Analysis of combined effect of synbiotic and LOLA in improving neuropsychometric function

Preetha Nandabalan and Suguna Bai Arone

Abstract
The most challenging factor after diagnosis of end stage liver disease like hepatic encephalopathy is choosing the definitive drug to improve the neuropsychometric performance of the patient. This study aims at analyzing the combined effect of Synbiotic and L-ornithine L-aspartate (LOLA) in improving brain function among patients admitted with covert hepatic encephalopathy. Methods: 40 cirrhotic patients with impaired psychometric performance were enrolled and randomized into control and study group receiving standard therapy and study drugs along with standard therapy respectively. Patients were evaluated using neuropsychometric tests on day 0, 7 and 14. Results were analysed statistically. In conclusion there is significant improvement in neurological function in patients receiving Synbiotics in combination with LOLA.

Keywords: Synbiotics, number connection test, line tracing test, encephalopathy

1. Introduction
Hepatic encephalopathy (HE) denotes a complication of liver disease and portosystemic shunting that represents as neuropsychiatric changes and altered consciousness. Based on clinical presentation HE is classified as overt hepatic encephalopathy (OHE) or covert hepatic encephalopathy (CHE). When the neurological changes are clinically apparent it is known as OHE. Whereas CHE is its mildest form, previously known as minimal or subclinical hepatic encephalopathy. In recognition of the dangerous consequences of CHE, the name of the condition has recently been changed from minimal to covert, a position endorsed by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism [1]. The impact of HE in quality of life make its early diagnosis imperative. Among the several diagnostic techniques ranging from simple clinical scales to sophisticated computerized tests, Psychometric tests seem to be promising due to their high sensitivity and low cost but results are variable depending on age and education [2-5]. Clinically CHE is known to be associated with deficits in driving skills [6-8], reduction in quality of life [9, 10], impairment of working capability [11].

1.1 Neuropsychometric Tests
Neuropsychometric tests include both ‘paper and pencil’ tests and computerized tests that can be used to identify impairments in visuo-spatial functioning, attention, processing speed and response inhibition [12]. These tests are cost effective, easy to administer and do not require skilled personnel or expensive equipment. However, their dependence on a patient’s age and education, total testing time and applicability restricted to lower grades of HE confers a disadvantage to diagnosis of HE. Present international consensus recommends use of the neuropsychometric tests for diagnosing and monitoring CHE depending on availability of local normative data [13].

These tests measures psychomotor speed and precision, visual perception, visuo-spatial orientation, visual construction, concentration, attention and memory, is simple to perform and can be completed in less than 20 minutes. the Portosystemic Encephalopathy (PSE) Syndrome Test, which includes the line tracing test (LTT), serial dotting test (SDT), digit symbol test (DST) and number connection test A and B (NCT A and B). The sensitivity and specificity of the PHES compared with the standard method of determining HE grade were 96% and 100%, respectively [14].

Line tracing test is considered as a measure of psychomotor speed. In LTT subjects are required to complete a course drawn on paper without touching or crossing the edges as fast and accurate as possible. The normal value is < 120 seconds [15]. Number connection test is
Considered as a measure of psychomotor speed and visual attention. In the number connection test, the subjects were asked to connect numbers 1 to 25 on the printed-paper consecutively as possible. Normal range falls between 15-30 seconds [16].

1.2 Standard therapy
Nonadsorbable disaccharides like Lacutlose and Lactitol are considered the firstline treatment option for HE. The reduction in potential pathogenic bacteria such as Escherichia coli and Staphylococcal species in stool at the end of treatment period with increase in non-urease producing Lactobacillus limits ammonia production. Moreover, lactulose is converted to lactic and acetic acid which results in acidification of colonic contents. The low pH decreases passive non-ionic diffusion of ammonia thus lowering its systemic concentration. Furthermore, with its prebiotic potential, lactulose also encourages growth of probiotic bacteria such as Bifidobacterium species that are known to have health-promoting [1] effects. Patients intolerant to nonabsorbable disaccharides are generally treated with antibiotics, to suppress the bacteria involved in ammonia genesis. There are few antibiotics which have been used for the treatment of HE which had shown limited benefit, which include neomycin, metronidazole, oral vancomycin, oral fluoroquinolones like Norfloxacain and very recently Rifaximin. In fact neomycin was used for treatment of HE, because of its limited systemic absorption, based on earlier studies. It has lost its use in HE in liver cirrhosis due to its ototoxicity and nephrotoxicity. Rifaximin, a minimally absorbed oral antibiotic is approved by Food and Drug Administration for the treatment of chronic HE.

1.3 Study drugs
Synbiotics are the combination of probiotics and prebiotics. Synbiotics acidify the gut lumen and inhibits the growth of urease producing pathogenic bacteria. It also normalizes the intestinal flora by promoting the growth of beneficial bacteria [17]. While this potential therapeutic target of modifying the gut microbiota using pre-pro or synbiotics has been evaluated in other conditions such as inflammatory bowel disease, irritable bowel syndrome, antibiotic-associated diarrhoea, this study proposes to assess the beneficial effect of these agents in hepatic encephalopathy. L-Ornithine L-Aspartate is shown to decrease serum ammonia levels and improve psychometric performance in subjects with hyperammonemia and hepatic encephalopathy. LOLA treatment stimulates ammonia detoxification, especially in skeletal muscle. Both oral and intravenous administration show reduction of ammonia levels and improvement in encephalopathy in patients with cirrhosis in certain control studies [18].

This study has been undertaken to analyse the additive effect of LOLA and synbiotics in improving psychometric performance in end stage liver disease.

2. Materials and methods
The study was conducted in Department of Hepatology, after obtaining the approval from Institutional Ethics Committee. Patients with clinical features of covert Hepatic Encephalopathy admitted for treatment as inpatient in the Department of Hepatology and their caregivers were briefed about the study purpose and procedures. The demographic details of the patients is obtained and recorded. Written informed consent was obtained from subjects willing to participate in the study, in the prescribed format.

<table>
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<th>Inclusion criteria</th>
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<td>Age -20 to 50 years</td>
<td>Patients with OHE/ hepatic coma</td>
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<td>patients admitted for cirrhosis of liver with covert hepatic encephalopathy</td>
<td>HE due to metabolic causes, intracranial disorders and toxins</td>
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<tr>
<td>Both genders</td>
<td>Recent GI bleed (&lt;6 weeks)</td>
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<td>Willing to give Written informed consent</td>
<td>Pregnant or lactating women</td>
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<td>associated significant systemic illness</td>
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As shown in Figure.2 in this study the diagnosis of covert Hepatic encephalopathy was done using quantitative psychometric analysis. The subjects were screened by complete medical history, clinical examination and laboratory investigations. Subjects who fulfilled the inclusion and exclusion criteria were enrolled in the study. They were
randomized to either of the study groups and treated for a period of 14 days. The enrolled patients were randomized into either Group A or Group B and received the respective therapy by simple randomization. The obtained data were analyzed statistically. The values were given as Mean ± SD.

The difference within the groups in Line Tracing and Number Connection tests was analyzed by repeated measures of ANOVA. Similarly the difference between Group A and Group B was analyzed using Student’s independent t-test. *p* < 0.05 is considered to be statistically significant.

**3. Results**

Comparison of age distribution among control and study group showed that there is no significant difference (*p* value = 0.463) in age between the two groups. Similarly, there was no difference in gender distribution among the two groups.

The normal time taken for Line Tracing Test is < 120 sec. On comparison of the two study groups as seen in Table 2, Mean time taken has decreased in the both groups on day 14. On further analysis, there is a difference within the Group A (*p* = 0.04) and within Group B (*p* = 0.01) which are statistically significant. However, the change within Group B is more significant compared to Group A group. The reduction in time taken shows no change between two groups on day 0 (*p* = 0.34), whereas there is a significant difference on day 7 (*p* = 0.04) and day 14 (*p* = 0.001). The difference is more significant on day 14 compared to day 7. Figure 3 is the diagrammatic representation of Time taken (in seconds) for Line Tracing Test in both the study groups.

Similarly the normal time taken for performing the number connection test is 15 – 30 seconds. Both Group A (*p* = 0.05) and the Group B (0.01) shows a significant difference in the time taken. The reduction in time taken, is more significant in Group B when compared to the Group A. The difference on day 14 is more significant compared to day 7 (Table 3). The diagrammatic representation of Time taken for Number connection Test in both the groups is shown in Figure 4.

**4. Discussion**

Once hepatic encephalopathy has been diagnosed it can be challenging for the physician to decide which agent would be the most effective in reversing the neurocognitive deficits. Inspite of different treatment options available there is yet no definitive therapy. This may be due to variable efficacy and side effect profile of the available options. This study fulfilled the aim of studying the effect of Synbiotic and LOLA in improving psychometric performance in the treatment of hepatic encephalopathy.

L-Ornithine L-Aspartate and synbiotics are not commonly used owing to reservations in their therapeutic benefit. Most of the available treatment strategies aim at reducing the synthesis of ammonia by bacteriological activity, whereas, LOLA improves the metabolism of ammonia by providing the substrates Ornithine and Aspartate, which are intermediates in the urea cycle in liver and glutamine synthesis in the muscles. Psychometric performance is assessed using Line Tracing Test and Number Connection Test. When compared to Day 0, the mean time taken to perform the Line Tracing Test (LTT) has decreased significantly in both groups on day 7 (*p* = 0.04) and day 14 (*p* = 0.001). Similarly, Number Connection Test showed a significant reduction in mean time duration in both the groups on Day 14 compared to Day 0. The reduction in time taken, is more significant in Group B (*p* = 0.01) when compared to Group A (*p* = 0.05).
This concurs with the study done by Kircheis, et al. \(^{[19]}\) and Poo, et al. \(^{[20]}\) in which there is improvement of psychometric performance with L-Ornithine L-Aspartate compared to standard treatment. Similarly, a study done to compare the effect of probiotics conclude that probiotics improve psychometric performance compared to lactulose \(^{[21]}\). Therefore, LOLA and Synbiotics show definite improvement in psychometric performance in hepatic encephalopathy patients when prescribed in combination. No adverse effects were reported with Synbiotic and L-Ornithine L-Aspartate combination during treatment period.

5. Conclusion
To conclude, Synbiotics in combination with LOLA along with Lactulose standard therapy have significant efficacy in improving neuropsychometric performance in end stage liver disease like hepatic encephalopathy.

6. Acknowledgements
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7. Declarations
Funding: Nil
No conflict of interest
Ethical approval: Obtained form the Institutional Ethical Comittee

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Table 2: Comparison of reduction in time taken using Line Tracing Test

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Table 3: Comparison of reduction in time taken using number connection test

8. References
9. Prakash R, Mullen K. Is poor quality of life always...