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Original Article

Can *Lactobacillus acidophilus* improve minimal hepatic encephalopathy? A neurometabolite study using magnetic resonance spectroscopy

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ABSTRACT

Background and study aims: Minimal hepatic encephalopathy (MHE) is diagnosed when hepatic patients perform worse on psychometric tests compared to healthy controls. This study aimed to evaluate probiotics as alternative therapy in MHE.

Patients and methods: This is an open-label randomised controlled trial, performed in the Department of Tropical Medicine and Infectious Diseases, Tanta University Hospitals, from March 2010 to January 2012. A total of 90 patients with MHE were allocated by simple randomisation to three parallel equal groups. Group A received lactulose, group B a probiotic (*Lactobacillus acidophilus*) and group C served as the control. After informed consent, patients were tested for gut microecology, fasting blood ammonia, liver functions and magnetic resonance spectroscopy (MRS) examination to study brain metabolites, mainly choline (Cho), myo-inositol (mI), glutamine + glutamate (Glx) and creatinin (Cre). Patients who developed overt encephalopathy were excluded from analysis. The whole battery of investigations was repeated in the same order after 4 weeks.

Results: The probiotic was better tolerated than lactulose. The relative risk reduction (RRR) of developing overt encephalopathy was 60% in the case of lactulose and 80% in the case of probiotic, with a number needed to treat (NNT) of 2.4 and 2.3, respectively. The differential but not total microecology count was significantly shifted towards saccharolytic rather than proteolytic bacteria. The mI/Cre and (Cho + mI)/Glx ratios were significantly increased and the Glx/Cre ratio was significantly reduced after 1 month-follow-up in the probiotic group compared to the lactulose group and in both treatment groups compared to the control group.

Conclusion: Both probiotic and lactulose therapy can improve blood ammonia and psychometric tests in MHE and reduce the risk of developing overt encephalopathy. MRS showed more improvement in the levels of brain neurometabolites in the probiotic group.

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Introduction

Minimal hepatic encephalopathy (MHE) is used to describe patients with chronic liver disease who are 'clinically normal' but show abnormalities in neuropsychometric and/or neurophysiological performance [1]. It affects the patients' ability to perform complex acts and impairs the health-related quality of life (HRQOL) [2,3]. Such impairments lead to major difficulties in safely performing routine activities of life [4]. The prevalence of MHE varies between 30% and 84% in patients with liver cirrhosis [2–6].

The pathogenesis of hepatic encephalopathy (HE) is multifactorial. However, gut-derived nitrogenous substances are thought to play a central role in all hypotheses [7]. Colonic bacteria break protein down into ammonia and carbon dioxide. The healthy liver converts ammonia back to urea to be excreted by the kidneys. If liver functions are impaired or there is a portosystemic shunt, the blood ammonia level and subsequently brain ammonia are increased as the blood–brain barrier is highly permeable to ammonia [8,9]. In the hyperammonaemia state, astrocytes protect the brain by converting ammonia into glutamine. Glutamine is not toxic, but it is osmotically active leading to astrocyte swelling and brain oedema. Astrocytes are responsible for the integrity of the blood–brain bar-

Abbreviations: MRS, magnetic resonance spectroscopy; MHE, minimal hepatic encephalopathy; Cho, choline; mI, myo-inositol; Glx, glutamine–glutamate; Cre, Creatinine; HRQOL, health-related quality of life; HE, hepatic encephalopathy; NCT-A, number connection test-A; NCT-B, number connection test-B; BDT, block design test; DST, digit symbol test; SDT, serial-dotting test; LTT, line tracing test; ANOVA, one-way analysis of variance; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat.

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rier; hence, their swelling facilitates further ammonia accumulation in the brain [10]. Other gut-derived toxins may also play a role in the pathogenesis of HE. For example, intestinal flora may produce benzodiazepine-like substances [11] or mercaptans [12], which can be additive or synergistic to the effect of ammonia.

Probiotics are viable bacteria given orally to improve health. They alter gut flora composition by inhibition of urease-producing bacteria resulting in decreased ammonia production and absorption [13]. They can also enhance intestinal epithelial viability and improve human intestinal permeability by providing essential nutritional support that inhibits the apoptosis of lumenal epithelial cells [14]. Additionally, experimental studies showed that administration of probiotics can affect neuronal signalling and transmission, both locally [15] and centrally [16], through modification of intestinal flora, reflecting the so-called gut–brain axis. Therefore, probiotics are expected to have multiple beneficial effects in HE through reduction of ammonia, pro-inflammatory cytokine signalling and oxidative stress [17].

There is no gold standard test for the diagnosis of HE, even if overt. However, normal mental status plus impairment in the performance of at least two of the following tests, number connection test-A (NCT-A), number connection test-B (NCT-B), block design test (BDT), digit symbol test (DST), serial-dotting test (SDT) and line tracing test (LTT), are accepted to diagnose MHE [1]. New modalities for diagnosis that are currently introduced include proton magnetic resonance spectroscopy (MRS) that use magnetic resonance imaging (MRI) to study specific tissue metabolites. Its ability to measure the metabolic abnormalities in the brain, including choline (Cho) myo-inositol (mI) and glutamine, was established [18,19].

The aim of this study was to evaluate the effect of a probiotic (*Lactobacillus acidophilus*) on MHE patients.

Patients and methods

The protocol for the research project was approved by Tanta Faculty of Medicine Ethical Committee and all cirrhotic patients attending the Tropical Medicine and Infectious Disease outpatient clinic and inpatient wards from March 2010 to January 2012 were encouraged to join this prospective randomised trial. The exclusion criteria were the presence of overt HE, alcohol intake, gastrointestinal haemorrhage or spontaneous bacterial peritonitis during the past 6 weeks, previous shunt surgery and associated heart, respiratory or renal failure as well as history of any neurologic or metabolic encephalopathies. Patients on psychoactive drugs, such as antidepressants or sedatives, were excluded. After informed consent, patients were screened using the following three tests, NCT-A, DST and SDT, to enrol 90 patients with MHE for randomisation. Twenty healthy volunteers were tested by psychometric tests prior to enrolment. Their mean and standard deviation (SD) were calculated as reference. Tests were considered abnormal when the test score was more than mean + 2 SD in comparison with that of age- and education-matched controls. Abnormalities in at least two tests diagnose MHE [20,21]. Next morning, patients with MHE were tested for gut micrecology, fasting blood ammonia level and liver function tests, followed by MRS examination to study brain metabolites, mainly Cho, mI and glutamine–glutamate (Glx). Patients were allocated by simple randomisation to three parallel equal groups of 30 patients each. Group A received lactulose (30–60 ml day^{-1}), group B received a probiotic (one capsule containing 10^6 *L. acidophilus* three times/day) and group C was the control. Patients were followed up weekly in the outpatient clinic to insure their adherence to therapy. Those patients who developed overt encephalopathy were discontinued from the study. The whole battery of investigations was repeated in the same order (a psychometric test followed by gut microecology study, ammonia level and brain metabolites using MRS) for patients who completed their follow-up after 4 weeks.

This study was designed as overtime open-label randomised controlled trial testing the role of a probiotic in comparison with lactulose or no therapy in MHE patients. Individual patients served as their own control subjects before and after therapy, as a time series design specifically controlled for innate variables, including age, sex, chronic disease, cultural differences, genetic factors and individual habits including diet [22].

Statistical analysis

Data processing was performed using the software package SPSS version 10 for Windows (SPSS, Chicago, IL, USA). Continuous outcomes are expressed as mean difference ± Standard deviation (MD ± SD). One-way analysis of variance (ANOVA) was used to compare different groups and a paired *t*-test to compare the same group before and after therapy. When normality failed, the Mann–Whitney test was used instead. A P value of $\leqslant 0.05$ was defined as significant. The relative risk ratio and number needed to treat (NNT) were calculated for each therapeutic modality. Relative risk reduction (RRR) of developing overt encephalopathy was calculated as the ratio of reduction of its incidence in treatment groups compared to the control group. Absolute risk reduction (ARR) = improvement rate in the intervention group – improvement rate in the control group; the NNT is the reciprocal of ARR.

Results

The demographic data of all patients are shown in Table 1.

Clinical efficacy and tolerability

In the lactulose group, 2/30 (6.7%) patients discontinued therapy due to poor tolerance. They were excluded from analysis in this work. The main side effects reported in patients who continued therapy were flatulence and nausea. Out of 24 patients who continued lactulose therapy, seven patients (29.2%) had flatulence and five (20.8%) had nausea. One patient on the probiotic lacked compliance to the three-times-daily regimen and refused to continue any therapy. He was also excluded from analysis. No side effects were reported in this group. One patient in the control group (4%) developed flatulence during follow-up (Fig. 1).

The RRR of developing overt encephalopathy was 60% in the lactulose therapy group and 80% in the probiotic therapy group.

Table 1
Demographic data of all studied patients.

	Lactulose group (A) (n = 24)	Probiotic group (B) (n = 26)	Control group (C) (n = 25)
Male/female	18/6	19/7	18/7
Age	48.8 ± 8.2	50.3 ± 7.8	51.2 ± 7.5
Child class A	2	3	3
B	14	14	13
C	8	9	9
INR	1.56 ± 0.44	1.58 ± 0.38	1.48 ± 0.18
Albumin(g dl^{-1})	2.73 ± 0.41	2.64 ± 0.39	2.63 ± 0.27
ALT (IU l^{-1})	34.15 ± 12.8	36.04 ± 18.66	36.03 ± 11.92
AST(IU l^{-1})	33.84 ± 11.30	37.08 ± 21.44	37.37 ± 10.89
Bilirubin (mg dl^{-1})	1.62 ± 0.8	1.57 ± 0.8	1.42 ± 1.5
Serum creatinine (mg dl^{-1})	1.51 ± 0.39	1.46 ± 0.33	1.54 ± 0.40
Serum ammonia	72.29 ± 24.50	71.1 ± 19.67	71.8 ± 15.01

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