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Original Article

Effects of Low-dose and High-dose Rifaximin in the Treatment of Covert Hepatic Encephalopathy

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Abstract

Background and Aims: Rifaximin is effective in preventing and treating hepatic encephalopathy (HE). This study aimed to investigate the efficacy and safety of different dosages of rifaximin in the treatment of cirrhotic patients with covert HE (CHE). ***Methods:*** In this single-center, randomized, controlled, open-label study, CHE was diagnosed using a combination of the psychometric HE score and the EncephalApp Stroop test. Cirrhotic patients with CHE were recruited and randomly assigned to low-dose rifaximin 800 mg/day, high-dose rifaximin (1,200 mg/day), and control groups, and were treated for 8 weeks. The sickness impact profile (SIP) scale was used to evaluate the health-related quality of life (HRQOL) of patients. Forty patients were included in the study, 12 were assigned to the low-dose group, 14 to the high-dose group, and 14 patients to the control group. ***Results:*** The percentage of patients with CHE reversal was significantly higher in both the low-dose (41.67%, 5/12) and high-dose (57.14%, 8/14) groups than in the control group (7.14%, 1/14) at 8 weeks (p=0.037 and p=0.005, respectively). In addition, both doses of rifaximin resulted in significant improvement of the total SIP score compared with the control group. There were no significant differences in the CHE reversal rate, total SIP score improvement, and incidence of adverse event between the low-dose and high-dose groups (p>0.05). ***Conclusions:*** Low-dose rifaximin reverses CHE and improves HRQOL in cirrhotic patients with comparable effects and safety to high-dose rifaximin.

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Keywords: Single-center open-label study; Randomized prospective study; Liver cirrhosis; Covert hepatic encephalopathy; Rifaximin.

Abbreviations: CHE, covert hepatic encephalopathy; HE, hepatic encephalopathy; HRQOL, health-related quality of life; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; SIP, sickness impact profile; TIPS, transjugular intrahepatic portosystemic shunt; MMSE, mini mental state examination; CT, computerized tomography; NP, neuropsychometric; ITT, intention-to-treat; mZ-score, mean Z-score.

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Introduction

Covert hepatic encephalopathy (CHE) is a mild form of HE defined as the presence of neuropsychological and/or neurophysiological abnormalities without directional disorder or flapping wing tremor.[1] CHE can have a negative impact on the health-related quality of life (HRQOL)[2] and reduce the socioeconomic potential of patients. CHE also increases the risk of development of overt HE (OHE)[3] and is as an independent risk factor for death and hospitalization of patients with liver cirrhosis.[4,5] Long-term treatment of CHE places a substantial economic burden on patients.[6,7]

Recent studies have highlighted the role of the gut microbiome in the pathogenesis of HE. Excessive growth or alteration of the gut microbiome contribute to hyperammonemia, high endotoxemia, and systemic inflammation, which lead to the development of HE. Targeting the gut microbiome by using antibiotics (e.g., rifaximin and nitazoxanide) has been an effective treatment of HE. Distinct from other antibiotics, rifaximin is a gut-selective broad-spectrum antibiotic and is rarely absorbed systemically. It remarkably inhibits the proliferation of urease-producing bacteria in the intestine and consequently reduces the production of ammonia and other intestinal toxins. Substantial evidence has clearly demonstrated the efficacy of rifaximin in the treatment of HE. It has also been demonstrated that either short- or long-term treatment rifaximin effectively reverses CHE and improves the HRQOL of patients.

Interestingly, the dosage of rifaximin adopted for various diseases varies. Clinical guidelines recommend 400 mg bid. of rifaximin for the treatment of traveler's diarrhea and *Clostridium difficile* infection.[8,9] This dosage has also been used for the treatment of inflammatory bowel diseases including Crohn's disease and ulcerative colitis.[10,11] However, the American College of Gastroenterology clinical guidelines recommend a dosage of 550 mg tid to treat symptomatic patients with small intestinal bacterial overgrowth.[12] Currently, the recommended dosage of rifaximin for the treatment of HE is 1,200 or 1,100 mg/day.[13] However, a study by Khokhar *et al*. demonstrated that rifaximin treatment at a dosage of 550 mg once or twice daily had similar efficacy for the prevention of HE in a local population in Pakistan.[14] We previously reported that low-dose (800 mg/day) rifaximin was comparable to high-dose (1,200 mg/day) rifaximin in reducing the serum endotoxin level after 2 weeks of treatment in Chinese patients with liver cirrhosis.[15] More recently, we reported that treatment with low-dose rifaximin (800 mg/day) for 6 months significantly decreased overall

complications and prolonged the survival of patients with decompensated liver cirrhosis.[16] The data suggest 800 mg/day of rifaximin might be sufficient for the treatment of HE, at least in Chinese patients. Accordingly, we conducted this prospective randomized controlled study to investigate the efficacy and safety of low-dose (800 mg/day) and high-dose (1,200 mg/day) rifaximin for the treatment of CHE.

Methods

Study patients

Patients with liver cirrhosis admitted to the Department of Gastroenterology, Shanghai Changzheng Hospital between May 2017 and May 2020 were enrolled in this study. Liver cirrhosis was confirmed by symptoms and signs, laboratory results, and radiological findings. All patients with liver cirrhosis without OHE were screened for CHE. The inclusion criteria were (1) an age of 18–70 years, (2) CHE diagnosed by both the psychometric hepatic encephalopathy score (PHES) and Stroop test, and (3) signing the informed consent form. The exclusion criteria were (1) allergy to rifamycin; (2) current or recent (<3 months) use of alcohol or inability to adhere to alcohol cessation during the study period, (3) use of antibiotics, lactulose/lactitol, probiotics, L-ornithine-L-aspart, zinc, metronidazole, neomycin, rifaximin, or psychoactive drugs within the previous 6 weeks, (4) infection or gastrointestinal hemorrhage within the previous 6 weeks, (5) OHE within the previous 3 months; (6) a history of portosystemic shunt surgery or transjugular intrahepatic portosystemic shunt (TIPS), (7) poor vision, color blindness, or motor defects that interfere with the performance of psychometric tests, (8) noncontrollable neurological or psychiatric problems that could affect cognitive function such as Alzheimer's disease, Parkinson's disease, or schizophrenia, (9) confirmed or highly suspect diagnosis of malignant liver tumors, (10) human immunodeficiency virus infection, (11) uncontrolled hypertension, diabetes, or other serious cardiac or pulmonary disease, (12) white blood cell count $<1\times10^9$/L, (13) pregnancy and breastfeeding, (14) participation in other clinical drug trials within 3 months.

Study design

The study protocol was approved by the Institutional Ethics Committee of Shanghai Changzheng Hospital, Naval Medical University (Shanghai, China) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The trial was registered at www.clinicaltrials.gov (No. NCT03077217). The protocol was explained to each patient and written informed consent was obtained from each participant before enrollment.

This study was designed as an open-label, prospective, randomized trial. A random assignment table was generated by the Statistical Teaching and Research Department of the Naval Medical University (Shanghai, China). Patients who met the eligibility criteria and signed the informed consent form were randomized to control, low-dose, or high-dose rifaximin groups. The control group did not receive rifaximin treatment. The low-dose group was given rifaximin 800 mg/day (400 mg, bid) for 8 weeks, and the high-dose group was given rifaximin 1,200 mg/day (600 mg, bid) for 8 weeks. With the exception of rifaximin, all other therapeutic drugs, such as diuretics, albumin, antiviral agent, and liver-protective drugs were the same in the three groups during the study period.

The trial involved three visits by each of the participants (Fig. 1), a screening visit, and visits after 4 and 8 weeks of treatment. The screening visit included (1) a detailed medical history and physical examination, (2) Mini Mental State Examination (MMSE), PHES, and Stroop tests; (3) HRQOL assessment, (4) laboratory examination including routine blood, liver, and kidney function tests, prothrombin time index, fasting blood sugar, electrolytes, alpha-fetoprotein, routine stool, and fecal occult blood tests; and (5) ultrasound type B of the abdomen or enhanced CT of the upper abdomen. The visit after 4 weeks of treatment included all the evaluations performed during the first visit except the HRQOL assessment. The visit after 8 weeks of treatment period included the same assessments that were performed at the first visit. The Child-Pugh score and model for end-stage liver disease (MELD) score were calculated to assess the stage and severity of cirrhosis.

Diagnosis of CHE

The MMSE was performed to exclude the presence of OHE and other illnesses that could affect the patient's neurological status. Patients with MMSE scores higher than 25 received neuropsychometric (NP) tests. Two NP tests, the PHES and EncephalApp Stroop tests, were used to screen for CHE in enrolled patients. CHE was diagnosed when the PHES and EncephalApp Stroop Test results were both positive. The PHES that was used included the number connection test A, number connection test B, line tracing test, serial dotting test, and digital symbol test. The five PHES tests were performed following the recommended methods,[1] interpretation of the PHES was as previously described, and a score ≤4 was considered pathological.[17] The EncephalApp Stroop Test was carried out as previously described.[18] A Stroop test time of >90 seconds was considered positive.[19]

Assessment of HRQOL

The sickness impact profile (SIP) questionnaire (John Hopkins University, Baltimore, MD, USA)[20] was used to assess HRQOL. The questionnaire consisted of 136 items grouped into 12 scales. Each category could be compared separately between the groups. Lower SIP scores indicated a better quality of life. Change in the total SIP score (ΔSIP) after 8 weeks of treatment served as the indicator for HRQOL improvement.

Efficacy and safety assessment

Two NP tests (PHES and Stroop) were performed in all patients at each of the three study visits. HRQOL evaluation with the SIP questionnaire was conducted at the screening and the end-of-treatment visits. The primary study end points were the reversal of CHE at 4 weeks and 8 weeks and the HRQOL improvement at 8 weeks. The secondary end points were the changes in NP tests at 4 and 8 weeks. Safety assessments consisted of monitoring adverse events and the results of clinical laboratory testing. Severe adverse events were defined as those that led to hospitalization, prolonged hospitalization, disability, reduced work capacity, life endangerment, or death.

Sample size and power analysis

Previous studies reported a reversal rates of 75.5% with rifaximin (1,200 mg/day) and 20% with placebo treatment

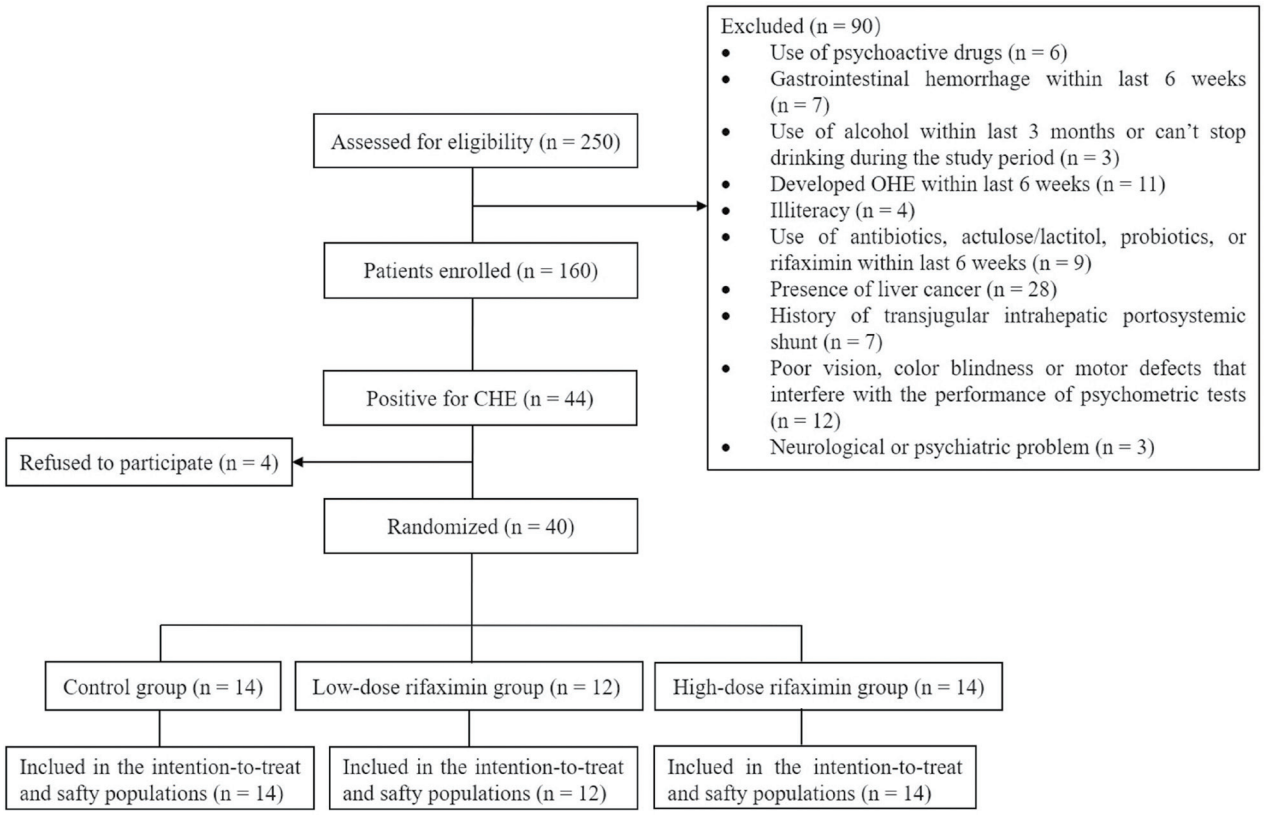

Fig. 1. Study flowchart. CHE, covert hepatic encephalopathy.

of CHE patients.[11] Assuming that low-dose rifaximin (800 mg/day) is as effective as high-dose rifaximin (1,200 mg/day), a sample size of at least 11 patients in each arm was required for a 5% type 1 error, 80% power, and a drop-out rate of 15%. We enrolled 14 in the control, 12 in the low-dose, and 14 in the high-dose groups, which were higher than required.

Statistical analysis

Efficacy data were analyzed for the intention-to-treat (ITT) population, including patients who received at least one dose of the study medication and completed one follow-up visit. Safety was determined for all enrolled individuals. Patients who were lost to follow-up during the study period, were included in the analysis using the last-observation-carried-forward method assuming that the outcome did not change from day 1 to 8 weeks.

Continuous variables with a normal distribution were reported as mean±standard deviation, and those that were not normally distributed were reported as medians and interquartile range. Student's *t*-test was used to compare the mean values of normally distributed data, and the Mann-Whitney U test was used to compare differences between groups with non-normally distributed data. Categorical variables were reported as numbers and percentages (%) or frequencies, and differences were compared with two-tailed $\chi 2$ or Fisher's exact tests. Spearman's rank correlation coefficient was used to assess correlations between SIP and the results of Stroop and PHES. $p<0.05$ was considered statistically significant. The statistical analysis was performed with SPSS 22.0 (IBM Corp., Armonk, NY, USA).

Results

Trial enrollment

A total of 250 hospitalized cirrhotic patients were screened, 160 (64%) met the eligibility criteria, and 90 (32%) were excluded (Fig. 1). The reasons for exclusion were use of psychoactive drugs (n=6), gastrointestinal hemorrhage within the previous 6 weeks (n=7), use of alcohol within the previous 3 months or inability to stop drinking during the study period (n=3), OHE within the previous 6 weeks (n=11), illiteracy (n=4), use of antibiotics/lactulose/lactitol/probiotics/rifaximin within the previous 6 weeks (n=9), presence of liver cancer (n=28), history of TIPS (n=7), poor vision/color blindness/motor defects that interfered with the performance of psychometric tests (n=12), and neurological or psychiatric problems (n=3). Of the 160 patients screened for CHE, 44 (27.5%, 44/160) were found to have CHE, four of whom refused to participate in this trial. The remaining 40 patients were included and randomly assigned to the control (n=14), low-dose rifaximin (n=12), and high-dose rifaximin (n=14) groups. All 40 patients were included in the ITT and safety populations.

Baseline characteristics

The baseline characteristics of the patients are shown in Table 1. There were no differences between the three groups in age, height, weight, duration of cirrhosis, etiology of cirrhosis, education, Child-Pugh grade, MELD score, and total SIP score ($p>0.05$). The three groups had similar baseline

Table 1. Baseline characteristics of patients

Characteristic	Control group (*n*=14)	Low-dose rifaximin (*n*=12)	High-dose rifaximin (*n*=14)	*p*-value
Age (years)*	61.00 (54.25–66.00)	63.50 (58.75–66.0)	57.00 (51.50–63.75)	0.796
Sex (male/female)	7/7	4/8	12/2	0.021
BMI (kg/m^2)*	23.98 (21.29–27.36)	22.15 (19.75–24.30)	23.66 (20.31–26.87)	0.235
Duration of cirrhosis (months)*	11.00 (1.00–82.0)	36.00 (16.00–81.50)	80.50 (45.00–109.00)	0.072
Etiology of cirrhosis, *n* (%)				
HBV	7 (50)	5 (41.67)	10 (71.43)	0.282
Primary biliary cholangitis	3 (21.43)	4 (33.33)	1 (7.14)	0.247
Alcoholic hepatitis	0 (0)	0 (0)	1 (7.14)	0.386
Schistosomiasis	1 (7.14)	0 (0)	0 (0)	0.386
Combined	0 (0)	3 (25)	2 (14.29)	0.153
Unknown	3 (21.43)	0 (0)	0 (0)	0.049
Education (years)*	6.00 (2.00–9.50)	9.00 (5.50–10.50)	9.00 (7.25–12.00)	0.225
Primary school, *n* (%)	7 (50)	4 (33.33)	3 (21.42)	0.282
Junior middle school, *n* (%)	5 (35.71)	5 (41.67)	5 (35.71)	0.938
High school, *n* (%)	1 (7.14)	3 (25)	4 (28.57)	0.320
Graduate, *n* (%)	1 (7.14)	0 (0)	2 (14.29)	0.386
Child-Pugh grade				
A, *n* (%)	7 (50)	8 (66.67)	4 (28.57)	0.149
B, *n* (%)	6 (42.86)	4 (33.33)	9 (64.29)	0.263
C, *n* (%)	1 (7.14)	0 (0)	1 (7.14)	0.637
MELD score*	11.00 (8.75–14.25)	10.00 (8.00–11.00)	13.00 (9.25–15.75)	0.114
Total SIP score*	5.68 (3.90–14.44	12.09 (5.74–21.25)	9.47 (7.84–19.62)	0.572

Data are *median (range) or *n* (%).

clinical and demographic characteristics, except for the male to female ratio (p=0.021).

Effects of rifaximin on CHE reversal

To determine the effects of different doses of rifaximin on CHE reversal in hospitalized cirrhotic patients, ITT analysis was conducted after rifaximin administration for 4 weeks and 8 weeks. There were no significant differences in the percentage of patients with CHE reversal at 4 weeks in the three groups (Fig. 2). The percentages of patients with CHE reversal in both the low-dose (41.67%, 5/12) and high-dose (57.14%, 8/14) rifaximin groups at 8 weeks were significantly higher than the percentage in the control group (7.14%, 1/14). There was no significant difference in the CHE reversal rates between the low-dose and high-dose rifaximin groups at 8 weeks (Fig. 2). The results confirmed that no obvious effects on CHE reversal occurred in the low-dose and high-dose groups at 4 weeks. Low-dose (800 mg/day) and high-dose (1,200 mg/day) rifaximin had similar effects on CHE reversal after 8 weeks of treatment.

Effects of rifaximin on HRQOL improvement

The SIP was used to compare the effects of different doses of rifaximin on HRQOL. Although no significant differences in the total SIP scores were found in the three groups after 8 weeks of treatment (Supplementary Table 1), ΔSIP was significantly higher in both the low-dose and high-dose rifaximin groups than that in the control group (Table 2). There was no significant difference in the ΔSIP score between the low-dose and high-dose rifaximin groups at 8

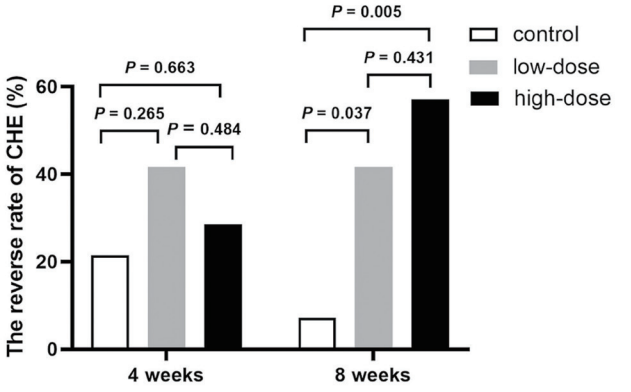

Fig. 2. Reversal of CHE in the control, low-dose, and high-dose groups after 4 and 8 weeks of treatment. There were no significant differences in the percentage of patients with CHE reversal at 4 weeks in the three groups. At 8 weeks, the percentages of patients with CHE reversal in both the low-dose (41.67%, 5/12) and high-dose (57.14%, 8/14) rifaximin groups were significantly higher than that in the control group (7.14%, 1/14). There was no significant difference in CHE reversal rates between the low-dose and high-dose rifaximin groups.

Table 2. Change in SIP score (ΔSIP) between baseline and 8 weeks in the control, low-dose rifaximin, and high-dose rifaximin group

	Control group (*n*=14)	Low-dose group (*n*=12)	High-dose group (*n*=14)	*p*-value[ζ]	*p*-value[*]	*p*-value[**]	*p*-value[***]
Physical							
Body care and movement	0 (0–2.20)	0 (−0.55–0)	0 (−5.07–0.00)	0.078	0.117	0.038	0.471
Ambulation	0 (0–0.06)	0 (−6.77–0)	0 (−1.31–0)	0.175	0.104	0.14	0.538
Mobility	0 (0–11.82)	0 (−27.96–0)	−4.59 (−22.81–0)	0.030	0.066	0.007	0.589
Total subscore	0 (−0.06–3.86)	−1.35 (−8.87–0)	−1.92 (−6.57–0)	0.019	0.041	0.005	0.980
Psychosocial							
Emotional	0 (−4.54–0)	0 (0–3.26)	0 (0–0)	0.520	0.364	0.614	0.345
Alertness behavior	0 (0–11.58)	0 (−5.41–3.80)	0 (−16.47–0)	0.044	0.195	0.015	0.201
Social interaction	0 (0–0.24)	−2.48 (−10.52–0)	−5.93 (−10.66–0)	0.002	0.006	0.001	0.458
Communication	0 (0–10.34)	0 (0–0)	0 (−14.10–0)	0.018	0.304	0.007	0.073
Total subscore	0.08 (0–4.72)	−0.98 (−6.19–2.53)	−3.94 (−11.91–0)	0.002	0.053	0.000	0.135
Independent scales							
Sleep and rest	0 (0–5.01)	0 (−18.74–0)	0 (−2.45–0)	0.269	0.112	0.467	0.374
Eating	0 (0–0)	0 (−11.13–0)	0 (−6.10–0)	0.172	0.304	0.028	0.849
Home management	0 (−5.16–5.76)	−10.63 (−42.11–0)	−7.33 (−46.59–0)	0.043	0.034	0.024	0.980
Work	0 (0–0)	0 (0–0)	0 (0–0)	0.839	1.000	0.694	0.563
Recreation and pastimes	0 (−6.04–0)	0 (−40.28–12.09)	−10.31 (−20.50–0)	0.345	0.505	0.105	0.623
Total SIP Score	0 (−1.15–3.50)	−1.98 (−9.24–0.67)	−4.00 (−10.80–0)	0.021	0.048	0.007	0.592

SIP, sickness impact profile; Δ, change. Data are median (interquartile range). [ζ]Control group vs. low-dose rifaximin group vs. high-dose rifaximin group; [*]Control group vs. low-dose rifaximin group; [**]Control group vs. high-dose rifaximin group; [***]Low-dose rifaximin group vs. high-dose rifaximin group.

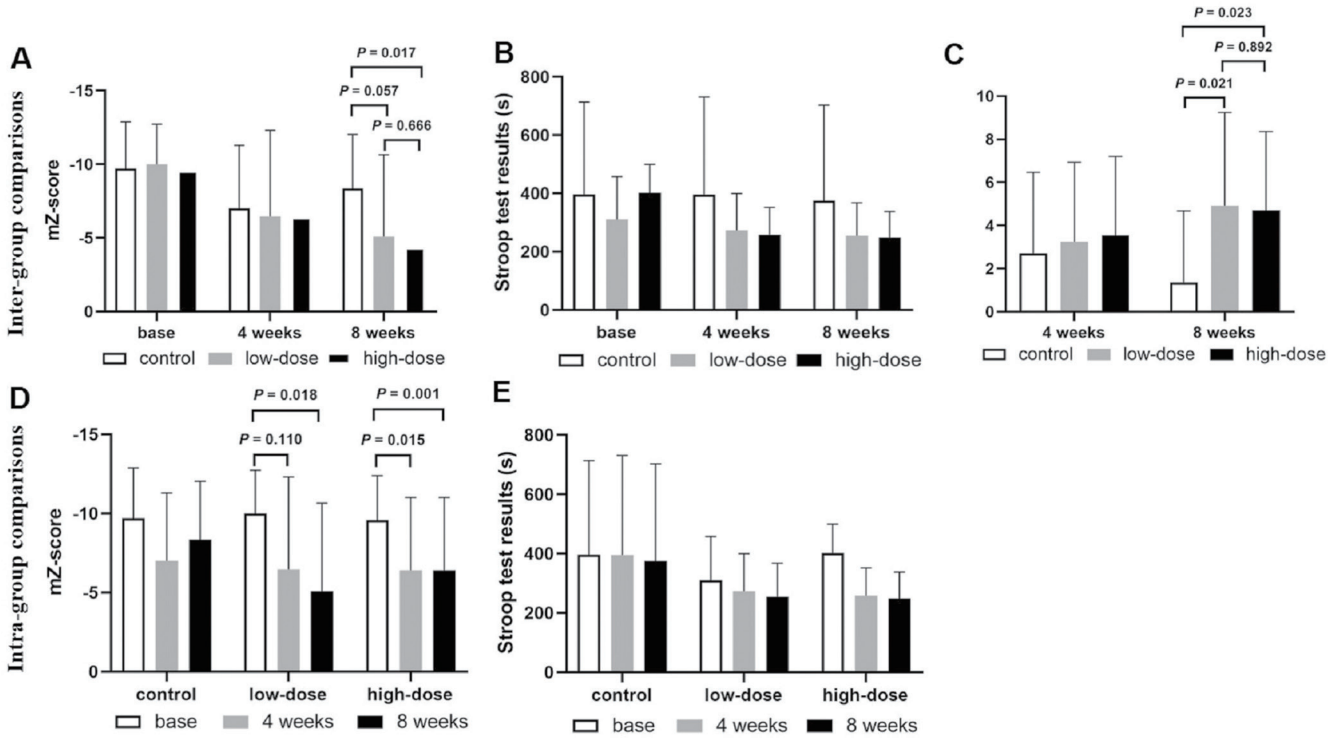

Fig. 3. NP test performance in the control, low-dose, and high-dose groups after 4 and 8 weeks of treatment. Intergroup comparisons showed no significant differences among the three groups in the mZ-scores at baseline and 4 weeks. The mZ-score of the high-dose rifaximin group at 8 weeks was higher than that of the control group (A). The Stroop results among the three groups were not significantly different at baseline, 4 weeks, and 8 weeks (B). Changes in the mZ (ΔmZ) scores of the low-dose and high-dose rifaximin groups were greater than that of the control group at 8 weeks. No significant difference was found in the ΔmZ-score between the low-dose and high-dose rifaximin groups at 8 weeks (C). Intragroup comparison showed that the mZ-scores and Stroop results were not significantly different at baseline, 4 weeks, and 8 weeks in the control group (D, E). In the low-dose group, the mZ-score was higher at 8 weeks than at baseline (D), whereas the Stroop results were not significantly different at different time points (E). In the high-dose group, the mZ-score was significantly improved at 4 weeks and 8 weeks compared with baseline (D).

weeks (Table 2). Subcategory analysis of the ΔSIP scores showed that both low-dose and high-dose rifaximin resulted in significant improvements in the total physical score, social interaction score, and home management compared with the control group. No differences were found in the changes in those scores between the low-dose and high-dose groups (p>0.05; Table 2).

Effects of rifaximin on NP test performance

To further evaluate the effects of rifaximin on CHE, we analyzed NP test performance in the three groups. As shown in Figure 3A, B, and Supplementary Table 2, there were no significant differences in the mean PHES Z-score (mZ-score) and the outcomes of the Stroop test at baseline and 4 weeks among the three groups. The PHES mZ-score of the high-dose rifaximin group at 8 weeks was significantly higher than that of the control group (p=0.017; Fig. 3A). However, the Stroop test results of the three groups at 8 weeks were not significantly different (p=0.261; Fig. 3B). Although no significant difference from baseline was found in the mZ-score in the low-dose rifaximin group after 8 weeks of treatment, changes in the mZ-scores (ΔmZ) of the low-dose and high-dose rifaximin groups at 8 weeks were significantly higher than that of the control group (4.92±4.32 vs. 1.36±3.32, p=0.021; 4.71±3.65 vs. 1.36±3.32, p=0.023, respectively). Interestingly, the ΔmZ-scores were comparable between the low-dose and high-dose rifaximin groups at 8 weeks (p=0.892; Fig. 3C). The data demonstrate that 8 weeks of rifaximin treatment at both doses significantly improved NP test performance in these CHE patients.

We further compared the efficacy of rifaximin for CHE at different times in each group. The results showed that the PHES mZ-scores and the outcomes of the Stroop test were similar at baseline, 4 weeks, and 8 weeks in the control group (p>0.05; Fig. 3D, E). In the low-dose rifaximin group, the mZ-score increased from −10.00±2.73 at baseline to −5.08±5.57 at 8 weeks (p=0.018), but the changes of the Stroop test scores at those times were not significant (Fig. 3D, E). It is noteworthy that the mZ-score improved after 4 and 8 weeks of high-dose rifaximin treatment (p=0.015 and p=0.001, respectively; Fig. 3D), but the Stroop test results did not decrease significantly (p>0.05; Fig. 3E). This results indicated that high-dose rifaximin enhanced the PHES performance of CHE patients at 4 weeks, which was earlier than low-dose rifaximin. At the end point of treatment (8 weeks), low-dose and high-dose rifaximin had similar effects on the PHES test in the CHE patients.

Safety

Differences in the incidence rates of adverse events in the three groups were not significant (p=0.142). Two patients in the high-dose rifaximin group experienced adverse events. One reported neutropenia (leukocyte count $<1\times10^9$/L) after 1 week of treatment. The leukocyte count returned to normal after withdrawal of the drug and administration of

a leucocyte-raising agent. The other patient experienced transient visual dysfunction 3 days after taking rifaximin and recovered spontaneously after stopping the medicine. No adverse events occurred in the control and low-dose rifaximin groups.

Discussion

CHE is a common complication of liver cirrhosis, and it severely affects patient quality of life. It is also a risk factor associated with the survival and prognosis of cirrhotic patients. Previous studies reported that CHE occurs in 20–80% of patients with liver cirrhosis.[6,21–23] CHE usually lacks obvious clinical manifestations, and its diagnosis is essentially based on neurophysiological and neuropsychological tests. Therefore, CHE is often overlooked, and can easily progress to OHE without effective intervention.

Rifaximin is recognized as an effective drug for preventing and treating HE. According to clinical guidelines, the recommended dose of rifaximin for cirrhotic patients is 1,100–1,200 mg/day.[13] However, cost-effectiveness has always been a concern of patients and doctors, especially in less developed countries and regions. The high medical burden may affect the compliance of patients during the treatment of HE. Bajaj *et al*. reported that rifaximin was not preferable for the treatment of CHE compared with lactulose when the economic benefits were taken into consideration.[7] Apparently, reducing the dosage of rifaximin is an important alternative to address this problem. A series of studies have been conducted at our center to explore the effects of low-dose rifaximin (800 mg/day) on chronic liver disease. Our previous studies revealed that the application of rifaximin 800 mg/day for 2 weeks reduced the serum endotoxin concentration in cirrhotic patients.[15] Long-term administration of rifaximin at 800 mg/day reduced the overall complications and prolonged survival in decompensated cirrhotic patients.[16] In this study, we discovered that low-dose rifaximin (800 mg/day) had therapeutic effectiveness comparable to high-dose rifaximin (1,200 mg/day) on CHE reversal and HRQOL improvement in patient with cirrhosis after 8 weeks of treatment. The lower dosage of rifaximin (800 mg/day) would probably be effective for the treatment of MHE in Chinese liver cirrhosis patients.

In the NP test, our data showed that 4 week treatment with high-dose rifaximin improved PHES test performance, which was not observed in the low-dose rifaximin group at the same time point. This result implied that the effect of high-dose rifaximin on CHE occurred earlier than that of low-dose rifaximin. However, the efficacy of low-dose rifaximin was similar to that of high-dose rifaximin in the PHES test in these patients after a longer treatment period (8 weeks). No significant changes in the Stroop test time were found in the high-dose and low-dose rifaximin groups until the end of treatment. Nevertheless, it should be noted that an obvious trend of improvement was observed in the Stroop test results in both groups at 4 and 8 weeks. A larger sample size and longer administration of rifaximin are required for confirmation in future studies.

As a gut-selective antibiotic, rifaximin has been demonstrated to be a drug with favorable safety. However, rifaximin may induce neutropenia and toxic epidermal necrolysis in some patients. Studies also showed that another antibiotic, nitazoxanide, might represent an alternative therapy for the treatment of HE to avoid the potential risks associated with the long-term use of rifaximin.[24,25] In this trial, no significant differences were found in the incidence rates of adverse events among the three groups evaluated. Nevertheless, one patient in the high-dose rifaximin group experienced leukopenia and another developed transient visual dysfunction. The leukopenia resolved following the withdrawal of rifaximin and administration of a leucocyte-increasing agent. The visual dysfunction resolved soon after discontinuing the medication. It should be noted that no adverse events occurred in the low-dose rifaximin group, implying that the dose would be preferable for the maintenance treatment of CHE. Our results indicate that low-dose rifaximin can help to prevent side effects associated with HE treatment, especially in countries where other antibiotics, such as nitazoxanide, are not an option.

There were some limitations in this study. First, we did not use an appropriate placebo for technical reasons. Therefore, the design of this study was not double-blind. Secondly, because it was conducted at a single center over a limited time, we did not employ a large sample size, which might have caused bias in the statistical analysis. Future studies with larger sample sizes are needed.

In conclusion, our study indicated that low-dose (800 mg/day) rifaximin had equivalent effectiveness and safety in terms of CHE reversal and HRQOL improvement to high-dose (1,200 mg/day) rifaximin in patients with cirrhosis after 8 weeks of treatment. A large-scale multicenter randomized controlled study is required to confirm the effects of low-dose rifaximin on MHE.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Designed the research and drafted the manuscript (WT, JW, WFX), presided over the enrollment and exclusion of patients (WT, XZ), followed up with the patients and collected the data (WT, PMS, LMF), checked the data (PMS, ZLY), statistical analysis of the data (WT, JW), revised the manuscript (XZ)

Data sharing statement

The data are available from the corresponding author upon request.

References

[1] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, *et al*. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60(2):715–735. doi:10.1002/hep.27210, PMID:25042402.

[2] Groeneweg M, Quero JC, De Bruijn I, Hartmann IJ, Essink-bot ML, Hop WC, *et al*. Subclinical hepatic encephalopathy impairs daily functioning. Hepatology 1998;28(1):45–49. doi:10.1002/hep.510280108, PMID:9657095.

[3] Hartmann IJ, Groeneweg M, Quero JC, Beijeman SJ, de Man RA, Hop WC, *et al*. The prognostic significance of subclinical hepatic encephalopathy. Am

J Gastroenterol 2000;95(8):2029–2034. doi:10.1111/j.1572-0241.2000.02265.x, PMID:10950053.
[4] Dhiman RK, Kurmi R, Thumburu KK, Venkataramarao SH, Agarwal R, Duseja A, *et al*. Diagnosis and prognostic significance of minimal hepatic encephalopathy in patients with cirrhosis of liver. Dig Dis Sci 2010;55(8):2381–2390. doi:10.1007/s10620-010-1249-7, PMID:20508990.
[5] Patidar KR, Thacker LR, Wade JB, Sterling RK, Sanyal AJ, Siddiqui MS, *et al*. Covert hepatic encephalopathy is independently associated with poor survival and increased risk of hospitalization. Am J Gastroenterol 2014;109(11):1757–1763. doi:10.1038/ajg.2014.264, PMID:25178701.
[6] Schomerus H, Hamster W. Quality of life in cirrhotics with minimal hepatic encephalopathy. Metab Brain Dis 2001;16(1-2):37–41. doi:10.1023/a:1011610427843, PMID:11726087.
[7] Bajaj JS, Wade JB, Gibson DP, Heuman DM, Thacker LR, Sterling RK, *et al*. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. Am J Gastroenterol 2011;106(9):1646–1653. doi:10.1038/ajg.2011.157, PMID:21556040.
[8] Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. Am J Gastroenterol 2016;111(5):602–622. doi:10.1038/ajg.2016.126, PMID:27068718.
[9] McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, *et al*. Clinical practice guidelines for clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66(7):e1–e48. doi:10.1093/cid/cix1085, PMID:29462280.
[10] Prantera C, Lochs H, Grimaldi M, Danese S, Scribano ML, Gionchetti P. Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn's disease. Gastroenterology 2012;142(3):473–481.e4. doi:10.1053/j.gastro.2011.11.032, PMID:22155172.
[11] Gionchetti P, Rizzello F, Ferrieri A, Venturi A, Brignola C, Ferretti M, *et al*. Rifaximin in patients with moderate or severe ulcerative colitis refractory to steroid-treatment: a double-blind, placebo-controlled trial. Dig Dis Sci 1999;44(6):1220–1221. doi:10.1023/a:1026648812439, PMID:10389700.
[12] Pimentel M, Saad RJ, Long MD, Rao SSC. ACG clinical guideline: Small intestinal bacterial overgrowth. Am J Gastroenterol 2020;115(2):165–178. doi:10.14309/ajg.0000000000000501, PMID:32023228.
[13] Montagnese S, Russo FP, Amodio P, Burra P, Gasbarrini A, Loguercio C, *et al*. Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF). Dig Liver Dis 2019;51(2):190–205. doi:10.1016/j.dld.2018.11.035, PMID:30606696.
[14] Khokhar N, Qureshi MO, Ahmad S, Ahmad A, Khan HH, Shafqat F, *et al*. Comparison of once a day rifaximin to twice a day dosage in the prevention of recurrence of hepatic encephalopathy in patients with chronic liver disease. J Gastroenterol Hepatol 2015;30(9):1420–1422. doi:10.1111/jgh.12970, PMID:25867912.
[15] Zeng X, Tang XJ, Sheng X, Ni W, Xin HG, Chen WZ, *et al*. Does low-dose rifaximin ameliorate endotoxemia in patients with liver cirrhosis: a prospective study. J Dig Dis 2015;16(11):665–674. doi:10.1111/1751-2980.12294, PMID:26474237.
[16] Zeng X, Sheng X, Wang PQ, Xin HG, Guo YB, Lin Y, *et al*. Low-dose rifaximin prevents complications and improves survival in patients with decompensated liver cirrhosis. Hepatol Int 2021;15(1):155–165. doi:10.1007/s12072-020-10117-y, PMID:33385299.
[17] Bajaj JS, Hafeezullah M, Franco J, Varma RR, Hoffmann RG, Knox JF, *et al*. Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. Gastroenterology 2008;135(5):1591–1600.e1. doi:10.1053/j.gastro.2008.07.021, PMID:18723018.
[18] Zeng X, Li XX, Shi PM, Zhang YY, Song Y, Liu Q, *et al*. Utility of the EncephalApp Stroop Test for covert hepatic encephalopathy screening in Chinese cirrhotic patients. J Gastroenterol Hepatol 2019;34(10):1843–1850. doi:10.1111/jgh.14656, PMID:30861191.
[19] Zeng X, Zhang LY, Liu Q, Lu CH, Wei J, Shi ZW, *et al*. Combined scores from the EncephalApp stroop test, number connection test B, and serial dotting test accurately identify patients with covert hepatic encephalopathy. Clin Gastroenterol Hepatol 2020;18(7):1618–1625.e7. doi:10.1016/j.cgh.2019.11.018, PMID:31712074.
[20] Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981;19(8):787–805. doi:10.1097/00005650-198108000-00001, PMID:7278416.
[21] Bajaj JS. Management options for minimal hepatic encephalopathy. Expert Rev Gastroenterol Hepatol 2008;2(6):785–790. doi:10.1586/17474124.2.6.785, PMID:19090738.
[22] Romero-Gómez M, Córdoba J, Jover R, del Olmo JA, Ramírez M, Rey R, *et al*. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. Hepatology 2007;45(4):879–885. doi:10.1002/hep.21586, PMID:17393525.
[23] Saxena N, Bhatia M, Joshi YK, Garg PK, Tandon RK. Auditory P300 event-related potentials and number connection test for evaluation of subclinical hepatic encephalopathy in patients with cirrhosis of the liver: a follow-up study. J Gastroenterol Hepatol 2001;16(3):322–327. doi:10.1046/j.1440-1746.2001.02388.x, PMID:11339425.
[24] Glal KAM, Abd-Elsalam SM, Mostafa TM. Nitazoxanide versus rifaximin in preventing the recurrence of hepatic encephalopathy: A randomized double-blind controlled trial. J Hepatobiliary Pancreat Sci 2021;28(10):812–824. doi:10.1002/jhbp.947, PMID:33768619.
[25] Abd-Elsalam S, El-Kalla F, Elwan N, Badawi R, Hawash N, Soliman S, *et al*. A randomized controlled trial comparing nitazoxanide plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. J Clin Gastroenterol 2019;53(3):226–230. doi:10.1097/MCG.0000000000001040, PMID:29668561.