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Research Article

Is L-ornithine-L-aspartate Effective in Hepatic Encephalopathy? or is it Just a Myth?

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Abstract

Hepatic Encephalopathy (HE), a complication of chronic liver disease, presents with neurological and psychiatric symptoms. It has four grades. Minimal Hepatic Encephalopathy (MHE) is the mildest form of HE. Over the last two decades, many Randomized Controlled Trials (RCTs) have been performed to understand the role of various treatments in HE. L-Ornithine L-aspartate (LOLA) has also been studied. It is a stable salt of two amino acids; L-Ornithine and L-aspartate. It acts in the liver to help utilize extra ammonia by the urea cycle and hence lowers the ammonia levels. This review aims to understand the role of LOLA in HE, MHE, and as a prophylaxis. PubMed was used as a search engine. A total of seven articles were retrieved. Our results demonstrated that LOLA can be very effective in lowering the ammonia levels and hence is not only effective for MHE and prophylaxis, but can play a very significant role in the treatment of HE.

Keywords: Hepatic Encephalopathy

1. Introduction

Hepatic Encephalopathy (HE) is a complication of cirrhosis. It manifests in the form of neurological and psychiatric symptoms. In early symptoms of HE, patients experience deficits of attention and visuospatial construction, as well as impaired motor speed and accuracy. Overt Hepatic Encephalopathy (OHE) is characterized by asterixis, stupor and can lead to coma. Coma is associated with poor prognosis and high mortality. Minimal Hepatic Encephalopathy (MHE) is the mildest form of HE. It is characterized by low-grade alterations of mental status generally diagnosed by psychometric testing [1]. 20% of patients with decompensated cirrhosis, present with overt hepatic encephalopathy. In patients with cirrhosis who have no evidence of neuropsychiatric impairment, the chance of developing an episode of HE within five years of presentation is about 5% to 25%. The presence of hepatic encephalopathy is associated with significant impairment in the performance of complex tasks, such as driving, and lays a detrimental effect on the quality of life, and safety [2]. Treatment for HE is based on measures to reduce the production and passage to the bloodstream of intestinal nitrogenous compounds such as ammonia. Traditionally, the first choice therapeutic option has been non-absorbable antibiotics such as neomycin, kanamycin sulfate, and paromomycin. These antibiotics decrease the number of bacteria responsible for producing nitrogenous compounds. Such antibiotic therapy has proved to be effective, but absorption of even a small fraction of these antibiotics can cause ototoxic and nephrotoxic side effects, hence this treatment is not common anymore. Recently, metronidazole, L-Ornithine L-aspartate (LOLA), and rifaximin use are advocated and their results are quite impressive [3].

L-Ornithine L-aspartate (LOLA), a stable salt of two endogenous amino acids, has ammonia-lowering properties. L-ornithine and L-aspartate are readily absorbed, distributed, and metabolized. L-ornithine acts as an important mediator in the urea cycle that takes place in periportal hepatocytes. It also acts as an activator of carbamoyl phosphate synthetase. L-ornithine as well as L-aspartate both are involved in transamination to glutamate via glutamine synthetase in perivenous hepatocytes. Furthermore, both these amino

acids play a crucial role in metabolic pathways where ammonia molecule is incorporated into urea and glutamine. It is the cellular and biological location of these pathways that confirms the application of LOLA as an effective ammonia-lowering strategy that can be used for the management and treatment of hepatic encephalopathy. These metabolic pathways were interpreted by experimental studies performed on animals and were confirmed by RCT trials performed on patients with severe liver diseases. More recent studies have indicated that LOLA may have a direct hepatoprotective effect as well [4]. In the current AASLD-EASL Guidelines [4], recommendations relating to the use of LOLA for the treatment of HE in cirrhosis were based upon the results of a single RCT with intravenous LOLA while the oral formulation was pointed out to be ineffective. The objectives of the present review are to provide an up-to-date evidence base for the efficacy of LOLA for the treatment of OHE and MHE in cirrhosis and to analyze where LOLA stands in terms of lowering ammonia levels.

2. Methods

A search of PubMed was performed to identify relevant research articles. Mesh keywords used included " Hepatic Encephalopathy" AND "Ornithylaspartate". The search was restricted to human studies, Randomized Control Trials, and those done in the last 15 years. Articles written in the English language were included. The pediatric population was not included and a filter of >18 years was applied. The exclusion criteria were animal studies.

3. Results

The total number of studies retrieved was 13 initially. After the primary and secondary screening, a total of 7 studies were retrieved and these studies are included in the review. The total number of subjects in our study was 847.

4. Discussion

Several randomized controlled trials have been done in the last 2 decades to explore the efficacy of LOLA in HE. Some studies explored its use in OHE, while others studied its role in MHE. These analyses were focused on comparing the effectiveness of LOLA to other treatments, and also compared oral versus intravenous formulation of LOLA. In this review, we sought to dig deeper to understand the role of LOLA in HE. Table 1 summarizes the characteristics of the studies which are included in our review article.

4.1 LOLA for prophylaxis

Aside from understanding the role of LOLA in HE patients for treatment, its role as an effective drug for prophylaxis is yet to be understood. It has been previously used for primary as well as secondary prophylaxis. Prophylactic management of patients to prevent the development of the first episode of HE is known as primary prophylaxis while preventing recurrence of HE in patients who had the previous episode of HE is classified as secondary prophylaxis [12]. In 2001, Mittal W et al. [9] made an effort to understand the role of LOLA in MHE. He selected patients with two or more abnormal psychometric tests. The patients in the experimental group were given LOLA 6 g three times per day. The duration of the study was 3 months. Interestingly, only 5% of the patients in the experimental group developed HE, while about 10% of the patients in the placebo went on to develop HE. The study concluded that LOLA can prevent the development of HE. Sharma K et al. [7] in 2014, performed an RCT to find out the effect of rifaximin, probiotics, and LOLA individually in the reversal of MHE. The patients were diagnosed to have MHE based on a critical flicker frequency (CFF) test and three neuropsychometric tests (NPTs). Results supported the evidence that LOLA can have a role in the reversal of MHE. In 2018, Varakanahalli et al. [5] studied the role

of LOLA as secondary prophylaxis in patients with previous episodes of HE. Primary endpoint was the development of HE. The RCT concluded that LOLA is effective in the secondary prophylaxis of HE and is associated with significant improvements in CFF scores, psychometric hepatic encephalopathy score, ammonia levels, and health-related quality of life. Table 2 further elaborates on these RCTs.

4.2 LOLA as a treatment for HE

Several different drugs can be used for the treatment of HE. The main goal of treatment is to reduce the levels of ammonia in the blood which can decrease its levels in the brain leading to the reversal of the condition. Antibiotics are often given empirically due to the frequency of infection as an underlying cause. Additional treatment measures include lactulose/lactitol (a non-absorbable osmotic laxative that helps convert ammonia to non-absorbable ammonium in the gastrointestinal tract), and zinc (to correct underlying deficiency common in cirrhotic patients) [14]. In 2018, Sidhu SS et al. [6] performed an RCT study on 193 patients having episodic OHE (grades 2–4). Intravenous LOLA, 30 g daily in three divided doses, was given to 98 patients in the treatment group (placebo=95). Meantime taken for recovery from OHE, venous ammonia levels and length of hospital stay in LOLA-treated patients were significantly reduced. It is important to note that in this trial, all patients, both LOLA and placebo-treated, received lactulose. However, despite receiving lactulose, patients in the placebo arm of the trial remained overtly encephalopathic and hyperammonemic. These lactulose-resistant features were shown to be significantly improved following intravenous LOLA. Abid S et al. [8] and Ahmad I et al. [10] also studied the role of LOLA in HE and demonstrated that LOLA could be used effectively for HE. Poo JL et al. [11] compared lactulose and LOLA and concluded that oral administration of lactulose or L-ornithine - L-aspartate to Mexican patients with cirrhosis and hyperammonemic encephalopathy significantly reduced serum ammonia levels in study groups and additionally improved mental status parameters, number connection test, asterixis scores, and EEG activity in the group receiving L-ornithine-L-aspartate. Table 3 further elaborates the role of LOLA in HE treatment.

Study	**Date of Publication**	**Study**	**Subject number**	**Patient population**
Varakanahalli S, et al, [5]	2018	Double-blind randomized controlled trial at a tertiary center.	150	Recovered from HE
Sidhu SS, et al. [6]	2018	Prospective, double-blind, randomized, placebo-controlled trial conducted at two tertiary care institutes in India	193	Patient with overt HE
Sharma K, et al. [7]	2014	--	124	MHE
Abid S, et al [8].	2011	Randomized placebo controlled study.	120	HE
Mittal VV, et al [9].	2011	--	160	MHE
Ahmad I, et al. [10]	2008	A randomized, placebo-controlled trial.	80	HE
Poo JL, et al. [11]	2006	--	20	HE

Table 1: Characteristics of studies included in the review.

Study	Main question of the study	Patient population	Dosage	Subject number	Time period	Response Assessment	Primary end point	Outcome
Varakanahalli S, 2018 [5]	Prevention of recurrence of encephalopathy (LOLA)	Recovered from HE	LOLA (6 g thrice daily)	150 patients 73/72	6 months	Assessed by psychometric HE scores using five paper-pencil tests, CFF test, arterial ammonia, and sickness impact profile scores at inclusion.	Overt HE.	LOLA is effective in the secondary prophylaxis of HE and is associated with significant improvements in psychometric hepatic encephal-opathy score, ammonia level, CFF scor-es, and health-related quality of life.
Sharma K, 2014 [7]	Find out the effect of rifaximin, prob-iotics, and LOLA individually in the reversal of MHE.	MHE	--	124 patients with MHE were randomized to receive LOLA (n = 31), rifaximin (n = 31) (probiotics (n = 32), placebo (n = 30).	2 months	Three neuropsychometric tests (NPTs) and CFF test.	Improvem ent in Status.	Rifaximin, LOLA, and probiotics are better than giving placebo in patients with MHE.
Mittal VV, 2011 [9]	LOLA as a treatment of MHE.	MHE	LOLA 6 g three times per day	--	3 months	Two or more abnormal psychometric tests.	Developm ent of overt HE	Only two (5%) patients on LOLA developed HE, while four (10%) developed HE in the placebo group.

Table 2: Illustrates the possible use of LOLA in primary prophylaxis and MHE.

Study	The main question of the study	Dosage	Subject number	Time period	Response Assessment	Primary endpoint	Outcome
Sidhu SS, 2018 [6]	Evaluated the efficacy of intravenous LOLA in the reversal of HE.	Intravenous infusion of LOLA, 30 g daily	193 LOLA (n = 98), or placebo (n = 95).	5 days	Fasting venous ammonia levels were estimated daily from 0 to 5 days. Serum TNF-alpha, interleukins, hemogram, and liver and renal function tests were performed at days 0 and 5.	Mental state grade on day 5 of treatment.	In patients with bouts of HE, intravenous LOLA (as an add-on therapy to lactulose and ceftriaxone) significantly improved the grade of HE over days 1-4, but not on day 5, and decreased venous ammonia, recovery time, and length of hospital stay.
Abid S, 2011 [8]	Efficacy of LOLA as adjuvant therapy in cirrhotic patients with HE.	--	120	--	Number connection test-A (NCT-A), ammonia level, clinical-grade of HE, and duration of hospitalization were assessed.	Improvement in HE.	In cirrhotic patients with advanced hepatic encephalopathy, treatment with LOLA was safe and associated with relatively rapid improvement and shorter hospital stay.
Ahmad I, 2008 [10]	Role of LOLA in HE	LOLA infusion	80 (LOLA, placebo)	5 days	Hyperammonemia and overt hepatic encephalopathy	Ammonia levels and HE grade	LOLA infusions were found to be effective in cirrhotic patients with hepatic encephalopathy
Poo JL, 2006 [11]	Efficacy of LOLA versus lactulose in Mexican patients with hepatic encephalopathy.	Oral LOLA	20 lactulose (n = 10) or LOLA (n = 10)	2 weeks	Hyperammonemia and overt hepatic encephalopathy.	Ammonia levels, mental status improvement.	Encephalopathy significantly improved, reduced serum ammonia levels in study groups, and additionally improved mental status parameters (number connection test, asterixis scores, and EEG activity) in the group receiving L-ornithine-L-aspartate.

Table 3: Findings of RCT studies done to evaluate the role of LOLA in HE.

5. Conclusion

To summarize, LOLA can be effective for the treatment of hepatic encephalopathy and minimal hepatic encephalopathy. The studies have found it an effective strategy to lower ammonia levels, which can help to reduce the grade of HE or in the case of MHE, help to improve the psychometric hepatic encephalopathy score, and health-related quality of life. It has also been shown to be effective for secondary prophylaxis. Having said that, there is a still need for large-scale RCTs to understand the role of LOLA as an effective drug for hepatic encephalopathy.

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