CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

Efficacy of L-Ornithine L-Aspartate in Acute Liver Failure: A Double-Blind, Randomized, Placebo-Controlled Study

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Background & Aims: **In acute liver failure (ALF), high blood ammonia levels have been documented that correlate with mortality and complications. L-ornithine L-aspartate (LOLA) reduces ammonia levels by increasing hepatic ammonia disposal and its peripheral metabolism. Present study evaluated efficacy and ammonia lowering effect of LOLA in ALF.** ***Methods:*** **This study was placebo-controlled and blinded. We randomized 201 patients with ALF between January 2005 and October 2007 to either placebo or LOLA infusions (30 g daily) for 3 days. Arterial ammonia was measured at baseline and daily for 6 days. The primary end point was improvement in survival. The study followed CONSORT guidelines and was registered at the ClinicalTrials.gov (Identifier: NCT00470314).** ***Results:*** **There was no reduction in mortality with LOLA treatment (mortality: 33.3% in placebo and 42.4% in LOLA; relative risk of death 1.27; 95% CI: 0.88–1.85; $P = .204$). By multivariate analysis, ammonia levels were an independent predictor of survival. There was significant decrease in ammonia levels in both groups with time ($P < .001$), but the levels of ammonia between the randomized groups at any time point, either during the 72 hours of LOLA infusion or during the follow-up were similar ($P = .492$). There was no difference between the 2 groups in the improvement in encephalopathy grade ($P = .418$), consciousness recovery time ($P = .347$), survival time ($P = .612$), or complications like seizures ($P = .058$) and renal failure ($P = .615$). The fetal outcome was also similar ($P = .172$). No adverse drug effect was noted.** ***Conclusions:*** **LOLA infusion did not lower the ammonia or improved survival in ALF.**

Acute liver failure (ALF) has high mortality. Survivors recover completely without any sequel. Liver transplantation is a definite treatment option in ALF but is logistically and financially difficult in countries with highest disease burden and requires lifelong immunosuppression. Therefore, new treatment options are needed to improve the survival of medically managed patients with ALF.

There is extensive experimental evidence that ammonia is the key neurotoxin in ALF. There is a substantial blood-to-brain ammonia transfer in ALF.[1] Ammonia can directly affect both excitatory and inhibitory central neurotransmission.[2] Removal of excess brain ammonia by glutamine synthesis in astrocytes leads to cellular edema. Increased brain ammonia concentrations result in altered expression of astrocyte proteins, a redistribution of cerebral blood flow from cortical to subcortical structures, up-regulation of the peripheral-type benzodiazepine receptors in astroglial mitochondria, and enhanced synthesis of neurosteroids, which are γ-aminobutyric acid (GABA) (A) receptor agonists.[3] Blood ammonia levels are higher in ALF than in cirrhotic patients. Higher blood ammonia levels in ALF have been correlated with higher mortality, higher grades of encephalopathy, increased frequency of raised intracranial hypertension, cerebral herniation, and complications in 4 human studies.[4–7] There is thus both an experimental and clinical rationale for using ammonia lowering therapies in ALF.

L-ornithine L-aspartate (LOLA) is a compound salt of ornithine and aspartate. In the periportal hepatocytes that synthesize urea, ornithine serves as an activator of ornithine transcarbamoylase and carbamoyl phosphate synthetase. In addition, ornithine itself acts as a substrate for urea genesis. Hence, LOLA can activate the periportal urea cycle in the liver.[8] Aspartate and ornithine, after conversion to α-ketoglutarate, also serves as carbon sources for perivenous glutamine synthesis. In the skeletal muscle, LOLA up-regulates glutamine synthesis by substrate provision for glutamine synthetase.[9,10] Ammo-

Abbreviations used in this paper: ALF, acute liver failure; LOLA, L-ornithine L-aspartate.

0016-5085/09/$36.00
doi:10.1053/j.gastro.2009.02.050

nia is consumed during urea formation and glutamine synthesis, and thereby LOLA decreases blood ammonia levels.[6–12]

LOLA is therefore a promising agent for use in ALF patients. It has a scientific rationale and has been found to be effective in reducing ammonia levels and improving psychometric performance in patients with cirrhosis.[11] In a rat model of acute liver injury, it was demonstrated that LOLA can effectively lower the ammonia levels and delay onset of hepatic encephalopathy.[12] There is, however, no human study evaluating LOLA in patients with ALF. LOLA has not been recommended to be used in patients with ALF, and a product information insert in commercial LOLA preparation in Europe does not recommend its use in ALF. Therefore, the present prospective randomized, double-blind, placebo-controlled trial was conducted to assess the clinical efficacy and ammonia lowering effect of LOLA in patients with ALF.

Patients and Methods

The Study Participants

Consecutive patients with ALF from January 2005 to October 2007 were evaluated for inclusion in this study. ALF was defined by the development of encephalopathy within 4 weeks of onset of symptoms in the absence of history of preexisting liver disease.[13] The patients were recruited at the Department of Gastroenterology, All India Institute of Medical Sciences (AIIMS), New Delhi, which is a tertiary referral center. An informed consent was taken from the nearest relative of the patient for enrollment in the trial. The study was approved by the Institutional Ethics Committee of AIIMS (approval number: A-38/29.1.2007) and conformed to the World Medical Association Declaration of Helsinki. The study followed the CONSORT guidelines for randomized controlled trials[14] and was registered at the ClinicalTrials.gov (identifier: NCT00470314).

Patients were excluded from enrollment if any of the following criteria were present:

1. Presence of 3 or more of the following adverse prognostic factors at the initial patient evaluation: age $\geq$40 years, clinical evidence of cerebral edema, bilirubin $\geq$15 mg/dL, and prothrombin time prolongation by $\geq$25 seconds.[15] Such patients are at advanced stage of liver failure and have high mortality rate of $>$90% with various complications, which itself influences the outcome.[15] In our earlier studies, we have documented that patients with 3 or more adverse prognostic factors had higher frequency of complications such as renal failure, seizures, sepsis, and gastrointestinal bleed, each of which can cause death and thereby may compromise the efficacy of LOLA. To evaluate the effect of LOLA, we therefore included patients with less than 3 adverse prognostic factors.
2. Previous treatment with LOLA, lactulose, or other ammonia lowering treatments before admission.
3. Suspicion of underlying cirrhosis, malarial hepatopathy, enteric hepatitis, alcoholic hepatitis, or ischemic hepatitis.
4. Renal insufficiency at admission, as defined by a urine output of $<$400 mL/day and/or creatinine level of $>$1.5 mg/dL.
5. Inability to randomize within 24 hours of admission.

The Study Intervention

The patients were randomized to receive either placebo or LOLA at a dose of 30 g daily, by infusion over 24 hours, for 3 days. LOLA was supplied as ampoules (each ampoule containing 5 g LOLA in 10 mL clear solution). Six ampoules (containing 30 g of LOLA) were infused through an infusion pump at a rate of 2.5 mL per hour. The placebo vials (10 mL isotonic saline in each vial) were identically supplied and similarly infused. Vials of placebo were indistinguishable from those containing LOLA (both were prepared and supplied by Intas Pharmaceutical, Ahmedabad, India.). The dose of LOLA (30 g in 24 hours) was based on the previously published data, demonstrating the effectiveness of this dose of LOLA in lowering ammonia levels and improving hepatic encephalopathy in patients with cirrhosis.[11]

The Study Objectives

In the current study, we tested the hypothesis that LOLA infusion will decrease plasma ammonia and will improve the clinical outcome of patients with ALF.

The Study Outcomes

Primary outcome measure: improvement in survival. In ALF, high arterial ammonia levels have been reported to be associated with higher mortality, and reduction in ammonia levels was associated with improved survival.[4–7] We presumed that, if LOLA decreases arterial ammonia, then it is likely to improve survival. Therefore, improvement in survival was considered to be the primary outcome measure.

Secondary outcome measures. (1) Reduction in ammonia levels during and at the end of 72-hour LOLA infusion, (2) improvement of encephalopathy by 1 or more grades, (3) reduction of consciousness recovery time among survivors, (4) prolongation of time to death among nonsurvivors, (5) prevention/reduction of cerebral edema, and (6) reduction of seizures frequency.

Sample Size

The survival rate of patients with ALF having $\leq$2 poor prognostic factors (as defined in the previous section) at our center was 50% in the previous years.[15] We believed that the survival rate would be similar in the placebo group and would improve to 75% in the LOLA group. Based on 0.8 power to detect a significant differ-