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THERAPEUTIC EFFICACY OF L-ORNITHINE L-ASPARTATE IN PATIENTS WITH HEPATIC ENCEPHALOPATHY

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ABSTRACT

Objectives: To determine the efficacy of ornithine-aspartate in reducing blood ammonia levels and clinical improvement, as a part of treatment in hepatic encephalopathy. **Material & method:** A randomized placebo controlled trial was conducted in 2013 in Jinnah medical and dental college hospital Korangi Karachi. One hundred patients with hepatic encephalopathy due to underlying chronic liver disease were randomly assigned into two groups with 50 patients each. One group received three days of ornithine-aspartate infusions (trial-treatment group) and the other group received three days of infusion of placebo (placebo group). Serum ammonia was measured in both groups on day 1 and day 3. Clinical improvement was assessed by West Haven's grading of hepatic encephalopathy. **Result:** The patients in trial group showed statistically significant improvement in serum ammonia levels and grading of hepatic encephalopathy as compared to placebo. **Conclusion:** L -Ornithinie L-Aspartate (LOLA) is effective in decreasing serum ammonia as well as results in clinical improvement in patients with hepatic encephalopathy and may be recommended for use in hepatic encephalopathy.

KEY WORDS: Hepatic Encephalopathy, Chronic Liver Disease, Serum Ammonia, Ornithine-Aspartate.

INTRODUCTION

Cirrhosis or end stage liver disease is destruction of normal liver parenchyma, replaced by regenerating nodules and scar tissue, due to various reasons common causes includes HBV, HCV, and alcoholic liver disease. Hepatic Encephalopathy is present in about 50-70% of all patients with cirrhosis.(1) Hepatic Encephalopathy is a complex neuropsychiatric syndrome associated with acute or chronic hepato- cellular failure and porto-systemic shunting of blood. It is one of the major complications of cirrhosis. Various neurotoxins have been known to involve in pathogenesis of hepatic encephalopathy. High levels of ammonia, glutamate, endogenous benzodiazepines, Gamma Amino butyric Acid (GABA) have been strongly associated with acute hepatic encephalopathy. [2] Among these, raised level of ammonia is thought to play a major role in pathogenesis of hepatic encephalopathy. [3,4] In hepatic encephalopathy the rate of ammonia metabolism decreases and its permeability to blood brain barrier increases, resulting in elevated ammonia levels in brain with variable changes in blood. This mechanism is also supported by the fact that cirrhotic patients are sensitive to conditions associated with excess ammonia (constipation, protein overload, internal bleeding or sepsis).[5] It also explains the reason why some patients have marginal elevation of arterial ammonia, despite hepatic encephalopathy.[6] Therefore reduction in ammonia levels in the body is important treatment strategy.[7] The L-ornithine L-Aspartate(LOLA) are salts of naturally occurring aminoacids ornithine and aspartate. They stimulate urea cycle and glutamine synthesis, which are major mechanisms of ammonia detoxification.[8] Over last 25 years, various studies were carried out regarding efficacy of LOLA in improvement of hepatic encephalopathy, showed controversial results. Blanco et al compared the standard treatment, with LOLA and concluded that LOLA was effective not only in reducing hyperammonemia and the severity of this disease, but also in improving the patient's perceived quality of life.[9] Sharma et al conducted a study in 2014and concluded that LOLA, probiotics and rifxamine were all superior to placebo, although this study was conducted on patients with minimal hepatic encephalopathy.[10] A meta-analysis done in 2009 reviewed four studies and concluded that although use of LOLA was associated with decreasing serum ammonia levels, no clinical improvement was

observed. But these studies were of small sample size and shorter follow ups.[11] Another meta-analysis done on three studies showed that LOLA therapy causes decrease in serum ammonia levels, and also clinical improvement.[12] Moreover most of the available data assessed role of LOLA in minimal encephalopathy, not the over encephalopathy. In the review of local data, there are only two authentic large trials available.[13,14] Therefore due to absence of large studies, controversial existing data and paucity of local data, we conducted a study to observe effect of LOLA on clinical improvement in most stages of hepatic encephalopathy.

MATERIAL & METHOD

After approval of Ethical review committee of Jinnah Medical and Dental College, a randomized, placebo-control trial was performed in medical department of Jinnah medical and dental college Hospital Korangi Karachi from July 2013 to June 2014. The trial was designed and reported according to CONSORT guidelines.[15] An informed consent was taken before entry in the trial. Data was collected by Interns and residents of the ward, who were trained by the authors for this study through workshops and meetings. Patients > 18 years of age, admitted in medical ward, diagnosed with Chronic liver disease (CLD) due to any cause, having grade II to grade IV Hepatic Encephalopathy were included in the study after informed consent. CLD was diagnosed by common complications like ascites, gastro-oesophagal varices, with sonographic findings of shrunken liver, splenomegaly, portal vein size > 1 cm, deranged clotting profile and and inverse albumin /globulin ratio. Hepatic encephalopathy was diagnosed on the basis of confusion, drowsiness, restlessness, disorientation and asterixis without any altered explanation of these symptoms. Clinical grading of hepatic encephalopathy was done by West Haven's criteria.[16] Patient having sepsis, hepatorenal syndrome, acute/ chronic kidney disease were excluded from the study because they might affect ammonia levels. Hypoglycemia and respiratory failure was excluded by measuring random blood sugar and arterial blood gases. The estimated sample size was 102 patients, considering 500 annual admissions in our ward. The patients meeting inclusion criteria were randomly allocated into two groups with 50 patients in each group. The Trial-Treatment group received L-Ornithine L-Aspartate; the Placebo group received normal saline. Both groups continued to receive all other standard supportive treatment including lactulose and metronidazole. The patients with precipitating factors such as infection, constipation, hypokalemia, dehydration, electrolyte imbalance, prolonged prothrombin time were treated accordingly. Performa was completed for each patient to record demographics, vitals, complete blood counts, liver function tests, prothrombin time, total proteins, electrolytes, serum ammonia, random blood glucose and renal status. In addition, ultra-sound of the whole abdomen was also done, to assess the size of liver, spleen and portal vein. Trial-Treatment group received a daily intravenous infusion of 20 g (4 ampoules) L-Ornithine L-Aspartate (Inj HepaMerz, Brooks pharma) diluted in 250 ml of 5% dextrose water administered slowly over 4 hours for three consecutive days. The Placebo group received a daily administration of 250 ml normal saline over 4 hours for three consecutive days. It was ensured that the infusions were given at the same specified time to both groups of patients. About 5 ml of blood of each patient was drawn on Day 1 and Day 3 under aseptic techniques, stored in rubber corked glass tubes for checking ammonia levels. The Tubes were frozen at 4 degrees centigrade temperature. The ammonia determination was performed according to the enzymatic determination of ammonia with glutamine dehydrogenase in a rapid and interference – free photomertric determination of NH4+ in native blood plasma. The testing was performed at a reliable laboratory of Karachi. Sample on Day 1, was collected as soon as a patient presented, before any treatment was started. The second sample was drawn on Day 3 i.e. after the patient received three days of the Trial-Treatment or Placebo. Clinical improvement in hepatic encephalopathy was noted by West Haven's criteria, on day 1 before LOLA infusion and on day III after infusion. Data was collected on the prescribed performa and analyzed using Statistical Package for Social Services (SPSS) V 17. Numerical data was recorded as mean and standard deviation, nominal data was recorded as frequency and percentage. Patients on treatment with Ornithine - Aspartate infusion and on placebo were compared by paired t-test. A p-value of < 0.05 was considered statistically significant.

RESULT

Out of 102, two patients were discharged or referred before collection of data. The remaining patients completed study. Half of the patients (50), received L-Ornithine L-Aspartate (LOLA) and half received Placebo (50). In LOLA group 20(40%) were female and 30(60%) were male. In placebo group were 22(44%) female and 28(56%) male. Mean age was 49.66+ 12.25 SD in trial group and 46.06 +9.83 SD in placebo group. Out of 100 people 43 % had HCV, 22 % had HBV, 4 % were non B-C and 8 % had both B and C virus. (Table: I) On Day I mean ammonia was 105.2 micromol/l in trial group. (Normal

range: 6-47 micromol/l). In placebo group mean ammonia level was 112.28 micromole /dl on Day I.(Table:II) On Day III mean ammonia level in the trial group was 74.16 micromol/L. In placebo group mean ammonia level was 110.52 micromol/L .On comparison of serum ammonia levels before(day 1) and after (day 3) L-ornithine L aspartate therapy ,the difference was statistically significant in trial group(p value 0.0013) while it was non significant in placebo group.(p value 0.124) (Table : II) To assess clinical improvement with LOLA, we used clinical grading of hepatic encephalopathy. In trial group, On Day I 10(20%) were in grade II, 17(34%) were in grade III and 23(46%) were in grade IV hepatic encephalopathy, while on day III 4(8%) were in grade zero, 18(36%) were in I, 20(40%) were in grade II, 8(16%) in grade III and zero were in grade IV hepatic encephalopathy. (Table:III) In placebo group on day I 12(24%) % were in grade II, 19(38%) were in grade III, 19(38%) were in grade IV hepatic encephalopathy, while on day III no patient % was in grade zero,10(20%) were in grade I, 12 (24%) were in grade II, 18(36%) were in grade III and 10(20%) were in grade IV hepatic encephalopathy. On Day I clinical difference in grading of hepatic encephalopathy between two groups was statistically non significant. (p-values > 0.05) while on Day III, significant clinical improvement was observed p value < 0.05.(Table: III)

DISCUSSION

In developing countries like Pakistan cirrhosis liver is more prevalent compared to developed countries.[17] In fact both hepatitis B virus (HBV) and hepatitis C virus (HCV) infections have become endemic in our community.[18,19] Hepatic Encephalopathy is a common neuro-psychiatric complication in CLD. High levels of ammonia in the body is a major cause of hepatic encephalopathy, that's why most of the treatments are targeted against the detoxification of ammonia. L Ornithine L aspartate (LOLA) stimulates the urea cycle and ammonia utilization that's why thought to be useful in acute hepatic encephalopathy. In our study, it was observed that the LOLA has beneficial effects not only in clinical improvement of encephalopathy but also obvious decrease in serum ammonia levels after infusion of LOLA. These results were comparable to other studies. Bai et al concluded after meta-analysis of 8 randomized clinical trials including 646 patients that, LOLA was beneficial in both overt and minimal hepatic encephalopathy, causes both clinical and biochemical detoxification of ammonia.[20] Another meta analysis done in 2011 supported the use of LOLA for neuro-psychiatric improvement as well as decreasing levels of ammonia.[21] Although regional data is sparse however, it is necessary to identify two clinical trials. In 2011 Abid et al conducted a study in Agha Khan university Hospital on 110 patients concluded that LOLA was safe and associated with rapid clinical improvement and shorter hospital stay.[14] Ahmed et al conducted a study in in Shaikh Zyed hospital Lahore on 80 patients in 2008 concluded that ornithine infusion was associated with rapid clinical recovery and decrease serum ammonia.[13] Considering the results of our trial and other national and international studies and meta analysis, we can recommend use of LOLA as addition to other standard therapies of hepatic encephalopathy since ornithine therapy is safe, with mild side effects like nausea and vomiting and is easily available, can be given both orally and parenterally and does not adds significant cost to treatment of hepatic encephalopathy. Future studies should be directed towards comparison of efficacy L ornithine therapy with others drugs used for standard treatment of hepatic encephalopathy like lactitol, rifixamine, Zinc supplements and branch chain amino acids.

CONCLUSION

LOLA is effective in decreasing serum ammonia as well as causes clinical improvement in patients with hepatic encephalopathy. It can be recommended that LOLA may be used in the patients with hepatic encephalopathy especially when not responsive to standard treatment regimen.

Table I: Distribution of patients according to characteristics

Characters	Trial group n= 50	Placebogroup n=50
Age	49.66+ 12.25	46.04 + 9.837
Male	30 (60%)	28(56%)
Female	20(40%)	22(44%)
Child-Pugh class A	3(6%)	zero
Child-Pugh class B	17(34%)	21(42%)
Child-Pugh class- C	29(58%)	29(58%)
Patients having HBV	12(24%)	10(20%)
Patients having HCV	35(70%)	33(66%)
Patient having Non-B/C CLD	_____	2(4%)
Patients with both B/C CLD	3(6%)	5(10%)

TABLE II: Distribution of patients according to mean serum ammonia levels on Day I and Day III:

	Day I	Day III	p-values
Trial group	105.24	74.16	0.0013
Placebo group	112.28	110.52	0.124

TABLE III : Distribution of patients according to grades of Hepatic encephalopathy on Day I & III:

DAY I	Trial group	Placebo Group	P values
Grade II	10(20%)	12(24%)	0.652
Grade III	17(34%)	19(38%)	0.648
Grade IV	23(46%)	19(38%)	0.324
DAY III			
Grade zero	4(8%)	------	
Grade I	18(36%)	10(20%)	0.0345
Grade II	20(40%)	12(24%)	0.0384
Grade III	8(16%)	18(36%)	0.0467
Grade IV	----	10(20%)	

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Author's contribution:

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Dr. Ajeet Kumar: Data collection, data analysis, manuscript writing, manuscript review

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