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RANDOMIZED CONTROLLED TRIAL OF LACTULOSE AND LACTULOSE PLUS PROBIOTICS IN THE TREATMENT OF MINIMAL HEPATIC ENCEPHALOPATHY

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HOW TO CITE THIS ARTICLE:

Mayank Sharma, Sanjay Bhat, Kalyan Dutt, Pulkit Sharma, Jasra Ali Bhat. "Randomized Controlled Trial of Lactulose and Lactulose Plus Probiotics in the Treatment of Minimal Hepatic Encephalopathy". Journal of Evidence based Medicine and Healthcare; Volume 1, Issue 9, October 31, 2014; Page: 1125-1135.

ABSTRACT: BACKGROUND AND AIM: Minimal hepatic encephalopathy (MHE) is associated with poor quality of life and increased work disability. Treatment with lactulose and probiotics has shown some benefit. We compared lactulose and a combination of lactulose plus probiotics in the treatment of MHE. **PATIENTS AND METHODS:** Fifty cirrhotic patients without overt encephalopathy were evaluated by psychometry (Number connection tests, Block design test and Digit symbol test). MHE was diagnosed by abnormal psychometry. Patients were randomized to receive lactulose [group 1 (n = 25): dose 30–60 ml/day], and probiotics plus lactulose [group 2 (n = 25) same dose of lactulose plus probiotic one capsule three times/ day, each capsule contained Streptococcus faecalis 60 million, Clostridium butyricum 4 million, Bacillus mesentericus 2 million, lactic acid bacillus 100 million]. Response was defined by normalization of the abnormal test parameters at six weeks treatment. **RESULTS:** MHE was diagnosed in 50 patients. Of the 50 patients, all had abnormal psychometry tests. Significant improvement was seen in abnormal psychometry tests in lactulose alone and lactulose plus probiotics groups after treatment. Normalization of abnormal psychometry was seen in 63%, and 60% of patients treated with lactulose alone and lactulose plus probiotics groups, respectively. **CONCLUSION:** All the patients with cirrhosis had MHE. Lactulose alone or combinations of both lactulose plus probiotic are equally effective in the treatment of MHE.

KEYWORDS: Cirrhosis, Lactulose, Probiotics, Minimal Hepatic Encephalopathy.

INTRODUCTION: Hepatic encephalopathy presents clinically as a combination of neuropsychiatric abnormalities characterized by alterations in mental status, personality, intellectual function, and changes in neuromuscular activity. It is frequently observed in those with both acute liver failure and liver cirrhosis.^(1,2) The pathogenesis of the syndrome is complex, but ammonia produced by intestinal bacteria is known to play an important role in its pathogenesis.⁽³⁾

In addition to clinically manifest hepatic encephalopathy, a subclinical stage known as minimal hepatic encephalopathy(MHE), defined as "a condition in which patients with cirrhosis exhibit various quantifiable neuropsychological defects but have a normal mental and neurological status on standard clinical examination."⁽⁴⁾ The prevalence of minimal hepatic encephalopathy (MHE) in patients with cirrhosis is estimated to vary from 30% to 84% because of differences in definitions of MHE used in the various studies and diagnostic methods.⁽⁵⁾ A major reason for the wide variation in the prevalence of MHE is the absence of a "gold standard" and consequently the lack of uniformity in the application of diagnostic tests. Psychomotor slowing, visual-constructive

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disabilities, attention deficits are among the few key features while fine motor performance is also impaired⁽⁶⁾

MHE may predict the development of overt hepatic encephalopathy. Various tools have been evaluated for the correct diagnosis of MHE, however, a combination of test methods is recommended to reliably diagnose MHE. Gut-derived nitrogenous substances are universally acknowledged to play a major role in the pathogenesis of hepatic encephalopathy, and the pathogenesis of MHE is thought to be similar to that of overt hepatic encephalopathy (HE). Specifically, ammonia is thought to be a critical factor in the pathogenesis. Ammonia-induced alterations in cerebral blood flow and glucose metabolism have shown that there is a significant decrease in glucose utilization of various cortical regions that correlate with the patient's cognitive functions.⁽³⁾

No study has, however, compared lactulose alone with lactulose plus probiotics. We performed a randomized controlled trial to compare the efficacy and safety of lactulose versus lactulose plus probiotics in the treatment of MHE.

AIMS AND OBJECTIVES: To study the role of lactulose alone and lactulose plus probiotics in patients of minimal hepatic encephalopathy.

MATERIAL AND METHODS: The study was prospectively conducted in the Department of Medicine in Acharya Shri Chander College of Medical Sciences, Jammu from November-2009 to October-2010 after getting approval from Hospital Ethical Committee and after obtaining informed consent from the patients in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

A total of 50 patients with cirrhosis diagnosed on a clinical basis including laboratory tests, endoscopic evidence, sonographic findings and liver histology, if available, were included.

Exclusion criteria were:

1. History of hepatic encephalopathy
2. History of taking lactulose or any antibiotics or alcohol intake in the past 6 weeks.
3. Gastrointestinal hemorrhage or spontaneous bacterial peritonitis during the past 6 weeks.
4. Earlier transjugular intrahepatic portosplenic shunt or shunt surgery.
5. Significant co-morbid illness such as heart failure, respiratory failure renal illness and any neurologic disease such as Alzheimer's disease, Parkinson's disease and non-hepatic metabolic encephalopathies.
6. Patients with color blindness and mature cataract, diabetic retinopathy and patients on psychoactive drugs such as anti-depressants or sedatives.

Patients were randomized according to a computer-generated randomization chart in two groups in a non-blinded manner: group 1 (lactulose n = 25), and group 2 (lactulose plus probiotics n = 25). Group 1 received 30–60 ml of lactulose/day, so that patients passed two to three semiformed stools per day. Group 2 received lactulose plus probiotics, 1 capsule three times per day (each capsule contained Streptococcus faecalis 60 million, Clostridium butyricum 4 million,

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Bacillus mesentericus 2 million, lactic acid bacillus 100 million) with water. Both the groups received treatment for six weeks. Compliance with treatment was checked by pill count and volume assessment of lactulose. Response was defined by normalization of the abnormal test parameters. Patients with normalization of psychometric tests before therapy were classified as responders, the parameters got normalized following treatment.

Minimal hepatic encephalopathy was diagnosed by mental status examination and impairment in performance of at least 2 of the following tests: -

1. Number connection test (NCT), is the most widely used test for the detection of minimal hepatic encephalopathy. It is a derivative of the Trail Making Test and measures cognitive motor abilities. Number connection test is a neuropsychological test of visual attention and task switching. The task requires a subject to 'connect-the-dots' of 25 consecutive targets on a sheet of paper or computer screen. Two versions are available: A, in which the targets are all numbers (1, 2, 3, etc.), and B, in which the subject alternates between numbers and letters (1, A, 2, B, etc.). The goal of the subject is to finish the test as quickly as possible, and the time taken to complete the test is used as the primary performance metric. Subjects are required to connect numbers printed on paper consecutively from 1 to 25 as quickly as possible. The test score is the time that the patient needs to perform the test, including the time needed to correct errors. A low score indicates a good performance.^(7,8)
2. Block design test (BL DES): The BL DES, adapted from the Wechsler Adult Intelligence Scale, yields a weighted index combining speed and accuracy. It describes the ability to construct designs or patterns from pictorial models. Block design is a subtest on many intelligence tests that measures visuospatial and motor skills. The test is required to take blocks that have all white sides, all red sides, and red and white sides and arrange them according to a pattern. They are timed on this task and compared to a normal sample. The maximum score is 24. Good performance on the block design test is indicative of appropriate functioning of the parietal and frontal lobes.⁽⁹⁾
3. Digit symbol test (DST): The DST is a subset of the Wechsler Adult Intelligence Scale and measures motor speed and accuracy. DST is a neuropsychological test sensitive to brain damage, dementia, age and depression. It is not sensitive to the location of brain-damage (except for damage comprising parts of the visual field). It consists of (e.g. nine) digit-symbol pairs (e.g. 1/-, 2/+, ... 7/\, 8/X, 9/=) followed by a list of digits.. The patient is given a list of digits from one to nine associated with symbols and is asked to fill in the blanks with symbols that correspond to each number. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (e.g. 90 or 120 sec) is measured. A high score indicates a good performance. (Kaufman, Alan and Elizabeth Lichtenberger 2002).

Tests were considered abnormal when test score was more than mean \pm 2 SD from the age-matched and education-matched controls.⁽⁹⁾ The normative values for NCT and BL DES DST were taken for patients of same educational and geographical background.

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DIETARY HABITS: Protein intake was not restricted in the enrolled patients. As most of our patients were strict vegetarian, they took vegetable-based protein (1gm/kg body weight) in supplementation with casein-based protein. Salt was restricted in every patient to < 2 gm/day. Their diets were routinely supplemented with vitamins. Patients, who were on diuretics or on beta-blockers for the prophylaxis of variceal bleeding, continued their medication. There was no significant difference in the intake of these medicines in the two groups.

ASSESSMENT OF MINIMAL HEPATIC ENCEPHALOPATHY: Patients without evidence for manifest HE, according to the mental state, (West Haven criteria) were defined as having no HE. MHE was defined by abnormal psycho-metric study (NCT or FCT and DST).

BLOOD TESTS AND BIOCHEMICAL EXAMINATIONS: After overnight fasting, a patient's venous blood was taken and analyzed for routine liver function tests and hematologic parameters by conventional methods.

STATISTICAL ANALYSIS AND DATA MANAGEMENT: Data processing was performed by using the software packages, SPSS Version 11 for Windows (SPSS, Chicago, Illinois, USA). Data were expressed as means \pm SD. Statistical analysis was performed using Student's paired t-test, Fisher's exact tests and analysis of variance. The probability level of $P < 0.05$ was set for statistical significance.

The end point of the study was improvement in the minimal hepatic encephalopathy by the above said drugs for a maximum of 6 week

OBSERVATION: A total of 50 patients with established cirrhosis without overt encephalopathy were screened for minimal hepatic encephalopathy irrespective of etiology. A sample of at least 25 patients was taken in each group i.e. group 1 who received lactulose only and group 2 who received lactulose and probiotic. All the patients underwent follow up on 4th and 6th week with respect to their baseline parameters i.e Sr. Creatinine, Sr. Bilirubin, SGOT, SGPT, ALP, Sr. Albumin, PTI and encephalopathy. There was no statistically significant difference in all their baseline parameters between the two groups at admission, 4th and 6th week.

Variables	Group 1	Group 2	P Value
Age (in years)	50.20 \pm 10.20	49.60 \pm 11.08	0.843
Sex	Male	19	19
	Female	6	6

Table 1: Showing mean age and sex of patients in two groups

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Variables	At Admission	At 4th week	At 6th week	P Value
Sr. Creatinine	1.44 ± 0.66	0.987 ± 0.25	0.945 ± 0.21	0.0001
Sr. Bilirubin	4.07 ± 1.89	2.51 ± 1.92	2.0 ± 1.06	0.0001
SGOT	99.56 ± 52.43	66.88 ± 30.24	60.92 ± 28.04	0.016
SGPT	88.88 ± 57.24	71.36 ± 51.63	61.20 ± 42.62	1.0
ALP	181.76 ± 53.53	173.84 ± 51.53	167.76 ± 48.11	1.0
Sr. Albumin	2.44 ± 0.93	2.59 ± 0.93	2.63 ± 0.91	1.0
PTI	2.42 ± 0.94	2.12 ± 0.82	2.12 ± 0.82	1.0
Encephalopathy	22	14	8	0.0001

Table 2: Comparison of variables in patients belonging to Group 1 at admission, at 4th week and 6th week

Variables	At Admission	At 4th week	At 6th week	P Value
Sr. Creatinine	1.54±0.71	0.988 ± 0.24	0.988 ± 0.24	0.002
Sr. Bilirubin	4.11 ± 1.68	2.0 ± 1.09	2.0 ± 1.09	0.0001
SGOT	93.88 ± 39.36	62.40 ± 16.95	62.40 ± 16.95	0.001
SGPT	80.88 ± 52.20	63.84 ± 26.85	63.84 ± 26.85	1.0
ALP	185.92 ± 56.14	167.32 ± 35.07	167.32 ± 35.07	1.0
Sr. Albumin	2.51± 0.97	2.62 ± 0.85	2.62 ± 0.85	1.0
PTI	2.46 ± 0.91	2.09 ± 0.55	2.09 ± 0.55	1.0
Encephalopathy	23	15	9	0.0001

Table 3: Comparison of variables in patients belonging to Group 2 at admission at 4th week and 6th week

	At Admission	4th week	6 Week
No. of Patients	22 (88%)	15 (56%)	8 (32%)

Table 4: Showing minimal hepatic encephalopathy at admission, at 4th and 6th week in Group I

	At Admission	4th week	6th Week
No. of Patients	23 (92%)	15 (60%)	9(36%)

Table 5: Showing minimal hepatic encephalopathy at admission, 4th and 6th week in Group 2

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	4th week	6th Week
No. of Patients	7(32%)	14(63%)

Table 6: Showing improvement in minimal hepatic encephalopathy at 4th and 6th week in Group I

	4th week	6th Week
No. of Patients	8(34%)	14(60%)

Table 7: Showing improvement in minimal hepatic encephalopathy at 4th and 6th week in Group 2

DISCUSSION: Minimal hepatic encephalopathy irrespective of the etiology, in our study was observed in 88% of group 1 and 92% of group 2 patients at the onset of the study. After follow up at 6th week the MHE significantly improved in the both groups i; e 68% in group 1 and 69% in group 2 but the difference was not significant among the two groups.

Prevalence of MHE in cirrhotics is variable ranging from 30 to 80% depending upon the criteria used for screening.^(5,10,11) All the groups showed significant improvement in the psychometric tests values after treatment.

The pathogenesis of MHE is thought to be similar to that of overt HE and ammonia plays a key role.^(3,12) Both the therapies were aimed at reducing ammonia levels. Treatment with lactulose is of benefit in a majority of patients with MHE.^(13,14,15,16)

Improvement in the lactulose group might be because of the acidification of gut causing growth of non-urease producing bacteria, as reflected in the decrease in venous ammonia levels.

Of the 25 patients who completed six weeks treatment with lactulose, we found 68% of them had a normalization of abnormal test parameters, which is consistent with that of earlier studies.^(17,18,19,20,21) We also noticed significant reduction in the serum transaminase which might be because of a reduction in the circulating endotoxin levels, which decreases the oxidative injury to liver cells. Therefore, lactulose is cost effective, easily available and effective in reducing blood ammonia in the management of MHE.^(22,23)

Liu et al.⁽²⁴⁾ reported an alternative and novel approach of modulating the gut microecology and acidifying the gut lumen for therapeutic benefit in cirrhotic patients with MHE by treatment with synbiotics. Such a modulation of gut flora was associated with a significant reduction in blood ammonia levels and a reversal of MHE in 50% of the patients. This concept of treating hepatic encephalopathy with probiotics is not new, as it has been tried earlier with variable efficacy.^(23,24,25,26,27,28) Experience with experimental animals suggests that oral supplementation with probiotics can protect against hepatocellular damage on account of alcohol-induced liver damage, and non-alcoholic liver disease via reduction in the intrahepatic expression of various molecular markers of inflammation, including nuclear factor kb and tumor necrosis factor α .⁽²⁹⁾ We also found that supplementing MHE patients with probiotics had an effect on the normalization of abnormal psychometric tests.

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We also randomized 25 patients to the lactulose plus probiotics group to know whether the combination hastened the reversal of MHE. Improvement in abnormal psychometry (92% to 36%) was seen. A total of 64% patients had a complete reversal of MHE, which is not statistically different in the two treatment groups. Possible mechanisms could be owing to the cathartic effect of lactulose, which may cause a washout of probiotics before it can have its effects or there is acidification of the gut lumen by lactulose, which interferes with the probiotics effect. Most of our patients tolerated lactulose without any significant diarrhea or abdominal pain. Probiotics treatment also had no side effect. One and half month of treatment with lactulose for MHE costs US\$20 each, whereas combination therapy had added to the cost (US\$40) of treatment without adding many benefits which has clear impact on treatment especially in developing countries where health is not insured.

CONCLUSION: In conclusion, the patients with cirrhosis with MHE treatment with lactulose, or lactulose plus probiotics were equally efficacious in the treatment of MHE.

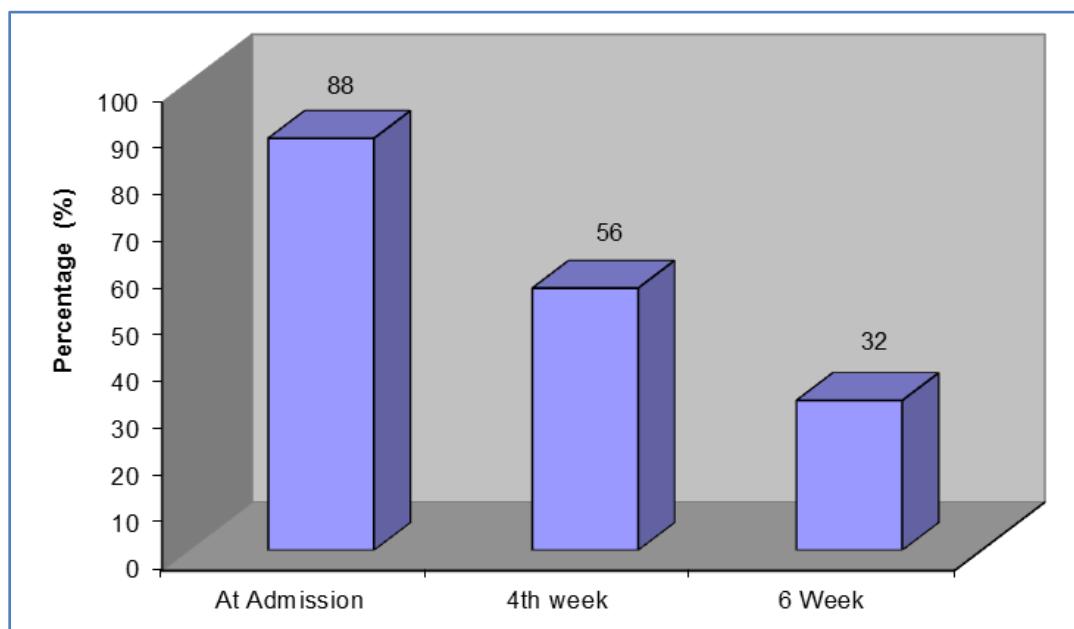


Fig. 1: Percentage of patients having Minimal Hepatic Encephalopathy at admission, 4th and 6th week in group 1

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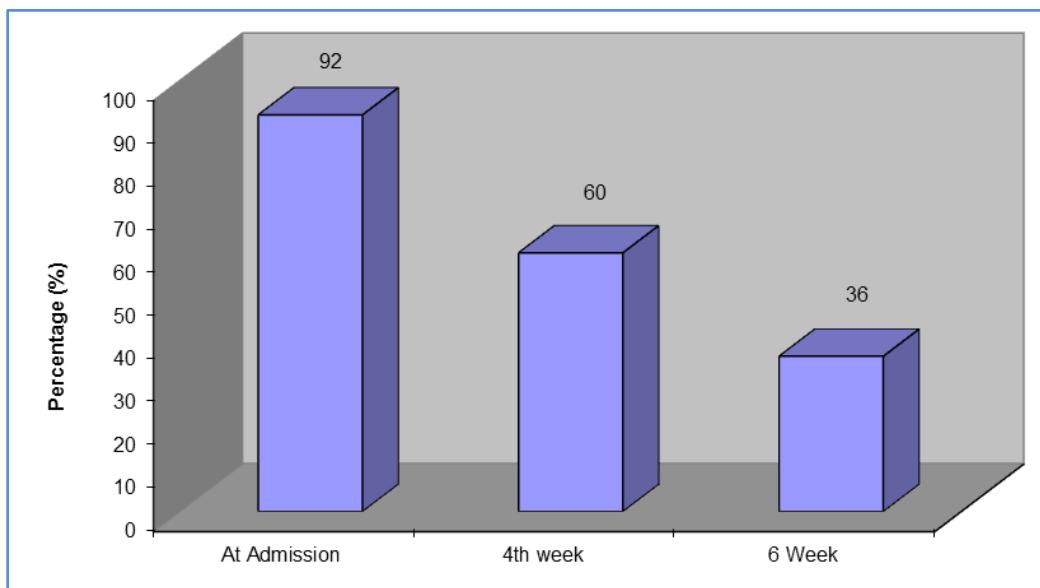


Fig. 2: Percentage of patients having Minimal Hepatic Encephalopathy at admission, 4th and 6th week in group 2

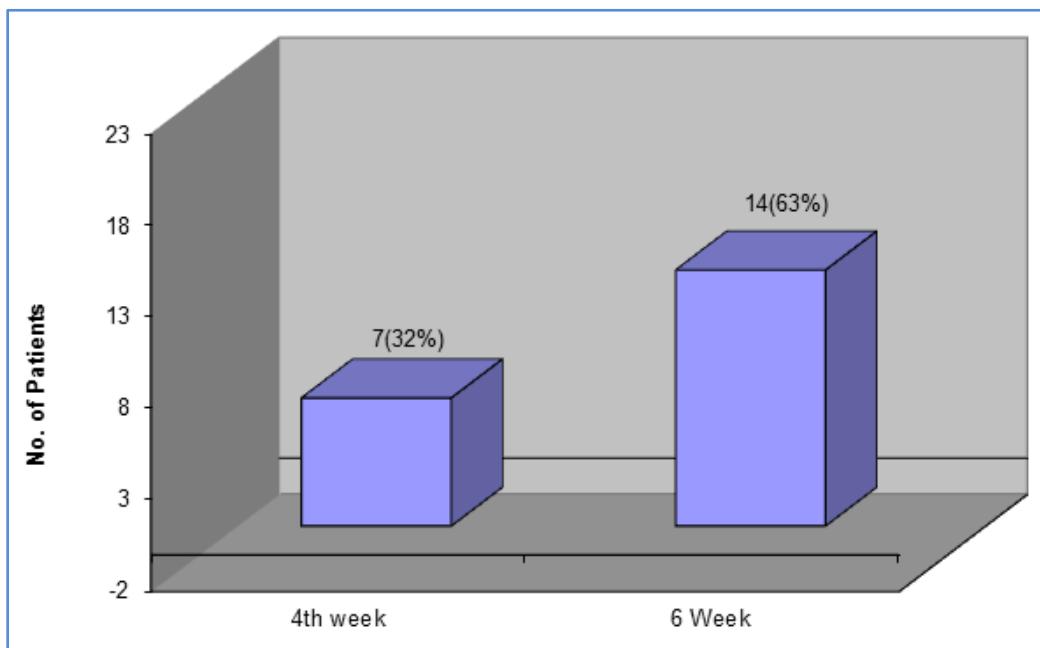


Fig. 3: Showing improvement in minimal hepatic encephalopathy at 4th and 6th week in Group I

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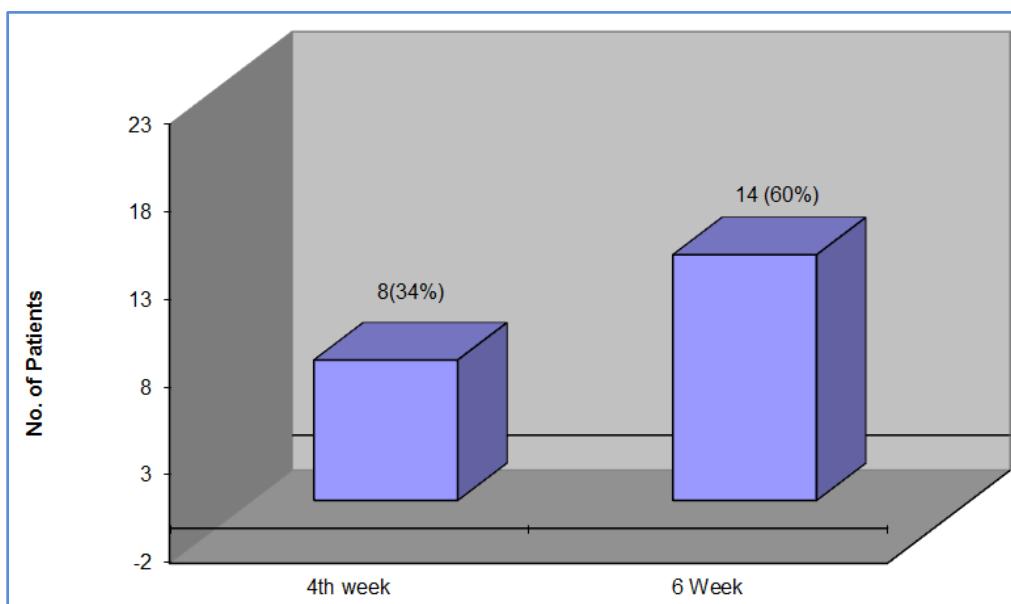


Fig. 4: Showing improvement in minimal hepatic encephalopathy at 4th and 6th week in Group II

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Date of Submission: 22/09/2014.
Date of Peer Review: 23/09/2014.
Date of Acceptance: 26/09/2014.
Date of Publishing: 17/10/2014.