Efficacy of lactulose in the prophylaxis of hepatic encephalopathy in cirrhotic patients presenting gastrointestinal bleeding

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Summary

Introduction: Hepatic encephalopathy (HE) is a bad prognostic factor in patients with liver cirrhosis and its incidence is associated with several triggering factors being the most prevalent gastrointestinal bleeding. Lactulose, despite its questionable efficacy in the literature, is considered a first line treatment in patients with HE.
Objective: To evaluate the effectiveness of lactulose in preventing HE in cirrhotic patients with gastrointestinal bleeding.
Method: A systematic review of the literature using the Medline scientific database. Only randomized controlled clinical trials evaluating the efficacy of lactulose for HE prophylaxis in cirrhotic patients with gastrointestinal bleeding were included.
Results: The incidence of HE in the intervention group was 7%, while the control group was 26% (p=0.01). There was no significant difference in the incidence of mortality in the group treated with lactulose compared to the group that was not treated (p=0.48).
Conclusion: Administering lactulose to cirrhotic patients with upper gastrointestinal bleeding reduces the incidence of hepatic encephalopathy.

Keywords: hepatic encephalopathy, gastrointestinal hemorrhage, lactulose, liver cirrhosis.

Introduction

Hepatic encephalopathy (HE) is a potentially reversible metabolically-induced neuropsychiatric disorder, characterized by changes in personality and intellect, sleep disturbances and depressed level of consciousness. It is a complication of patients with acute or chronic liver failure, especially in cases of cirrhosis, and is generally associated with triggering factors such as gastrointestinal bleeding, bacterial infections and electrolyte disturbances.[1,2]

The main mechanisms responsible for the development of HE are severe intrinsic liver dysfunction and the presence of portosystemic shunts leading to portal blood deviation to the systemic circulation before the removal of intestinal toxic substances.[2,3]

Non-absorbable disaccharides, including lactulose as their main representative, are considered first-line treatment in patients with HE despite their questionable efficacy in the literature. These substances act by reducing the concentration of aminogenic substrate in the intestinal lumen, decreasing the pH of the colon through the production of organic acids by bacterial fermentation and osmotic cathartic mechanism.[4,5]

The aim of this study is to evaluate the effectiveness of non-absorbable disaccharides for HE prophylaxis in cirrhotic patients with gastrointestinal bleeding.

Method

Selection criteria

Only randomized controlled clinical trials evaluating the efficacy of non-absorbable disaccharides for HE prophylaxis in cirrhotic patients with gastrointestinal bleeding were included. To be included in the review, the trial should adequately describe the methods of randomization and blinding of patients, as well as the loss of patients to follow-up, according to the Jadad score criteria.[6] The internal validity of each study was based on Consort[7] recommendations.

The study population included patients over 18 years old and diagnosed with liver cirrhosis, regardless of etiology, and gastrointestinal bleeding. Exclusion criteria were patients who had used lactulose in the past six weeks, were hemodynamically unstable or had severe comorbidities.

The intervention group included patients treated with lactulose aiming to obtain two or three bowel movements with pasty stools per day.

The analyzed primary outcome was the incidence of hepatic encephalopathy during hospitalization. Mortality and adverse effects from the use of lactulose were also evaluated.

Search strategies

The Medline database was searched via PubMed (http://www.ncbi.nlm.nih.gov/pubmed) using the following search strategy: (liver cirrhosis) AND (gastrointestinal bleeding) AND (lactulose OR lactitol OR disaccharides) AND (hepatic encephalopathy), until September 2014.

The references of the selected studies were also consulted manually to select studies that may not have been retrieved in electronic searches.

Statistical analysis

All data were examined based on intention to treat analysis, and patient assessment was conducted within each randomization group, regardless of the treatment protocol and irregularities.

The measures of effectiveness or harm expressed in absolute numbers were analyzed as the absolute risk difference using a 95% confidence interval. When there was a statistical difference between the groups, the number needed to treat (NNT) or number needed to harm (NNH) was calculated.

Results

The electronic and manual searches resulted in a total of 28 studies. After reading their titles and summaries, two studies that met the inclusion criteria were selected and evaluated for methodology.

The results of this review were based on data provided by two controlled clinical trials[8,9] totaling 200 patients, 100 in lactulose group and 100 in the control group.

Both articles describe randomization and patient allocation to each group appropriately. Blinding of patients was considered impossible due to the sweet taste and the cathartic effect of lactulose. To minimize this bias, the analysis of the incidence of hepatic encephalopathy was carried out by independent evaluators. None of the patients were lost to follow-up. Therefore, both studies were classified as score 3 on the Jadad scale (Table 1).

Demographic, laboratory and clinical data, etiology of cirrhosis and bleeding source are described in Table 2. There were no significant differences among patients randomized to each group in each primary study.

Incidence of hepatic encephalopathy

The overall incidence of hepatic encephalopathy was 16.5% (33 cases), ranging from 10 to 28.6% in primary studies. In the lactulose group, one patient developed HE grade 1; three developed grade 2; two developed grade 3; and one developed grade 4. In the control group, three patients developed HE grade 1; fourteen developed grade 2; seven developed grade 3; and one developed grade 4. In the group of patients who received lactulose, the incidence of HE was 7% while in the control group it was 26%. This means a reduction of 19% in absolute risk (95CI 0.04 to 0.33; p=0.01; I^2=47%) so that six patients need to be treated to obtain such benefit (Figure 1).

Mortality

The mortality rate was 5%, ranging between 0.7 and 12.9% in the primary studies. Liver failure was the main cause of death (70%) followed by failure to control bleeding (30%). There was no difference in the incidence of mortality between the group treated with lactulose and the

TABLE 1 Characteristics of primary studies.

Reference Period Location	Lactulose	Description of the randomization and allocation methods	Description of blinding	Description of patient loss	Jadad
Wen J, 2013 2007 – 2011 Beijing, China	10-30 mL 2-3x/day for 7 days until 2-3 bowel movements with pasty stools	Table of random numbers generated by computer	Non-blinded	Yes	3
Sharma P, 2011 2008 – 2010 New Delhi, India	30 mL 3-4x/day for 5 days until 2-3 bowel movements with pasty stools	Opaque envelopes numbered by computer	Non-blinded	Yes	3

TABLE 2 Demographic data referring to the primary studies.

	Sharma P, 2011		Wen J, 2013	
	Lactulose (n=35)	**Control (n=35)**	**Lactulose (n=65)**	**Control (n=65)**
Age (years)	41.6±12.9	37.2±16.0	53.0±13.3	50.4±10.2
Gender				
Female	5 (14%)	7 (20%)	20 (30.8%)	18 (27.7%)
Male	30 (86%)	28 (80%)	45 (69.2%)	47 (72.3%)
Hemoglobin (mg/dL)	8.4±1.5	9.3±2.3	8.6±2.1	8.6±1.9
Albumin (g/L)	2.8±0.5	3.0±0.6	3.3±0.6	3.2±0.7
Creatinine (mg/dL)	1.1±0.3	0.9±0.3	1.6±0.1	1.6±0.1
Serum potassium (mmol/L)	4.1±0.6	4.2±0.4	4.3±0.5	4.2±0.4
Bilirubin (mg/dL)	2.0 (0.5-8.6)	2.1 (0.8-6.8)	1.9 (0.5-10.5)	1.5 (0.4-9.8)
INR	1.9±0.5	1.9±0.3	-	-
PAT	-	-	16.9 (12-28.5)	17.0 (12.8-29.2)
AST (IU/L)	43 (17-250)	50 (25-180)	32 (14-423)	40 (17-468)
ALT (IU/L)	30 (15-198)	32 (11-150)	33.5 (12-270)	39.3 (13-287)
Child-Pugh Score	9.6±1.4	9.6±1.5	6 (4-12)	6 (4-12)
Source of bleeding				
Varicose	35	35	43	42
Non-varicose	-	-	22	23
Etiology of cirrhosis				
Alcoholic	19	14	5	7
HBV	9	11	44	42
HCV	3	3	6	4
Other	4	7	10	12

INR: international normalized ratio; PAT: prothrombin activation time; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HBV: hepatitis B virus; HCV: hepatitis C virus.

untreated group (3 *vs.* 7%, 95CI -0.12 to 0.06; p=0.48; I^2=40%), according to Figure 1.

Adverse effects of lactulose

The main adverse effects related to the use of lactulose were diarrhea (5%) and bloating (2.5%). Two patients (1%) needed to interrupt the intake of lactulose due to side effects. There were no significant adverse effects such as significant abdominal pain, dehydration and electrolyte disturbances during the study periods.

Discussion

The prognosis of a cirrhotic patient worsens quickly after hepatic encephalopathy develops. The estimated survival rate is 50% in one year, and 25% in three years after an episode of HE.[10,11]

It is known that hepatic encephalopathy is caused by reversible factors in over 80% of patients. These factors include gastrointestinal bleeding, bacterial infection, intestinal obstruction, electrolyte disturbances, protein overload and the use of sedatives and tranquilizers. Thus, identifying and correcting reversible precipitating factors before deterioration of hepatocellular function may be beneficial to prevent and treat most episodes of hepatic encephalopathy.[10-12]

Most therapies for HE are aimed at reducing the nitrogen load in the intestinal lumen, an approach that is consistent with the hypothesis that this disorder results from the accumulation of neurotoxins derived from the intestine in patients with hepatic impairment and portosystemic shunts.[13]

Non-absorbable disaccharides have been used for decades and are considered first-line therapy in the management of HE, although there is no evidence in comparative studies that actually proves its benefits in a consistent manner.[4,5] They act by reducing the production and absorption of ammonia in the intestinal lumen. Acidification of the contents of the colon due to metabolism of ammonia into acetic acid and lactic acid creates a harsh environment for the survival of intestinal bacteria involved in ammonia production, and facilitates the conversion of NH3 into NH4 (non-absorbable). Moreover, its cathartic effect causes increased fecal excretion of nitrogenous compounds.[14]

Study	Lactulose		Control			Difference in risk	Difference in risk
	n	Total	n	Total	Weight	M-H, Random, 95CI	M-H, Random, 95CI
Incidence of hepatic encephalopathy							
Sharma P, 2001	5	35	15	35	20.1%	-0.29 [-0.49, -0.08]	
Wen J, 2013	2	65	11	65	26.9%	-0.14 [-0.24, -0.04]	
Total (95CI)		**100**		**100**	**47.1%**	**-0.19 [-0.33, -0.04]**	
Total of events	**7**		**26**				
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.89$; df = 1 (p = 0.17); $I^2 = 47\%$							
Overall effect test: Z = 2.53 (p = 0.01)							
Mortality							
Sharma P, 2001	3	35	6	35	23.3%	-0.09 [-0.24, 0.07]	
Wen J, 2013	0	65	1	65	29.7%	-0.02 [-0.06, 0.03]	
Total (95CI)		**100**		**100**	**52.9%**	**-0.03 [-0.12, 0.06]**	
Total of events	**3**		**7**				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.68$; df = 1 (p = 0.20); $I^2 = 40\%$							
Overall effect test: Z = 0.71 (p = 0.48)							

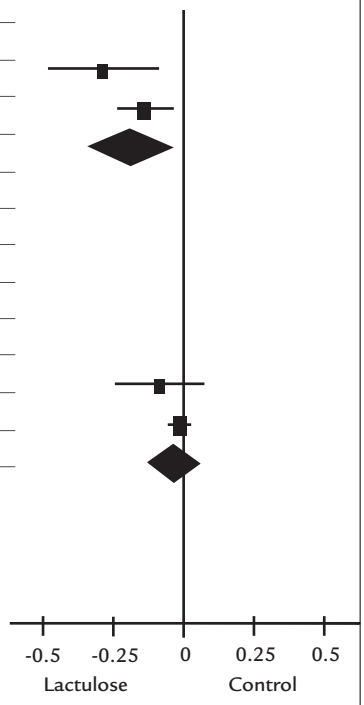

FIGURE 1 Meta-analysis of the incidence of hepatic encephalopathy and mortality.

So far, there is no evidence to defend the prophylactic use of lactulose in cirrhotic patients presenting triggers for HE.[15] Based on the reasoning of the pathophysiology of HE and the potential benefits of lactulose, the clinical trials included in this review used lactulose prophylactically to reduce the incidence of HE.

Both had a significant reduction in the incidence of HE. Meta-analysis of the data showed a decrease of approximately 20% (range 10 to 28%) in the absolute risk HE. The difference in incidence of HE between the primary studies can be explained by the fact that in the study by Sharma et al. patients had higher Child-Pugh scores (9 *vs.* 6 points), which means worst liver performance. In addition, the authors included only patients with gastrointestinal bleeding of varicose source, which is known to occur when the liver function is already considerably compromised. Another difference observed was the etiology of liver disease. In the study by Sharma et al., alcoholic etiology prevailed, while in the study by Wen et al.[9] the main cause of liver disease was chronic infection with hepatitis B virus.

There was no difference in the overall incidence of mortality. The highest number of deaths observed in the study by Sharma et al. is explained by the same reasons mentioned above.

The most common adverse events arising from the administration of lactulose are diarrhea, abdominal cramps, nausea and flatulence. Although these side effects are common, they seldom lead to discontinuation of treatment.

It should be noted that the summary of the evidence in this review may be biased by the low statistical power of the sample in the primary studies.

Conclusion

Administering lactulose to cirrhotic patients with upper gastrointestinal bleeding reduces the incidence of hepatic encephalopathy.

Resumo

Eficácia da lactulose na profilaxia de encefalopatia hepática em pacientes cirróticos apresentando hemorragia digestiva

Introdução: encefalopatia hepática (EH) é fator de mau prognóstico no paciente com cirrose hepática e sua inci-

dência está associada a vários fatores desencadeantes, sendo a hemorragia digestiva o mais prevalente. A lactulose, apesar de apresentar eficácia discutível na literatura, é considerada tratamento de primeira linha em pacientes com EH.

Objetivo: avaliar a eficácia da lactulose na prevenção de EH em pacientes cirróticos apresentando hemorragia digestiva.

Método: realizou-se revisão sistemática da literatura pela base de dados Medline. Foram incluídos apenas ensaios clínicos controlados e randomizados que avaliaram a eficácia da lactulose na profilaxia de EH em pacientes cirróticos com hemorragia digestiva.

Resultados: a incidência de EH no grupo intervenção foi de 7% enquanto no grupo controle foi de 26% (p=0,01). Não houve diferença significante na incidência de mortalidade entre o grupo que recebeu lactulose e o que não recebeu (p=0,48).

Conclusão: a administração de lactulose em pacientes cirróticos apresentando hemorragia digestiva alta diminui a incidência de encefalopatia hepática.

Palavras-chave: encefalopatia hepática, hemorragia gastrointestinal, lactulose, cirrose hepática.

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