A CRITICAL ANALYSIS OF STUDIES ASSESSING L-ORNITHINE-L-ASPARTATE (LOLA) IN HEPATIC ENCEPHALOPATHY TREATMENT

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ABSTRACT – Context - Experimental and clinical studies suggest that LOLA may have a favorable influence on hepatic encephalopathy due to the effect on the reduction of ammonia, and improvement of the symptoms and laboratory findings. Objectives - To evaluate and to critically analyze the efficacy and/or effectiveness results of the use of LOLA when compared to placebo in the treatment of hepatic encephalopathy. Data sources - LILACS, SciELO, MEDLINE, PubMed database and Cochrane Collaboration Register of Controlled Trials were searched from 1966 to September of 2006. The review has included all the randomized controlled double-blind clinical trials performed in humans in English language. Results - Four studies published between 1993 and 2000 were selected and reviewed. LOLA was showed as being able to reduce hyperammonemia in patients with hepatic encephalopathy, when compared to patients in the placebo group. Conclusions - Although the trials have shown efficacy of LOLA in reducing hyperammonemia of hepatic encephalopathy, sufficient evidence of a significant beneficial effect of LOLA on patients with hepatic encephalopathy was not found. The studies performed in this area were small, with short follow-up periods and half of them showed low methodological quality.

HEADINGS - Hepatic encephalopathy. Dipeptides.

INTRODUCTION

Change in the brain function is a characteristic complication of acute or chronic liver failure. In addition to the traditional presentation, as frank hepatic encephalopathy (HE), a subclinical manifestation form is currently known, where the patient has a normal neurological status, but manifests motor and cognitive deficits detected only by specific tests. Minimum hepatic encephalopathy (MHE) is an entity of unquestionable clinical importance due to the high prevalence, occurring in up to 84% of cirrhotic patients. Furthermore, MHE may potentially evolve to frank HE in about 56% in 3 years negatively interfering in the survival of these individuals. This survival is not bigger than 20% in 5 years, following the identification of the clinically manifested disease.

In spite of a silent course, studies have shown that daily activities and quality of life of cirrhotic individuals with MHE are compromised. Use of lactulose in the treatment MHE was related to improvement in the detection tests of the disease, in addition to the impact in the quality of life of these individuals; however, its routine usage in the clinical practice is questionable and more prospective, randomizes trials are necessary.

Most of therapeutic measures currently in use aim the reduction of serum levels of ammonia, principally through a smaller production of enteric ammonia. Experimental and clinical trials, started more than 25 years ago, suggest that L-ornithine L-aspartate (LOLA) may have a favorable influence on HE due to the effect on the reduction of ammonia, and improvement of symptoms and laboratory findings related to HE.

However, few controlled trials are known to have reached theses results, as the possibility of spontaneous resolution without specific therapeutics is known. As there is a current lack of consensus related to the usage of LOLA in HE, the present study has the purpose of evaluating and critically analyzing efficacy and/or effectiveness studies of the use of LOLA when compared to placebo in the treatment of HE.

METHODS

Criteria for consideration of studies in this review

Type of studies

The review has included all the randomized controlled double-blind clinical trials performed...
Type of participants
Patients with cirrhosis, hyperammonemia, and HE, any gender, age or ethnicity were included.

Type of intervention
Experimental intervention could be LOLA dosed by oral or parenteral route in any dosage or duration. Control group could be a placebo.

Searching strategy for identification of the studies
A comprehensive searching strategy was formulated, in order to identify all the relevant studies. LILACS, SciELO and MEDLINE (1966-9/2006) were searched, by using the following terms: “ornithine” and “aspartate” and (“hepatic encephalopathy”). PubMed (1966-9/2006) was searched, by using the terms “L-ornithine-L-aspartate” or “ornithine-aspartate”. Cochrane Collaboration Register of Controlled Trials (CCRCT) was also searched, by using the term “ornithine”.

Critical analysis of the papers
The methodological quality of the papers included was evaluated according to the following schedule(17):

a. Was the patient allocation randomized?
   i. Was the follow-up complete?
   ii. Were the patients analyzed according to the randomization?

b. Were all the patients who took part in the trial properly evaluated?

c. Were the patients, health professionals and researchers blinded?

C. Were the groups similar in the beginning of the trial, except for the intervention?

d. Were the groups equally followed-up?

f. What were the results?
   i. How large was the effect of the treatment?
   ii. How accurate was the estimation of the effect of the treatment?

g. Can the results help in the treatment of my patients?
   i. Can the results be applied to my patients?
   ii. Were all the clinically important outcomes considered in the trial?
   iii. Are the probable benefits of the treatment worth the potential costs and hazards?

Evaluation of the methodological quality of the studies was finished by using JADAD et al.(26) scale, composed by three items, quantifying the probability of bias related to the trial according to the description of randomization, masking, withdrawals and dropouts. Scores vary from 1 to 5; studies that present scores 1 or 2 are considered as showing low quality and studies that present scores 3 to 5 are considered as showing high quality.

RESULTS

Search results
A total of 271 references was identified by electronic search in MEDLINE (n = 22), PubMed (n = 97) and Cochrane Collaboration Register of Controlled Trials (n = 152). No paper was found in LILACS and SciELO database. Fifty nine duplicate references and 145 references considered as irrelevant after reading the abstracts were excluded.

From the remaining 67 references, 63 were excluded, 16 reviews(5, 6, 7, 12, 13, 27, 28, 31, 32, 38, 44, 51, 56, 67, 69, 72), 1 letter to the editor(33), 7 abstracts (21, 29, 39, 40, 46, 53, 55), 1 presentation in congress(54), 14 other study design(1, 3, 14, 15, 20, 25, 37, 42, 57, 58, 61, 65, 68, 71), 17 in another language(2, 4, 5, 9, 10, 19, 24, 35, 39, 43, 45, 48, 52, 59, 60, 62, 66, 73), and 7 clinical trials that have not met our inclusion criteria (11, 18, 22, 25, 36, 41, 49). Remaining references are four randomized, controlled clinical trials that met the inclusion criteria(30, 54, 63, 64). Figure 1 shows the results from the search and Figure 2 describes the included studies.

Description of the studies
Four trials were included in this analysis. All four trials were reviewed as complete papers. Details of the trials were described in Figure 2. Two trials used parallel groups design and two trials used crossover groups design.
To investigate the therapeutic efficacy of LOLA in patients with cirrhosis, hyperammonemia and frank, stable, chronic HE, and MHE

To investigate the therapeutic efficacy of LOLA in patients with cirrhosis, hyperammonemia and chronic, persistent HE.

To evaluate the effects of LOLA in plasma concentration of ammonia and amino acids from patients with cirrhosis

Randomized, controlled, two-fold crossover, double-blind, placebo controlled clinical trial

Randomized, controlled, double-blind, placebo controlled clinical trial

Randomized, controlled, double-blind, placebo controlled clinical trial

Randomized, controlled, four fold crossover, double-blind, placebo controlled clinical trial

A critical analysis of studies assessing L-ornithine-L-aspartate (LOLA) in hepatic encephalopathy treatment

A total of 217 patients were randomized in the trials. Mean number of patients in each trial was 54 (varying from 10 to 126). Mean ages varied from 52 to 57 in these trials. All 217 patients had cirrhosis. The etiology of cirrhosis was alcohol (81%), hepatitis (14%), and others (5%). Patients had some kind of hepatic encephalopathy (three trials), minimum hepatic encephalopathy (two trials) and grade I and II hepatic encephalopathy (two trials). (Table 1)

With respect to the administration of ornithine-aspartate, three trials used parenteral dosing and one trial used oral dosing. Average amount of LOLA was 18 g/day (ranging from 5 to 40 g) and mean duration of the treatment was 7 days (ranging from 2 to 14 days) (Table 2).

Placebo was used as comparator for LOLA in all four trials. Ornithine aspartate administration was accompanied by special nutritive diets (0.8-1 g of protein/kg of weight/per day) in three trials. LOLA administration was accompanied by ingestion of 20 g of oral glutamine. Overall, LOLA group and control group received a similar caloric regimen in all four trials.

All four trials evaluated the improvement in the clinical outcomes caused by the use of LOLA. Clinical outcomes were analyzed by plasma concentration of ammonia post-meal and in fasting condition, plasma concentration of some amino acids, psychometric tests such as NCT-A, mental status grade, PSEI, CRT (patients’ choice reaction time) and electroencephalogram. Figure 3 presents the effects of the use of LOLA.

### Table 1. Description of the patients according to the trial included

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Total number of patients (n)</td>
<td>15</td>
<td>66</td>
<td>120</td>
<td>15</td>
<td>217</td>
</tr>
<tr>
<td>Male</td>
<td>NA</td>
<td>42(64)</td>
<td>91(72)</td>
<td>8(80)</td>
<td>141(70)*</td>
</tr>
<tr>
<td>Female</td>
<td>NA</td>
<td>24(36)</td>
<td>35(28)</td>
<td>2(20)</td>
<td>61(30)*</td>
</tr>
<tr>
<td>Age (years) (mean)</td>
<td>52</td>
<td>57</td>
<td>57</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>Cirrhosis etiology</td>
<td>14(93)</td>
<td>54(82)</td>
<td>100(79)</td>
<td>80(80)</td>
<td>176(81)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1(7%)</td>
<td>6(12)</td>
<td>20(16)</td>
<td>2(20)</td>
<td>31(14)</td>
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<tr>
<td>Hepatitis</td>
<td>0(0)</td>
<td>4(6)</td>
<td>6(5)</td>
<td>0(0)</td>
<td>10(5)*</td>
</tr>
<tr>
<td>Other</td>
<td>0(0)</td>
<td>23(35)</td>
<td>53(42)</td>
<td>0(0)</td>
<td>76(35)</td>
</tr>
<tr>
<td>HE Grade</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MHE</td>
<td>0</td>
<td>25(38)</td>
<td>53(42)</td>
<td>0</td>
<td>76(35)</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>18(27)</td>
<td>20(16)</td>
<td>0(0)</td>
<td>38(17)</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>38(58)</td>
<td>64(51)</td>
<td>102(49)**</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh Grade</td>
<td>12(80)</td>
<td>21(32)</td>
<td>50(40)</td>
<td>NA</td>
<td>81(40)*</td>
</tr>
<tr>
<td>B</td>
<td>3(20)</td>
<td>7(16)</td>
<td>12(9)</td>
<td>22(11)**</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**IV = Intravenous
LOLA = L-ornithine-L-aspartate
NA = Not available

### Table 2. Description of LOLA administration, control and additional therapy according to the trial included

<table>
<thead>
<tr>
<th>Studies</th>
<th>Total number of patients</th>
<th>Study medication/duration of the treatment</th>
<th>Number of patients included in each group</th>
<th>Age (years) Mean (SD) or variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>REES et al. (1997)</td>
<td>15</td>
<td>LOLA 5 g/IV</td>
<td>15</td>
<td>52 (NA)</td>
</tr>
<tr>
<td>Placebo/IV</td>
<td>15</td>
<td>52 (NA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stauch et al. (1997)</td>
<td>66</td>
<td>LOLA 18 g/oral Placebo/oral</td>
<td>34</td>
<td>48.5 (64.6)</td>
</tr>
<tr>
<td>Placebo/IV</td>
<td>32</td>
<td>70.9 (74.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kircheis et al. (1997)</td>
<td>126</td>
<td>LOLA 20 g/IV Placebo/IV</td>
<td>63</td>
<td>53.9 (12.4)</td>
</tr>
<tr>
<td>Placebo/IV</td>
<td>63</td>
<td>52.3 (13.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staedt et al. (1997)</td>
<td>10</td>
<td>LOLA 5 g/IV</td>
<td>10</td>
<td>53 (10)</td>
</tr>
<tr>
<td>Placebo/IV</td>
<td>10</td>
<td>53 (10)</td>
<td></td>
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</tr>
<tr>
<td>Placebo/IV</td>
<td>10</td>
<td>53 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo/IV</td>
<td>10</td>
<td>53 (10)</td>
<td></td>
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</tbody>
</table>
necesssary in order to evaluate whether the difference among the groups was statistically significant.

Withdrawals and drop outs were described in only two of the studies. Ten patients (5%) withdrew prematurely. Common reasons were lack of compliance to the treatment or adverse effects.

Report of any adverse effect occurred in seven patients (3%), consisting of moderate gastrointestinal disorders, such as nausea and vomiting.

Quality was evaluated using Jadad scale, with scores varying from 1 to 5. Five was the maximum value, higher quality, and 3 the minimum score of acceptable quality. Two of the selected papers presented score 2 (54, 63), and the other two studies presented score 5 (32, 64).

Figure 4 presents a summary of the critical analysis schedule and Jadad scale score from the studies analyzed.

**DISCUSSION**

Evaluation of efficacy of ornithine aspartate in reducing serum levels of ammonia and increasing neuropsychiatry status in HE has been studied during at least the last 3 decades. However, few double-blind, randomized, placebo-controlled clinical trials were able to detect such effect. Reduction of ammonia and improvement of encephalopathy clinical status, measured by psychometric tests (generally numeric connection test (NCT)) or mental status through the clinical scoring of encephalopathy has been the form of evaluating drug efficacy. Tolerance and the appearance of adverse effects shown by the patients have also been subject to evaluation in most of these studies.

Generally, the studies selected here showed that LOLA was able to reduce hyperammonemia in patients with

<table>
<thead>
<tr>
<th>Reference</th>
<th>Plasma concentration of ammonia</th>
<th>NCT-A</th>
<th>Mental status</th>
<th>PSEI</th>
<th>CRT</th>
<th>EEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rees et al. (54)</td>
<td>In the patients without TIPS: there was a significant improvement in LOLA-treated patients.</td>
<td>In the patients without TIPS and in the patients with TIPS: there was no statistically significant difference in LOLA-treated patients</td>
<td>NA</td>
<td>NA</td>
<td>In the patients without TIPS: there was no statistically significant difference in LOLA-treated patients.</td>
<td>In the patients without TIPS and in the patients with TIPS: there was no statistically significant difference in LOLA-treated patients.</td>
</tr>
<tr>
<td>Stauch et al. (54)</td>
<td>There was a statistically significant improvement in LOLA-treated patients.</td>
<td>In the subgroups HE I and HE II: there was a statistically significant improvement in LOLA-treated patients.</td>
<td>There was a statistically significant improvement in LOLA-treated patients.</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Kircheis et al. (63)</td>
<td>In the subgroups HE I and HE II: there was a statistically significant improvement in LOLA-treated patients.</td>
<td>In all the subgroups analyzed there was a statistically significant improvement in LOLA-treated patients.</td>
<td>There was a statistically significant improvement in LOLA-treated patients.</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Staedt et al. (64)</td>
<td>There was a significant improvement only in the patients treated with 40 grams of LOLA.</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NCT-A = Numeric connection test A; PSEI = Portal systemic encephalopathy index; CRT = Patients’ choice reaction time; EEC = Electroencephalogram; TIPS = Transjugular intrahepatic portosystemic shunts; NA = Not applicable.

FIGURE 3. Clinical parameters used to evaluate the effect of L-ornithine-L-aspartate compared to placebo.

FIGURE 4. Summary of critical analysis of the papers included in the review.

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Soárez PC, Oliveira AC, Padovan J, Parise ER, Ferraz MB. A critical analysis of studies assessing L-ornithine-L-aspartate (LOLA) in hepatic encephalopathy treatment

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HE, when compared to the group that used placebo. This reduction could be detected in the first hours following the infusion of intravenous drug (IV), in a crossover study with 10 cirrhotic patients from different etiologies. This finding was more pronounced when a higher dose of LOLA was used (40 g/day) (295 ± 216 mg/dL, P < 0.005) and even more following diet with higher protein content (0.5 g/kg/weight) in this same dosage[63]. In a bigger casuistic, with 126 cirrhotic patients, KIRCHEIS et al.[30], observed significant reduction in serum ammonia on the 7th day following the beginning of the IV infusion (17 ± 37 µmol x 6 ± 32 µmol, P < 0.05), which was more expressive in the grade II encephalopathy subgroup than in the subclinical encephalopathy or grade I encephalopathy subgroup. This reduction was accompanied by improvement in the NCT-A performance and not necessarily by mental status measured by PSE index.

Efficacy measured in terms of reduction of circulating ammonia levels must be considered with caution. As seen before, there is no relation between this serum determination and the hepatic encephalopathy grade. Hence, there is a need for clinical parameters for this evaluation. On the other hand, numeric connection test, when used alone, do not represent a high sensitivity and specificity test in the evaluation of minimum and initial HE. During the last years, a number of psychometric tests and sensorial stimuli has been used, together or alone, and represent more sensitive forms to evaluate encephalopathy in these patients.

In these studies, different protein overloads were used in the induction of serum increase of ammonia, varying from 0.25 to 1 g/kg/day. In addition, there were few references related to the origin of the protein, whether animal or vegetable, as differences in the ammoniogenic potential between them are known and possibly in the response to the treatment.

Oral drug efficacy was evaluated by STAUCH et al.[64], in 1998, considering a reduction in the bioavailability to 82.2% ± 28%. This study documented a progressive reduction in the level of ammonia through the 2 weeks of the study in both groups. However, this result was faster and more pronounced on the 14th day of drug dosing in patients who used oral LOLA, when compared to values of the beginning of the study (40 µmol x 60 µmol; P < 0.001). This reduction in ammonia was also accompanied by improvement in NCT-A time (51 sec to 40 sec). The test was improved in 9 of 11 patients in MHE; one of the patients showed normalization of NCT-A time (<30 sec). However, improvement in mental status was more enhanced in individuals with frank HE, where 79% showed improvement versus 40% in the placebo group, a non-detected difference in MHE. This difference in the behavior of MHE may be in the own definition of subclinical encephalopathy, where the patients do not show evident clinical manifestations of encephalic disease, making mental status evaluation difficult. On the other hand, higher drug dose and/or longer period of use might be necessary in this group.

In conclusion, the studies were able to demonstrate efficacy of LOLA in reducing hyperammonemia of HE, which was accompanied by improvement of the psychometric tests used; however, there might be the need for standardizing the amount and quality of the protein used in order to induce increase of ammonia in these cirrhotic patients, in addition to discussing and using more sensible HE detection tests, principally in the evaluation of MHE. There is a lack of trials with this drug in the more severe HE (grade II and III) compared, for instance, to a control group of patients, not without medication, but using standardized drugs and usually used in frank HE.

However, sufficient evidence of a significant beneficial effect of LOLA on patients with hepatic encephalopathy was not found. The trials performed in this area were small, with short follow-up periods and half of them showed low methodological quality.

We believe performing more randomized controlled clinical trials with solid design and methodology is necessary. All the trials must be reported according to the recommended guidelines (www.consort-statement.org).

Studies should include a greater number of patients and a longer follow-up period. Choice of more appropriate clinical parameters for evaluation of the drug effect such as combination of at least two psychometric tests, application of neurophysiologic tests in order to evaluate the visual (P100) or auditory (P300) evoked potential, magnetic resonance and spectroscopy to evaluate encephalic glutamine concentration, etc, has fundamental importance. Moreover, further outcome analyses which measure the improvement in the quality of life of these patients must be added in future studies.


REFERENCES

4. Because hepatic encephalopathy is a frequent contributing factor. Patients with liver cirrhosis are poorer drivers. MMW Fortschr Med. 2003;145:61.


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