

## L-ORNITHINE ASPARTATE AMONG CIRRHOTIC PATIENTS WITH HEPATIC ENCEPHALOPATHY: DOES IT MAKE A DIFFERENCE?

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### ABSTRACT

**Background:** Hepatic Encephalopathy is a complication of liver failure. Over the last two decades, studies have shown the beneficial use of "ammonia lowering" drugs, particularly amino acids, such ornithine-aspartate among patients with hepatic encephalopathy.

**Objectives:** To determine the effectivity of L-ornithine aspartate among patients with cirrhosis complicated with hepatic encephalopathy. Search strategy: An electronic search using MEDLINE, Pubmed, Medscape, Science Direct, and Cochrane Library Documents. Search terms included L-ornithine aspartate searched with liver cirrhosis and/ or hepatic encephalopathy.

**Selection criteria:** Randomized controlled trials comparing the effect of L-ornithine aspartate and placebo for at least 7 days among patients diagnosed with cirrhosis and hepatic encephalopathy. Decisions regarding inclusion of data were duplicated while disagreements were resolved by discussion or a third party.

**Data collection & analysis:** Three reviewers assessed trial quality and compared outcomes independently. Weighted Mean Difference (WMD) and relative risk ratios were computed using Revman Manager 4.2.8. Heterogeneity was determined using forest plots,  $\chi^2$  and  $I^2$  tests.

**Main results:** Three RCTs met the criteria and were included in the study (n = 277). Treatment with L-ornithine aspartate showed that there was a significant improvement to patient's mental state after therapy as compared to placebo with a fixed OR 0.42 (CI 95% 0.23, 0.78). However, there was no significant change in the mean PSE Index between therapy and placebo (WMD 0.09 CI 95% 0.05, 0.13). On the other hand, no summary statistics can be derived from the pooled data with regards to change in the mean ammonia level because of the significant heterogeneity in the included trials.

**Reviewers' conclusions:** Although the evidence from the three RCTs suggests that L-ornithine aspartate is effective in improving the mental state gradient, more high quality trials are required to conclusively determine the benefit of L-ornithine aspartate among cirrhotic patients.

**Category:** Liver; **Article:** Meta-analysis; **Key words:** L-ornithine aspartate, hepatic encephalopathy, Portal systemic encephalopathy index or PSE index

### INTRODUCTION

Hepatic Encephalopathy is a major, reversible complication of liver failure, whether it may be from an acute or chronic liver disease. It presents a spectrum of non specific, neurologic abnormalities which can lead to poor long-term prognosis if not treated and recognized in time.

The precise pathophysiologic mechanisms of hepatic encephalopathy remains unknown, however, several hypotheses have surfaced to explain this neuropsychiatric complication, the most important of which are the impaired neurotransmission and increase in blood concentrations of substances, particularly ammonia and manganese that are potentially neurotoxic. Studies have demonstrated that there is a significant alteration in the glutamatergic and monoaminergic mechanisms in the brain of patients with hepatic encephalopathy. Glutamine, formed from glutamate, is a major metabolite and excitatory neurotransmitter, which is invariably increased in hepatic encephalopathy with exposure to even low levels of ammonia. Likewise, it has also been shown that there are increased serotonin, homovanillic acid and GABA levels and activation of the opioid system with concomitant decrease in serotonin levels. On the other hand, significant levels of ammonia has been very much

implicated as a major cause of hepatic encephalopathy with PET studies demonstrating an increase in the permeability of ammonia in the blood-brain barrier. The effects of ammonia in the brain consist of both direct and indirect mechanisms and there is little doubt that ammonia plays a major role in the pathogenesis of hepatic encephalopathy.<sup>9</sup>

In cirrhotic patients, carbamylphosphate synthetase and glutamine synthetase, both major ammonia detoxifying enzymes for the production of urea and glutamine are impaired, consequently leading to hyperammonemia.<sup>3,4</sup> Over the last two decades, studies<sup>5</sup> involving use of L-ornithine aspartate in patients with liver cirrhosis have demonstrated beneficial effects. Proposed mechanisms<sup>2,4</sup> as basis for the use of “ammonia lowering” drugs, particularly amino acids, such ornithine-aspartate include the following: 1) in cirrhotic patients, aspartate and citric dicarboxylates may serve as carbon sources for impaired glutamine synthetase flux in the perivenous scavenger hepatocytes; and 2) ornithine improves the flux through the impaired urea cycle enzyme system, especially through carbamylphosphate synthetase, localized in the periportal hepatocytes.

Despite several studies demonstrating its beneficial effects, L-ornithine aspartate is still not as frequently used among patients with hepatic encephalopathy and there are still some hesitations and issues with regards to its real benefit. Hence, this study aims to confirm the effectiveness of L-ornithine aspartate among cirrhotic patients with hepatic encephalopathy and determine if it does make any difference.

## **OBJECTIVES:**

### *A. General Objective:*

To determine the effectiveness of L-ornithine aspartate on cirrhotic patients complicated with hepatic encephalopathy.

### *B. Specific Objectives:*

1. To be able to determine the effect on the improvement of mental state gradient with the use of L-ornithine aspartate.
2. To determine the effect on the change in mean ammonia blood level with the use of L-ornithine aspartate.
3. To determine the effect on the change in mean PSE Index with the use of L-ornithine aspartate.

## **METHODOLOGY**

### *Literature Search*

Two investigators independently searched the published English literature using MEDLINE, Pubmed, Medscape, Science Direct, and Cochrane Library Documents. Search terms included *L-ornithine aspartate* search with *Liver cirrhosis* and/ or *Hepatic Encephalopathy*. Review of other cited bibliographies and reference lists were made to increase our yield. No language and date restrictions were used.

### *Study Selection Criteria*

Studies were included if they met the following criteria: 1) randomized controlled trials; 2) population consisted of established cirrhotic patients (either sonographically, histologic or based on clinical grounds) with hyperammonemia (> 50 umol/l), and presence of stable, spontaneous, chronic, overt Hepatic encephalopathy; 3) outcomes of blood ammonia level, mental state gradient and PSE Index were measured in the RCT.

Studies were excluded if they did not include encephalopathic patients, were not randomized controlled trials, studies where they induced hyperammonemia (e.g., by giving glutamine challenge).

### *Quality Assessment and Data Abstraction*

Studies accepted for meta-analysis were reviewed and assessed independently by three reviewers using the critical appraisal form for quality assessment of controlled trials. This included concerns in randomization,

allocation concealment, blinding, similarities in baseline characteristics, and intention to treat analysis. Assessment was then done and each included trial was graded A, B, or C or high quality, fair-quality or low-quality. Decisions regarding inclusion of data were duplicated, disagreements were resolved by discussion or a third party.

Reviewers independently and in duplicate abstracted the information on patient population (inclusion/exclusion criteria), methods, interventions, outcome of treatments, particularly those that were pertinent to this review which includes the mean change in blood ammonia level, improvement in mental state gradient and the change in mean portosystemic encephalopathy index.

### **Statistical Analysis**

Data were entered and analyzed using Review Manager 4.2.8. For dichotomous variables, individual and pooled statistics were reported as odds ratio (OR). For continuous variables, the weighted mean differences (WMD) were calculated.

For one study which did not mention the actual mean, data extrapolation was done from the pertinent available graph presented in the paper and the standard deviation calculated as the half of the inter quartile range.

For studies that did not give the standard deviation (SD), the change from baseline to post treatment was computed by assuming a correlation coefficient ( $\rho$ ) of 0.5 and applying this to the following equation:

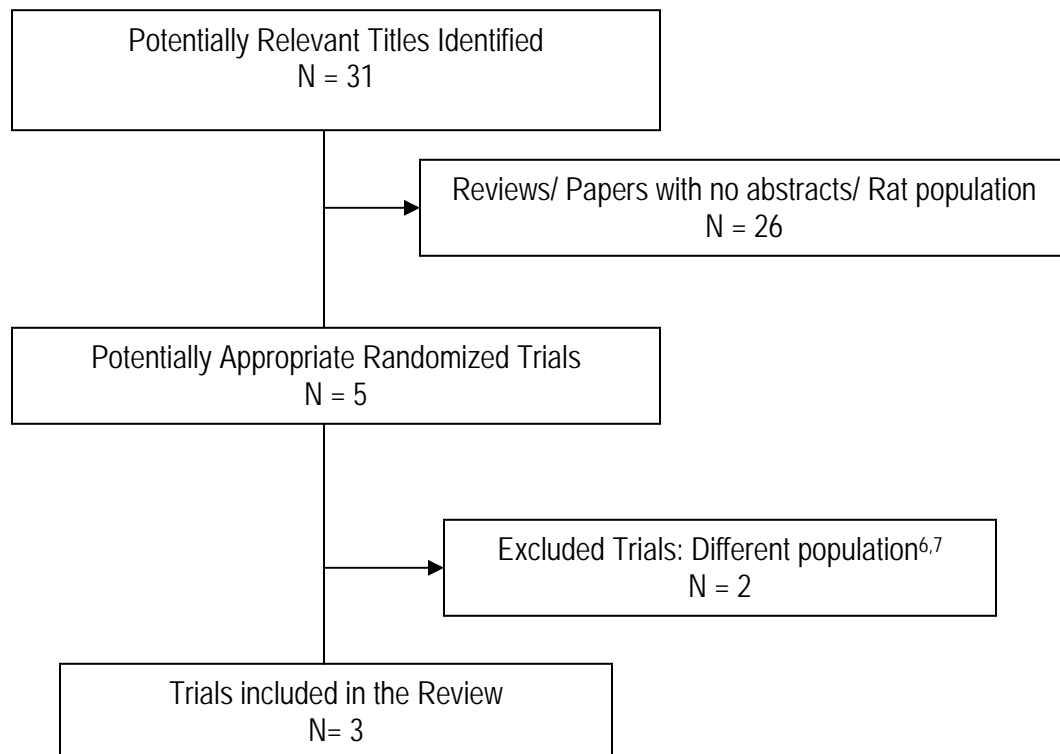
$$\text{Var}(\overline{\Delta\chi}) = \text{Var}(\overline{\chi_{\text{pre}}}) + \text{Var}(\overline{\chi_{\text{post}}}) - 2\rho\sqrt{(\text{Var}\chi_{\text{pre}})(\text{Var}\chi_{\text{post}})}$$

Heterogeneity between comparable trials were tested using a standard chi square test and considered significant if  $p < 0.05$ . Likewise, an  $I^2$  test was used to determine heterogeneity.

### **RESULTS**

A total of 31 potentially relevant titles were identified and of these, only 3 trials<sup>1,4,8</sup> satisfactorily fulfilled the inclusion criteria. Papers that used non human population (4), different treatment arms/ outcomes (3) as well as review papers (8) were rejected. In addition, there were 12 papers that had no abstracts and full text materials were also unavailable. (See Figure 1).

Figure 1. Identification of Potentially Relevant Studies for Review



Two trials<sup>4,8</sup> were assessed as high quality (A) based on the Quality Scale for Meta-Analytic Review. One trial<sup>1</sup> was written in simplified Chinese text and quality assessment can not be performed because of lack of an English translation. All trials included patients (n=277) diagnosed with liver cirrhosis either proven histologically or confirmed by ultrasound with stable, spontaneous, chronic overt hepatic encephalopathy with ammonia level >50  $\mu\text{mol}$ . Patients with active, major complications of portal hypertension, serious non hepatic diseases, severe hepatic encephalopathy, pregnant or lactating persons, patients who were on anti hepatic encephalopathy medications were all excluded from the studies. Majority of the patients were graded with Child-Pugh scoring of A-B. Most common causes of cirrhosis among these patients were due to alcohol and hepatitis. The trials measured all the outcomes relevant to the review.

The study medication was consisted of L-ornithine aspartate which differed in the route and dosing regimen among the trials. Two of the three trials used the 40 ml or 20 grams of L-ornithine aspartate via intravenous route (Chen and Kircheis), while the study made by Stauch used 6 grams oral L-ornithine aspartate. In all trials, L-ornithine aspartate was given for at least 7 days to 14 days compared with placebo only. Table 1 shows the tabulated summary of included trials in the review.

### ***Effect on the Mental State Gradient***

Two trials measured the outcome of L-ornithine aspartae on the improvement of mental state gradient among cirrhotic patients with hepatic encephalopathy. Pooled data showed a significant effect with the use of the treatment arm as compared to placebo with an OR 0.42 (0.23, 0.78 at 95% CI). See Figure 2.

Table 1. Characteristics of Included Studies

Study	Methods	Participants	Intervention	Outcomes	Quality
Chen et al. <sup>1</sup>	RCT, blinded	85 cirrhotic patients complicated by liver cirrhosis	intravenous 40 ml LOLA* in 250 ml 10% glucose water and saline (once daily for 7 days) vs no treatment	Blood ammonia and liver function (Total bilirubins, ALT)	C
Kircheis, G. et al. <sup>4</sup>	RCT, double-blinded study, randomization performed by random generator blocks of 4	126 cirrhotic patients. Inclusion criteria: chronic (persistent), manifest HE (mental state grade I/II) or SHE (mental state grade 0 and NCT-A performance time > 30 seconds); hyperammonemia (venous ammonia concentration > 50 umol); histologically proven cirrhosis or overt clinically proven cirrhosis confirmed by ultrasound.	Intravenous infusions of 20 g OA (4 ampules of 10 ml each) in 5% fructose for 4 hours vs. placebo solution (4 ampules of 10 ml each in 250 ml 5% fructose) for 7 consecutive days.	post prandial venous ammonia, NCT-A performance test time, Mental state gradation, and portosystemic index (PSEI), fasting ammonia levels	A
Stauch, S. et al. <sup>8</sup>	RCT, randomization by random generator in blocks of 4	66 cirrhotic patients with stable, spontaneous, chronic overt HE (mental state grade I or II) or SHE (mental state grade 0 and NCT-A performance time > 30 seconds); with hyperammonemia (fasting venous blood ammonia level > 50 umol/l), cirrhosis diagnosed by histology, sonographic or on clinical grounds.	6 grams LOLA vs 5 grams fructose, given three times a day, dissolved in water before meals for 14 consecutive days	post prandial venous ammonia concentrations, Number Connection Test performance times, Mental state grade and PSE Index	A

\* LOLA: L-ornithine L-aspartate

Review: L-ornithine Aspartate among Cirrhotic Patients with Hepatic Encephalopathy: Does it make a difference?  
 Comparison: 01 Efficacy of L-ornithine Aspartate  
 Outcome: 02 improvement in mental status

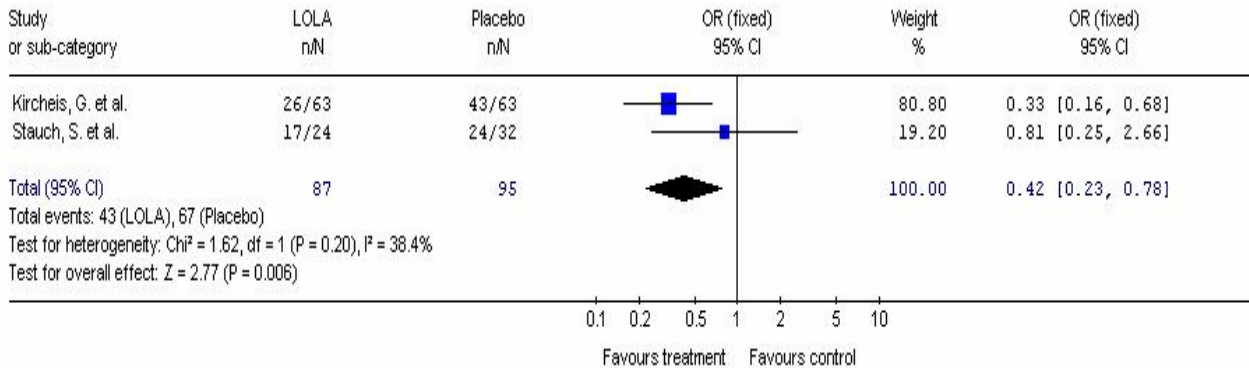


Figure 2. Mean Change in Mental State Gradient

**Effect on the Blood Ammonia Level**

Three trials measured the effect of L-ornithine aspartate on the mean change in blood ammonia levels after 7 days of treatment. Pooled data analysis however, showed significant heterogeneity with  $\chi^2 = 21.40$  ( $P < 0.0001$ ) among the included trials thus no summary statistic can be derived for this outcome. See Figure 3.

Review: L-ornithine Aspartate among Cirrhotic Patients with Hepatic Encephalopathy: Does it make a difference?  
 Comparison: 01 Efficacy of L-ornithine Aspartate  
 Outcome: 01 change in mean of blood ammonia level

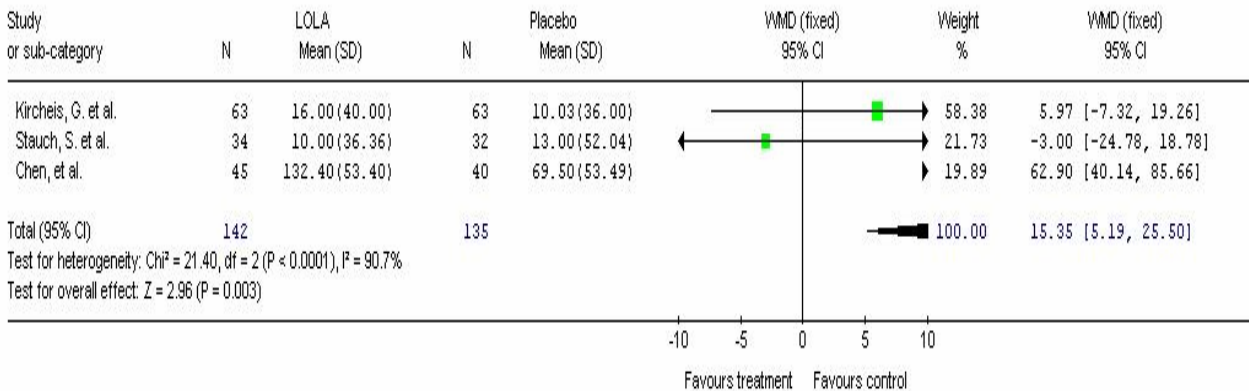


Figure 3. Mean Change in Blood Ammonia Level

**Effect on the Portosystemic Encephalopathy Index**

Data from the pooled homogenous data ( $P=0.83$ ) showed that L-ornithine aspartate has no significant effect on the portosystemic index when used among cirrhotic patients with hepatic encephalopathy with a WMD 0.09 (0.05, 0.13 at 95% CI). See Figure 4 below.

Review: L-ornithine Aspartate among Cirrhotic Patients with Hepatic Encephalopathy: Does it make a difference?  
 Comparison: 01 Efficacy of L-ornithine Aspartate  
 Outcome: 03 change in mean PSE Index

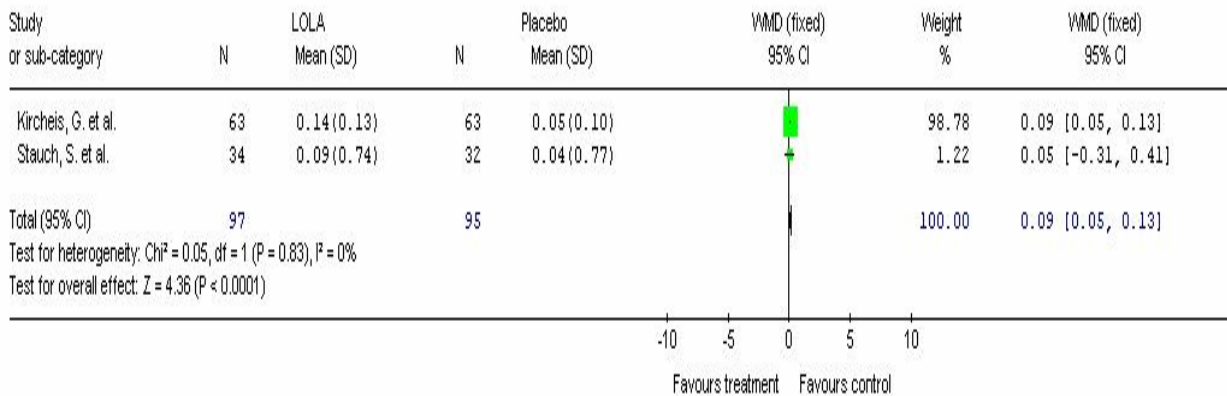


Figure 4. Mean Change in PSE Index

**DISCUSSION**

This study reviewed the effectiveness of L-ornithine aspartate among cirrhotic patients with hepatic encephalopathy with regards to its effect on the mental state gradient, blood ammonia levels and PSE Index. A total of three trials met the inclusion criteria with a total population of 277 patients, most of whom had Child-Pugh grade of A-B.

From the pooled analysis, this review showed only significant benefit with the use of L-ornithine in terms of improvement in mental state gradient, whereas no benefit can be derived for its effect on the blood ammonia level and change in PSE index. In hepatic encephalopathy, clinical outcome of the patient is more helpful in determining whether the patient’s status is improving or not. Therefore, despite the results of this review, the improvement in the mental state of the patient is already significant and important.

Also in this review, significant heterogeneity was seen in the included trials, which could be attributed to the fact that they differed in the route and dosing regimen of L-ornithine aspartate. (Chen et al. used intravenous 40 ml L-ornithine aspartate in 250 ml 10% glucose water, Kircheis et al. gave 20 g of L-ornithine aspartate in 5% fructose whereas Stauch et al. used an oral L-ornithine aspartate of 6 grams 3x a day). This review also may not have the power to detect significant benefit among the outcomes measured primarily because of limited population of the included trials.

**LIMITATIONS**

The following are the limitations of this review:

- 1) There was significant heterogeneity among the trials primarily because of differences in the methodology, including treatment protocols;
- 2) The trials included in the review had small populations.
- 3) The investigators were unable to extract the full text articles of some studies because of financial constraints, hence limiting also the number of trials properly assessed for inclusion in this review.

**CONCLUSION**

Although the evidence from the three randomized controlled trials suggests that L-ornithine aspartate is effective in improving the mental state gradient, more high quality trials are required to conclusively determine the benefit of L-ornithine aspartate among cirrhotic patients.

## IMPLICATIONS FOR RESEARCH AND HEALTHCARE

L-ornithine aspartate is a potential, non invasive alternative in the treatment of patients with hepatic encephalopathy. In order to be able to give conclusive evidence of significant benefit, large population, high quality randomized controlled trials comparing L-ornithine aspartate with placebo should be undertaken.

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