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ORIGINAL ARTICLE

Efficacy of L-ornithine-L-aspartate as an Adjuvant Therapy in Cirrhotic Patients with Hepatic Encephalopathy

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ABSTRACT

Objective: To evaluate the efficacy of L-ornithine-L-aspartate (LOLA) as an adjuvant therapy in cirrhotic patients with hepatic encephalopathy (HE).

Study Design: Randomized placebo controlled study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi in the year 2003-2004.

Methodology: Patients with HE were randomized to receive LOLA or placebo medicine as an adjuvant to treatment of HE. Number connection test-A (NCT-A), ammonia level, clinical grade of HE and duration of hospitalization were assessed.

Results: Out of 120 patients, there were 62 males with mean age of 57 ± 11 years. Improvement in HE was higher (n=40, 66.7%) in LOLA group as compared to the placebo group (n=28, 46.7%, p=0.027). In patients with grade I or less encephalopathy, improvement was seen in 6 (35.3%) and 3 (20%) patients in LOLA and placebo groups respectively (p=0.667). Patients with HE grade II and above showed improvement in 34 (79.1%) and 25 (55.6%) cases in LOLA and placebo group respectively (p=0.019). On multivariate analysis patients with HE of grade II and above showed prothrombin time, creatinine level and use of LOLA influencing the outcome. Duration of hospitalization was 93.6±25.7 hours and 135.2±103.5 hours in LOLA and placebo groups respectively (p=0.025). No side effects were observed in either groups.

Conclusion: In cirrhotic patients with advanced hepatic encephalopathy treatment with LOLA was safe and associated with relatively rapid improvement and shorter hospital stay.

Key words: *Hepatic encephalopathy. Liver cirrhosis. L-ornithine-L-aspartate.*

INTRODUCTION

Hepatic encephalopathy is characterized by the development of impaired central nervous system function that may range from trivial abnormalities of consciousness, personality, behaviour and/or intellectual function to deep coma. Hepatic encephalopathy may be clinically invisible, i.e. minimal or sub-clinical, a syndrome that can only be detected by the demonstration of subtle psychometric or electrophysiological abnormalities.[1,2] The most common presentation is overt hepatic encephalopathy (HE), which occurs frequently in patients with advanced cirrhosis with a well developed portal-systemic collateral circulation.[3,4]

HE is one of the major complications of cirrhosis. Five years after the diagnosis of cirrhosis, the probability of developing at least one episode of this specific form of decompensated cirrhosis is 26%.[5] The probability of survival at 5 years is just 16-22%, once clinical decompensation has occurred, compared with a survival probability of 55-70% in cirrhotic patients without HE.[5,6] Therefore, prevention and effective treatment of HE may have important prognostic implications in cirrhotic patients.

A number of toxins are implicated in the pathogenesis of HE, with ammonia remaining the main candidate neurotoxin.[7] The neurotoxin ammonia plays a decisive role in the pathogenesis of HE by a variety of postulated mechanisms.[8]

Episodes of hepatic encephalopathy in patients with liver cirrhosis are usually induced by precipitating factors like dehydration, constipation, gastrointestinal bleeding, infections, hypokalemia, hypoxemia, the use of psychotropic drugs, or alcohol intake.[4] Precipitating factors seem to relevantly increase body ammonia levels and their identification and alleviation remains a keystone in the treatment of HE. In general, the majority of therapeutic measures are directed towards reducing blood ammonia levels, mainly by diminishing the enteric ammonia production via treatment with lactulose and metronidazole.[9] However, not all of these therapeutic options comply with the standards of evidence based medicine.[10]

L-ornithine-L-aspartate (LOLA), the stable salt of the amino acids ornithine and aspartic acid, in several clinical trials has shown to reduce blood ammonia levels and improve psychometric performance in patients with

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HE. LOLA stimulates the urea cycle and glutamine synthesis, which are important mechanisms in ammonia detoxification.[11,12] Ammonia lowering effect of LOLA is controversial. Some studies have demonstrated a decrease in ammonia level in patients with HE who were treated by LOLA.[13,14] While, a recently published study in patients with acute liver failure did not show the ammonia lowering effect of LOLA.[15]

Currently no large controlled clinical trial of specific treatment of proven efficacy is available for HE according to the standards of evidence based medicine. Moreover, only patients with minimal HE or grade 1 were enrolled in previous clinical trials of LOLA.[12,16] Therefore, this study aimed to assess the efficacy and safety of L-ornithine -L-aspartate as an adjuvant therapy in cirrhotic patients with all grades of HE, starting from minimal hepatic encephalopathy to overt HE of grades 1-4.

METHODOLOGY

This was a randomized, double-blind, placebo-controlled, prospective study conducted at The Aga Khan University Hospital, Karachi, during 2003-04. The formal approval from the institutional ethical review committee (ERC) of the hospital was granted before start of the trial. The trial was also registered through Clinic Trial. gov, Protocol Registration System (identification number NCT00433368).

A written informed consent was taken from the patient or attendant (in cases where patients were unable to understand and sign consent due to advanced HE) before enrolment to the study.

Patients who met the following inclusion criteria were eligible for the study: 1) cirrhosis, diagnosed on the basis of clinical findings, ultrasonic and/or histologic basis; (2) patients age more than 18 years, with HE grades 1-4 according to West Haven criteria; 3) patients were grouped as minimal HE if NCT-A completion took more than 30 seconds and no other sign of encephalopathy present;[17-19] (4) hyperammonemia (fasting venous blood ammonia level greater than 60 µmol/l); and (5) patients with or without a single reversible precipitating factor of HE such as constipation, hypokalemia, urinary tract infection, respiratory tract infection, spontaneous bacterial peritonitis (SBP), or dehydration.

A diagnostic paracentesis was performed in all patients with ascites to diagnose SBP. Similarly, urine culture and chest X-ray were done in all patients to diagnose urinary tract infection (UTI) and respiratory tract infection (RTI) respectively. Hypokalemia was labeled when serum potassium level on admission was < 3.5 meq / liter. SBP and other infections were treated with appropriate intravenous antibiotics for 3 days followed by oral form if HE improved.

Exclusion criteria were hepatocellular carcinoma, severe septicemia with compromised hemodynamic status, active gastrointestinal bleeding, hepatorenal syndrome, acute superimposed liver injury, advanced cardiac or pulmonary disease and end stage renal failure. Patients taking sedatives, antidepressants, or benzodiazepines and patients with chronic HE on metronidazole or lactulose prior to admission were also not included.

Patients admitted to the hospital via outpatient clinic or emergency room were assessed at randomization (Day 0, before start of treatment). The randomization was performed within 12 hours of admission in the hospital. Patients were randomly allocated to two treatment groups, i.e. L-ornithine-L-aspartate (LOLA) or placebo, using sequentially numbered, sealed, opaque envelopes. Both groups were given lactulose and metronidazole as per routine management of hepatic encephalopahty.

Intravenous infusions were administered daily over 4 hours from 08:00 to 12:00 a.m for 3 consecutive days and contained either 20 g LOLA (4 ampoules of 10 ml each) or placebo (4 ampoules of 10 ml distilled water each) both mixed in 250 ml 5% dextrose. The active agent and placebo were indistinguishable in colour and appearance.

Concomitant medications were required for the treatment of precipitating factor, such as antibiotics for infection, potassium replacement for hypokalemia, and intravenous dextrose saline for dehydration. Diuretics and beta-adrenergic blocking drugs were stopped and a salt restricted diet was started in both treatment groups.

Improvement/deterioration in HE grade (based on NCT-A and West Haven criteria) was defined as the primary outcome variable. Improvement in length of hospital stay, improvement in fasting ammonia level, and mortality rate were recorded as secondary outcome variables. The mental state was graded on a 0-4 scale according to the West Haven criteria.[17,18] Number connection test (NCT-A) was performed in patients with minimal hepatic encephalopathy (MHE) and grade-I HE.[21] NCT time was checked daily with the help of four parallel variations of NCT test, validated to be of equal difficulty, as demonstrated in literature.[4] In patients with minimal and grade-I HE, "definite improvement" was achievement of HE- 0 at end of treatment according to West Haven criteria. In patients with HE grade ≥ II, HE was "definitely improved" whenever it improves to two grades from baseline; and rated as "partially improved" when a decrease of 1 grade according to West Haven criteria was observed between baseline and Day 3, but not reaching to grade 0; "no improvement/ deterioration", when HE has not improved or deteriorated. Physicians were trained for correct and consistent use of mental state grading and NCT-A prior to start of study.

Samples for ammonia were drawn into heparinized vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey), and analyzed within 30 minutes. Initial venous ammonia levels were checked in all the patients on day 0 at the time of admission. Thereafter, the postprandial venous ammonia levels were checked from day 1 to day 3 of treatment in both the groups after 4 hours of infusion of LOLA or placebo.

Hospital stay was monitored (in hours) of patients and in-hospital mortality in the LOLA and placebo groups of treatment. Laboratory parameters were determined on Days 0 and 3 and included haematology (haemoglobin, haematocrit, white blood cell count, platelets) and liver function tests (alanine aminotransferase, gamma glutamyl transferase serum bilirubin, serum albumin and prothrombin time).

Patients who received at least 95% of study medication were considered compliant. All adverse events were assessed by the investigator according to usual clinical evaluations. Any clinical or laboratory findings observed during trial were monitored and recorded until their normalization was observed or their correlation with investigational medication could be explained.

A sample size of 55 patients from the LOLA group and 55 patients from the placebo group achieve 80% power at a 5% significance level using equivalence test of proportions by assuming 20% higher improvement in LOLA as compared to placebo group. While improvement in placebo group was used as 40% and the maximum allowable difference between the group proportions that still results in equivalence (the range of equivalence) is 5%.

All analyses were carried out by using the Statistical Package for Social Sciences (SPSS) 19. Descriptive analysis was applied to demographic data and baseline characteristics. Quantitative variables were summarized by presenting means ± standard deviation with normally distributed data, however, median with range were presented for skewed data. Frequencies and percentages were given for qualitative variables. Between groups, mean differences in quantitative outcome parameters were assessed using independent t-tests or Mann Whitney U-test. Proportions were compared by Pearson's chi-square, where appropriate. Paired sample t-tests were used to analyze the within-group changes in ammonia concentration and NCT-A from baseline to the end of treatment.

Multiple logistic regression analysis was used to assess the factor associated with improvement. All those variables which were significant at 20-25% level of significance were considered for multivariate analysis. P-values < 0.05 were considered to be statistically significant. For assessment of primary outcome we analyzed MHE and grade-I HE separately from grade-II and above HE.

RESULTS

Out of 307 consecutive patients, a total of 120 patients with liver cirrhosis and portal hypertension fulfilled the criteria of inclusion into this clinical investigation. The data presented are based on total study sample (intent-to-treat analysis), which included 60 patients in each group. The two random groups were matched in age {mean age 57±11 years; 62 males (52%)}, etiology of cirrhosis, Child-Turcotte-Pugh (CTP) class, laboratory parameters (haemoglobin, urea, creatinine, electrolytes), grades of HE and precipitating factors (Table I).

Baseline severity of hepatic encephalopathy and improvement after LOLA or placebo administration Table II. NCT-A score among LOLA patients was 122 $\pm$ 13 seconds at baseline that has improved to 71 $\pm$ 25 seconds ($p < 0.001$) while in placebo group NCT-A was 122 $\pm$ 7 improved to 78 $\pm$ 22 seconds), ($p < 0.001$); however, 3 patients in placebo group deteriorated and hence, NCT was not calculated. A comparison in NCT was not done between LOLA and control groups as 3 patients who deteriorated from control group were unable to perform NCT.

Table I: Patients characteristics of L-ornithine-L-aspartate (LOLA) and placebo group.

Characteristics	LOLA n=60	Placebo n=60
Age (years, mean ± SD)	57.1 ± 11.5	57.5 ± 11
Gender, n (%)		
Male	30 (50)	32 (53.3)
Female	30 (50)	28 (46.7)
Etiology of cirrhosis, n (%)		
Hepatitis C	41 (68.3)	40 (66.7)
Hepatitis B	05 (8.3)	06 (10.0)
Non-B/non-C hepatitis	13 (21.7)	10 (16.7)
Ethnol	01 (1.7)	04 (6.6)
Child Pugh grade, n (%)		
B	13 (21.7)	08 (13.3)
C	47 (78.3)	52 (86.7)
Laboratory data*		
Hemoglobin (g/L)	10.4 (5.9 to 15.5)	10.7 (6.3 to 16.1)
Leukocytes (x10E9/L)	9.3 (2.9 to 38.3)	8.5 (2.7 to 27)
Platelets (x10E9/L)	105 (7.9 to 342)	112 (5 to 279)
Total bilirubin (mg/dl)	2.9 (0.9 to 40)	4.3 (0.9 to 62)
ALT (IU)	34 (14 to 1048)	45.5 (17 to 703)
Alk. Phosphatase (IU)	111 (42 to 430)	134 (53 to 330)
PT (control 12)	19.9 (13 to 44)	19.5 (12.6 to 58)
Albumin (g/dl)	2.1 (1.2 to 3.9)	2 (1.3 to 3.8)
Potassium (mEq/l)	4.1 (2.2 to 6.3)	4.1 (2.4 to 6.8)
Creatinine (mg/dl)	1.2 (0.5 to 3.3)	1.3 (0.5 to 3.2)
Ammonia level (µmol/l)	135.5 (33 to 497)	127.5 (53 to 304)
Precipitating factors, n (%)		
Constipation	13 (21.7)	18 (30.0)
Hypokalemia	06 (10.0)	04 (6.7)
Urinary tract infection	11 (18.3)	05 (8.3)
Respiratory tract infection	02 (3.3)	–
SBP	14 (23.3)	17 (28.3)
None	16 (26.7)	19 (31.7)

*SD=Standard deviation, * result presented as median (range).*

Table II: Hepatic encephalopathy grade wise improvement in the two treatment groups.

	L-Ornithine L-aspartate (LOLA) (n=60)			Placebo (n=60)		
Grade of HE*	Complete improvement	Partial improvement	No improvement/ deterioration	Complete improvement	Partial improvement	No improvement/ deterioration
MHE	6/6 (100)	-	-	3/6 (50)	-	3/6 (50)
Grade I	11/11 (100)	-	-	-	9/9 (100)	-
Grade II**	14/18 (78)	2/18 (11)	2/18 (11)	10/18 (55)	5/18 (28)	3/18 (17)
Grade III**	15/18 (83)	1/18 (6)	2/18 (11)	11/19 (58)	2/19 (10)	6/19 (32)
Grade IV**	5/7 (72)	1/7 (14)	1/7 (14)	4/8 (40)	3/8 (38)	1/8 (12)

** Analyzed combined all grade showed significant improvement in LOLA group compared to placebo (p = < 0.001).*
*** Analyzed together showed better improvement in LOLA group compared to placebo (p=0.019).*

Table III: Factor associated with definite improvement for grade II and above in univariate analysis.

Factors	Partial improvement n=29 (%)	No-completer improvement n=59 (%)	p-value
Age (years, mean ± SD)	57.5 ± 11	57.1 ± 11.5	0.893†
Treatment group			
Placebo	20 (44.4)	25 (55.6)	0.019‡
LOLA	9 (20.9)	34 (79.1)	
Laboratory data*			
Hemoglobin (g/L)	9.1 (6.6 to 15)	11.1 (5.9 to 16.1)	0.014§
Leukocytes (x10E9/L)	9.0 (2.7 to 27)	9.3 (2.9 to 38.3)	0.648§
Platelets (x10E9/L)	122 (32 to 292)	112 (5.9 to 342)	0.445§
Total bilirubin (mg/dl)	4.9 (1.2 to 40)	2.7 (0.9 to 62)	0.053§
ALT (IU)	48.5 (17 to 481)	46.5 (15 to 1048)	0.657§
Alk. Phosphatase (IU)	137.5 (42 to 430)	127 (48 to 330)	0.969§
PT (control 12)	24.1 (12.6 to 44)	18.2 (12.8 to 58)	0.016§
Albumin (g/dl)	1.7 (1.3 to 3.9)	2.2 (1.3 to 3.9)	0.018§
Potassium (mEq/l)	3.7 (2.7 to 5.8)	4.1 (2.4 to 6.8)	0.261†
Creatinine (mg/dl)	1.5 (0.6 to 3.3)	1.3 (0.5 to 3.1)	0.089§
Ammonia level (µmol/l)	130 (52 to 497)	134 (33 to 345)	0.327†

*SD=Standard deviation; * result presented as median (range); † p-value calculated based on t-test; ‡ based on Pearson chi-square; § calculated based on Mann Whitney U test.*

Table IV: Independent factor associated with definite improvement for grade II and above in logistic regression.

Variables	Adjusted odds ratio	95% C.I for adjusted odds ratio	p-value
Treatment groups			
Placebo	1¶		
LOLA	3.9	(1.30, 11.74)	0.015
Creatinine	0.35	(0.15, 0.83)	0.017
PT	0.95	(0.89, 1.00)	0.064

¶ Reference category.

Table V: Blood ammonia levels in L-ornithine L-aspartate and placebo groups.

Grade of HE	L-ornithine-L-aspartate		Placebo	
	Day 0 n (mean ± SD)	Day 3 n (mean ± SD)	Day 0 n (mean ± SD)	Day 3 n (mean ± SD)
Minimal HE/grade 1	17 (126 ± 42)	17 (105 ± 19)	15 (140 ± 44)	15 (143 ± 57)
HE grade 2	18 (129 ± 51)	18 (116 ± 51)	18 (151 ± 79)	18 (131 ± 42)
HE grade 3	18 (148 ± 70)	18 (134 ± 56)	19 (150 ± 60)	19 (152 ± 99)
HE grade 4	7 (151 ± 59)	7 (109 ± 25)	8 (185 ± 36)	8 (153 ± 81)

Mean change with (95% C.I.) in LOLA group 18.8 (5.3, 32.3) p=0.007, in placebo group 8.7 (-13.3, 30.8) p=0.431.

Overall definite improvement in LOLA group was higher 40/60 (66.7%) as compared to placebo group 28/60 (46.7%), p < 0.001; moreover, 17/17 (100%) patients who received LOLA with grade-I or MHE improved while in placebo group 3/15 (20%) showed definite improvement (p < 0.001).

Patients with HE grade II and above who received LOLA 34/43 (79%) improved compared to 25/45 (55.6%) in placebo group (p=0.019). Overall factors were not found significant when the whole group was evaluated.

On subset analysis only patients with HE of grade-II and above showed that prothrombin time, creatinine level and use of LOLA influencing the outcome of HE (Tables III and IV). There was a significant decline in ammonia levels in LOLA group; the mean difference and CI between day 0 and day 3 in ammonia level was 18.8 (5.3, 32.3) p=0.01. The change in ammonia level was, however, not significant in the placebo group even after excluding those patients who deteriorated from MHE to higher grades; 13.3 (-8.3, 34.9) p=0.182 (Table V). The median duration of hospitalization was significantly shorter following treatment with LOLA compared to placebo; 96 hours (range 48-574) and 96 hours (range 90-240) respectively (p=0.025). Overall, 4/60 patients (7%) receiving LOLA infusions died during in-patient care as compared to 7/60 (12%) patients treated with matching placebo group (p=0.343).

A compliance of 100% was achieved for both the active medication and treatment with placebo in this clinical trial. No adverse drug reactions in terms of symptoms or biochemical laboratory deviations were observed in either group.

DISCUSSION

The present study aimed at exploring the efficacy of intravenously administered LOLA in a randomized, placebo controlled, double blind trial in a defined population of cirrhotic patients with encephalopathy. In this trial all grades of encephalopathy were included ranging from minimal to overt hepatic encephalopathy.

L-ornithine L-aspartate was found safe as an adjuvant therapy in the management of HE along with standard management. Moreover, LOLA showed significant improvement in patients with grade-I or minimal HE

compared to placebo. This apparent beneficial effect of LOLA could be due to the fact that 3 patients in the placebo group actually deteriorated. Whether LOLA prevented a similar deterioration of HE in the active treatment arm cannot be determined from this study.

Another interesting finding is better outcome of patients with advanced grades of encephalopathy in LOLA group compared to placebo, which was statistically significant.

This study is the first randomized, placebo-controlled investigation that has included patients with all stages of HE. Moreover, unlike previous studies patients with a variety of precipitating factors were included that were equally distributed in the two treatment groups. Therefore, the selection of study subjects in the present study was closer to the real-time clinical situation where patients with or without precipitating factors and various grades were subjected to randomized treatment. This has also reduces the element of selection bias in this study. Previously reported controlled studies of LOLA were performed in patients with HE of milder severity (grades I and II),[11,12,16,17] and did not include the patients with precipitating factors.

A significant drop in fasting ammonia concentrations was observed in patients given LOLA, compared to their baseline values this effect was not evident in the placebo group, similar results were found in the other studies elsewhere.[4,20,21] A recently conducted double blind study from Austria has demonstrated an improvement in posturographic control in patients with HE.[22] This study also suggested a possible augmentation in the improvement of clinical condition of patients with HE by using LOLA in addition to intravenous fluids.

A significant decrease in the length of hospital stay was observed in patients who received LOLA compared to those who were on placebo as an adjuvant therapy. However, any clinical significance of this shorter hospital stay cannot be concluded from this observation. A similar trial from another region of Pakistan had found LOLA as an effective agent in cirrhotic patients with HE.[23]

There are certain limitations to this study. Firstly, use of venous ammonia sample was not ideal especially while assessing the role of LOLA which induce the urea cycle in muscles and may cause falsely reduced level of ammonia in venous sample. Therefore, the reduction in ammonia level in this study may have potential of misinterpretation. Secondly, a shorter course of LOLA was used compared to other studies; this was based upon the observation that majority of patients improve within 3-5 days. It was presumed that 72 hours therapy would be appropriate than a longer duration of therapy. A relatively longer follow-up could not be obtained in these patients and a repeat estimation of ammonia as rebound rise in ammonia level and worsening of HE was a possible theoretical risk associated with such patients. Finally, the effect of other medicines like lactulose, metronidazole and antibiotics received by patients can not be eliminated. Since both the arms were randomized, the distribution of precipitating factors were equal and all patients received identical supportive treatment with lactulose and metronidazole, therefore, it may be presumed that the results of this study were not modified by these factors.

CONCLUSION

Three days adjuvant therapy with LOLA is safe and beneficial, it is better in improving hepatic encephalopathy as adjuvant compared to placebo, especially in higher grade of encephalopathy. Moreover, LOLA administration was associated with shorter duration of hospital stay. The present study second the recently published meta-analysis of three trials which concluded that the use of LOLA was beneficial in cirrhotic patients with overt HE, but not with minimal HE.[24]

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