Original Article

Factors associated with nonresponse to lactulose in patients with cirrhosis and hepatic encephalopathy

Muhammad Omar Qureshi, Farzana Shafqat, Mohammad Salih, Nasir Khokhar

Department of Gastroenterology, Shifa International Hospital, Islamabad, Pakistan

Objective: To evaluate the factors associated with non response to lactulose in patients with liver cirrhosis and hepatic encephalopathy (HE).

Methodology: This prospective non-interventional study was conducted at Shifa International Hospital, Islamabad, Pakistan from August 2011 to February 2013.A total of 250 patients with liver cirrhosis and hepatic encephalopathy were included. They were treated with lactulose. Non response was defined if patient remained in HE after 10 days of treatment or died while in HE. The data were analyzed using SPSS v 16.

Results: Out of 250 patients, 193(77.2%) responded to lactulose vs 57 (22.8%) patients who did not respond. Patients not responding to lactulose had high MELD,and CTP score, increasex TLC, ammonia levels, low platelets and sodium levels in comparison to lactulose responsive patients ($p<0.001$).

Conclusion: Majority of patients with HE responded to lactulose. High baseline MELD,CTP score, TLC, ammonia levels, low platelets and low serum sodium levels were associated with non response to lactulose. (Rawal Med J 2014;39: 115-118).

Key Words: Hepatic encephalopathy, Liver cirrhosis, Lactulose.

INTRODUCTION

Hepatic encephalopathy (HE) is a clinical syndrome characterized by alterations in mental status, personality, intellectual function, and changes in neuromuscular activity. It is frequently observed in those with both acute liver failure and liver cirrhosis.[1] Hepatic encephalopathy may occur in 50 to 70 percent of all patients with cirrhosis, including those with abnormalities demonstrable only by psychometric testing.[2] Most manifestations of HE are reversible with pharmacological management. Some patients with hepatic encephalopathy have progressive debilitating syndromes, such as dementia, spastic paraparesis, cerebellar degeneration and extra pyramidal movement disorders, associated with structural abnormalities of the central nervous system.[3] The presence of HE is a poor prognostic sign, with 1-year mortality rates of almost 60%.[4]

Although a number of other possible factors have been proposed to play a role in the pathogenesis of HE, such as, the production of central benzodiazepine agonists, endogenous opioids and false neurotransmitters, ammonia is still viewed as the key contributor.[2] Thus, the main focus of treatment for HE revolves about reducing the production and absorption of ammonia in the gut, and to improve its excretion by drug therapy or modification in diet.

Currently, lactulose and nonabsorbable antibiotics are most commonly used therapeutic agents to treat HE.[5] Lactulose is currently recommended as the first-line pharmacological treatment for HE by the practice guidelines by the American College of Gastroenterology.[6] Lactulose has multiple effects on gut flora and reduces ammonia levels by decreasingits production and absorption.[7]However, not all patients respond and its efficacy varies from 40-70% in some studies.[8] The factors which contribute to failure of lactulose have been studied by few International studies.[7,8] This study was aimed to determine the predictive factors of nonresponse to lactulose in patients with HE in our setting.

METHODOLOGY

This prospective study included 250 patients admitted to the Department of Gastroenterology, Shifa International Hospital, Islamabad from August 2011 to February 2013. Patients of age greater than 18 years with diagnosis of liver cirrhosis of any etiology and HE were included in the study. Patients with comorbid conditions like stroke, sepsis etc were excluded from the study. The Ethics committee of the hospital approved the study

and informed consent was obtained from all study participants. Cirrhosis was confirmed by clinical, biochemical and ultrasonographic findingsand diagnosis of HE was based on exclusion. HE was graded according to the West Haven classification system (Table 1).

Table 1. West Haven Criteria for Grading of Hepatic Encephalopathy.

Grade	Criteria
Grade 0	No signs or symptoms
Grade 1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
Grade 2	Lethargy or apathy
	Minimal disorientation for time or place
	Subtle personality change
	Inappropriate behavior
	Impaired performance of subtraction
Grade 3	Somnolence to semistupor but responsive to verbal stimuli
	Confusion
	Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Patients were treated with lactulose and correction of any associated precipitating factors. Dose of lactulose was adjusted in each patient, so that patients passed at least three to four semi-formed stools per day. Response to the treatment was checked on daily basis. Nonresponse was defined if patient remained in HE after 10 days of treatment or died while in HE.

The demographic profile of the patient and etiology of liver disease were noted. The severity of liver disease was assessed according to Child-Pugh score. They were assessed for ascites and were graded according to International Ascites Club. All patients had complete blood counts, serum electrolytes, creatinine, LFT 's, serum albumin, INR and ammonia levels.

The data were analyzed using SPSS v 17. Chi square test was used to assess categorical variables and Student t test for continuous variables. All statistical tests were two-sided, and a $P<0.05$ was considered statistically significant.

RESULTS

Out of 250 patients, 149 (59.6%) had HCV as cause of their cirrhosis, with mean age of 50±9.9 years, mean MELD score of 18.7 6.2 and majority were in Child class C (Table 1).

Table 1. Baseline characteristics of study population.

Characteristics Value (%)	
Male	135 (54%)
Female	115(46%)
Age (Years)	50± 9.9
Cause of Cirrhosis	
HCV	149(59.6%)
HBV	36 (14.4%)
Others	65(26%)
Child class	
A11(4.4%)	
B	102 (40.8%)
C	137(54.8%)
MELD Score (Mean ± SD)	18.9± 6.2
Laboratory values	
TLC (cells/$mm^3$9900 ± 1200	
Platelets(cells/l) 103 x 10^9± 45 x 10^9	133± 5
Sodium levels(mmol/l)	177± 26
Ammonia levels (mg/dl)	
Complications	
Ascites	121(48.4%)
GI BLEED	78 (31%)
SBP	31(12.4%)

Table 2. Comparison of hepatic encephalopathy patients responding to lactulosevsnonresponders.

Parameters	Responders (n = 193)	Nonresponders (n = 57)	P values
Age (Years)	46 ± 11.2	57 ± 10.7	<0.001
MELD score	17 ± 4.7	24 ± 3.9	<0.001
CTP score	9 ± 3.0	11 ± 3.7	<0.001
TLC (cells/mm^3)	8800 ± 2600	12000 ± 3000	<0.001
Platelets (cells/l)	127 x 10^9 ± 22 x 10^9	75 x 10^9± 32 + 10^9	<0.001
Creatinine (mg/dl)	1.07 ± 0.57	3.23 ± 0.91	<0.001
Sodium (mmol/l)	135 ± 4.0	129 ± 5.2	<0.001
Ammoni a (mg/dl)	145 ± 15	209 ± 19	<0.001
SBP	14(7.25%)	17 (29.8%)	<0.001
GI bleed	55 (28.4%)	13 (22.08%)	0.321

Out of 250 patients, 193(77.2%) responded to lactulose vs 57 (22.8%) did not respond (Table 2).

DISCUSSION

Hepatic encephalopathy is a life threatening complication of liver cirrhosis. Multiple factors are responsible for HE but the development of HE is explained, to some extent, by the effect of neurotoxic substances, which occur in patients with cirrhosis and portal hypertension.[9] Cirrhosis is a common cause of mortality amongst Pakistani population and a frequent cause of admission in our hospitals.[10] HE results from failure of the liver to detoxify noxious agents of gut origin because of hepatocellular dysfunction and porto systemic shunting.[11]It results from the combined effect of multiple factors.[12]

Ammonia has been regarded as the most important factor in the progress of the HE. It reaches the systemic circulation via portosystemic shunting.[13]It is believed that this contributes to the increase occurrence of motor dysfunction and the extra pyramidal symptoms seen in HE. It is reported that in 60-80% of patients with HE, arterial blood samples show greater ammonia levels suggesting its important role in the pathogenesis of HE.[14]

Most studies have shown an improvement in psychomotor functions by reducing the ammonia level.[15,16] The efficacy of oral lactulose for the treatment of HE has been established in controlled trials.[2] The daily dose should be titrated to result in two to four soft, acidic (pH less than 6) stools daily. For most patients, the daily dose is between 30 and 60 g. Lactulose lowers the colonic pH as a result of the production of organic acids by bacterial fermentation. The decrease in pH creates an environment that is hostile to the survival of urease-producing intestinal bacteria and may promote the growth of nonurease-producing lactobacilli, resulting in reduced production of ammonia in the colonic lumen.[2] Water enemas are ineffective, suggesting that acidification rather than bowel cleansing alone, is responsible for the therapeutic effect.[2]

In our study, we treated patients of HE with lactulose as per standard protocol. 77% patients responded to lactulose while 22% patients did not improve with treatment. The main purpose of the study was to evaluate the factors associated with nonresponse of HE to lactulose therapy. We found that all patients with HE had a lower serum sodium level (133$\pm$5.0 mmol/L) and patients who did not respond to lactulose had significantly lower serum sodium as compared with responders (129$\pm$5.2 vs 135$\pm$4.0mmol/L, P = 0.001). A recent study proposes a role of low-grade cerebral edema in the pathogenesis of HE. According to this hypothesis, ammonia and other neurotoxins act synergistically to induce a low-grade cerebral edema as a result of swelling of astrocytes, which is mainly because of an increased intracellular content of glutamine, secondary to ammonia metabolism.[15,16] Both hyperammonemia and hyponatraemia have the ability to produce swelling of susceptible cells by altering the osmotic balance andhence contributes to HE.[17]

We found venous ammonia levels to be higher (177$\pm$26) in our all patients of HE. Venous ammonia was even higher in nonresponders as compared with responders (209$\pm$19 vs 145$\pm$ 15mmol/L, P <0.001). Similarly, increasing age, higher MELD and CTP scores, lower platelets, presence of renal failure, SBP and infections were found to be associated with nonresponse to lactulose therapy, while GI bleed did not affect the outcome of HE. Sharma et al. reported high baseline MELD, high total leukocyte count, low serum sodium, low mean arterial pressure and presence of hepatocellular carcinoma as a predictors of nonresponse to lactulose.[18] In another study, a low serum sodium and a high venous ammonia level were significantly associated with a low response to lactulose.[7]

Our study had few limitations. Effects of co morbid conditions were not checked for their effect on HE. Though the main drug used was lactulose, some patients also had additional regimens depending upon their condition and needs, that may have effect on the outcome.

CONCLUSION

Majority of patients with HE responded to lactulose. High baseline MELD, CTP score, total leukocyte count, ammonia levels, creatinine levels, low

platelets and low serum sodium levels were associated with nonresponse to lactulose.

Author contributions:
Conception and design: Muhammad Omar Qureshi
Collection and assembly of data: Muhammad Omar Qureshi
Analysis and interpretation of the data: Mohammad Salih
Drafting of the article: Farzana Shafqat
Critical revision of the article for important intellectual content: Nasir Khokhar
Statistical expertise: Muhammad Omar Qureshi
Final approval and guarantor of the article: Nasir Khokhar
Corresponding author email: Dr_omar211@hotmail.com
Conflict of Interest: None declared
Rec. Date: Dec 11, 2013 Accept Date: Jan 30, 2014

REFERENCES

1. Lizardi-Cervera J, Almeda P, Guevara L, Uribe M. Hepatic encephalopathy: a review. Ann Hepatol 2003;2:122-30.
2. Riordan SM, Williams R. Treatment of Hepatic Encephalopathy. N Engl J Med 1997;337:473-9.
3. Gitlin N. Hepatic encephalopathy. In: Zakim D, Boyer TD, eds. Hepatology: a textbook of liver disease. 3rd ed. Vol. 1. Philadelphia: W.B. Saunders, 1996:605-17.
4. Dbouk N, McGuire BM. Hepatic encephalopathy: a review of its pathophysiology and treatment. Curr Treat Options Gastroenterol 2006;9:464-74.
5. Bosch J, Bruix J, Mas A, Navasa M, Rodes J. Rolling review: the treatment of major complications of cirrhosis. Aliment Pharmacol Ther1994;8:639-57.
6. Blei AT, Cordoba J. Hepatic encephalopathy. Am J Gastroenterol 2001;96:1968-76.
7. Sharma P, Sharma BC, Sarin SK. Predictors of nonresponse to lactulose for minimal hepatic encephalopathy in patients with cirrhosis. Liver Int 2009;29:1365-71.
8. Prasad S, Dhiman RK, Duseja A. Lactulose improves cognitive function and health-related quality of life in cirrhotic patients with minimal hepatic encephalopathy. Hepatology 2007; 45:549-59.
9. Butterworth RF. The neurobiology of hepatic encephalopathy. Semin Liver Dis 1996;16:235-44. 10.Almani SA, Memon AS, Memon AI, Shah I, Rahpoto Q, Solangi R. Cirrhosis of liver: Etiological factors, complications and prognosis. J Liaquat Uni Med Health Sci 2008;7:61-6.
11. Lawrence S, Friedman. Liver, Biliary Tract, & Pancreas Disorders. In: Current Medical Diagnosis & Treatment. 49th edition: Mc Graw Hil Lange; 2010.622-23.
12. Jones EA. Pathogenesis of hepatic encephalopathy. Clin Liver Dis 2000;4:467-85.
13. Chatauret N, Butter worth RF. Effects of liver failure on inter-organ trafficking of ammonia: Implications for the treatment of hepatic encephalopathy. J Gastroenterol Hepatol 2004;19:219-23.
14. Rodes J. Clinical menifestations and therapy of hepatic encephalopathy. Adv Expt Med Biol 1993;341:39-44.
15. Haussinger D. Low grade cerebral edema and the pathogenesis of hepatic encephalopathy in cirrhosis. Hepatology 2006;43:1187-90.
16. Kale RA, Gupta RK, Saraswat VA. Demonstration of interstitial cerebral edema with diffusion tensor MR imaging in type C hepatic encephalopathy. Hepatology 2006;43:698-706.
17. Restuccia T, Gomez-Anson B, Guevara M. Effects of dilutionalhyponatremia on brain organic osmolytes and water content in patients with cirrhosis. Hepatology 2004;39:1613-22.
18. Sharma P, Sharma BC, Sarin SK. Predictors of nonresponse to lactulose in patients with cirrhosis and hepatic encephalopathy. Eur J Gastroenterol Hepatol 2010;22:526-31.