COMPARISON OF RIFAXIMIN, LACTULOSE WITH RIFAXIMIN, LACTULOSE, BRANCHED CHAIN AMINO-ACIDS (BCAA) IN GRADE 1 TO GRADE 3 OF HEPATIC ENCEPHALOPATHY- NON RANDOMIZED CONTROLLED TRIAL STUDY

Abhishek Basappanamalige Lokesh Reddy[1], Sabeena Kizhedath[2], Bindhu Vasudevan[3]

[1]Senior Resident, Department of Pharmacology, Government Medical College, Manjeri.
[2]Associate Professor, Department of Pharmacology, Government Medical College, Ernakulam.
[3]Associate Professor, Department of Community Medicine, Government Medical College, Ernakulam.

ABSTRACT

BACKGROUND

Hepatic encephalopathy is presented clinically as a combination of neuropsychiatric abnormalities. It is frequently observed in those with both acute and chronic liver diseases, such as hepatic cirrhosis, alcoholic liver disease. Insufficient hepatic clearance of toxins absorbed from the intestine, can result in neurochemical abnormalities across the blood brain barrier. Presently, non-absorbable disaccharides like Lactulose and antibiotics like Rifaximin are the mainstay of therapy. In cirrhosis of liver there is severe catabolic state, and consequent degradation of body protein is the major determinant of the characteristic amino acid imbalance with increased aromatic amino acid and decreased branched chain amino acid. So branched chain amino-acids could be effective in the treatment of hepatic encephalopathy.

The aim of the study is to compare the efficacy of treatment of group who take Rifaximin, and Lactulose (group A) with the group taking Rifaximin, Lactulose and Branched Chain Amino-Acids (Group B) in Grade 1 to Grade 3 of hepatic encephalopathy.

MATERIALS AND METHODS

A non-randomised controlled trial study was done among 50 patients with grade 1 to grade 3 of hepatic encephalopathy. Group A (n = 25) patients received Rifaximin at 1200 mg per day in three divided doses plus Lactulose at 90 mL a day. Group B (n = 25) patients were those who receive Rifaximin plus lactulose plus Branched chain amino-acids (BCAA) at 20 g per day. The treatment duration was 14 days. Clinical parameters like grade of mental status (MS), flapping tremors (FT), number connection test (NCT), blood ammonia levels (BAL) were performed at baseline, 7th day and 14th day and estimation of Hepatic encephalopathy indexes (HEI) was done using these parameters.

RESULTS

Both groups showed significant improvement in HEI from baseline to 7th and 14th day. Even though the improvement was more for group B, the difference in the improvement of HEI between Group A and B was not statistically significant during the treatment period except for the severity of flapping tremor on 14th day of treatment.

CONCLUSION

Since the study conducted was as a non-randomised controlled trial, for better assessment of effectiveness, either a similar study with more sample size or a randomised controlled trial is desired.

KEYWORDS

Rifaximin, Lactulose, BCAA, Hepatic Encephalopathy, Grade of Mental status, Flapping Tremors, NCT, Blood Ammonia, Hepatic Encephalopathy Index.

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BACKGROUND

Hepatic encephalopathy (HE) or Portosystemic encephalopathy (PSE) is a complex and reversible neuropsychiatric syndrome characterised by disturbances in consciousness and behaviour, personality changes, fluctuating neurologic signs, asterixis or flapping tremor and distinctive EEG changes.[1] HE may be acute and reversible or chronic and progressive. In severe cases, irreversible coma and death may occur. Acute episodes may recur with variable frequency [2,3,4] HE also impacts patient survival.[5,6]

Hepatic encephalopathy is an important complication of hepatic cirrhosis. The pathogenesis of the syndrome is complex, but ammonia produced by intestinal bacteria is known to play an important role in its pathogenesis. Neurochemical abnormalities across the blood brain barrier can occur due to insufficient hepatic clearance of toxins absorbed from the intestine.

The symptoms of hepatic encephalopathy, manifested on a continuum, are deterioration in mental status with psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration, disorientation, even coma and death. Episodes of overt hepatic encephalopathy result in frequent hospitalisations and pose a formidable burden on the healthcare system. The

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Corresponding Author:
Dr. Sabeena Kizhedath,
Associate Professor,
Department of Pharmacology,
Government Medical College, Ernakulam.
E-mail: drsabeenak123@gmail.com
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treatment of hepatic encephalopathy has focused on reducing both the production and absorption of gut-derived ammonia. Presently, non-absorbable disaccharides and antibiotics are the mainstay of therapy.[7]

Up to now, non-absorbable disaccharides such as lactulose (β-galactoside, fructose) and Lactitol (β-galactoside, sorbitol) have been the first-line drug for the treatment of Hepatic encephalopathy. They are directed at reducing the serum level of ammonia, since they decrease the absorption of ammonia through cathartic effects and by altering the colonic pH. The side effects of non-absorbable disaccharides include abdominal pain, flatulence, and severe diarrhoea, which may lead to the cessation of therapy.[8] A few patients dislike the sweet taste of the preparations, so dilution with water or administering the preparation with fruit juice can mask the taste.[9,10,11]

Rifaximin is a semi-synthetic, gut-selective, and non-absorbable oral antibiotic, derived from rifamycin and a structural analogue of rifampin. Rifaximin is minimally absorbed after oral administration and acts locally in the gastrointestinal tract, with systemic adverse effects that are similar to placebo. It is active against a variety of aerobic and anaerobic Gram-positive and Gram-negative organisms, as well as protozoal infections.[12,13] Rifaximin acts by inhibiting bacterial ribonucleic acid (RNA) synthesis. The primary mechanism for developing resistance to Rifaximin is chromosomal alteration of the drug target, i.e., DNA-dependent RNA polymerase, which is in contrast with the plasmid-mediated resistance that affects other antibiotics. Therefore, resistance to Rifaximin is not transmissible easily between bacteria.[14,15] Several studies have been conducted to support the use of rifaximin instead of or in addition to Lactitol/lactulose in the treatment of acute hepatic encephalopathy.[16-23]

In patients with hepatic encephalopathy, plasma concentration of aromatic amino acids (AAA) such as phenylalanine, tyrosine, tryptophan, methionine, aspartic acid and glutamic acid are elevated whereas branched amino acids (BCAAs) such as leucine, isoleucine and valine are decreased.[24] Branched chain amino-acids should be effective in the treatment of hepatic encephalopathy.

They are thought to be able to interrupt the chain of events linking the hypercatabolic state to hepatic encephalopathy in at least three possible ways-

- They reduce protein breakdown and stimulate protein synthesis,
- They normalise the plasma amino-acid pattern either by decreasing proteolysis or by increasing the use of aromatic amino acid for protein synthesis,
- They provide the bulk of competition across the blood brain barrier, thus preventing aromatic amino-acid from accumulating in the brain.[25]

Therefore, this non-randomised controlled trial was conducted to compare the efficacy of Rifaximin plus Lactulose regimen with Rifaximin, Lactulose plus Branched chain amino-acids regimen for the treatment of Hepatic encephalopathy patients.

MATERIALS AND METHODS

Study Design

It is a non-randomised controlled trial study.

Study Setting

The study conducted in both outpatients & inpatients attending Gastroenterology Department, Govt. Medical College Thrissur, a tertiary care hospital.

Study Period- 12 months.

Study Population

Outpatients & inpatients attending Gastroenterology Department in Government Medical College, Thrissur, who has cirrhosis of liver with first to third degree of hepatic encephalopathy.

Inclusion Criteria

- Both sexes,
- Patients with signs and symptoms of acute and chronic hepatic encephalopathy,
- Patients in the age group more than 18 years.
- Patients with Model End-Stage Liver Disease Scale (MELD) score <25.

Exclusion Criteria

- Serum creatinine level more than twice normal,
- Advanced medical problems like congestive cardiac failure, advanced pulmonary disease or renal insufficiency or electrolyte imbalance,
- Hepatocellular carcinoma,
- History of Portosystemic shunt surgery or transjugular intrahepatic Portosystemic shunt,
- Pregnancy and breastfeeding,
- Use of Interferon or psychoactive drugs like benzodiazepines, psychotropic drugs,
- Antiepileptics within the last 6 weeks,
- Presence of a major neuropsychiatric illness which interferes with psychometric analysis,
- Poor vision or motor defects which interfere with the performance of number connection tests.

Sample Size

According to the results of a study conducted by Aftab Soomro et al, mean and SD of blood ammonia level at 6th day of treatment was 70.4 and 13.9 for a group of treatment with Branched Chain Amino Acid and the same values for the control group was 50.8 and 8.16. Based on this data and using formula,

$$\frac{(Z\alpha + Z\beta)^2 \times SD^2}{} \times 2/ d^2$$

The minimum sample size in each group was determined as 7.

Zα = 5%, Zβ = 10% with the power of 90%, d = difference in Means

$$SD = \frac{SD_1 + SD_2}{2}$$ [28]

It was decided to include 25 in each group for statistical purpose which made the total sample size of 50.

Ethical Clearance
Ethical clearance was obtained from institutional Ethics Committee, Government Medical College, Thrissur.

Study Procedure
A non-randomised controlled trial study was conducted in the Department of Gastroenterology in patients with first to third degree hepatic encephalopathy. Patients affected by decompensated liver cirrhosis and Hepatic encephalopathy, showing signs of the first to third degree Hepatic encephalopathy, according to Conn's modification of Parsons-Smith classification considered and divided into two groups based on the treatment they receive. Group A patients were those who receive Rifaximin at 1200 mg per day in three divided doses plus Lactulose at 90 mL a day. Group B patients were those who receive Rifaximin plus lactulose plus Branched chain amino-acids at 20 g per day. The treatment duration was 14 days unless symptoms worsened or serious side effects occurred.

Selection of the Participants
The first participant in group A & group B were the first persons who were given the corresponding treatment by the treating physician during the study period, and then all the consecutive patients based on the treatment prescribed by the physician were included in the corresponding group till the sample size was obtained.

Drug administration was discontinued in the event of-
A serious cirrhotic complication such as acute variceal bleeding, or spontaneous bacterial Peritonitis.

A patient's refusal to participate in the trial.

Grade of mental status, flapping tremors, number connection test (NCT), blood ammonia levels were assessed and estimation of HE indexes determined in both groups accordingly at Baseline and on 7th day & 14th day of treatment.

Grade of Mental Status
Examined semi-quantitatively using Conn's modification of the Parsons-Smith classification with grades 0 to 4.

Grade 0- No abnormality; Grade 1- Trivial loss of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction performance; Grade 2- Lethargy, disorientation with respect to time, obvious personality change, inappropriate behaviour; Grade 3- Somnolence to semi-stupor, responsive to stimuli, confusion, gross disorientation, bizarre behaviour; Grade 4- Coma, unable to test mental function.

Severity of Flapping Tremor
Determined by extending the patient's arms and forearms with the wrists dorsiflexed for at least 30 seconds with Grades 0 to 3.

Grade 0- No flapping motion; Grade 1- Infrequent flapping motion; Grade 2- Continual flapping motion; Grade 3- Unable to test.

Number Connection Test (NCT)
It is the time taken to connect 25 progressive numbers; Graded 0 to 4. Grade 0- < 30 sec (normal); Grade 1: 31-50 sec; Grade 2: 51-80 sec; Grade 3: 81-120 sec; Grade 4: > 120 sec.

Blood Ammonia Levels
Measured & graded 0 to 4.
Grade 0: < 75 μM/L; Grade 1: 76-150 μM/L; Grade 2: 151-200 μM/L; Grade 3: 201-250 μM/L; Grade 4: > 251 μM/L.

Hepatic Encephalopathy (HE) Index
Defined as the total of the weighted grades of all the parameters, and had a possible range of 0 to 23 points, i.e., HE index = (Grade of mental state) × 3+ (grade of number connection test) + (grade of flapping tremor) + (grade of blood ammonia).

Analysis of Data
Data was collected, coded and entered in MS Excel and analysed using SPSS statistical software. Qualitative data was summarised into frequency and percentage. Quantitative data was summarised using mean and standard deviation. Association between qualitative data was assessed using chi-square test. Association between quantitative data was determined using independent sample t test, Mann-Whitney U test and Wilcoxon signed rank test. Significance level was fixed at a p value of <0.05.

RESULTS
A non-randomised controlled trial was conducted between two treatment regimens for the first to third degree hepatic encephalopathy. Comparison of Grades of mental state (MS), Flapping tremors (FT), Number connection test (NCT), Blood ammonia levels, Hepatic encephalopathy index (HEI) was determined and results were analysed.

Table 1 shows comparison of baseline parameters between both groups. Mean value of age between two groups noted and p value was obtained by using independent sample t test. Frequencies of gender, Grade of hepatic encephalopathy (HE), Grade of MS, severity of FT, NCT, Blood ammonia levels, at baseline in both Group A and Group B were noted and compared using Chi square test. On comparison, the baseline parameters were comparable between two groups since there was no statistically significant difference between the groups regarding the baseline parameters.

Table 2 shows comparison of parameters between group A and group B on 7th day of treatment. Frequencies of Grade of MS, severity of FT, NCT, Blood ammonia levels in both groups were compared using Chi square test. On comparison, the parameters on 7th day of treatment showed no statistically significant difference between two groups.

Similarly, Table 3 shows comparison of the same parameters between group A and group B on 14th day of treatment, these parameters were compared using Chi square test, which showed no statistical significance between the groups, but only one parameter i.e., severity of FT showed significant difference with a p value 0.03* between two groups.

Table 4 shows comparison of groups based on HE Index, its mean value was noted at baseline, 7th and 14th day of treatment and was compared between group A and group B using Mann-Whitney U test. The index was improving with the treatment in both the groups at various points of treatment, but the difference was not statistically significant between the groups at any of the treatment evaluation point.

Table 5 shows comparison of difference of HE index at various treatment points between groups. Means of

difference of HE index between baseline and 7th day, difference between baseline and 14th day, difference between 14th and 7th day was noted and was compared using Mann-Whitney U test. There was no statistically significant difference in improvement of HE index between the groups at any point of treatment.

Table 6 and Table 7 shows comparison of difference of HE Index within Group A and group B respectively. Means of difference of HE index between baseline and 7th day, difference between baseline and 14th day, difference between 14th and 7th day noted and p value was obtained by Wilcoxon signed rank test. There was statistically significant improvement of HE index in both groups at 7th and 14th day.

Figure 1, 2, 3, 4 shows comparison of group A & B based on Grade of MS, FT, NCT, Blood ammonia levels at baseline, on 7th & 14th day of treatment.

	Group A	Group B	P value
Age	52.84 ± 9.65	55.32 ± 8.4	0.33
Gender (Male/Female)	24/1 (96%/4%)	22/3 (88%/12%)	0.29
Grade of HE	1 (24%) 2 (48%) 3 (28%)	1 (12%) 2 (48%) 3 (40%)	0.46
Grade of MS	1 (24%) 2 (48%) 3 (28%)	1 (12%) 2 (48%) 3 (40%)	0.46
Severity of FT	1 (24%) 2 (48%) 3 (28%)	1 (28%) 2 (36%) 3 (36%)	0.68
NCT	0 (4%) 1 (16%) 2 (20%) 3 (32%) 4 (28%)	0 (0%) 1 (16%) 2 (4%) 3 (28%) 4 (52%)	0.23
Blood Ammonia Levels	0 (0%) 1 (0%) 2 (36%) 3 (40%) 4 (24%)	0 (4%) 1 (4%) 2 (24%) 3 (40%) 4 (28%)	0.61

Table 1. Comparison of Baseline Parameters

HE- Hepatic encephalopathy, MS- Mental status, FT- Flapping tremors, NCT- Number connection test,

	Group A	Group B	P value
Grade of MS	0 (20 %) 1 (48 %) 2 (28 %) 3 (4 %)	0 (28 %) 1 (52 %) 2 (16 %) 3 (4 %)	0.75
Severity of FT	0 (4 %) 1 (56 %) 2 (36 %) 3 (4 %)	0 (12 %) 1 (52 %) 2 (32 %) 3 (4 %)	0.77
NCT	0 (12 %) 1 (32 %) 2 (32 %) 3 (16 %) 4 (8 %)	0 (8 %) 1 (32 %) 2 (32 %) 3 (24 %) 4 (4 %)	0.92
Blood Ammonia levels	0 (16 %) 1 (36 %) 2 (32 %) 3 (12 %) 4 (4 %)	0 (20 %) 1 (60 %) 2 (12 %) 3 (8 %) 4 (0 %)	0.27

Table 2. Comparison of Parameters of both Groups on 7th day of Treatment

	Group A	Group B	P value
Grade of MS	0 (64 %) 1 (32 %) 3 (4 %)	0 (88 %) 1 (8 %) 3 (4 %)	0.10
Severity of FT	0 (36 %) 1 (56 %) 2 (4 %) 3 (4 %)	0 (76 %) 1 (20 %) 2 (0 %) 3 (4 %)	0.03*
NCT	0 (40 %) 1 (40 %) 2 (16 %) 4 (4 %)	0 (52 %) 1 (40 %) 2 (4 %) 4 (4 %)	0.53
Blood Ammonia levels	0 (76 %) 1 (20 %) 3 (0 %) 4 (4 %)	0 (84 %) 1 (12 %) 3 (4 %) 4 (0 %)	0.45

Table 3. Comparison of Parameters of both Groups on 14th day of Treatment

*Significant difference, p value <0.05

HEI	Group A (Mean ± SD)	Group B (Mean ± SD)	P value
Baseline	14.08 ± 4.56	14.56 ± 4.04	0.69
7th day	8.16 ± 4.72	7.08 ± 4.34	0.40
14th day	3.32 ± 4.29	1.72 ± 3.91	0.17

Table 4. Comparison of Groups Based on HE Index

	Difference between Baseline and 7th day of HEI	Difference between Baseline and 14th day of HEI	Difference between 7th Day and 14th of HEI
Group A	8.16 ± 4.72	10.76 ± 3.67	2.6± 6.00
Group B	7.08 ± 4.34	12.84 ± 4.68	5.76 ± 5.65
P value	0.4	0.08	0.77

Table 5. Comparison of Difference between Groups in HE Index

Group A			
	Difference between Baseline and 7th Day of HEI	Difference between Baseline and 14th Day of HEI	Difference between 7th Day and 14th of HEI
Mean	8.16 ± 4.72	10.76 ± 3.67	2.6 ± 6.0
P value	0.001*	0.001*	0.04*

Table 6. Comparison of Difference in HE Index within Group A

*Significant difference, p value <0.05

Group B			
	Difference between Baseline and 7th Day of HEI	Difference between Baseline and 14th Day of HEI	Difference between 7th Day and 14th of HEI
Mean	7.08 ± 4.34	12.84 ± 4.68	5.76 ± 5.65
P value	0.001*	0.001*	0.001*

Table 7. Comparison of Difference in HE Index within Group B

* Significant difference, p value <0.05

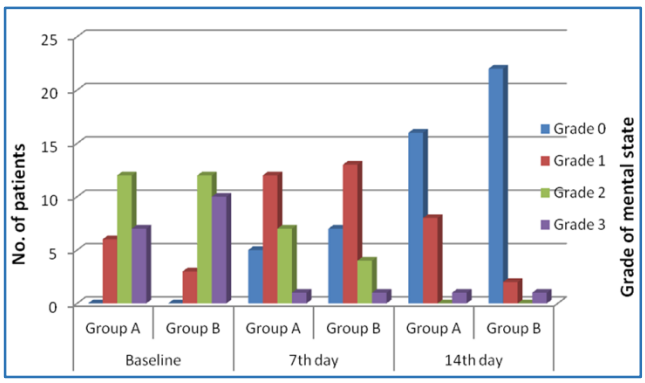

Figure 1. Comparison of Groups based on Grade of Mental State at Baseline, 7th day and 14th day of Treatment

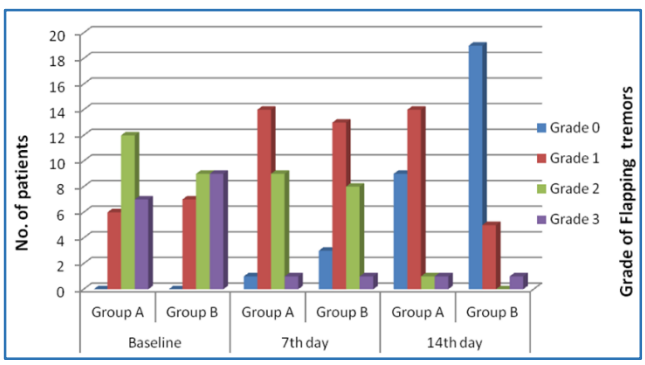

Figure 2. Comparison of Groups based on Severity of Flapping Tremors at Baseline, 7th day and 14th day of Treatment

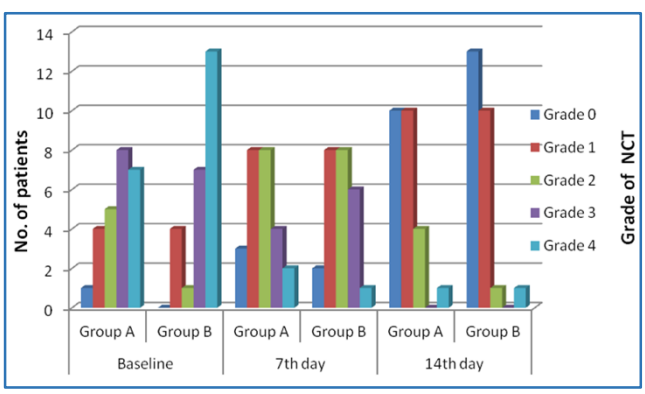

Figure 3. Comparison of Groups based on NCT at Baseline, 7th day and 14th day of Treatment

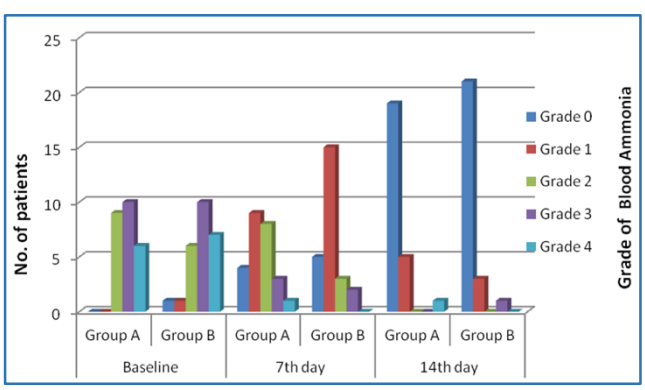

Figure 4. Comparison of Groups based on Blood Ammonia levels at baseline, 7th day and 14th day of Treatment

DISCUSSION

Hepatic encephalopathy is one of the recurrent and difficult to treat complication of Liver cirrhosis. Prevention of episodes of hepatic encephalopathy is an important goal, since symptoms of overt encephalopathy are debilitating and decrease the ability for self-care, leading to improper nutrition and non-adherence to a therapeutic regimen, which in turn leads to severe symptoms, frequent hospitalizations, and a poor quality of life. Currently, Lactulose and non-absorbable antibiotics like Rifaximin are most commonly used therapeutics to treat HE. The objective of this present study was to compare the treatment of Rifaximin, Lactulose (Group A) regimen with Rifaximin, Lactulose plus Branched chain amino-acids (Group B) regimen in Grade 1 to Grade 3 of hepatic encephalopathy.

Comparison of groups based on Grade of mental status, showed that in Group A patients at baseline 48% of patients were in Grade 2, while on 7th day of treatment majority of patients were in grade 1 with 48% and on 14th day of treatment maximum patients were in Grade 0 (64 %), similarly in Group B, 48 % of patients were in Grade 2 at baseline, while on 7th day of treatment 52% patients were in grade 1 which is more when compared to 48% in Group A and on 14th day of treatment 88% were in Grade 0 when compared to 64% in Group A. Improvement in Grade of mental status from baseline to 7th day and baseline to 14th day was seen in both groups which could be due to effect of treatment. On comparing the two groups, no significant difference between Group A and Group B regimen in grade of mental state was found on 7th and 14th day. A study done by Paik et al reported that both rifaximin and lactulose were effective with significant improvement in mental state.[7]

Comparison of severity of flapping tremor showed that at baseline 48% of patients were in Grade 2 in Group A patients, and 36% each in Grade 2 and Grade 3 respectively among the Group B patients. On 7th day of treatment, majority of patients in Group A (56%) were in grade 1 as compared to 52% in Group B & on 14th day of treatment more patients of Group B were in Grade 0 (76%), as compared to 36% in Group A. Both groups showed improvement in Grades of severity of flapping tremor from baseline to 7th and 14th day of treatment. On comparing Group A regimen and Group B regimen, there was a statistical significant improvement of flapping tremor grade in Group B as compared to group A on 14th day of treatment with P value 0.03. This finding is in agreement with the study done by Horst D et al showing a statistically significant improvement of flapping tremor with BCAA supplement.[27]

Comparison of groups based on NCT showed that among the Group A patients at baseline, 32% of patients were in Grade 3, while 52% patients of Group B were in Grade 4. On 7th day of treatment, majority of patients were seen in Grade 1 and Grade 2 (32% each). A similar picture was seen among Group B patients also. On 14th day of treatment, 40% of patients in Group A were in Grade 0 and Grade 1, while Group B showed 52% of patients in Grade 0 which was more when compared to Group A. Both groups showed improvement in Grade of NCT from baseline to 7th and baseline to 14th day of treatment. On comparing, no significant difference was found between Group A and Group B in NCT on 7th and 14th day of treatment. A study done by Eriksson L S et al also showed that there was no significant difference in psychometric tests on treatment with BCAA compared to placebo.[28]

Comparison of groups based on blood ammonia levels showed that among Group A and Group B patients at baseline, 40% of patients were in Grade 3, while on 7th day of treatment Group B showed 60% of patients in grade 1 which is more when compared to 36% of Group A. On 14th day of treatment, 84% of patients were in Grade 0 in Group B when compared to 76% of patients in Group A. The Grade of Blood Ammonia level was improved from baseline to 7th and baseline to 14th day of treatment in both groups. On comparing, statistically significant difference was not seen in both the groups on 7th and 14th day of treatment. Similar results were seen in a study done by Sharma BC et al which showed no statistical significance in blood ammonia levels.[29]
Comparison of groups based on Hepatic Encephalopathy Index (HEI) showed that the Mean value of HEI in Group A at baseline was 14.08, on 7th day of treatment it was 8.16 and on 14th day it was 3.32, while the Mean value of HEI in Group B at baseline was 14.56, on 7th day of treatment mean was 7.08 and on 14th day of treatment mean was 1.72. The mean value of HEI reduced from baseline to 7th day and baseline to 14th day of treatment in both Group A and Group B which might be due to effect of treatment. There was no statistically significant difference of HEI grade between Group A and Group B at any treatment point.

Similarly, on comparison between Group A and Group B based on HEI difference between baseline and 7th day, between baseline and 14th day, between 7th and 14th day, no statistically significant difference was found between two groups. On comparing HEI difference between baseline and 7th day, between baseline and 14th day, between 7th and 14th day within group A and within group B respectively showed a significant improvement. A study done by Marchesini G et al showed that the PSE or HE index significantly improved in patients on treatment with BCAA,[30] also the study of Paik YH et al shows that HE index improved in both rifaximin and lactulose treatment.[7]

CONCLUSION

In this non-randomised controlled trial study, treatment between Rifaximin, Lactulose (Group A) regimen and Rifaximin, Lactulose, BCAA (Group B) regimen were compared and the study shows that both treatment regimens were improving the HE index and the various parameters of HE index. But the difference in the improvement was not statistically significant between the groups except the grading of flapping tremor on 14th day of treatment. Since the study is an observational study with small sample size a similar study with a bigger sample size or a randomised control trial may be needed to reach at a definite conclusion.

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