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Research Article

Comparison of Lactulose versus Lactitol in Patients with Acute Hepatic Encephalopathy (HE)

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ABSTRACT

Background*:* Hepatic encephalopathy (HE), a syndrome observed in some patients with cirrhosis, with depressed level of consciousness. Lactulose as well as lactitol has been used in the treatment of HE. Lactitol is comparable to lactulose in the treatment of HE with fewer side effects and better tolerated. However, literature showed equal efficacy of both drugs. So we conducted this trial to find better drug to implement its use in future.
Objective: To compare the effectiveness of lactulose and lactitol in patients with acute hepatic encephalopathy.
Study Design: Randomized Controlled Trial
Duration of study: 6 months
Place: Department of Medicine OPD and Emergency (East, West, North, South), Mayo Hospital, Lahore
Patients & Methods: 570 patients were included through non-probability, consecutive sampling after informed consent. Initial grade of HE was assessed and patients were randomly divided in two groups by using lottery method i.e. lactulose or lactitol. Patients were admitted to ward for management and kept under observation for 5 days. After 5 days, HE grades was measured again, then improvement in grade of HE (effectiveness) was measured. All data was entered and analyzed by using SPSS version 21.0. Chi-square was applied to compare both groups for effectiveness taking p-value≤0.05 as significant.
Results: In this study the mean age of the patients was 44.22 ±11.81 years, the male to female ratio of the patients was 2.4:1. The mean duration of the cirrhosis of the patients was 3.73±1.61 months. In our study the effectiveness was achieved in 538 (94.39%) patients, out of which 263 cases were from lactulose group and 275 were from lactitol group and the difference was significant (p<0.0.5).
Conclusion: Our study results concluded that Lactitol is better choice for the treatment of patients with acute hepatic encephalopathy as compared to lactulose. More efficacy was achieved in lactitol group patients than in lactulose group patients.

Keywords: Lactulose, Lactitol, Cirrhosis, Hepatic Encephalopathy,

INTRODUCTION:

Cirrhosis is defined as the end result of hepatocellular injury resulting in fibrosis and nodular regeneration of liver.[1] Cirrhotic liver is becoming more and more prevalent in our country due to the increasing incidence of Hepatitis C.[2] Prevalence of cirrhosis in Pakistan is 234,112 people.[3] Hepatic encephalopathy (HE) affects up to 80% of the cirrhotic patients.[4] HE is a condition associated with disordered central nervous system function resulting from failure of the liver to detoxify noxious agents of gut origin because of

hepatocellular dysfunction and portosystemic shunting.[1]

Pathogenesis of HE in cirrhosis is complex, however there is a consensus that ammonia is a key toxin in HE, which may sensitize the brain to different precipitating factors.[5,6]

Lactulose is the most commonly utilized non-absorbable disaccharide for HE. Lactulose (1:4, B-galactosido-fructose), a synthetic disaccharide, is comprised of the monosaccharide lactose and galactose, and is available as syrup. Doses are generally titrated to achieve two to four semi-soft stools daily, with typical doses of 20 g/30mL orally three to four times per day. A second non-absorbable disaccharide, lactitol (B-galactosido-sorbitol), has also been used in the treatment of HE. It is a disaccharide analog of lactulose which is neither absorbed nor broken down in the small intestine, but is extensively metabolized by colonic bacteria. It is available in a highly soluble crystalline powder form. Clinical trials have reported lactitol dosages of 10-12 g every 6 hours, titrated to two bowel movements daily to be effective in treatment of HE.[7]

Lactitol is comparable to lactulose in the treatment of HE with fewer side effects. Lactitol is better tolerated and more palatable because of its more pleasant taste, moreover cathartic effect is more predictable.[8]

In a study lactitol was considered more palatable.[9] While Heredia et al. reported that complete clinical resolution of HE occurred in 5 (25%) patients given lactulose and in 6 (30%) cases given lactitol. These results indicate that lactitol is as effective as lactulose in the management of HE.[10]

Another study reported that favorable response to treatment was obtained in 19 (86%) of the patients receiving lactitol and in 14 (78%) of those receiving lactose.[11]

Rationale of this study is to compare the effectiveness of lactulose v/s lactitol in patients with acute hepatic encephalopathy. It has been observed in literature that lactitol and lactulose, both have equal effectiveness in terms of resolution of symptoms, but one study had showed that lactitol has more benefits as compared to lactulose. There is no local study available, so we have designed this study to see that which is the most effective drug for resolution of HE in cirrhotic patients and also to resolve the disparity as observed in literature.

MATERIAL AND METHODS:

This randomized clinical trial conducted at Department of Medicine, Mayo Hospital, Lahore for 6 months after the approval of synopsis from the hospital ethical review committee. Sample size of 570 (285 patients in each group) was calculated with 80% power of test, 5% level of significance and expected percentage of effectiveness i.e. 86% with lactitol and 78% with lactulose in HE patients. 570 cirrhotic patients (cirrhosis for $\geq$6 months) of 15-65 years age of both genders with clinical diagnosis of hepatic encephalopathy and with history of drowsiness were included through non-probability, consecutive sampling and written informed consent was taken. Patients with neuropsychiatric problems due to causes other than hepatic cirrhosis (on medical record) like uremic encephalopathy (eGFR <30ml/min/1.73m^2 and ultrasonography showing echogenic kidneys), septicemia (TLC <4000 or >11,000/ul ,hypo or hyperthermia, tachycardia, tachypnea) and those with other systemic problems like diabetes and cardiac problems (abnormal ECG) on previous medical record were excluded. Patients were labeled having cirrhosis when coarse echo texture of liver is seen on ultrasound abdomen for at least 6 months. Acute hepatic encephalopathy was defined when these cirrhotic patients presented with a compliant of drowsiness < 24 hours (GCS < 8/15) with West Haven criteria score $\geq$ 1 grade. After accessing the initial grade of HE, patients were randomly divided in two groups by using lottery method i.e. lactulose (30 ml/day) or lactitol (12 g/day) for treatment. Demographic data like name, age, gender and address was noted. Patients were admitted in the ward for management of HE as per protocol. One group was given lactulose and the other group lactilol and was kept under observation for 5 days for improvement of

symptoms and grade of HE. Effectiveness was measured after 5 days of start of initial treatment by using West Haven criteria[12] i.e. improvement in grade of the patient was labeled as effectiveness. All data was collected on a predesigned proforma and later entered and analyzed by using SPSS version 21.0. Numerical variables like age was represented as mean±SD and categorical variable like gender and effectiveness was expressed as frequency and percentages. Chi-square was applied to compare both groups taking p-value≤0.05 as significant. Data was stratified for age, gender, grade of HE, duration of cirrhosis to deal with effect modifiers. Post-stratification chi-square test was applied. p-value ≤0.05 was considered as significant.

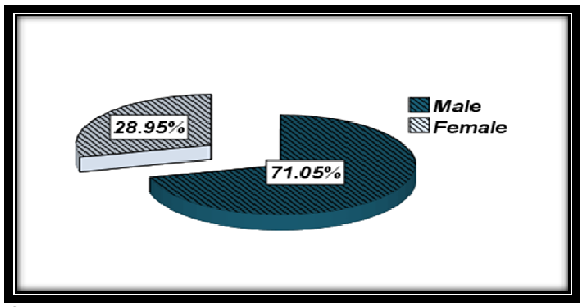
RESULTS:

In this present study total 570 cases were enrolled. The mean age of the patients was 44.22±11.81 years with minimum and maximum ages of 25 & 6 years respectively.

Table#1: Descriptive statistics of age (years)

Age (years)	N	570
	Mean	44.22
	SD	11.81
	Minimum	25
	Maximum	65

In this study 71.05% patients were males and 28.95% patients were females. The male to female ratio of the patients was 2.4:1**.**



Fig#1: Frequency distribution of gender

The study results showed that the mean duration of the cirrhosis of the patients was 3.73±1.61 months with minimum and maximum duration of 1 & 7 months respectively.

Table#2: Descriptive statistics of duration of cirrhosis (months)

Duration of cirrhosis	n	570
	Mean	3.73
	SD	1.61
	Minimum	1.00
	Maximum	7.00

The study results showed that before treatment HE two grade was found in 232(40.7%) patients, three grade was found in 168(29.5%) patients and grade four was found in 170(29.8%) patients.

Table#3 :Frequency distribution of HE grade before treatment

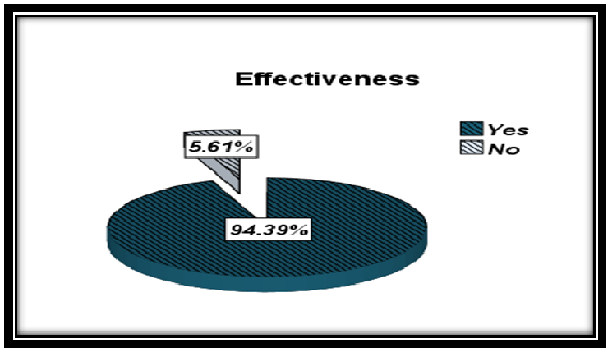
		Frequency	Percent
HE Grade before treatment	Two	232	40.7
	Three	168	29.5
	Four	170	29.8
	Total	570	100.0

In our study zero grade after treatment was observed in 213 (37.4%) patients, one grade was observed in 133(23.3%) patients, two grade was found in 143(25.1%) patients, three was found in 57(10%) patients and four was found in 24(4.2%) patients.

Table#4: Frequency distribution of HE grade after treatment

		Frequency	Percent
HE Grade after treatment	Zero	213	37.4
	One	133	23.3
	Two	143	25.1
	Three	57	10.0
	Four	24	4.2
	Total	570	100.0

In this study the overall effectiveness was achieved in 94.39% patients and it was not achieved in 5.61% patients.



Fig#2: Frequency distribution of effectiveness

The study results showed that the effectiveness was achieved in 538 cases in which 263 cases were from lactulose group and 275 were from lactitol group, similarly the efficacy was not achieved in 32 cases in which 22 were from lactulose group and 10 were from lactitol group. Statistically there is significant difference was found between the study groups and effectiveness of the patients. i.e p-value=0.029

Table#5: Comparison of effectiveness in both study groups

		Study Group		Total	P value
		Lactulose	Lactitol		
Effectiveness	Yes	263	275	538	0.029
	No	22	10	32	
Total		285	285	570	

Chi value=4.77, p-value=0.029 (Significant)

Table#6 Comparison of effectiveness in both study groups stratified by gender

			Study Group		Total	p-value
			Lactulose	Lactitol		
Effectiveness	Male	Yes	190	193	383	0.201
		No	14	8	22	
	Female	Yes	73	82	155	0.044
		No	8	2	10	

In this study in male patients the effectiveness was acheived in 383 cases in which 190 were from lactulose group and 193 were from lactitol group, similarly in female patients the effectiveness was achieved in 155 cases in which 73 cases were from lactulose group and 82 were from lactitol group. Statistically there is significant difference was found between the study groups and effectiveness in female patients. i.e p-value=0.044 (**Table#6)**

In our study in below 4 months cirrhosis duration patients the effectiveness was aceived in 356 cases in which 184 cases were from lactulose group and 172 were from lactitol group, similarly in above 4 months cirrhosis duration patients the effectiveness was achieved in 79 cases in which 103 cases were from lactulose group and 82 were from lactitol group. Statistically there is significant difference was found

between the study groups and effectiveness in below 4 months cirrhosis duration patients. i.e p-value=0.05 **Table#7**

In our study in patients with HE grade before treatment, the effectiveness in grade two HE patients was achieved in 231 cases in which 117 cases were from lactulose group and 114 were from lactitol group, the effectiveness in three HE grade was found in 161 cases, similarly the effectiveness in grade four HE patients was achieved in 146 cases in which 61 cases were from lactulose group and 85 were from lactitol group. Statistically there is significant difference was found between the study groups and effectiveness in before treatment HE grade four patients. i.e p-value=0.008 **Table#8**

The study results showed that in patients with HE grade after treatment, the effectiveness in grade two HE patients was achieved in 142 cases in which 61 cases were from lactulose group and 81 were from lactitol group, similarly the effectiveness in grade three HE patients was achieved in 50 cases in which 18 cases were from lactulose group and 32 were from lactitol group. Statistically there is insignificant difference was found between the study groups and effectiveness in after treatment HE grades. i.e p-value=0.43 & 0.411 respectively (**Table#9**)

Table#7: Frequency distribution of effectiveness in accordance with study groups stratifying by cirrhosis duration

Effectiveness			Study Group		Total	p-value
			Lactulose	Lactitol		
Duration of cirrhosis	Below 4	Yes	184	172	356	0.05
		No	16	6	22	
	Above 4	Yes	79	103	182	0.30
		No	6	4	10	

Table#8: Frequency distribution of effectiveness in accordance with study groups stratifying by HE grade before treatment

Effectiveness			Study Group		Total	p-value
			Lactulose	Lactitol		
HE Grade before Treatment	Two	Yes	117	114	231	0.50
		No	1	0	1	
	Three	Yes	85	76	161	0.56
		No	4	3	7	
	Four	Yes	61	85	146	0.008
		No	17	7	24	

Table#9: Frequency distribution of effectiveness in accordance with study groups stratifying by HE grade after treatment

Effectiveness			Study Group		Total	p-value
			Lactulose	Lactitol		
HE Grade after treatment	Two	Yes	61	81	142	0.43
		No	1	0	1	
	Three	Yes	18	32	50	0.411
		No	4	3	7	

DISCUSSION:

This present randomized control trial was conducted at Department of Medicine OPD and Emergency, Mayo Hospital, Lahore to compare the effectiveness of lactulose v/s lactitol in patients with acute hepatic encephalopathy.

Hepatic encephalopathy (HE) is one of the major complications of liver cirrhosis. It has a considerable socioeconomic impact as it reduces the individual's quality of life and needs repeated admission in hospital for its treatment. Lactulose is the most commonly utilized non-absorbable disaccharide for HE

In our study the overall efficacy was achieved in 538(94.39%) patients in which 263 cases were from lactulose group and 275 were from lactitol

group, similarly the efficacy was not achieved in 32 cases in which 22 were from lactulose group and 10 were from lactitol group. Statistically there is significant difference was found between the study groups and effectiveness of the patients. i.e p-value=0.029. Our study result showed that lactitol is more efficacious as compared to lactulose group. Some of the studies are discussed here in support of our findings and few are in contrary as.

Marsha Y et al resulted in their study that at the end of the trial, 67% of the patients in the lactitol group and 69% of the lactulose group were clinically normal. However, patients treated with lactitol responded significantly more quickly than patients treated with lactulose.[9]

A study by Uribe M et al showed that favorable response to treatment was obtained in 19 (86%) of the patients receiving lactitol enemas and in 14 (78%) of those receiving lactose enemas. They concluded that acidifying agents like lactose and lactitol are effective and superior to tap water enemas for the treatment of acute nitrogenous portal-systemic encephalopathy.[11]

One study enrolled 53 patients with acute hepatic encephalopathy which were treated with lactitol 60g/day for 5-10 days concluded lactitol to be effective in 81% of patients.

A metaanalysis by Camma et al showed that lactitol was as effective as other disaccharides in the treatment of encephalopathy: pooled odds ratio was 0.83, 95% confidence interval was 0.38-1.82.[13]

Pai et al demonstrated in their study that both lactitol and lactulose are effective in the treatment of PSE, though the effect of lactitol seems slightly superior to that of lactulose in our study. Lactitol is more acceptable to our patients due to better palatability and less side effects. Lactitol is another good alternative in the treatment of PSE.[14]

Pierre Blanc in 1992 described that no statistical difference between therapeutic effects of lactitol and lactulose, but it does show a higher frequency of flatulence with lactulose. This suggests that lactitol should be preferred to lactulose for the treatment of chronic HE.[15]

On contrary the study conducted by D. Heredia et al in 1987 showed that no side effects attributable to therapy were observed in either group. The results indicate that lactitol is as effective as lactulose in the management of patients with cirrhosis and acute PSE.[10]

Dr. Oliviero Riggio et al conclude in their study that lactitol is as effective as lactulose in the long-term prevention of episodes of HE in cirrhotics with portal-systemic shunt and may be better tolerated.[16]

Heredia et al. reported that complete clinical resolution of HE occurred in 5 (25%) patients given lactulose and in 6 (30%) cases given lactitol. These results indicate that lactitol is as effective as lactulose in the management of HE.[10]

CONCLUSION:

Our study results concluded that Lactitol is better choice for the treatment of patients with acute hepatic encephalopathy as compared to lactulose. More efficacy was achieved in lactitol group patients than in lactulose group patients. Now in future, we can implement the use of lactitol instead of lactulose for management of HE.

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