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Randomized controlled trial of lactulose and lactulose with probiotic in the treatment of minimal hepatic encephalopathy in chronic liver disease

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ABSTRACT

Introduction: Minimal Hepatic Encephalopathy (MHE) has impact on future clinical outcomes, such as occurrence of overt hepatic encephalopathy, quality of life and survival.

Objectives: To compare lactulose and lactulose with probiotic in treatment of MHE in chronic liver disease and to determine Prevalence of minimal hepatic encephalopathy in patients with chronic liver disease.

Methodology: This was stratified randomized controlled trial. A total of 62 patients with MHE were analyzed. Child-Pugh Score was used to stratify the patients into three blocks of Child-Pugh Class (CPC) i.e., CPC-A, B and C. Patient in each block were randomized into two groups (lactulose alone and lactulose with probiotic). The primary end point was to evaluate cognitive status after one month of treatment with Figure Connection Test (FCT) A and B scores in comparison to the baseline. The secondary end points were to estimate the prevalence of MHE in chronic liver disease and assess association of inflammatory markers, total leucocyte count (TLC) and MHE.

Results: The prevalence of MHE was 41.33%. There was improvement in FCT A and B in 90% of patients in both the groups of CPC-A. Lactulose improved FCT A and B in 45.45% and 40% while lactulose with probiotic improved it in 54.54% and 30% in CPC-B and C respectively. Patients with higher baseline values had less improvement in FCT A and FCT B. Those who didn't improve had higher TLC in all the groups.

Conclusion: There was no difference in cognitive status between lactulose alone and lactulose with probiotic in treatment for chronic liver disease patients with MHE. High baseline FCT scores and TLC had poor recovery.

INTRODUCTION

Minimal Hepatic Encephalopathy (MHE) is defined as the presence of measurable cognitive defects in patients with liver disease and or portal- systemic shunting, that are not identified by clinical history and neurological examination, but are detected by abnormal neuropsychometric or neuropsychological tests.[1] The prevalence of MHE varies between 24 – 72%.[2,3,4] Figure connection test (FCT) A and B has been validated as a neuropsychologic test.[5] MHE has an impact on clinical outcomes, like occurrence of overt HE, quality of life and survival.[6] Ammonia plays a key role in the pathogenesis of MHE. Inflammation and imbalance of intestinal flora among cirrhotics contribute further. Lactulose decreases blood ammonia levels and improves psychometric performance in cirrhotic patients with MHE.[1,2] Probiotics improve endotoxin level, reduces blood ammonia level. Reversal of MHE in 50% of patients has been reported with the use of probiotics.[7] This study was conducted to assess the effectiveness of lactulose alone and in combination with probiotics in the treatment of MHE.

METHODOLOGY

The study was conducted as block stratified randomized controlled trial for the duration of 12 months from September 2015 to September 2016 in B P Koirala Institute of Health Sciences, Nepal after ethical approval was obtained from the institutional review committee. The diagnosis of cirrhosis was based on ultrasonography findings (irregular margins of liver parenchyma or portal vein diameter greater than 12 mm with or without enlarged spleen) and laboratory tests (platelet count less than 140000 or serum albumin less than 3.5 grams per deciliter or coagulopathy with INR greater than or equal to 1.5). All cirrhotic patients aged 18 years or more were included in the study. Patient who didn't give consent, overt hepatic encephalopathy or history of OHE during the past 2 weeks, recent (<2 weeks) use of drugs affecting psychometric performances like benzodiazepines, anti-epileptic or psychotropic drugs, significant comorbidity such as congestive heart failure, pulmonary disease, uremia, neurological or psychiatric disorder etc. were excluded from the study. OHE was defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of brain disease characterized by personality changes, intellectual impairment, and a depressed level of consciousness.8,9

All cirrhotic patients were allocated to different blocks of Child-Pugh class (CPC) according to Child-Pugh score and randomized by computer-generated table of random numbers. This study was an open-label study. Detailed neurological examination along with mini-mental state examination of the Nepalese version for gross neurological deficits was performed. This version of MMSE has been used by other study.10 Patients without gross neurological deficits and mini-mental state examination score (MMSE) ≥ 24 were considered for psychometric tests. FCT-A and FCT-B were the psychometric tests used and tests was considered abnormal when the test score was more than the mean +2SD from age and education-matched controls. Patient was considered to be in MHE when both FCT-A and FCT-B were abnormal. Patients diagnosed as MHE were randomized and stratified according to CPC into the standard treatment group (lactulose) and standard treatment plus probiotic group (lactulose plus probiotic). The principle investigator enrolled and assigned participants to interventions. Figure 1.

Probiotic capsules contained Streptococcus faecalis T-110 30 million CFU plus clostridium butyricum TO-A 2 million CFU plus Bacillus mesentericus TO-A 1 million CFU plus Lactobacillus sporogenes 50 million CFU. Commercially available probiotic capsules from one manufacturer available at the hospital pharmacy containing above flora were used. These capsules were given twice daily and patients were advised to conserve drug blisters. Compliance was confirmed by checking the drug-free blisters. All patients received usual medications for cirrhosis as per their disease status. Randomized patients were followed up at 1 month and assessed again with FCT A and B. The principal investigator was assessing the compliance as well as FCT A and B during follow-up visits at one month in medicine opd.

The response of treatment was based on the primary end point i.e.cognitive status interpreted by FCT-A and FCT-B scores in comparison to the baseline after one month of treatment. The secondary endpoints were the estimation of the prevalence of MHE in patients with chronic liver disease and to assess association of MHE and inflammatory markers.

Sample size was calculated by considering difference in proportion in two groups using following equation.

$$n \text{ (size per group)} = \frac{2\,(\bar{A})\,(1-\bar{A})(Z\beta + Z\alpha/2)2}{(p1-p2)2}$$

On the basis of results of three previous published studies, 1,2,7 we estimated an average improvement of 15% in MHE in the control group and an improvement of 60% in MHE in the treatment group with lactulose and

p1- probability of improvement in treatment group i.e; 0.6

p2 - probability of improvement in control group without treatment i.e; 0.15

$\bar{A}$- (p1 + p2) /2 i.e.; 0.375

Zβ- 1.28 at 90% power

Zα/2- 1.96 at 95% confidence interval

Considering above equation sample size was calculated as at least 20 patients in each arm to detect a difference in improvement in MHE, that is, the proportion of patients with MHE at 1 month, with a 5% type 1 error and 90% power for a two-tailed log-rank test.

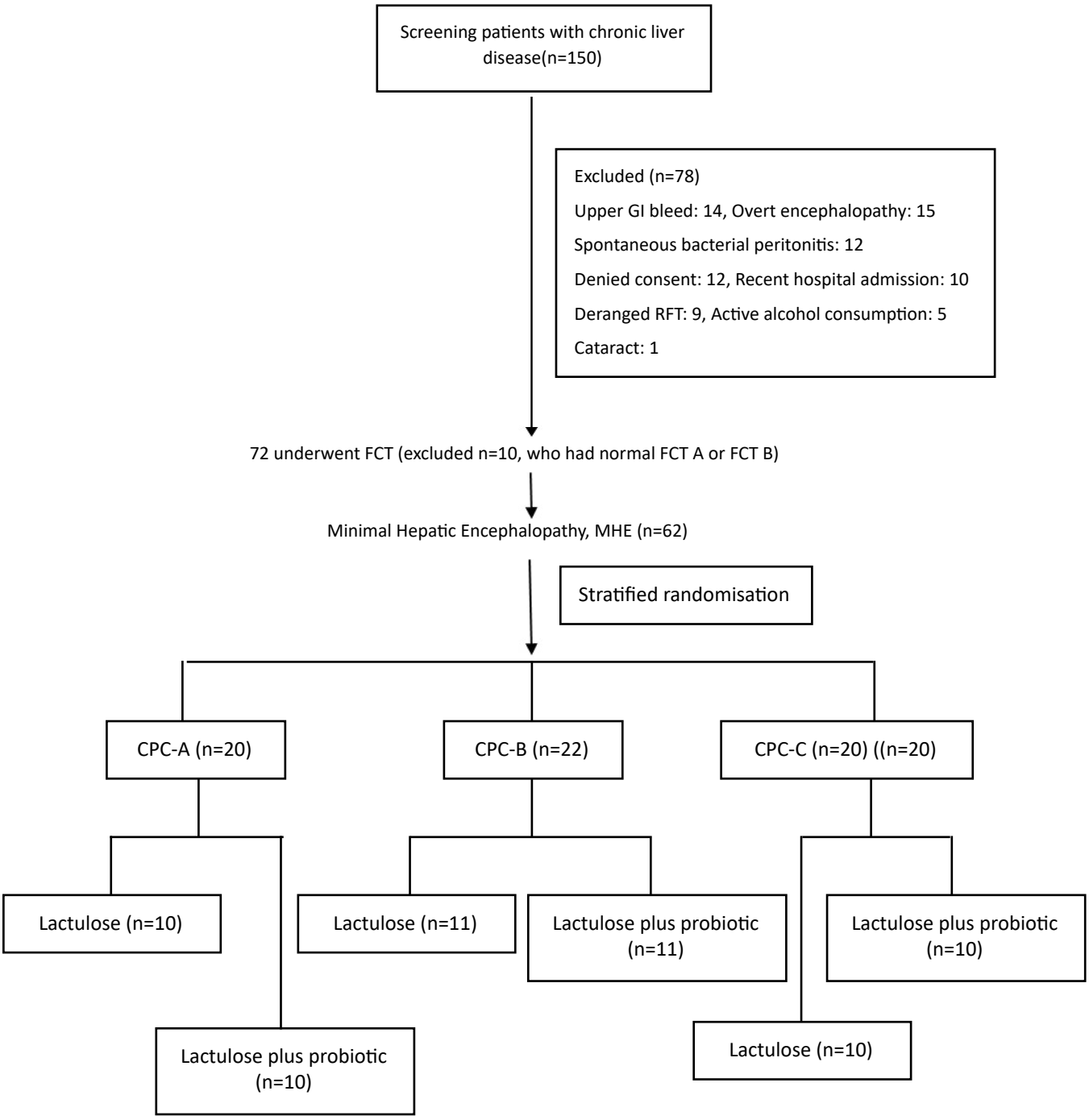
Data processing was performed by using the software packages SPSS version

11.1 for Windows (SPSS, Chicago, Illinois, USA). Data was expressed as

mean ± SD. Statistical analysis was performed by using Student's paired t-test,

Fischer's exact tests. The probability level of $P<0.05$ was set for statistical analysis.

Figure 1. Flowchart of screening and randomization of study subjects



RESULTS

Out of 150 chronic liver disease patients screened for MHE, 62 were included in the study, with a prevalence of 41.3%. Patients were stratified into three groups according to Child-Pugh scores. Patients in each group were randomized to receive lactulose or lactulose with probiotics (Figure 1). The etiology of cirrhosis was alcohol consumption (n=58), chronic hepatitis B (n=2) and chronic hepatitis C (n=2). Baseline characteristics of the patients in each group were similar except Child-Pugh Score in CPC-B (Tables 1, 2 and 3). All the baseline variables in each randomised group were similar except Child-Pugh Score between groups in CPC-B. Among CPC-B, Child-Pugh Score was either 8 or 9 in lactulose group while four patients in lactulose with probiotic group had Child-Pugh Score of 7 (p=0.02) (Table 2).

There was no significant difference in FCT A and FCT B between

the two groups in CPC-A (Table 4). Two patients failed to normalize the FCT A (one in each group), were older (mean age 53.50 vs. 47.28, p= 0.290) and of higher baseline FCT A (mean value 123.5 vs. 97.22, p= 0.297). Total leukocyte count was higher in those two patients who didn't improve (9000 vs. 6455.56, p= 0.005). One patient failed to have normal FCT B after treatment, was older (62 vs. 47, p= 0.058). Total leukocyte count was higher in the patient who didn't improve (9100 vs. 6584.21, p= 0.058). Sex, education status, Child-Pugh score and Model for end stage liver disease score (MELD) were not found to be significantly different in those with and without improvement (Table 4).

There was no significant difference in FCT A and FCT B between the two groups in CPC-B (Table 4). Five patients in the lactulose group and six patients in the lactulose plus probiotic group failed to show improvement in MHE. The mean age of the patients who didn't improve was lower (46.38 vs. 49, p= 0.43). Baseline mean FCT A and FCT B was higher in those who didn't improve, (mean value 164.55 vs. 115.18 and 272.18 vs. 206.73 with p= 0.007). Total leucocyte count was also higher in those who didn't normalized FCT (mean 8318.18 vs. 5198.18, p= 0.00). No significant difference was found with haemoglobin, platelet, albumin, bilirubin, AST, ALT, INR, creatinine and MELD scores. (Table 4)

There was no significant difference in FCT A and FCT B between two groups in CPC-C (Table 4). Thirteen patients (six in lactulose and seven in lactulose with probiotic) failed FCT normalization. Age was higher in those without FCT normalization (mean age 55.08 vs. 44, p= 0.001). Baseline FCT A and FCT B was higher in those without improvement (FCT A 176.23 vs. 159.86, p= 0.414 and FCT B 295.38 vs. 277.57, p = 0.482). Total leukocyte count was higher in those without normalization (mean TLC values 10143.08 vs. 5157.14, p= 0.00). INR (mean 2.05 vs. 1.8 p= 0.057) was significantly higher in those without normalization so is the MELD score (19.08 vs.16.14, p= 0.003) (Table 4).

Overall, 58 % (36/62) of our patients had FCT normalization after treatment for one month. FCT A and B was normalized in 17 patients (54.83%) in the lactulose group and 19 patients in the lactulose and probiotic group (61.29%). Patients with CPC-A had a greater frequency of improvement compared with CPC-B and CPC-C (90% vs. 50% vs. 35%) (Figure 2). High total leukocyte count was associated with non-improvement in FCT (Table 5). Sex, education and liver function test parameters weren't significantly different between improved and non-improved patients. The INR and MELD score was higher (2.05 vs. 1.8, p= 0.057 and 19.08 vs.16.14, p= 0.003 respectively) among non-improved CPC-C patients.

Table 1: Baseline characteristics of the group CPC-A

		CPC-A				p value
		Lactulose (N=10)	Lactulose + Probiotic (N=10)			
Age ¶		48.9±7.66	46.9±8			0.575
Sex (M/F)º		6/4	5/5			0.653
Educationº	Illiterate	7	6			0.639
	Sub graduate	3	4			
	Graduate	0	0			
	Post graduate	0	0			
Addressº	Hilly	1	3			0.264
	Terai	9	7			
Child-Pugh Scoreº		5	3	5	5	0.361
		6	7	6	5	
FCT A¶		103.10±32.590	96.60±34.786			0.671
FCT B¶		192.80±39.443	185.90±42.485			0.711
Hemoglobin (g/dl)¶		11.06±1.020	10.40±0.871			0.137
Total leukocyte count¶		6760±1601.5	6660±1016.7			0.869
Platelets¶		208500±65591.75	231300±71816.20			0.468
Total bilirubin(mg/dl)¶		1.21±0.6	1.13±0.5			0.771
Albumin (gm/dl)¶		3.40±0.29	3.64±0.20			0.049
AST¶		68±48.14	82.9±60.86			0.551
ALT¶		34.6±20.98	49.90±35.85			0.259
INR¶		1.35±0.17	1.42±0.16			0.412
Creatinine¶		0.79±0.21	0.73±0.14			0.482
MELD¶		10.80±1.98	11.10±1.91			0.735

¶ : mean ± standard deviation ºː frequency

Table 2: Baseline characteristics of the group CPC-B

		CPC-B				p value
		Lactulose (N=11)		Lactulose+Probiotic (N=11)		
Age ¶		47.45 ± 7.17		47.91 ± 8.54		0.894
Sex (M/F)º		6/5		7/4		0.5
Educationº	Illiterate	7		9		0.66
	Sub graduate	2		1		
	Graduate	1		1		
	Post graduate	1		0		
Addressº	Hilly	4		1		0.31
	Terai	7		10		
Child-Pugh Scoreº		7	0	7	4	0.02
		8	9	8	3	
		9	2	9	4	
FCT A¶		130.55±52.20		149.18±37.03		0.346
FCT B¶		227.18±68.44		251.73±49.77		0.348
Haemoglobin (g/dl)¶		10.19±1.11		9.89±0.87		0.490
Total leucocyte count¶		6672.73±2116.64		6843±1770.23		0.839
Platelets¶		168181±35968.92		155090±29737		0.363
Total bilirubin(mg/dl)¶		2.1±1.06		2.22±1.55		0.838
Albumin (gm./dl)¶		3.14±0.35		3.17±0.31		0.850
AST¶		99.18±48.39		85.45±61.13		0.566
ALT¶		41.91±21.57		35.91±19.20		0.499
INR¶		1.66±0.25		1.58±0.231		0.45
Creatinine¶		0.78±0.27		0.74±0.18		0.720
MELD¶		15.09±2.02		14.18±3.68		0.48

¶ : mean ± standard deviation º: frequency

Table 3: Baseline characteristics of the group CPC-C

		CPC-C				p value
		Lactulose (N=10)		Lactulose + Probiotic (N=10)		
Age ¶		50.5 ± 8.15		51.9 ± 8.37		0.709
Sex (M/F)º		5/5		5/5		0.67
Educationº	Illiterate	7		8		0.58
	Sub graduate	2		2		
	Graduate	1		0		
	Post graduate	0		0		
Addressº	Hilly	3		3		0.68
	Terai	7		7		
Child-Pugh Scoreº		10	2	10	3	0.6
		11	4	11	2	
		12	4	12	5	
FCT A¶		160.50±48.33		180.50±32.67		0.293
FCT B¶		278.90±59.58		299.40±44.44		0.395
Hemoglobin (g/dl)¶		8.47±1.17		9.11±1.17		0.240
Total leucocyte count¶		8238±3271.59		8558±2517.82		0.809
Platelets¶		94300±48034.82		111300±33370.14		0.370
Total bilirubin(mg/dl)¶		3.51±1.65		2.74±0.87		0.211
Albumin (gm/dl)¶		2.34±0.25		2.41±0.26		0.557
AST¶		76.10±48.56		90.60±39.93		0.475
ALT¶		35.10±20.27		39.80±17.05		0.582
INR¶		1.98±0.29		1.94±0.29		0.725
Creatinine¶		0.77±0.34		0.73±0.20		0.752
MELD¶		18.80±2.04		17.30±2.31		0.142

¶ : mean ± standard deviation º: frequency

Table 4: Response of treatment in the study groups

	Lactulose		p value(CI)	Lactulose+Probiotic		p value(CI)
	Before treatment	After treatment		Before treatment	After treatment	
CPC-A						
FCT A	103.1±32.6	72.6±28.9	0.00 (17.52-43.57)	96.6±34.7	73.3±28.1	0.00 (17-29.6)
FCT B	192.8±39.4	131.7±37.9	0.00 (42.5-79.6)	185.9±42.4	134.2±37.4	0.00 (39.3-64.1)
CPC-B						
FCT A	130.6±52.2	86.2±42.1	0.00 (31.6-57.2)	149.2±37.0	102.6±33.8	0.00 (32.7-60.4)
FCT B	227.2±68.4	147.5±55.8	0.00 (63.7-95.7)	251.7±49.8	172.3±49.2	0.00 (56.6-102.3)
CPC-C						
FCT A	160.5±48.3	124.4±56.2	0.015 (8.8-63.4)	180.5±32.6	142.6±55.7	0.01 (9.74-66.1)
FCT B	278.9±59.6	214.4±73.6	0.005 (24.6-104.4)	299.4±44.4	237.4±83.6	0.011 (17.9-106)

Table 5: Association of Response of treatment and total leukocyte count

	Figure Connection Test (Normalization)		p value
	Yes	No	
TLC(FCT A)	5818.89±1403.3	9283.08±1414.5	0.00
TLC(FCT B)	5991.79±1486.4	9441.7±1413.5	0.00

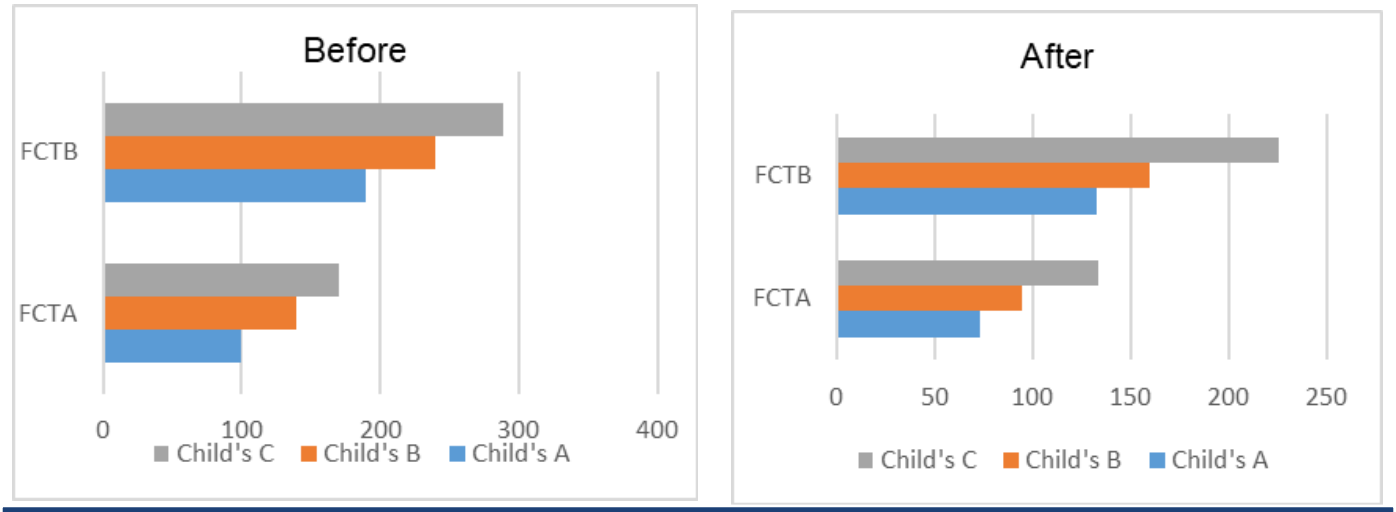


Fig 2: Comparison of FCT A and FCT B between different Child-Pugh classes

DISCUSSION

This study showed that probiotics in addition to standard treatment with lactulose does not have added advantage in treatment of MHE. Liu et al [11] showed that modulation of gut micro ecology and acidification of gut lumen in patients with liver cirrhosis and MHE by treatment with synbiotics (probiotics and prebiotic) resulted in increased faecal content of non-urease producing Lactobacillus species whereas the number of urease producing pathogenic Escherichia coli and Staphylococcal species decreased. This effect persisted for 14 days after cessation of supplementation. It was associated with significant reduction in blood ammonia and endotoxin levels and MHE reversal in 50% of the patients. Malaguarnera et al.[12] studied bifidobacterium longum with fructooligosaccharide treatment in MHE patients and showed improvement in blood ammonia levels and psychometric scores in synbiotic treated group.

A possible explanation for the similar efficacy between lactulose and lactulose plus probiotic might be because of the lactulose cathartic effect causing probiotic clearance in feces.[13] Also lactulose causes acidification of gut lumen that can interfere with the probiotic effect. Zhao et al.[14] demonstrated varying degrees of imbalance of intestinal flora among cirrhotic compared to normal healthy controls; there was an increase in the counts of aerobes and anaerobes and a decrease in the count of Bifidobacterium. The severity of imbalance in gut flora matched the degree of liver dysfunction, with the most serious imbalance observed in patients in CPC-C. This may be the reason for the decreased frequency of improvement seen in CPC-C patients compared with CPC-A and B in this study (CPC-A vs. B vs. C: 90% vs. 45-55% vs. 30-40%) (Figure 2).

After screening 150 patients with chronic liver disease, we found 62 patients had MHE, a prevalence of 41.33%. Studies have shown that markers of inflammation are higher in patients with MHE than those without it.[15] Our, this study with similar findings further emphasizes that inflammation has a role in the maintenance of MHE. The FCT A and B failed to normalize in all Child-Pugh classes with higher total leukocyte count. The major limitations of this study are non- blinding of study participants and the lack of a placebo in the lactulose group. We conclude that lactulose alone and the addition of probiotics to lactulose, both are equally effective for the treatment of MHE. Improvement in FCT score was less with treatment with higher baseline FCT values. The improvement was also correlated with baseline inflammatory state as improvement in FCT scores was significantly less with increased total leukocyte count.

CONCLUSION

There was no difference in cognitive status between lactulose alone and lactulose with probiotics in treatment for chronic liver disease patients with MHE. High baseline FCT scores and TLC had poor recovery. The prevalence of MHE was 41.33%.

LIMITATIONS OF THE STUDY

We couldn't compare FCT A and FCT B with other modalities

of diagnosis like venous ammonia, neurophysiological tests or magnetic resonance imaging and spectroscopy

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CONFLICT OF INTEREST None

FINANCIAL DISCLOSURE None

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