Secondary Prophylaxis of Hepatic Encephalopathy in Cirrhosis: An Open-Label, Randomized Controlled Trial of Lactulose, Probiotics, and No Therapy

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OBJECTIVES: **Lactulose is effective in secondary prophylaxis of hepatic encephalopathy (HE). Probiotics improves minimal hepatic encephalopathy (MHE), which predisposes to HE. No study has been conducted on the secondary prophylaxis of HE using probiotics. Our objective was to study the effects of lactulose and probiotics for secondary prophylaxis of HE.**

METHODS: **Consecutive cirrhotic patients who had recovered from HE were randomized to receive lactulose (Gp-L, 30 ml three times per day), three capsules of probiotics (Gp-P) per day containing 112.5 billion viable lyophilized bacteria per capsule, or no therapy (Gp-N). All patients were assessed by psychometry (number connection test (NCT-A, B), figure connection test if illiterate (FCT-A, B), digit symbol test (DST), and block design test (BDT)), critical flicker frequency (CFF) test, and arterial ammonia at inclusion. The patients were followed up monthly. The primary end point was development of overt HE according to West Haven criteria or a follow-up of 12 months.**

RESULTS: **Of 360 patients who recovered, 235 (65.2%) met the inclusion criteria (Gp-L, $n=80$; Gp-P, $n=77$; and Gp-N, $n=78$). In all, 38 patients (16.1%) were lost to follow-up and 77 patients developed HE (Gp-L, $n=18$; Gp-P, $n=22$; and Gp-N, $n=37$). There was a significant difference between Gp-L and Gp-N ($P=0.001$) and between Gp-P and Gp-N ($P=0.02$) but no difference between the Gp-L and Gp-P groups ($P=0.349$). The rate of readmission for causes other than HE (Gp-L, Gp-P, and Gp-N, 19:21:28; $P=0.134$) and deaths (Gp-L:Gp-P:Gp-N = 13:11:16; $P=0.56$) in all three groups were similar. There was a high prevalence of abnormal psychometry test results (NCT-A, 71.5%; NCT-B, 69.2%; DST, 76.9%; and BDT, 85.2%), and FCT-A and -B were abnormal in 35 of 48 patients (72.7%). CFF was <38 Hz in 118 patients (50.2%). Upon multivariate analysis, recurrence of overt HE was significantly associated with two or more abnormal psychometric tests and arterial ammonia after the recovery of an episode of HE.**

CONCLUSIONS: **Lactulose and probiotics are effective for secondary prophylaxis of HE in patients with cirrhosis.**

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INTRODUCTION

Hepatic encephalopathy (HE) represents a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after the exclusion of other known brain diseases (1). A challenging complication of advanced liver disease, HE occurs in approximately 30–45% of patients with cirrhosis and 10–50% of patients with a transjugular intrahepatic portosystemic shunt (2–5). Increases in the frequency and severity of such episodes predict an increased risk of death (6–8). Lactulose has been shown to be useful in the treatment of acute, chronic, recurrent portosystemic HE and in the secondary prophylaxis of HE (9,10). Bass *et al.* (11) recently showed that, over a 6-month period, treatment with rifaximin maintained remission from HE more effectively than did placebo. This treatment also significantly reduced the risk of hospitalization involving HE. The majority of these patients were also on lactulose. Minimal hepatic encephalopathy (MHE) occurs in 25–80% of cirrhotic patients without overt HE, and it has been shown to be the marker of development of overt HE (12–14). Lactulose has shown efficacy in the treatment of MHE; however, convincing data for the treatment of acute episodes of HE are lacking (15). Rifaximin has been shown to play a role in the treatment of MHE, acute episodes of overt HE, and secondary prophylaxis

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of HE. There have been two studies on the use of lactulose and rifaximin for secondary prophylaxis of HE (10,11). However, because there is no definitive recommendation or consensus on secondary prophylaxis, the use of lactulose or rifaximin for prevention of HE is not routine practice.

Probiotics alter the gut flora, resulting in decreased ammonia production and absorption due to decreased intraluminal pH. Probiotics have been shown to alter short-chain fatty acid production, decrease intestinal permeability and improve Child Pugh Score, and decrease endotoxin levels in patients with cirrhosis (16,17). Studies have shown improvement in MHE with the use of probiotics and reduction of overt low-grade HE over follow-up (16–19). However, data on the use of probiotics for treatment of overt HE are limited, and none exist for the secondary prophylaxis of HE. Long-term use of probiotics in patients with cirrhosis has also not been evaluated. MHE defined by more than two psychometric tests has been shown to predict an episode of overt HE in patients who have never had HE (7). Psychometric tests assess psychomotor speed, visual–spatial reasoning, and attention, and critical flicker frequency (CFF) is a measure of visual discrimination and general arousal (1,20). These cognitive functions have been shown to be affected by an episode of overt HE and to predict future episodes without any prophylaxis of HE (10,11,21,22). Ammonia has been regarded as the key precipitating factor in HE, and astrocytes have been the most commonly affected cells neuropathologically. Lower ammonia levels have been shown to improve HE (10,16,17). In this study we assessed the effects of lactulose and probiotics for secondary prophylaxis of HE in patients with cirrhosis.

METHODS

Study patients

From October 2008 to December 2009, consecutive patients with cirrhosis who had no overt HE but a previous history of HE and were attending the outpatient department of the Department of Gastroenterology, G.B. Pant Hospital (New Delhi, India) were enrolled. The participants were 18–70 years of age.

Cirrhosis was diagnosed on a clinical basis involving laboratory tests, endoscopic evidence, sonographic findings, and liver histology, if available.

Patients were excluded for the following reasons: (i) a history of taking lactulose in the past 6 weeks; (ii) alcohol intake during the past 6 weeks; (iii) receiving secondary prophylaxis for spontaneous bacterial peritonitis (SBP); (iv) previous transjugular intrahepatic portosystemic shunt or shunt surgery; (v) significant comorbid illness, such as heart, respiratory, or renal failure, and any neurological disease, such as Alzheimer's disease, Parkinson's disease, and nonhepatic metabolic encephalopathies; (vi) hepatocellular carcinoma; (vii) receiving psychoactive drugs, such as antidepressants or sedatives; and (viii) resumption of alcohol consumption during follow-up. The study was approved by the ethics committee of the hospital, and informed written consent was obtained from each patient before enrollment. The ethics committee of the hospital strictly followed the study, and data were monitored regularly.

Evaluation for psychometric tests

All patients underwent neuropsychometric testing using a battery of tests, including two number connection tests (NCTs), parts A and B; two figure connection tests (FCTs), parts A and B; and two performance subtests of the Wechsler Adult Intelligence Scale: the block design test (BDT) and the digit symbol test (DST). These tests were easy to administer and could be performed in 30–40 min. In principle, the FCT was similar to the NCT except figures were used instead of numbers. The FCT is a universally applicable test for the assessment of mental state that transcends the barriers of illiteracy and linguistic differences. Patients were categorized as illiterate (those unable to read and write) or being at an undergraduate (< 12 years of formal education) or graduate (holders of a bachelor's degree with 15 years of formal education) level. The psychometric test for NCT/FCT was considered abnormal when both NCT-A and NCT-B or FCT-A and FCT-B were abnormal. The test score is the time required to complete the test, including the time needed to correct any errors. NCT, FCT, and DST were analyzed as time to completion, and BDT was measured as a raw score. Tests were considered abnormal when test scores were 2 s.d. less than those of the age- and education-matched controls (23,24).

Measurement of CFF threshold

The CFF was measured in a quiet, semidarkened room without distracting noises. A portable, battery-powered analyzer was used (Hepatonorm Analyzer; Acc-136, Kusterdingen, Germany). Each patient was instructed about the fundamentals of performing the test, and an exercise involving five trial runs was performed before patient response was recorded. Flicker frequencies were measured eight times and the mean value calculated. This procedure took 15–20 min. Measurement of the CFF thresholds was performed via intrafoveal stimulation with a luminous diode. With the frequency of the light pulses decreasing from 60 Hz downward, the CFF threshold was determined when the impression of fused light turned to a flickering one. CFF was considered abnormal when the value was < 38 Hz (20). Determinations of the CFF thresholds and psychometric measurements were performed on the same day.

Blood tests, imaging, and biochemical examinations

Serum bilirubin, serum creatinine, albumin levels along with the prothrombin time, and other hematologic parameters were analyzed from patients' venous blood taken after overnight fasting using conventional methods. Arterial ammonia concentration was determined immediately after psychometric testing at baseline and at the 3-month follow-up. Arterial ammonia was measured using the ammonia Test Kit II for the PocketChem BA device (Arkay, Kyoto, Japan).The blood sample was collected onto ice and tested immediately after collection. The continuous measurement range is 7–286 μmol/l; the normal blood ammonia level for healthy adults for this device is < 54 μmol/l. An ultrasound scan of the abdomen and Doppler test were performed to check for large, spontaneous shunts, which were also confirmed by CT scan of the abdomen.

Standard treatment and nutrition

All patients were treated according to standard treatment recommendations, including diuretics, β-blockers, antiviral treatment for hepatitis B, and endoscopic treatment for variceal bleed. Patients were advised to follow a salt-restricted diet (< 2 *g* sodium intake). Protein intake was not restricted. Patients were encouraged to take supplemental casein-based protein, approximately 1 g/kg per day. Patients who were on diuretics or on β-blockers for the prophylaxis of variceal bleeding continued their medication. There was no significant difference in the intake of these medicines in the three groups.

Study design

Consecutive cirrhotic patients who recovered from HE were randomized to receive either lactulose (Gp-L) or probiotics (Gp-P) or to a no-therapy group (Gp-N) along with previous treatment. Previous episodes of HE were documented by examining the patients' medical records. The study was not blinded, and randomization was performed using tables of computer-generated random numbers by an independent person who was unaware of the patient characteristics. All randomization numbers were concealed in separate envelopes, each of which was marked with a patient number. All subjects were followed up every month to assess treatment compliance and record any complications. Patients who did not report for follow-up were contacted by telephone and instructed to return for a check-up. In the Gp-L group, patients received 30–60 ml of lactulose in two or three divided doses so that each patient passed two to three semisoft stools per day; in the Gp-P group, patients received three capsules per day containing 112.5 billion viable lyophilized bacteria per capsule (each capsule contained four strains of *Lactobacillus* (*L. casei*, *L. plantarum*, *L. acidophilus*, and *L. delbrueckii* subsp. *bulgaricus*), three strains of *Bifidobacterium* (*B. longum*, *B. breve,* and *B. infantis*), and one strain of *Streptococcus salivarius* subsp. *thermophilus* (referred to hereafter as *S. thermophiles*)); Gp-N patients merely continued their previous therapy. Compliance with therapy was ascertained by checking for increased stool frequency and a change to a softer consistency as well as by bottle and sachet counts. All patients were assessed by means of psychometry test, CFF, and arterial ammonia levels at baseline—arterial ammonia, considered a causative agent for HE and lactulose, was measured again after 3 months of follow-up. Probiotics have been shown to decrease levels of arterial ammonia (16–19), so it was repeated after 3 months of therapy to assess the effect of therapy on arterial ammonia. Primary end points were the development of overt HE or a follow-up of 12 months. HE was assessed by West Haven criteria (1).

We defined secondary prophylaxis as the prevention of recurrence of HE during the follow-up period in patients who had recovered from a previous episode of HE. Patients who developed SBP during follow-up were treated with cefotaxime for 5 days and albumin per the standard protocol and later put on secondary prophylaxis of SBP with 400 mg of norfloxacin per day. Patients admitted with variceal bleed were also given 1 g of ceftriaxone for 5 days. Similarly, admissions for other infective causes were treated with antibiotics according to the culture and sensitivity of the organisms. The patients and their relatives were instructed to contact the hospital immediately in the event of any complication. The flow diagram of the study is shown in **Figure 1**.

Statistical analysis

We calculated that a sample size of at least 60 patients in each arm would be required to detect a difference in prophylaxis of HE, that is, with a 5% type 1 error and 90% power for a two-tailed log-rank test. Results of previously published studies (10,24) indicate that lactulose is effective in 70% of patients in preventing recurrence of HE, and we presumed an efficacy of 30% by placebo in the control group. Our hypothesis was that lactulose is as effective as probiotics in the secondary prophylaxis of HE. Taking into account that 20% of patients will be lost to follow-up, the average number of patients in each arm corresponds to 72 patients. Data processing was performed using the SPSS software packages (SPSS, Chicago, IL). Data were expressed as means±s.d. Statistical analyses were performed by one-way analysis of variance. For a comparison of categorical variables, χ^2 and Fisher's exact tests were used, and for continuous variables, a Mann–Whitney test for unpaired data and a Wilcoxon rank sum test for paired data were used, as appropriate. Correlations between variables were examined with a Pearson correlation, and a multivariate analysis was performed. A probability level of $P < 0.05$ was set for statistical significance.

RESULTS

Study patient

Between October 2008 and December 2009, 360 patients with cirrhosis recovering from an episode of HE were screened; 235 patients (65.2%) who had recovered from HE and met the inclusion criteria were included in the study. The etiologies of cirrhosis were alcohol ($n = 94$), chronic hepatitis B ($n = 49$), chronic hepatitis C ($n = 36$), primary biliary cirrhosis ($n = 2$), autoimmune hepatitis ($n = 3$), and cryptogenic cirrhosis ($n = 51$). A total of 125 patients (34.8%) were excluded from the study because of a history of recent alcohol intake ($n = 42$), renal impairment ($n = 38$), hepatocellular carcinoma ($n = 16$), recent use of drugs affecting psychomotor performance ($n = 1$), or a severe medical problem ($n = 20$) or because they were not willing to participate in routine follow-up ($n = 8$). Patients with chronic hepatitis C were decompensated in the form of ascites and were not treated with interferon-α during the follow-up period. The clinical and demographic characteristics of the patients in the three groups were comparable (**Table 1**).

Recurrence of HE

Of 235 patients, 38 (16.2%) were lost to follow-up, with a median follow-up of 4 months (range 1–7 months), 12 in Gp-L, 13 in Gp-P, and 13 in Gp-N. The compliance with follow-up in our study was 83.8%; 68 patients in Gp-L, 64 patients in Gp-P, and 65 patients in Gp-N were followed up for 12 months.

During the study period, 77 (39.1%) of 197 patients developed an episode of HE (**Figure 2**). In all, 18 (26.5%) of 68 in Gp-L

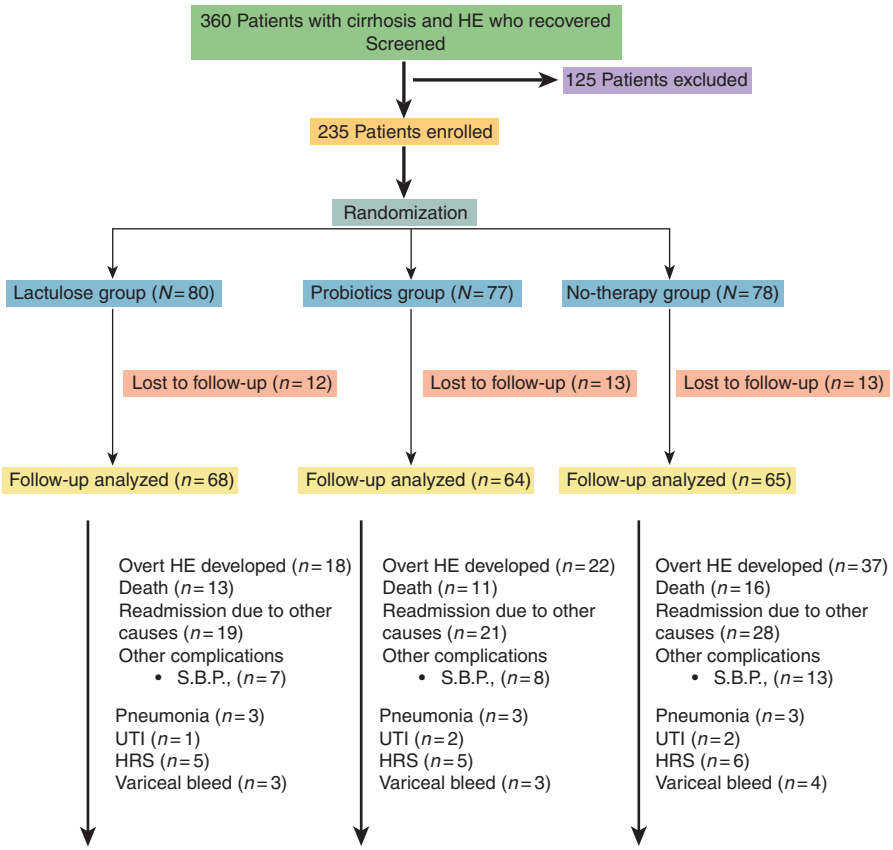

Figure 1. Flow chart of the study. HE, hepatic encephalopathy; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection.

(grade 1, $n=2$; grade 2, $n=9$; grade 3, $n=6$; and grade 4, $n=1$), 22 (34.4%) of 64 in Gp-P (grade 1, $n=2$, grade 2, $n=11$; grade 3, $n=6$; and grade 4, $n=3$;), and 37 (56.9%) of 68 in Gp-N (grade 1, $n=5$, grade 2, $n=21$; grade 3, $n=8$; and grade 4, $n=3$;) developed HE ($P=0.001$). Lactulose therapy, as compared with no therapy, was significantly more effective in secondary prophylaxis (26.2% vs. 56.9%, $P=0.001$). Similarly, probiotics therapy, as compared with no therapy, was associated with a lower incidence in recurrence of HE (34.4% vs. 56.9%, $P=0.02$), but no significant difference was found between lactulose and probiotics therapy (26.2% vs. 34.4%, $P=0.349$). There was a significant difference in recurrence of HE on intention-to-treat analysis considering patients lost to follow-up who had developed HE (30 [37.5%] of 80 in Gp-L, 35 [45.4%] of 77 patients in Gp-P, and 50 [64.1%] of 78 patients in Gp-N; $P=0.003$). The etiologies of precipitating factors are shown in **Table 2**, and there was no significant difference among the causes of HE.

There was no significant difference in patients who were on β-blockers and developed HE among the three groups (Gp-L, $n=5$; Gp-P, $n=7$; and Gp-N, $n=9$; $P=0.631$). Similarly, no difference was seen in large spontaneous shunts among the three patients who developed HE (Gp-L, $n=4$; Gp-P, $n=4$; and Gp-N, $n=6$; $P=0.43$).

Hospitalizations other than for HE

Hospitalizations other than for HE occurred in 19 (27.9%) of 68 patients in Gp-L (SBP, $n=7$; pneumonia, $n=3$; upper gastrointestinal bleed, $n=3$; urinary tract infection, $n=1$; and hepatorenal syndrome, $n=5$), 21 (32.8%) of 64 patients in Gp-P (SBP, $n=8$; pneumonia, $n=2$; upper gastrointestinal bleed, $n=3$; urinary tract infection, $n=3$; and hepatorenal syndrome $n=5$), and 28 (43.0%) of 65 patients in Gp-N (SBP, $n=13$; upper gastrointestinal bleed, $n=4$; urinary tract infection $n=2$; pneumonia, $n=3$; and hepatorenal syndrome, $n=6$) ($P=0.134$). A total of 40 patients died during follow-up (Gp-L:Gp-P:Gp-N = 13:11:16; $P=0.56$). All patients who died were decompensated at baseline.

Results of psychometric tests and CFF

All patients could perform the BDT and DST, 187 patients could perform the NCT, and the remaining 48 performed FCT because of illiteracy. There was a high prevalence of abnormal psychometry test results (NCT-A, 71.5%; NCT-B, 69.2%; DST, 76.9%; and BDT, 85.2%), and FCT-A and B were abnormal in 35 of 48 patients (72.9%; **Table 3**). There was a high prevalence of two or more abnormal psychometry test in these groups ($n=167$, i.e., 71.0%). Patients who developed HE had significantly higher NCT (71.2±15.5 vs. 53.3±17.8 s, $P=0.001$), FCT (83.8±18.7 vs. 69.6±20.5 s, $P=0.001$), DST (128.6±21.4 vs. 107.1±19.1 s, $P=0.001$), and BDT raw scores (27.0±3.6 vs. 29.0±3.8, $P=0.001$) compared with patients who did not develop HE. Arterial ammonia level was not significantly higher in patients with two

Table 1. Clinical and demographic profile of the patients

Parameter	Lactulose group (*n*=80)	Probiotics group (*n*=77)	No-therapy group (*n*=78)	*P* value
Age (years)	41.7±10.7	45.4±11.7	46.0±11.2	0.104
Male:female	68:12	70:7	61:17	0.72
Hemoglobin (g%)	10.2±1.67	9.5±1.89	10.0±1.82	0.09
Total leukocyte count (mm³/dl)	6,235±2,607	6,265±2,459	5,837±2,003	0.578
INR	2.20±0.85	2.30±.72	2.10±0.5	0.562
Serum bilirubin (mg/dl)	3.90±2.40	3.7±2.9	3.0±2.1	0.312
AST (IU/l)	65.7±33.9	79.6±46.2	67.2±33.2	088
ALT (IU/l)	41.7±21.8	42.9±142.9	44.2±24.5	858
Serum albumin (g%)	2.90±0.50	2.82±0.80	2.79±0.47	0.311
Child score	10.1±1.2	10.5±1.1	10±1.1	0.105
MELD	19.2±5.5	19.5±5.1	18.5±4.2	0.622
Serum sodium (mmol/l)	134.0±4.5	134.6±6.4	133.9±9.4	0.875
β-Blocker therapy, *n* (%)	25 (31.3%)	28 (36.4%)	27 (34.6%)	0.858
Large spontaneous shunts, *n* (%)	13 (16.2%)	14 (18.1%)	14 (17.9%)	0.965
≥2 Abnormal psychometry test results (*n*)	57 (71.2%)	53 (68.8%)	57 (73.1%)	0.845
Ammonia (μmol/l)	93.2±19.0	88.2±20.6	89.8±18.6	0.408
No. of HE episodes within 1 year before enrollment (median)	1 (range, 1–3)	1 (range, 1–3)	1 (range, 1–3)	0.398

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HE, minimal hepatic encephalopathy; INR, international normalized ratio; MELD, model for end-stage liver disease.

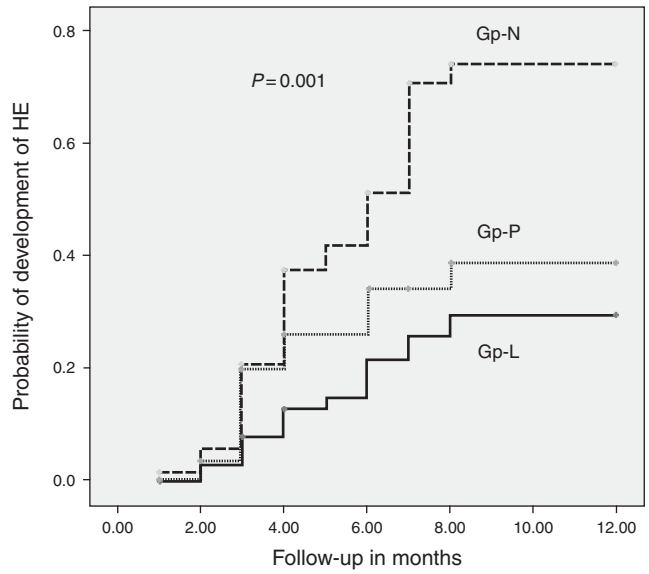

Figure 2. Probability of developing hepatic encephalopathy (HE) in patients receiving lactulose or probiotics treatment or no therapy.

or more abnormal psychometric tests compared with patients with fewer than two abnormal psychometric tests (91.8±17.9 vs. 86.9±22.4 μmol/l, *P*=0.142).

Table 2. Precipitating factors of HE

Precipitating factor	Lactulose group (*n*=68)	Probiotics group (*n*=64)	No-therapy group (*n*=65)
Variceal bleed	4	4	5
UTI with sepsis	0	1	2
SBP	4	3	7
Pneumonia with sepsis	2	0	3
Constipation	3	5	8
Unknown	5	9	12

HE, hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection.

All patients could perform CFF. CFF was <38 Hz in 118 patients (50.2%; **Table 3**). In all, 62 patients had psychometric impairment without CFF impairment, 12 had CFF impairment without psychometric impairment, and 106 had both CFF and psychometric impairments. Patients diagnosed with two or more abnormal psychometric tests had a CFF that was significantly lower than those with fewer than two abnormal tests (37.7±1.6 vs. 39.5±2.0 Hz, *P*=0.001). CFF, when used alone for the diagnosis of patients with two or more abnormal psychometry tests, had a sensitivity and specificity of 63.2% and 83.6%, respectively. There was a significant difference in baseline CFF in patients who developed HE vs. those who did not (37.7±1.6 vs. 38.5±1.96 Hz, *P*=0.008).

Table 3. Prevalence of abnormal psychometry and critical flicker frequency

Psychometric test	Lactulose group (*n*=80)	Abnormal tests, *n* (%)	Probiotics group (*n*=77)	Abnormal tests, *n* (%)	No-therapy group (*n*=78)	Abnormal tests, *n* (%)	*P* value
NCT-A (s)	54.4±8.7	49 (61.3)	51.3±19.8	42 (54.5)	50.1±14.5	45 (57.6)	0.481
NCT-B (s)	109.9±8.1	47 (58.8)	98.8±39.2	41 (53.2)	105.4±9.9	42 (53.8)	411
FCT- A (s)	73.2±20.2	12 (70.5)	79.5±23.5	10 (76.9)	75.0±21.4	13 (72.2)	0.806
FCT-B (s)	172.3±37.4	12 (70.5)	181.1±39.7	10 (76.9)	179.2±39.4	13 (72.2)	0.750
DST (s)	113.5±24.1	46 (57.5)	116.1±22.6	50 (64.9)	116.5±25.5	48 (61.5)	0.835
BDT (raw score)	28.8±3.9	65 (81.3)	28.7±3.7	65 (84.4)	27.5±3.9	67 (85.9)	0.221
CFF (Hz)	38.5±2.3	40 (50)	38.2±1.7	39 (50.6)	37.9±1.6	39 (50)	0.654

BDT, block design test; CFF, critical flicker frequency; DST, digit symbol test; FCT, figure connection test; NCT, number connection test.

Table 4. Arterial ammonia level in the three groups at baseline and at 3-month follow-up

	Arterial ammonia at baseline (μmol/l)	Arterial ammonia on follow-up (μmol/l)	*P* value
Lactulose group	93.2±19.0	82.97±12.9	0.03
Probiotics group	88.2±20.6	75.20±20.9	0.04
No-therapy group	89.8±18.6	85.20±16.7	0.597

Arterial ammonia levels

Arterial ammonia levels were analyzed in all study patients at baseline and at the 3-month follow-up. Mean levels for arterial ammonia were 90.3±19.4 μmol/l. Analysis of the change in mean arterial ammonia levels in the study groups at baseline and follow-up of 3 months of treatment showed a significant decrease in ammonia levels in Gp-L ($P=0.03$) and Gp-P ($P=0.04$) but not in Gp-N ($P=0.597$; **Table 4**).

Safety

All patients were able to tolerate and remained compliant with lactulose therapy in Gp-L. Of 68 patients, 18 (26.4%) had diarrhea, 11 (16.2%) had abdominal bloating, and 12 (17.6%) had distaste to lactulose. In these patients, the dose was reduced but not stopped. In Gp-N, constipation was reported in 14 (21.5%) patients and was managed by dietary modifications. In the Gp-P group, 9 (14%) patients complained of abdominal distension and 14 (21.8%) of constipation managed with dietary advice and on-and -off use of proton pump inhibitors. None of the patients in the Gp-P group developed increased frequency of stools, fever, or rash related to probiotics.

Correlation of HE with baseline parameters

CFF, baseline arterial ammonia, two or more abnormal psychometric tests, and Child-Turcotte-Pugh scoring (CTP) score were significantly associated with the development of HE upon univariate analysis (**Table 5**). On multivariate analysis, recurrence of overt HE was significantly associated with the presence of two or more abnormal psychometric test results and baseline arterial ammonia level (**Table 6**).

Table 5. Correlation of hepatic encephalopathy with baseline parameters

Parameter	Pearson's coefficient (*r*)	*P* value
MELD Score	0.012	0.877
Child score	−0.180	0.02
Ammonia	−0.252	0.001
CFF	0.200	0.01
Two or more abnormal psychometry tests	0.375	0.001
Serum sodium	−0.142	0.07
Serum creatinine	−0.053	0.504

CFF, critical flicker frequency; MELD, model for end-stage liver disease.

DISCUSSION

HE develops in 50–70% of patients with cirrhosis, and its occurrence is an indicator of a poor prognosis, with projected 1- and 3-year survival rates of 42% and 23%, respectively, without liver transplantation (25). HE is now considered a continuous spectrum of neurocognitive abnormalities, which range from no dysfunction (HE0) to MHE (detected with psychometric tests) and overt encephalopathy (grades 1–4). We and others have previously shown the high prevalence of cognitive abnormalities assessed by psychometry tests after clinical recovery of HE (21,22). The secondary prophylaxis of HE is an emerging concept; however, there is no definitive recommendation or consensus on secondary prophylaxis of HE and therefore the use of lactulose or rifaximin for the prevention of HE is not yet routine practice.

This study showed that the use of lactulose and probiotics as compared with no therapy is more effective in secondary prophylaxis of HE. Of 197 patients, 77 (39.1%) developed an episode of overt HE over a follow-up period of 12 months. In all, 18 (26.2%) in Gp-L, 22 (34.4%) in Gp-P, and 37 (56.9%) in Gp-N developed HE ($P=0.001$). In our previous study, 12 (19.6%) of 61 patients in the HE-L group and 30 (46.8%) of 64 in the HE-NL group ($P=0.001$) developed HE over a median follow-up of 14 months (range 1–20 months), and we have shown that lactulose is better than no

Table 6. Multivariate analysis of those factors associated with the recurrence of HE

Variable	CI (95%)	*P* value
CFF	0.663–1.05	0.138
Two or more abnormal psychometry tests	2.86–27.7	0.001
Child score	0.984–1.78	0.06
Ammonia	0.947–0.988	0.002

CFF, critical flicker frequency; HE, hepatic encephalopathy.

treatment for the secondary prophylaxis of HE (10). The results of this study corroborate those of our previous study, which indicated that lactulose is more effective than no therapy for secondary prophylaxis of HE. Recently, Bass *et al.* (11) also showed that, over a 6-month period, treatment with rifaximin and lactulose in the majority of such patients maintained remission from HE more effectively than did placebo. However, lactulose causes diarrhea and is not tolerable by some patients, and long-term rifaximin poses a risk of gastrointestinal infection with *Clostridium difficile*; evaluating long-term safety in cirrhotics requires more data (26).

Lactulose works in part by altering gut flora to decrease ammonia production and absorption. The evidence suggests that the lactulose effects occur because lactulose serves as a "prebiotic" ingredient, encouraging the growth of endogenous bacteria that resemble those found in many probiotics (27,28). Thus, the concept that therapeutic manipulation of the endogenous gut bacterial flora (gut flora therapy) by probiotics might hold for HE (16–18). Probiotics have been used to treat HE by decreasing urease-producing bacteria and promoting the growth of non-urease-producing bacteria. They may be particularly useful in scenarios of noncompliance or intolerance to lactulose. Loguercio and colleagues reported in a pilot study that *Enterococcus faecium* was as effective as lactulose in reducing ammonia levels and improving mental status among chronic HE patients (18). Similarly, in a randomized trial on the use of probiotic yogurt on psychometric performance of cirrhotic patients with MHE, the number of episodes of HE at follow-up was significantly lower than that observed in the no-treatment arm of the study (29). Probiotics have been used for the treatment of MHE and have been shown to improve the Child score in patients with cirrhosis (16–19). All published studies on the effect of probiotics on HE have demonstrated efficacy. These studies used high doses of non-urease-producing bacteria, either *L. acidophilus* or *E. faecium* SF68. The mechanisms of action of these probiotic strains in liver disease or HE are uncertain and require validation in future trials. We found that probiotics were as efficacious as lactulose and better than no therapy for the secondary prophylaxis of HE with minimum side effects. Hence, probiotics is a good alternative to secondary prophylaxis of HE.

Gut-derived nitrogenous substances are universally acknowledged to play a major role in HE. Specifically, ammonia is thought to be a critical factor in its pathogenesis. Increased levels of ammonia have been implicated in the pathogenesis of HE, and nonabsorbable disaccharides and minimally absorbed antibiotics have been effective in reducing the activity of colonic bacteria involved in the production of ammonia (16–19). The results of this study substantiate our previous findings that the baseline arterial ammonia and two or more than two abnormal psychometry tests independently predict future episodes of HE.

CFF appears to detect a broad spectrum of neurophysiological abnormalities ranging from visual signal processing (retinal gliopathy) to cognitive functions, and CFF < 38 Hz is predictive of further bouts of overt HE (20). We also found that CFF used alone for the detection of patients with two or more abnormal psychometry test results had a sensitivity and specificity of 63.2% and 83.6%, respectively, and patients developing HE had significantly lower CFF at baseline than those who did not. We found it to be a simple bedside tool for identifying patients with abnormal psychometric tests, even after recovery from overt HE. However, in this study we did not find CFF to be a predictor of recurrence of HE upon multivariate analysis.

The limitation of this study is that it was not blinded; however, because treatment with lactulose induces changes in bowel habits, it is difficult to remain blind to treatment and it would have been wiser to evaluate the changes in bacterial flora of the gut before and after therapy. We used a high concentration of probiotics and the results could be strain-specific, which could not be identified with treatment of another probiotics with a different strain and hence require validation with other probiotic combinations. Treatment with lactulose and probiotics caused few side effects, which could be managed well without stopping drug treatment. In conclusion, lactulose and probiotics were equally effective in secondary prophylaxis of HE.

CONFLICT OF INTEREST

Guarantor of the article: Barjesh Chander Sharma, MD, DM.
Specific author contributions: Amit Agarwal collected data; Barjesh Chander Sharma supervised the study and collected data; Praveen Sharma analyzed data and wrote manuscript; Shiv Kumar Sarin supervised and edited the manuscript.
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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Secondary prophylaxis should be used for hepatic encephalopathy.
- ✓ Lactulose is effective in secondary prophylaxis of hepatic encephalopathy.
- ✓ Not all patients can tolerate lactulose because of its side effects.

WHAT IS NEW HERE

- ✓ Lactulose and probiotics are equally effective in secondary prophylaxis of hepatic encephalopathy.
- ✓ Probiotics are well tolerated.

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