



LACTULOSE VERSUS LACTITOL IN ACUTE HEPATIC ENCEPHALOPATHY (HE).

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Article received on:

15/10/2019

Accepted for publication:

25/12/2019

INTRODUCTION

The end result of hepatocellular injury resulting in fibrosis and nodular regeneration of liver is called Cirrhosis.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

ABSTRACT... 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. **Setting:** Department of Medicine OPD and Emergency (East, West, North, South), Mayo Hospital, Lahore. **Period:** 6 Months June 2017 to Dec 2017. **Material & 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 $p\text{-value} \leq 0.05$ 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 ($p < 0.05$). **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.

Key words: Cirrhosis, Hepatic Encephalopathy, Lactulose, Lactitol.

Article Citation: Rasool S, Azhar S, Munir T, Ahmad MS, Akhtar S, Abbas R, Ahsan M. Lactulose versus lactitol in acute hepatic encephalopathy (HE). Professional Med J 2020; 27(8):1595-1601. DOI: 10.29309/TPMJ/2020.27.08.4245

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}

The most utilized non-absorbable disaccharide for HE is Lactulose.(1:4, B-galactosido-fructose) Lactulose, a synthetic disaccharide, is comprised of the monosaccharide lactose and galactose, and is available as syrup. Doses are generally titrated with typical doses of 20 g/30mL orally three to four times per day to achieve two to four semi-soft stools daily. A second non-absorbable disaccharide has also been used in the treatment of HE which is lactitol (B-galactosido-sorbitol), It is a disaccharide analog of lactulose which is

extensively metabolized by colonic bacteria in the small intestine. But neither absorbed nor broken down. It is accessible in a profoundly dissolvable crystalline powder Form. Clinical preliminaries have detailed lactitol to be an effective in treatment of HE with dosage of 10-12 g every 6 hours, titrated to two bowel movements daily.⁷

Lactitol has fewer side effects in the treatment of HE compared to lactulose. It 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 thorough clinical resolution of HE occurred in 5 (25%) patients given lactulose and in 6 (30%) cases given lactitol. These outcomes demonstrate that in the administration of HE lactitol is as compelling as lactulose.¹⁰

Another examination revealed that good reaction to treatment was gotten for 19 (86%) patients getting lactitol and in 14 (78%) of those accepting lactose.¹¹

Basis of this study is to compare the viability of lactulose v/s lactitol for acute hepatic encephalopathy among patients. 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 & METHODS

After the approval of synopsis from the hospital ethical review committee a randomized clinical trial was conducted for 6 months at Department of Medicine, Mayo Hospital, Lahore. size of the sample was 570 (285 patients per 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 >6 months) of 15-65 years age of both genders with clinical diagnosis of hepatic encephalopathy and with history of drowsiness were incorporated through non-probability, consecutive sampling and written assent was taken. Patients with neuropsychiatric problems due to causes other than hepatic cirrhosis (on medical record) like uremic encephalopathy (eGFR <30ml/min/1.73m² 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 isolated in two gatherings by utilizing lottery technique 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 lactitol 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 criteria¹² i.e. improvement in grade of the patient was labeled as effectiveness.

Data collected on predesigned proforma was closely handled SPSS 20. Numerical variables like age was represented as mean \pm 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 \leq 0.05 as significant. Data was characterized 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

570 cases were enrolled in this present study. 44.22 ± 11.81 years was the mean age of the patients with least and most extreme ages of 25 and 65 years respectively. Table-I

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

Table-I. Descriptive statistics of age (years).

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

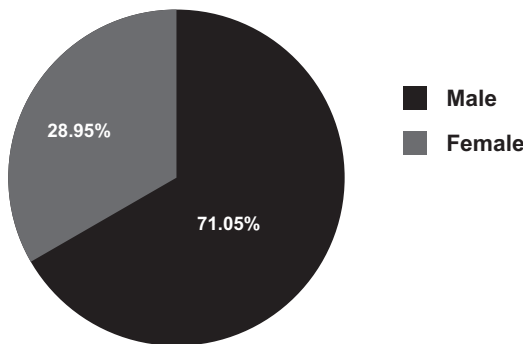


Figure-1. Frequency distribution of gender.

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

Table-II. Descriptive statistics of duration of cirrhosis (months).

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-III

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

Table-III. Frequency distribution of HE grade before treatment.

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

		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

Table-IV. Frequency distribution of HE grade after treatment.

In this examination the general effectiveness was accomplished in 94.39% patients and it was not accomplished in 5.61% patients.

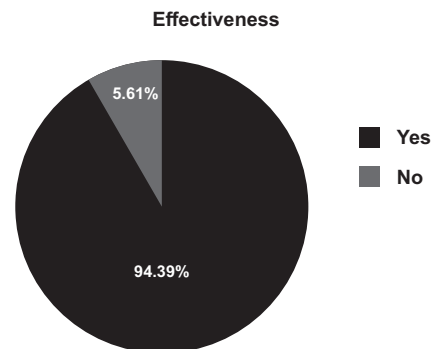


Figure-2. Frequency distribution of effectiveness.

The study results demonstrated that effectiveness was accomplished in 538 cases, 263 cases of lactulose group and 275 of lactitol group, comparably the adequacy was not accomplished in 32 cases, 22 from lactulose group and 10 of lactitol group. There is noteworthy distinction

found statistically between the study groups and effectiveness of the patients. i.e p-value=0.029. Table-V

		Study Group		Total	P-Value
		Lactu-lose	Lactitol		
Effective-ness	Yes	263	275	538	0.029
	No	22	10	32	
Total		285	285	570	

Table-V. Comparison of effectiveness in both study groups.
Chi value=4.77, p-value=0.029 (Significant).

		Study Group		Total	P-Value	
		Lactu-lose	Lactitol			
Effective-ness	Male	Yes	190	193	383	0.201
		No	14	8	22	
	Female	Yes	73	82	155	0.044
		No	8	2	10	

Table-VI. Comparison of effectiveness in both study groups stratified by gender.

In this study among male patients the viability was achieved in 383 cases, 190 of them were lactulose group and 193 of lactitol group, while in female patients the effectiveness was accomplished in 155 cases, 73 cases were of lactulose group and 82 were of lactitol group. Noteworthy distinction was found statistically between the investigation groups and effectiveness in female patients. i.e p-value=0.044 Table-VI.

In our study in below 4 months cirrhosis duration

the effectiveness was achieved in 356 cases, 184 of them were of lactulose group and 172 of lactitol group, comparably in over 4 months cirrhosis term patients the viability was accomplished in 79 cases, 103 cases from lactulose group and 82 of lactitol group . Factually huge contrast was found between the examination groups and effectiveness in below 4 months cirrhosis duration patients. i.e p-value=0.05 Table-VII.

In the study of patients with HE grade before treatment, the effectiveness in grade two HE patients was accomplished in 231 cases, 117 cases from lactulose group while 114 from lactitol group, In 161 cases the effectiveness in grade three HE was found, similarly the effectiveness in grade four HE patients was accomplished in 146 cases, 61 cases of lactulose group and 85 of lactitol group. There is noteworthy contrast found between the study groups and effectiveness in before treatment HE grade four patients. i.e p-value=0.008 Table-VIII.

The study results demonstrated that in patients with HE grade after treatment, the effectiveness in grade two HE patients was accomplished in 142 cases, 61 cases of lactulose group and 81 of lactitol group, similarly the effectiveness in grade three HE patients was accomplished in 50 cases, 18 of lactulose group and 32 of lactitol group. There is no noteworthy contrast statistically found between the study groups and effectiveness in after treatment HE grades. i.e p-value=0.43 & 0.411 respectively Table-IX.

Effectiveness		Study Group		Total	P-Value
		Lactulose	Lactitol		
Duration of cirrhosis	Below 4	Yes	184	172	0.05
		No	16	6	
	Above 4	Yes	79	103	0.30
		No	6	4	

Table-VII. Frequency distribution of effectiveness in accordance with study groups stratifying by cirrhosis duration.

Effectiveness		Study Group		Total	P-Value
		Lactulose	Lactitol		
HE Grade before Treatment	Two	Yes	117	114	0.50
		No	1	0	
	Three	Yes	85	76	0.56
		No	4	3	
	Four	Yes	61	85	0.008
		No	17	7	

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	

Table-IX. Frequency distribution of effectiveness in accordance with study groups stratifying by HE grade after treatment.

DISCUSSION

The trial was directed at Department of Medicine OPD and Emergency, Mayo Hospital, Lahore to look at the viability of lactulose v/s lactitol in patients with acute hepatic encephalopathy.

One of the intricacies of liver cirrhosis is Hepatic encephalopathy (HE). It has an extensive financial effect as it reduces the individual's personal life quality and it becomes a necessity for the patient to be admitted to the hospital for treatment regularly. For HE, lactulose is the most generally used non-absorbable disaccharide.

In our study, overall efficacy was achieved in 538(94.39%) patients in which 263 cases were from lactulose group and 275 were from lactitol group, likewise the efficacy was not possible in 32 cases, 22 were from lactulose group and 10 were from lactitol group. Measurably essential differentiation was found between the assessment groups and effectiveness of the patients. i.e p-value=0.029. Our result's demonstrated that lactitol is more efficacious as related to lactulose. A portion of the studies considered here are in support and while few are contrary of our findings.

Marsha Y et al brought about their investigation that toward the conclusive part of the arrangement, The patients in the lactitol gathering about 67% and from lactulose gathering about 69% were clinically in good health. In any case, the patients that were administered with lactulose reacted altogether quite sluggishly than the patients that were administered with lactitol.⁹

A Study by Uribe M et al demonstrated it showed that a great reaction to treatment was obtained from the patients receiving lactitol and lactose enemas ie 19 (86%) patients treated with lactitol

and 14 (78%) patients treated with lactose. They reasoned that acidifying agents like lactose and lactitol are compelling and better for the treatment of acute nitrogenous portal-systemic encephalopathy than faucet water enemas.¹¹

53 patients with acute hepatic encephalopathy were enrolled in one study, for 5-10 days they were treated with lactitol 60g each day, In 81% of patients lactitol was found to be compelling.

Camma et al demonstrated in the investigation that encephalopathy treated by lactitol turned out to be as successful as various disaccharides: pooled chances proportion was 0.83, 95% confidence interval was 0.38-1.82.¹³

Pai et al exhibited in their Study that lactitol and lactulose are successful 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

In 1992 Pierre Blanc portrayed that no quantifiable differentiation between helpful impacts of lactitol and lactulose, yet it demonstrates a higher repeat of flatulence with lactulose. This recommends lactitol ought to be required than lactulose for the treatment of chronic HE.¹⁵

On contrary the study directed by D. Heredia et al in 1987 demonstrated that no reactions owing to treatment were seen in either gathering. In the administration of patients with cirrhosis and acute PSE the outcomes demonstrate lactitol is as successful as lactulose.¹⁰

Dr. Oliviero Riggio et al deduced in their study that

lactitol may be better endured and for the long haul aversion of Episodes of HE in cirrhotics with Portal-Systemic Shunt is as viable as lactulose.¹⁶

Heredia et al. reported that thorough clinical constancy of HE occurred in 5 (25%) patients given lactulose and in 6 (30%) cases given lactitol. In the association of HE outcomes exhibit that lactitol is as viable as lactulose.¹⁰

CONCLUSION

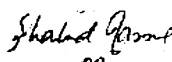




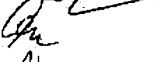
Our study results concluded that compared to lactulose the better decision for the treatment of patients with acute hepatic encephalopathy is Lactitol. More efficacy was achieved in lactitol group patients than in lactulose group patients. Now in future, we can implement the use of lactitol instead of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

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5	M. Saeed Akhtar	Data collection, Paper writing.	
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