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ORIGINAL ARTICLE

A Study on the Role of Lactulose on Hepatic Encephalopathy Among Cirrhotic Patients with Acute Upper Gastrointestinal Bleeding

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ABSTRACT

Aim: To determine the efficacy of lactulose as prophylaxis on hepatic encephalopathy among cirrhotic patients of acute upper gastrointestinal bleeding.

Material and methods: We carried out this randomized control trial in multi centers including Mian Rashid Hussain Shaheed Memorial Hospital Pabbi Nowshera. KPK and Isra University Hospital, Hyderabad from February 2022 to July 2022 (06 months) with total no of 80 patients. Group A patients received lactulose while group B patients received sweet syrup placebo. Both groups were assessed for Hepatic encephalopathy as primary outcome. Chi Square test was used for assessment of outcomes between both groups keeping P value < 0.05 as statistically significant.

Results: Eighty patients were divided into two groups equally using lottery method. Group A patients received lactulose treatment while group B patients received placebo. The mean age in group A was 44.36±15.37 years while the mean age in group B was 38.71±18.56 years. Hepatic encephalopathy was observed in 2.5% patients in group A while in group B 10% patients had HE, the difference was statistically significant. Diarrhea, abdominal pain and mortality between both groups were no statistically significant.

Conclusion: Lactulose is effective in preventing hepatic encephalopathy in patients with cirrhosis and an acute upper gastrointestinal bleeding.

Keywords: Lactulose, hepatic encephalopathy, cirrhosis, acute upper gastrointestinal bleeding

INTRODUCTION

It is conceivable for patients with severe liver dysfunction to recover from a syndrome known as hepatic encephalopathy (HE). A range of neuropsychiatric disorders caused by neurotoxic chemical buildup in the circulation characterizes the condition [1]. Typical manifestations include a lowered state of awareness along with symptoms like muddled thinking, personality shifts, and disorientation. In the first stages, patients frequently exhibit an inverted sleep-wake pattern, in which they sleep during the day and remain up at night [2]. Patients typically show a worsening of disorientation, tiredness, and behavioral abnormalities throughout the middle stages. Hepatic encephalopathy can cause unconsciousness and perhaps even death in its latter stages [3].

Renal failure, bleeding from the gastrointestinal tract, constipation, infection, medication non-compliance, high protein intake in the diet, dehydration, electrolyte imbalance, alcohol consumption, and the use of certain sedatives, analgesics, or diuretics can all lead to HE [4]. Hepatic encephalopathy is a rare but serious complication of a trans-jugular intrahepatic portosystemic shunt [5].

Through its effects on brain edema and astrocyte dysfunction, excess plasma ammonia contributes to the onset of HE [6]. As a result, the majority of HE treatments now aim to either stop the body from producing HE or speed up its disposal. Lactulose, a non-absorbable disaccharide, is useful for treating HE and preventing further episodes [7]. In addition to its laxative effects, lactulose has prebiotic effects because its metabolites, acidify the gut lumen, which reduces intestinal ammonia absorption and promotes non-ammonia genic lactobacilli [8].

Esophageal varices are common in cirrhotic patients and are prone to bleeding. Nearly 80% of cirrhotic patients, according to an endoscopic research, reported with acute upper gastrointestinal bleeding due to the varices [9]. Patients with cirrhosis who develop HE after AUGIB have a bad prognosis [10]. Bleeding is one of the most common cause of HE, and triggers a rise with in intestinal absorption of hazardous chemicals such as ammonia [7]. Therefore, gastrointestinal irrigation has been employed for blood loss prevention. On the other hand, this tactic is not advocated and rarely implemented outside of experimental settings [11].

Gastrointestinal bleeding has indeed been determined to be the most common precipitating factor of HE in patients with chronic liver disease. Current regulations cannot definitively state suitable strategies for preventing HE after AUGIB in patients with cirrhosis due to a dearth of adequate evidence. Therefore, this study was carried out to determine the efficacy of lactulose as prophylaxis against hepatic encephalopathy in cirrhotic patients with acute upper gastrointestinal bleeding**.**

MATERIAL AND METHODS

This randomized controlled trial was conducted in multi centers including Mian Rashid Hussain Shaheed Memorial Hospital Pabbi Nowshera. KPK and Isra Univeristy Hospital Hyderabad from February 2022 to July 2022 (06 months). After taking ethical approval from the hospital's ethical committee we enrolled 80 patients presenting with liver cirrhosis with AUGIB. Clinical observations, laboratory results, ultrasound pictures, CT scan results, and liver histology, if available, were used to make the diagnosis of cirrhosis. On endoscopy, the acute UGB diagnosis was confirmed. Patients under 18 years of age and over 60 years of age, pregnant women, patients who had taken lactulose since last six days before commencing the study, patients with neurological disorders or previously diagnosed for HE were excluded from the study. Patients were divided in group A Group B equally. Group A received 30 ml of lactulose 2 to 3 times a day while the patients in group B received a sweet syrup like lactulose 2 to 3 times a day. Patients in both groups were observed for passing the stool 2 to 3 times a day. Two senior consultants with more than 20 years of hepatology experience evaluated the HE episode clinically and independently. We selected the West Haven criteria for the evaluation of HE. The primary outcome variable was hepatic encephalopathy while secondary outcomes were diarrhea, abdominal bloating and mortality.

Data was analyzed using IBM SPSS 23. Frequency and percentage were calculated for categorical variables while mean and SD were calculated for numerical variables. Outcome variables were assessed between both groups using Chi Square test keeping P value < 0.05 as statistically significant.

RESULTS

This study was conducted on 80 patients divided in two groups. Group A patients received lactulose treatment while group B patients received placebo. The mean age in group A was 44.36±15.37 years while the mean age in group B was 38.71±18.56 years. Regarding the gender distribution, we found that male gender had a higher prevalence as compared to the female gender. The baseline parameters, hemoglobin, albumin, creatinine and serum potassium in both groups are shown in table 1. Child-pugh score was 8.9±1.2 in group A while 9.1±1.7 in group B.

The primary and secondary outcomes are presented in table 2. We found that hepatic encephalopathy was significantly lower in the lactulose group as compared to the placebo group (P = 0.04). Diarrhea was observed in 3.8% patients in group A while 6.2% patients in group B, the difference was not statistically significant. Abdominal bloating was seen in 6.2% patients in group A while 10% patients had abdominal bloating in group B, the difference was not statistically significant. The rate of mortality was 1.2% in group A while in group B the rate of mortality was 2.5%, the difference was not statistically significant.

Table 1: Baseline Characteristics

Demographic variables		Group A (n = 40)	Group B (n = 40)
Age		44.36±15.37	38.71±18.56
Gender	Male	21 (52.5%)	24 (60%)
	Female	19 (47.5%)	16 (40%)
Hemoglobin (mg/dL)		7.4±1.8	8.3±3.3
Albumin (g/L)		2.1±0.8	3.7±0.9
Creatinine (mg/dL)		1.1±0.3	017±0.6
Serum potassium (mmol/L)		3.8±0.2	4.7±0.8
Child-Pugh Score		8.9±1.2	9.1±1.7

Table 2: Primary and Secondary Outcomes

Primary and secondary variables		Groups				P value
		Group A		Group B		
		n	%	n	%	
Hepatic encephalopathy	Yes	2	2.5%	8	10.0%	0.04
	No	38	47.5%	32	40.0%	
Diarrhea	Yes	3	3.8%	5	6.2%	0.45
	No	37	46.2%	35	43.8%	
Abdominal bloating	Yes	5	6.2%	8	10.0%	0.36
	No	35	43.8%	32	40.0%	
Mortality	Yes	1	1.2%	2	2.5%	0.55
	No	39	48.8%	38	47.5%	

DISCUSSION

Lactulose, a non-absorbable disaccharide, is frequently prescribed to cirrhotic patients who have recent upper gastrointestinal bleeding as a preventative measure against hepatic encephalopathy (HE) (AUGIB). HE is a cirrhosis complication that develops when toxic compounds like ammonia build up in the blood, which can cause brain malfunction. A severe cirrhosis complication that can cause major morbidity and mortality is AUGIB.[12]

A chronic liver illness called cirrhosis causes the liver to become dysfunctional by replacing healthy liver tissue with scar tissue. The liver is crucial in cleansing the blood and getting rid of dangerous chemicals like ammonia. Because the liver cannot adequately eliminate these poisons in cirrhotic people, they build up in the blood and can cause HE.[13]

After hepatic encephalopathy manifests, the prognosis of a cirrhotic patient rapidly deteriorates. After a hepatic encephalopathy episode, the expected survival rate is 50% in the first year and 25% in the third year.[14]

Hepatic encephalopathy is a severe cirrhosis complication that can happen at any stage of the condition. Several symptoms, such as bewilderment, disorientation, and even coma, describe it. Another cirrhosis consequence that can have a substantial impact on morbidity and mortality is AUGIB[15]. Bleeding from the upper gastrointestinal system, such as the esophagus, stomach, or duodenum, is what is meant by the definition. Over 80% of people with hepatic encephalopathy have recognized reversible causes for the condition. The use of sedatives and tranquillizers, intestinal blockage, bacterial infection, electrolyte imbalances, protein overload, and gastrointestinal haemorrhage are some of these risk factors. Therefore, preventing and treating the majority of episodes of hepatic encephalopathy may be facilitated by recognizing and addressing reversible triggering causes prior to impairment of hepatocellular function.[16]

The majority of hepatic encephalopathy treatments focus on lowering the nitrogen load in the intestinal lumen, which is in line with the theory that patients with hepatic impairment and portosystemic shunts develop HE as a result of a buildup of neurotoxins originating from the gut.[17]

Although there isn't any evidence from side-by-side comparison studies that consistently demonstrates the benefits of non-absorbable disaccharides, they have been used for decades and are regarded as first-line therapy in the management of hepatic encephalopathy. They work by reducing the amount of ammonia produced and absorbed in the intestinal lumen. The colon's contents get acidified as a result of the metabolism of ammonia into acetic acid and lactic acid, which makes it difficult for intestinal bacteria that produce ammonia to survive and speeds up the transformation of NH3 into NH4 (non-absorbable). Additionally, its cathartic effect results in a rise in the excretion of nitrogenous substances from the faeces.[18]

HE is a neuropsychiatric illness that can be reversed and is primarily associated with chronic liver disease. It is characterized by cognitive and psychomotor dysfunctions of varied degrees of severity. The recommended course of action is still to address the precipitating factor prophylactically in high-risk circumstances to prevent HE due to the substantial morbidity and mortality that are linked with it.[19] Within a few hours of the start of GI bleeding, the amount of blood urea nitrogen rises and peaks 24 to 48 hours later. Therefore, remaining blood in the GI tract can result in significant ammonia production. Additionally, blood in the bowel may create an environment that is favourable for intestinal bacteria to proliferate, which encourages the production of ammonia. Previous clinical studies have demonstrated the value of whole gut irrigation for preventing HE in cirrhotic patients following an episode of AUGIB. However, it was uncertain whether lactulose therapy to eliminate blood from the GI system would be effective for the prevention of HE.[18]

Lactulose works by reducing ammonia absorption in the gut and increasing ammonia excretion in the stool. This can aid in lowering blood ammonia levels and preventing HE. Lactulose is a non-absorbable disaccharide that colonic bacteria degrade to produce lactic acid and short-chain fatty acids. This causes the intestinal contents to become more acidic and its pH to drop, both of which lower the solubility of ammonium ions and the colon's ability to absorb ammonia.[12]

Lactulose has been tested in a number of randomized controlled trials to see if it can prevent HE in cirrhotic patients with AUGIB. In comparison to placebo or no treatment, lactulose dramatically decreased the incidence of HE in cirrhotic individuals with AUGIB, according to several investigations. In cirrhotic individuals with AUGIB, lactulose was linked to a decreased incidence of HE and mortality, according to a different study.[20]

Our study was conducted on 80 patients, we divided the patients in two groups. Group A received lactulose and group B received lactulose like placebo treatment. The incidence of HE in group A was 2.5% while in the placebo group the incidence of HE was 10%, the difference was statistically significant. Our results are comparable to a study[16] which reported significantly lower incidence of HE in lactulose group. We did not observe any significant difference between groups in the secondary outcomes like diarrhea, abdominal bloating and mortality.

CONLCUSION

From our study we conclude that lactulose can effectively prevent hepatic encephalopathy in patients with cirrhosis and an acute upper gastrointestinal bleeding.

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