracts, letters to the editor, conference presentations and preliminary.

RESULTS

Were identified 48 references (17 using PubMed, 12 using Medline and 19 using the Cochrane database). Of these six were selected as having met the inclusion criteria.¹¹⁻¹⁶ A total of 623 patients were randomized in these publications. Their ages ranged from 22 to 65 years. In total, 422 patients (67%) were diagnosed with cirrhosis and the remainder had acute liver failure. The etiology of chronic liver failure was reported:

- 76% of cases were caused by excessive alcohol consumption.
- 19% were associated with post-viral hepatitis.
- 5% had other causes.

Acute liver failure was most frequently observed in patients with fatty liver of pregnancy (53%). The degree of encephalopathy was grade to a three-point scale using the West-Haven clinical criteria. L-ornithine L-aspartate was administered parenterally in

all the studies; the mean dose was 20 g/d (range 5-40 g/d) and the duration of treatment ranged from 24 h to 7 d. LOLA was always compared with a placebo. Hepatic encephalopathy status was monitored in all studies and clinical results were analyzed. Plasma ammonia concentration was available for most, but not all studies. The results of psychometric tests to assess mental status and of the number connection test-A, were analyzed. One of the studies compared a LOLA group with a group in which an osmotic laxative was administered.¹⁶ Endpoints were defined in terms of the stage of hepatic encephalopathy, blood ammonia level or hospital stay.

Efficacy and response to treatment

Expressed relative to the placebo treatment, responses to the LOLA infusion were the follows.

- The number connection test results differed between the LOLA and placebo groups on day 4 of treatment (55 ± 19 s and 58 ± 23 s, respectively) ($p = 0.0078$) and on day 7 of treatment ($p = 0.0006$).
- Venous ammonia concentration improved in the LOLA group. The decrease in blood ammonia after 7 d was 17 ± 37 $\mu\text{mol/L}$ in the LOLA group vs. 6 ± 32 $\mu\text{mol/L}$ in the placebo group ($p < 0.05$).
- The stage of encephalopathy on day 7 was 0.14 ± 0.13 units lower than that before treatment in the group receiving LOLA and 0.05 ± 0.1 units lower than that before treatment in the placebo group ($p = 0.001$). The Wilcoxon test for two samples showed that LOLA decreased ($p = 0.0003$) the stage of encephalopathy.¹¹⁻¹⁵

A study published by Abdo, *et al.*¹⁶ showed that LOLA infusion reduced the number of days spent in hospital compared with an osmotic laxative (oral lactulose). The accumulated number of days of hospitalization for patients who received LOLA was 264 d vs. 443 d in patients who received the osmotic laxative (40% reduction in hospital stay).

Encephalopathy recovery time was faster in patients who received LOLA than in those who received lactulosa (4.32 d vs. 10.15 d, respectively).¹⁶

Adverse effects were observed in only 5% of patients and presented nausea and vomiting which were always associated with the rate of drug infusion and were resolved by reducing the rate of infusion or stopping the treatment.

DISCUSSION

The efficacy of LOLA for reducing serum ammonia level and increasing hepatic neuropsychiatric status in encephalopathy has been studied for many years. Despite this, few double-blind, randomized, placebo-controlled studies have been conducted to evaluate the effects of LOLA. Appropriate measures of the effectiveness of LOLA are serum levels of ammonia, the clinical state of encephalopathy assessed using the West Haven score for encephalopathy and mental status, usually assessed using psychometric tests (such as the number connection test). Studies have demonstrated that LOLA reduces blood ammonia level in patients with hepatic encephalopathy. A reduction in blood ammonia level was observed shortly after infusing the drug intravenously in a cross-sectional study with 10 patients with cirrhosis of different etiologies,¹¹ and was most evident at a high dose of LOLA (40 g/d) (note that patients also consumed a diet containing 0.5 g protein per kg of weight).

Kircheis, *et al.*¹² observed a significant reduction in blood ammonia level on the seventh day of LOLA infusion (17 ± 37 μmol vs. 6 ± 32 μmol $p < 0.05$). It should be noted that the etiology of hepatic encephalopathy is multifactorial and depends not only on the increase in blood ammonia but also on a triggering mechanism (such as infection, bleeding or an electrolyte disorder). Abdo, *et al.* provide evidence that LOLA treatment reduces hospital stay compared with an osmotic laxative, an alternative treatment for hepatic encephalopathy. Replacement of an osmotic laxative with LOLA will reduce the cost of treatment and the shorter hospital exposure associated with LOLA treatment will reduce the risk of nosocomial infection.

CONCLUSION

The available scientific evidence supports the adoption of LOLA infusion as a treatment for clinical encephalopathy in patients with liver failure because it has been shown to improve neuropsychiatric status and decrease serum levels of ammonia with a low incidence of adverse effects (less than 5%).

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