ORIGINAL ARTICLE

L-Ornithine-L-Aspartate Infusion Efficacy in Hepatic Encephalopathy

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ABSTRACT

Objective: To determine the efficacy of L-ornithine-L-aspartate in treatment of hepatic encephalopathy.
Study Design: Randomized, placebo-controlled trial.
Place and Duration of Study: Department of Gastroenterology and Hepatology, Sheikh Zayed Hospital, Lahore, from February to August 2005.
Methodology: Cirrhotic patients with hyperammonemia and overt hepatic encephalopathy were enrolled. Eighty patients were randomized to two treatment groups, L-ornithine-L-aspartate (20g/d) or placebo, both dissolved in 250mL of 5% dextrose water and infused intravenously for four hours a day for five consecutive days with 0.5 g/kg dietary protein intake at the end of daily treatment period. Outcome variables were postprandial blood ammonia and mental state grade. Adverse reactions and mortality were also determined.
Results: Both treatment groups were comparable regarding age, gender, etiology of cirrhosis, Child-Pugh class, mental state grade and blood ammonia at baseline. Although, improvement occurred in both groups, there was a greater improvement in L-ornithine-L-aspartate group with regard to both variables. Four patients in the placebo group and 2 in L-ornithine-L-aspartate group died.
Conclusion: L-ornithine-L-aspartate infusions were found to be effective in cirrhotic patients with hepatic encephalopathy.

Key words: *L-ornithine-L-aspartate. Hepatic encephalopathy. Ammonia.*

INTRODUCTION

Hepatic Encephalopathy (HE) is a major cause of morbidity and mortality in cirrhosis, which is caused by gut-derived toxins that reach the systemic circulation as a result of portosystemic shunting or reduced hepatic clearance.[1] Amongst these toxins, ammonia is thought to be the most important substance.[2] Concentration of ammonia is high in systemic circulation and cerebrospinal fluid of patients with HE.[3] In brain, high level of ammonia results in impaired neurotransmission, either alone or in combination with endogenous benzodiazepine agonists, manganese, tryptophan or other substances.[4-7]

L-ornithine-L-aspartate (OA) is a stable salt of the amino acids ornithine and aspartic acid and provides substrates for ureagenesis and glutamine synthesis, which are important mechanisms in ammonia detoxification.[8] It has been shown in randomized, double-blind, placebo-controlled studies to reduce fasting and postprandial blood ammonia levels and improve the symptoms of hepatic encephalopathy compared to placebo treated patients.[8-10]

The objective of this study was to assess the efficacy, in terms of lowering of blood ammonia and improvement in mental state, of OA infusions in the treatment of HE with hyperammonemia and to compare it with placebo.

METHODOLOGY

The trial was conducted from February to August 2005 at the Department of Gastroenterology and Hepatology, Sheikh Zayed Hospital, Lahore.

Adult cirrhotic patients (>18 years of age), diagnosed on the basis of clinical, laboratory and ultrasonographic features, who met the following criteria were included in the study: (1) clinically overt encephalopathy (graded 1-4 according to the West-Haven criteria)[11] developed spontaneously without any precipitating factor; and (2) hyperammonemia (venous blood ammonia concentration >50 µmol/l). Exclusion criteria were existence of specified precipitating factors; mental state grade IV HE; active, major complications of portal hypertension, such as gastrointestinal bleeding, hepatorenal syndrome, or spontaneous bacterial peritonitis; acute superimposed liver injury; hepatocellular carcinoma; serious non-hepatic diseases, such as heart, respiratory or renal failure; and presence of infections other than

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spontaneous bacterial peritonitis necessitating antibiotic therapy.

Detailed history including presence of associated conditions like diabetes mellitus was taken from each included patient on the day of admission (day 0), thorough examination was done and investigations (complete blood count, liver and renal function tests, electrolytes, prothrombin time and serum albumin) were sent. Patients were randomized to two treatment groups i.e., trial drug group (OA) and placebo group, using treatment assignment derived from computer-generated random numbers. Study medications were started on next day (day 1). These consisted of intravenous infusions of 20 g OA (4 ampoules of 10 ml each) in 250 ml of 5% of dextrose or the placebo drug (4 ampoules of 10 ml distilled water) in 250 ml of 5% dextrose, each administered daily over 4 hours (8.00 AM to 12.00 PM) for 5 consecutive days. Standard treatment including lactulose and metronidazole were given to all patients in both groups.

All patients were given a nutritious diet containing 1 g meat-vegetable-dairy protein per kg body weight per day. The quantity of protein was divided among 3 main meals of each day in such a way that the quantity of protein consumed with breakfast was 0.25 g/kg body weight and that consumed with lunch was 0.5 g/kg body weight.

Efficacy of study drugs was assessed by decrease in venous blood ammonia and improvement in mental state. These primary outcome variables were checked at 1.00 PM (one hour after the completion of infusion and lunch) each study day (day 1-5). Other recorded variables were adverse reactions to medicine and in-hospital mortality.

Study protocol was approved by Institutional Ethical Review Committee. A written informed consent was obtained from the patient or relative before enrolment in the study. SPSS 10 software (SPSS, Chicago, Illinois, USA) was used for statistical analysis. Means were compared by using student's t-test; qualitative variables were compared by using X^2 test and Fisher's two-tailed exact test. A p-value of <0.05 was considered to be significant.

RESULTS

Eighty cirrhotic patients were randomly assigned to receive OA (n=40) or placebo (n=40). The two groups were similar in demographic characteristics, etiology and severity of cirrhosis as determined by the Child-Pugh criteria (Table I). The age of patients ranged from 27-76 years in OA group and 22-73 years in placebo group. There was no marked difference between the two groups regarding blood counts, prothrombin time and biochemical parameters (total bilirubin, albumin, sodium and creatinine levels in serum). Ten patients in OA group and 9 in placebo group had Diabetes mellitus.

The pre-treatment plasma ammonia concentrations were similar in both treatment groups (Table I). The reduction in ammonia level on each study day was more in OA group than in placebo group (Table II), and the difference was significant on day 4 (p = 0.041) and day 5 (p = 0.022).

At baseline, the two treatment groups had comparable HE grades (Table I). During the treatment, 37/40 (92.5%) patients achieved HE grade 0 in OA group compared to 31/40 (77.5%) in placebo group but this difference was not significant (p=0.060). This difference in improvement of mental state and achievement of grade 0 HE started from day 1 and became more evident from day 3 onwards (Table III).

One patient in OA group developed nausea/vomiting, which responded to intravenous metoclopramide without necessitating withdrawal of trial drug. No side effect was seen with placebo. A total of 6 patients died; 4 in placebo group and 2 in OA group. In OA group, both patients died on day 4; in placebo group, one patient died on day 3, one on day 4 and 2 on day 5. Four patients died of end-stage liver disease, and 2 had developed massive upper gastrointestinal bleeding.

Table I: Baseline data of 80 patients with hepatic encephalopathy.

Parameter	OA group (n=40)	Placebo group (n=40)
Age (in years), mean±SD	51.68±10.80	52.03±11.70
Gender		
Male	28 (70%)	31 (77.5%)
Female	12 (30%)	9 (22.5%)
Etiology		
HCV	37 (92.5%)	38 (95%)
HBV	1 (2.5%)	1 (2.5%)
Others	2 (5%)	1 (2.5%)
Child-Pugh score, mean±SD	10.65±1.89	10.85±1.85
Child-Pugh class		
A	1 (2.5%)	1 (2.5%)
B	12 (30%)	12 (30%)
C	27 (67.5%)	27 (67.5%)
HE grade		
I	10 (25%)	10 (25%)
II	20 (50%)	26 (65%)
III	10 (25%)	4 (10%)
Ammonia, mean±SD	95.18±40.56	93.03±41.10

OA=L-Ornithine-L-Aspartate, SD=standard deviation, HE=hepatic encephalopathy

Table II: Postprandial plasma ammonia at 1.00 PM on each study day.

Day	OA group (mean±SD)	Placebo group (mean±SD)
Day 0	95.18 ± 40.56	93.03 ± 41.10
Day 1	75.08 ± 18.77	74.85 ± 32.09
Day 2	60.65 ± 19.63	68.38 ± 35.48
Day 3	54.58 ± 15.24	64.83 ± 34.92
Day 4	49.88 ± 17.32	64.06 ± 32.12
Day 5	44.42 ± 14.80	65.55 ± 27.23

Table III: Number of patients who achieved HE grade 0 at days 1-5 in OA and placebo groups.

Treatment groups	Day 1	Day 2	Day 3	Day 4	Day 5
OA group	5 (12.5%)	11 (27.5%)	25 (62.5%)	33 (82.5%)	37 (92.5%)
Placebo group	2 (5%)	9 (22.5%)	18 (45%)	25 (62.5%)	31 (77.5%)

DISCUSSION

Hepatic encephalopathy represents a reversible deterioration in neuropsychiatric functions in cirrhotic patients, commonly precipitated by constipation, gastrointestinal bleeding and infections.[12-14] The first step in the management of HE is to identify and correct these precipitating factors. The second step involves measures directed at lowering elevated blood ammonia levels. Among these measures, most commonly used as standard treatment are those that involve removing the source of ammonia in gut (reduction of dietary protein, enemas), that inhibit ammonia production in the colon (antibiotics) and that trap ammonia in the colon and reduce its absorption (lactulose).[15]

OA decreases blood ammonia by increasing its removal.[8] Its ammonia lowering effect has been shown in three well-controlled studies;[8-10] two of them also demonstrated clinical improvement in HE.[9,10] Ammonia-lowering effect of OA has been demonstrated after inducing hyperammonemia by dietary protein load[8-10] (as in this study) or by oral glutamine challenge.[16] OA was compared with placebo, but as all patients (in both trial drug groups) were given lactulose and metronidazole (agents that reduce intestinal ammonia production) contrary to above-mentioned studies, which excluded such patients, the therapeutic efficacy of OA or placebo was over and above that of lactulose and metronidazole.

Despite the relatively short treatment period in our study, a clinical benefit of OA over placebo was evident in both primary outcome variables which favours previous studies.[8-10] Ammonia lowering effect was significantly greater in OA group and, although, difference in improvement in mental state did not achieve statistically significant levels, it was simply more in OA group than in the placebo group. A recent study which supported the efficacy of OA also showed that the duration of hospital stay was shorter in the OA group.[17] The observed safety and tolerability of OA confirms the results of previous studies.[9,10]

Data available so far makes the efficacy of OA unquestionable and it can be recommended to add OA in patients of HE who do not respond to standard treatment, but before incorporating OA in standard treatment of HE, much more has to be done. Investigations are required, which should include large number of patients, enrolling patients with severe HE as well, giving more importance to clinical improvement than ammonia level reduction and having longer study period (at least 7 days). These studies should also find out whether OA reduces hospital stay, and if it does so, is it cost-effective; and in patients with more severe grades of HE, whether OA reduces in-hospital mortality.

CONCLUSION

In cirrhotic patients with HE, OA infusions resulted in greater improvement in postprandial ammonia and mental state grade than placebo; also, OA was safe and well-tolerated. Studies with larger sample size and longer treatment period are required to confirm these findings.

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