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CONSERVATIVE ORAL THERAPY VERSUS RIFAXIMIN PLUS LACTOSE: WHICH IS A BETTER OPTION TO MANAGE RECURRENCE ONSET OF HE (HEPATIC ENCEPHALOPATHY)

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Abstract:

Objective: *To have a comparison of the recurrence or frequency of HP (hepatic encephalopathy) with a liver cirrhosis patient having treatment with Rifaximin plus Lactulose as opposed to oral conventional treatment by Lactulose only.*

Materials & Methods: *This research started from January and ended in August 2017 at the Department of Medicine, Jinnah Hospital, Lahore. In this research, a total number of 200 HE patients were considered and divided into two groups: a group of getting treatment patients and a placebo group. The recurrence or frequency of HE was evaluated amid these two groups.*

Results: *A comparison of 200 HE patients was carried out. The mean of the patient age was (44.78 ± 11.87) years in which the group under treatment was of mean ages (44.33 ± 10.45) years and the placebo group mean ages were (43.33 ± 10.13) years. After comparison, the cases of the group under treatment were 22 (22%) and cases of the placebo group were 47 (47%). There were significantly higher (P = 0.000) HE recurrence in the placebo group as opposed to the group under treatment.*

Conclusion: *For decreasing the recurrence or frequency of HE the use of rifaximin plus lactulose is better than conventional treatment by lactulose only.*

Keywords: *Rifaximin, Hepatic Encephalopathy (HE), Oral, Recurrence and Lactulose.*

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INTRODUCTION:

Over one hundred and seventy million of the population of the world is affected by the dangerous disease of HCV (Hepatitis C Virus) [1]. HE shows a range of reversible and transient psychiatric and neurologic dysfunction of patients having severe diseases of the liver [2]. The hospitals are filled with 30 to 45% of the patients suffering from liver diseases [3]. Long-term policies are focused on the reduction and elimination of ammonia (gut-derived) as well as to raise the environment to prevent HE. Bacteria of the colon digest the lactulose (which is a synthetic disaccharide non-absorbable syrup) and fatty acids are short-chained to acidify the colon contents. As a result of acidification, ammonium ion is formed in NH4NH3 + H+ equation; NH3 is neurotoxic and absorbable whereas NH4+ is non-absorbable. The intake of lactulose alters the bowl flora resulting in the lesser presence of organisms which form ammonia [1, 2]. In acute situations lactulose is effective but other antibiotics are necessary for a sound cure [4 – 6].

The oral type of antibiotics having complete absorption such as neomycin, vancomycin, metronidazole and paromomycin are taken for decreasing ammonium gut flora but its longer use is not good for ototoxicity, peripheral neuropathy and nephrotoxicity [4]. Without any manifestations, rifaximin decreases the production of ammonia through diminishing bacteria in the colon. A complete evaluation shows that rifaximin is as effective, rather superior, in eliminating symptoms of HE of mild or moderately severe nature, antimicrobials and non-absorbable disaccharides [4 – 6]. Rifaximin is recommended in the small researches and is tolerated very well but a few types of research prove its effectiveness in reducing HE in the long term and no such study is present for the population of Pakistan [4].

A long-term study was undertaken to calculate recurrence or frequency of HE by using rifaximin. The recurrence of HE in the group using rifaximin was 22.1% as opposed to placebo group whose frequency was 45.9%. The HE patients using rifaximin were hospitalized in the percentage 13.6% in contrast to 22.6% of patients of the placebo group (P=0.01) [4].

There are devastating explicit occurrences of HE patients because it happens abruptly and makes the patient unable to take care of himself, that is why the patient is hospitalized. Even if the appearance, of these HE occurrences, seems not to be the reason for liver diseases but the rise in the severity and frequency of such occurrences are predictors of a high death risk [9]. Rifaximin prevents the recurrence of HE promisingly [4, 5]. There is a difference in the habits of taking food as well as gut flora of the population of Pakistan, while compared to its western counterpart, because of various meats consumptions which lead to the production of ammonia [7]. In case our research, of preventing the recurrence of HE by using Rifaximin combined with Lactulose, gives superior results, the rate of mortality due to CLD (Chronic Liver Diseases) may be minimized and the burden on hospitals may be reduced.

Chronic Liver Disease:

A liver of coarse texture and small in size (size<13 cm) was identified by ultrasonography, having additionally; Splenomegaly: spleen size i.e., length > 13cm (by ultrasound), Ascites: positive fluctuating dullness shown through ultrasound and diameter of portal vein >10mm.

Hepatic Encephalopathy:

Conn score evaluated HE through examinations in the clinic and the history of the patient by 0, 1, 2, 3 and 4 with respective explanation of having no behavioral or personality abnormality clinically, disturbance in the pattern of sleeping during day and night as the patient now sleeps more during the day as compared to sleeping at night, the capability of adding or subtracting is damaged as the patient sequentially unable to subtract 7starting from 100, inability to tell time exactly (mostly incorrect in telling exact day of week or of the month, year, month or the season), quivering of hands and explicit changes in personality through medical evaluations, Space disorientation (when the patient is wrong in telling the place or city, it is positive that he is an HE), may response due to a stimulus only and Coma (when the patient does not respond to the hurting provocation or stimulus) When Conn's score is ≥2 the HE is considered positive.

Recurrence:

It is also considered positive when patients of HE shows Conn's score ≥2 who were having Conn's score <2 at the time of discharge, three months before, from the hospital.

MATERIAL AND METHODS:

This research started from January and ended in August 2017 at the Department of Medicine, Jinnah Hospital, Lahore. In this research, a total number of 200 HE patients, regardless of sex, age 20 to 60 years, having at least six months' duration of CLD (Chronic Liver Disease), were considered and divided into two groups: a group of getting treatment patients and a placebo group. The patients of liver transplant were excluded from the study. The existence of precipitants for positive HE (in 90 days gastrointestinal depletion, 3 months earlier than the visit for screening), Difficulty in respiration, Prolonged inadequacy of

renal nature (creatinine level, >2.0mg per deciliter), An electrolyte abnormality (serum sodium level, <125mEqper liter; serum calcium level, >10 mg per deciliter [2.5 mmol per liter]; Inter-current infection, or active spontaneous bacterial peritonitis4). potassium level, <2.5 mmol per litre), or Anemia (haemoglobin level, <8 g per deciliter).

The distribution of patients was random in the placebo and the treatment groups from arbitrary tables with arbitrary statistics. For the patient of the group under treatment, along with Lactulose of 30 to 60 ml in three or two doses in a day, the Rifaximin tab of 550 mg two times a day was advised. The placebo group remained at the conventional prescription of 30 to 60 ml of Lactulose in three or two doses in a day. Each and every patient was cleared from the hospital when their Conn's score of HE was<2. But these patients were tracked for the recurrence of HE on a "yes or no" for a duration of three months. The findings were recorded on an already designed proforma and then the data was examined by SPSS. Percentages and frequencies were determined to categorize data while SD and mean were calculated for the data numerical in nature.

RESULTS:

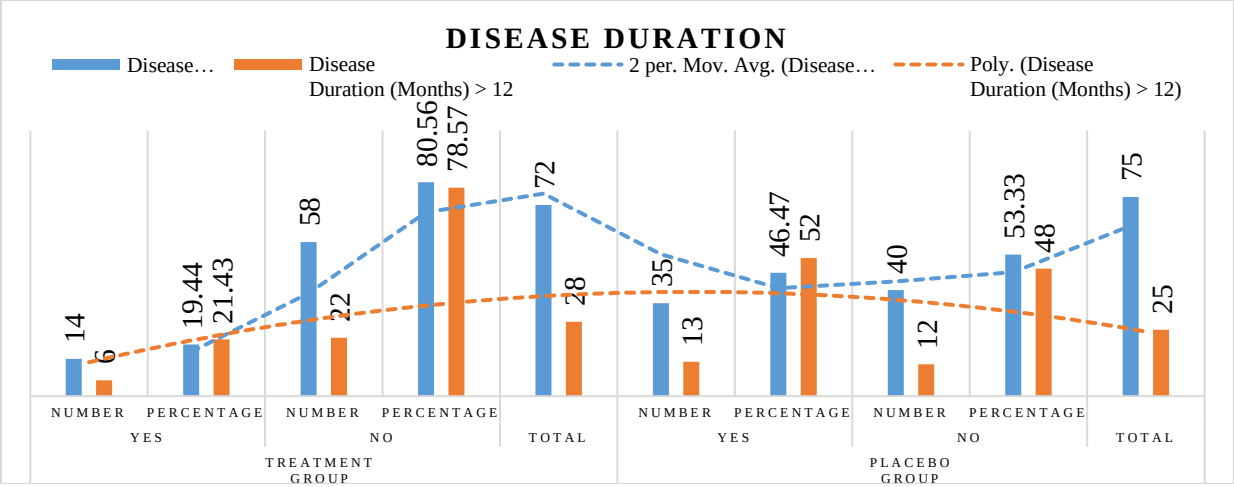
In this research, a total of 200 patients were chosen for comparison of recurrence of hepatic encephalopathy. The mean of the patient age was (44.78 ± 11.87) years in which the group under treatment was of mean ages (44.33 ± 10.45) years and the placebo group mean ages were (43.33 ± 10.13) years. The groups were compared for the recurrence of HE. HE recurrence in the cases of the group under treatment was 22 or twenty-two percent while that of the placebo group was 47 or forty-seven percent cases. The HE recurrence was higher significantly (P = 0.000) in the group considered as a placebo by comparing it with the group under treatment. In HE groups, during the period of six to twelve months, the recurrence of HE in the group under treatment was 14 (19.44%) cases while that of the placebo group was 35 (46.47%) cases. There was a significant difference in recurrence statistically amid the group under treatment and the placebo group (P = 0.000). The recurrence of HE in the group under treatment was 6 (21.43%) cases while that of the placebo group was 13 (52%) cases and there was significant difference statistically (P = 0.025). The data were classified according to ages. In the ages ranging from 20 to 30 years, the group under treatment was having HE recurrence of 5 (26.32%) while the placebo group HE recurrence was 20(50%) but statistically, it was not a significant difference (P = 0.190). In the ages ranging from 41to 50 years, the group under treatment was having HE recurrence of 5 (26.32%) while the placebo group HE recurrence was 25 (41.67%) and statistically it was a significant difference (P = 0.020). The male patients in the placebo group showed higher recurrence of HE (45.45% vs 21.92%) and there was a significant difference (P = 0.000). in the patients of the female sex, the recurrence rate in the group under treatment was 5 (18.82%) patients and 13 (43.75%) patients of the placebo group and there was a significant difference (P = 0.013).

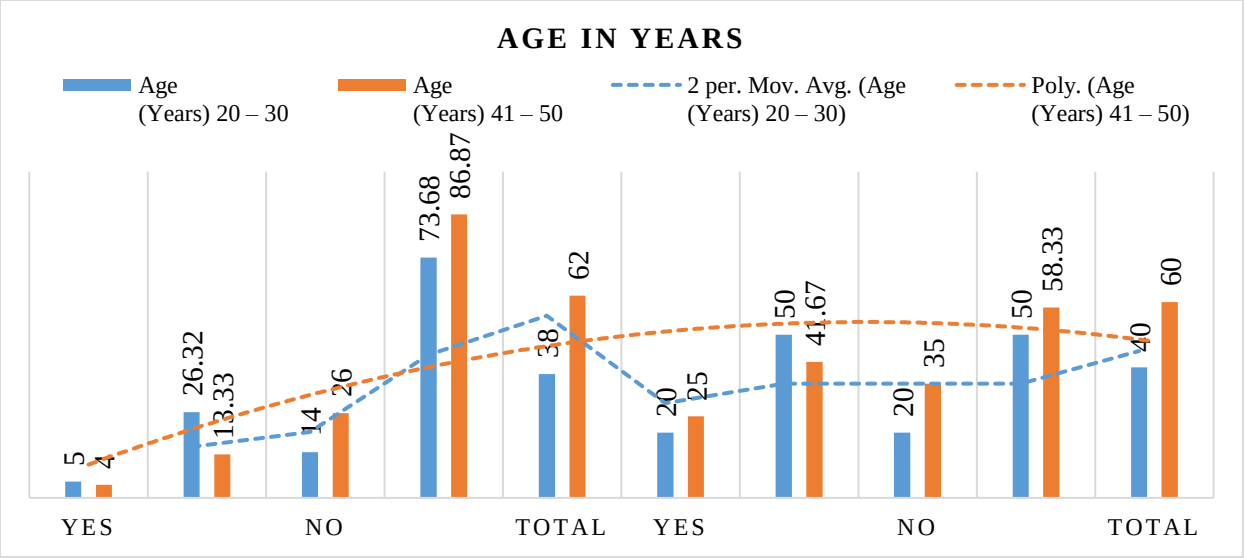
Table – I: Group Wise HE Recurrence

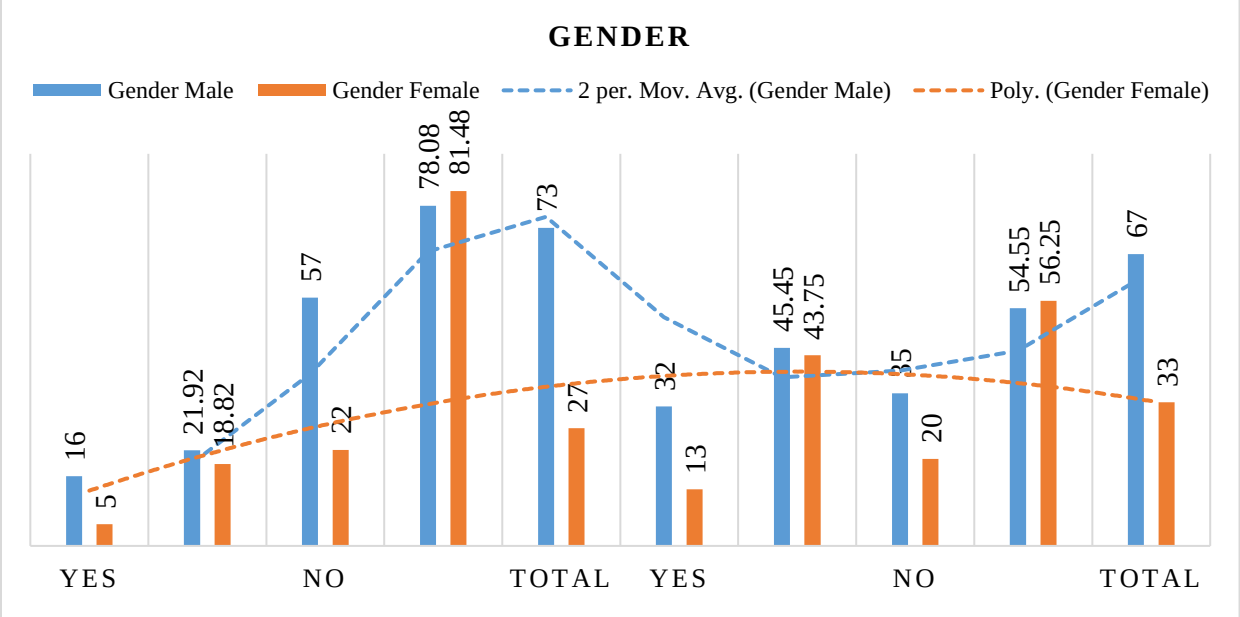
HE Recurrence	Yes	No	P-Value
Treatment Group	22	78	0.000
Placebo Group	47	53	

Table – II: HE Recurrence with respect to Gender, Age and Disease Duration

HE Recurrence			Disease Duration (Months)		Age (Years)		Gender	
			6 – 12	> 12	20 – 30	41 – 50	Male	Female
Treatment Group	Yes	Number	14	6	5	4	16	5
		Percentage	19.44	21.43	26.32	13.33	21.92	18.82
	No	Number	58	22	14	26	57	22
		Percentage	80.56	78.57	73.68	86.87	78.08	81.48
	Total		72	28	38	62	73	27
Placebo Group	Yes	Number	35	13	20	25	32	13
		Percentage	46.47	52	50	41.67	45.45	43.75
	No	Number	40	12	20	35	35	20
		Percentage	53.33	48	50	58.33	54.55	56.25
	Total		75	25	40	60	67	33
P-Value			0.000	0.025	0.190	0.020	0.000	0.013







DISCUSSION:

In this research, a total of 200 patients were chosen for comparison of recurrence of hepatic encephalopathy. The groups were compared for the recurrence of HE. HE recurrence in the cases of the group under treatment was 22 or twenty-two percent while that of the placebo group was 47 or forty-seven percent cases. The HE recurrence was higher significantly (P = 0.000) in the group considered as a placebo by comparing it with the group under treatment. A long-term study was undertaken to calculate recurrence or frequency of HE by using rifaximin. The recurrence of HE in the group using rifaximin was 22.1% as opposed to placebo group whose frequency was 45.9%. The HE patients using rifaximin were hospitalized in the percentage 13.6% in contrast to 22.6% of patients of the placebo group (P=0.01) [4].

A multicenter published a study 2010 explaining that Rifaximin has established itself effective in preventing recurrence of HE [10]. The patients had two occurrences of HE was given Rifaximin or categorized in the placebo group and kept under observation for six months. Most of the patients about (90%) were given Rifaximin along with lactulose and other (10%) in the placebo group. The Rifaximin group was able to save itself from the recurrence of HE in a more effective manner (having less adverse effects and more

tolerability) than the placebo group. It is probable that in the future Rifaximin will lead the treatment of recurrence of HE [10].

Presently, lactulose is practised as the most effective treatment for HE although Rifaximin debate is continued. Patients having, HE recurrence, 299 in number, were given Rifaximin and the placebo group, Rifaximin was more effective. The 550 mg dose two times a day of Rifaximin decreased the risk of recurrence HE (HR 0.42; 95% CI [0.250-0.64]) and the risk to be hospitalized because of HE recurrence (HR 0.50; 95% CI [0.29 – 0.87]). Lactulose of baseline was given to 90% of the HE patients and the 10% were without lactulose. In the without lactulose group, the use of Rifaximin was unable to bring any changes. Rifaximin has proved to positive results and it is tolerated well [11].

At present, lactulose with Rifaximin is the most issued prescription. Sharma in his study showed that Rifaximin with lactulose is better than simple lactulose. In Sharma research 120 HE patients were observed (>80%grade 3 or 4) having Rifaximin plus lactulose or only lactulose. Baseline Child-Pugh was mainly Class B and C and Mean MELD was (24.5 ± 4.2). Among them, 55 patients already faced a recurrence of HE and were under treatment. The patients suffering from recurrence of HE in ten days' duration (76% vs. 44% lactulose alone; p = 0.004) [12].

There are many types of research that prove Rifaximin in combination with lactulose as best tolerated and better treatment than lactulose alone. Nevertheless, due to the absence of proof to use Rifaximinas only treatment of HE as Rifximin is costlier than lactulose. The data which is accessible and the latest policies AASLD, lactulose is recommended as the sole treatment of recurrence of HE while Rifaximin is used as an add-therapy [13 – 14].

A trial (double-blind, prospective, controlled and randomized) of 94 HE patients was conducted. In eight weeks, duration, two Rifaximin 200 mg tablets (400 mg) 3 times in a day to the group under treatment (n= 49) the placebo group (n=45) was not given Rifaximin. Eight weeks' duration, primary result was reverse of the definition of HE that it decreases the abnormal NP tests mean number. The secondary result was in reverse to two weeks of HE and SIP score improvement in eight weeks. In a comparison of baseline for two and eight weeks, Rifaximin was able to decrease the abnormal NP scores mean number [15].

A trial (double-blind, prospective, controlled and randomized) of 120 HE patients were compared, with Rifaximin 400mg thrice a day with lactulose two times a day in 30-60 ml (n=63) with lactulose two times a day in 30-60 ml (n=57) for judging the safety and efficacy of both therapies versus single therapy for HE treatment. These patients had lactulose before as a treatment or as a prophylactic therapy using lactulose presently. The West Haven criteria showed that primary result was in reverse to episodes of HE while the secondary result shows the duration of hospitalization and mortality. The more patients belonging to the mixed group while comparing with lactulose had HE reversal (76% vs.44%, p=0.004) [16].

CONCLUSION:

We showed that to decrease the recurrence or frequency of HE, the use of Rifaximin plus lactulose is better than conventional treatment by lactulose only. It is, therefore, recommended that Rifaximin plus Lactulose may be utilized as a primary method of treatment for the prevention of recurrence of hepatic encephalopathy.

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