Effect of rectal lactulose administration with oral therapy on time to recovery from hepatic encephalopathy: a randomized study

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Hepatic encephalopathy is one of the most disturbing late features of decompensated cirrhosis of the liver.[1] Hepatic transplantation is the only definite treatment at this stage. Various treatments have been evaluated to manage chronic encephalopathy and intermittent episodes of encephalopathy in cirrhosis of the liver. Treatment modalities vary according to putative mechanism of encephalopathy, e.g. low protein diet,[2] receptor antagonism in the brain,[3] changing gut flora,[2] and reducing ammonia production.[4] Administration of the non-absorbable disaccharides, lactulose and lactitol, have become standard treatment of chronic and intermittent hepatic encephalopathy.[5] When given orally, lactulose passes mostly unchanged in the small intestine and is fermented in the large intestine by bacteria, lowering pH, trapping ammonia and changing gut flora.[2] The latter may be more relevant in chronic encephalopathy while pH change and ammonia trapping are seemingly responsible for the initial phase of improvement in encephalopathy.[4,6] We, therefore, thought that administration of lactulose retention enema at the ultimate site of action may shorten the initial period of improvement of encephalopathy.

Patients and Methods

In a parallel, open-label prospective trial, we randomized patients having episodic (intermittent) hepatic encephalopathy[7] to lactulose or a tap water enema with a treatment allocation ratio of 1:1. Oral administration of lactulose was continued as the base line treatment in both groups at doses of 20 to 30 ml every 6 to 8 hours to produce 2 to 3 additional semisolid stools.[2]

The trial was designed to determine time to improvement in episodic deterioration of hepatic encephalopathy. For inclusion in the trial, the current episode of encephalopathy must have been precipitated within the last 48 hours. Diagnosis of cirrhosis was confirmed by prior biopsy or by a combination of clinical and ultrasonographic findings.[1] The patient could be in any grade of encephalopathy deeper than sub clinical and grade I, as rapid improvement at this subtle level of encephalopathy is difficult to appreciate.[7] Patients who had a clear precipitating event of encephalopathy were excluded as treatment is primarily directed towards removing the insult. Patients who had significant concomitant diseases that could impair or contribute to the impairment of consciousness were excluded clinically and by appropriate investigations.

Lactulose was administered as a retention enema within one hour of presentation to hospital. The large intestine was cleaned first by plain water enema. Later 250-300 ml of standard lactulose preparation, diluted with normal saline to a total of 700 ml, was given in the right lateral position. Thereafter, enema administration was continued at 12 hourly intervals. Evaluation of the improvement was done primarily by the West Haven hepatic encephalopathy grades recommended for clinical trials at a congress on evaluation of hepatic encephalopathy in 1998.[7] Another clinical scoring for hepatic encephalopathy described by Jones and Gammal was also used.[8] Both of these evaluations were done daily by a resident trained in such evaluation and also by one of the two consultant staff members at entry, at 48 hours and at the end. Ammonia levels were done at entry and at the end by the enzymatic method using semimicro procedure in a Microlab 200 (Randox Laboratory, United Kingdom). Dietary protein was standardized at 0-10 g/day in grade II to IV coma and was liberally increased up to 40 g/day once the patient aroused sufficiently to talk.[2] Other concomitant medications were continued as required e.g. insulin, ACE inhibitors, and others. The composite scoring system, the portal systemic encephalopathy (PSE) index,[9] was also calculated at entry and at the end to double check the maximum level of improvement in encephalopathy at the end of the study period. This scoring system is based on ammonia levels, grades of encephalopathy and performance on the number connection test or digit symbol test. We used the digit symbol system, as most of our patients were illiterate.[10]

The primary end point of the study was time to improvement in hepatic encephalopathy according to clinical scoring.

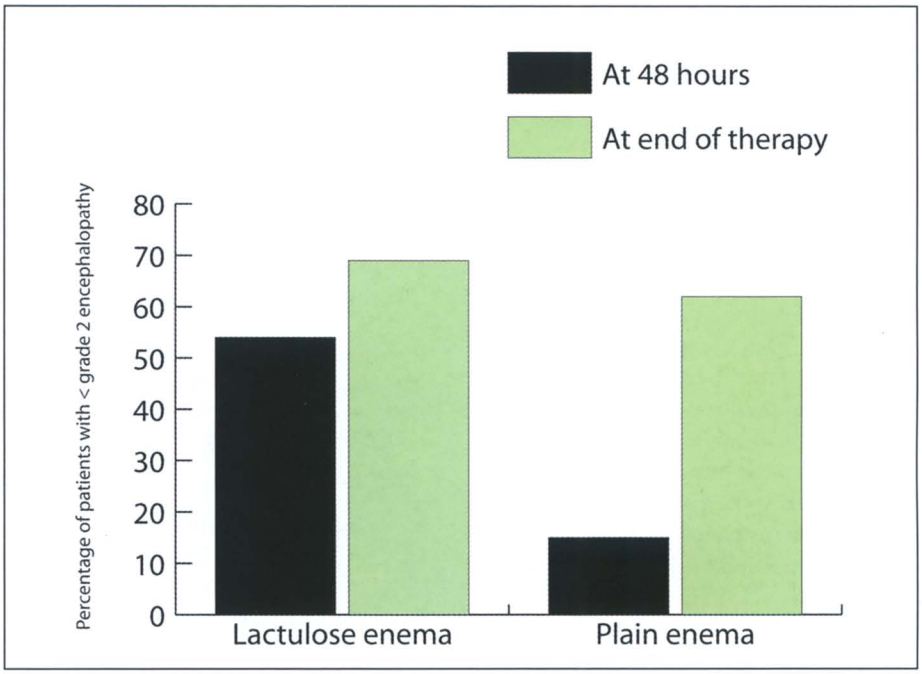

Figure 1. Percentage of patients moving to lighter (< West Haven grade 2) encephalopathy after intervention.

The maximum level of recovery was also noted at the time of discharge by the two clinical scoring systems and the PSE index. Improvement in scores at 48 hours and at the end of treatment were compared with scores at the start of treatment by the paired sample *t* test. An intergroup comparison of the same scores was done with the independent sample *t* test. A *P* value of <0.05 was considered statistically significant.

Results

Small differences in age and grade of encephalopathy between the control and intervention group at presentation were not statistically significant (Table 1). Patients in both groups had advanced liver disease to a comparable extent by the Child's score. There was a statistically significant improvement at 48 hours in the PSE score and the West Haven encephalopathy grading in those administered lactulose enema (Table 2). There was no statistically significant changes in those given plain enema. Table 3 compares data from the three scoring systems at the beginning, at 48 hours and at the end of therapy. Encephalopathy improved to a comparable extent in the control and intervention groups at the end of treatment (Table 3). However, when degree of improvement in the two clinical scoring systems were compared at 48 hours, the differences were statistically significant in favor of lactulose enema. Encephalopathy improved earlier in patients administered lactulose enema, while there was a lag of almost 48 hours before any appreciable improvement was noticed in the group given lactulose by the oral route alone. At 48 hours, most of the patients given the lactulose enema had moved to a lighter (< West Haven grade 2) encephalopathy (62% vs. 15%) (Figure 1). Similar improvements with oral lactulose alone occurred mostly after 48 hours.

There were three deaths in grade IV encephalopathy; two in groups administered plain water enema and one in patients administered lactulose enema. These deaths were not considered to represent failure of treatment and no separate scoring was allotted for them.

Table 1. Comparison of demographic, etiological and clinical features at the beginning of study.

	Lactulose Enema	Plain Enema	*P* value
Age (years)	55.08	52.38	0.36
Male	5	6	
Female	13	7	
HBsAg	3	4	
Anti-HCV	8	6	
HBsAg + Anti-HCV	2	3	
Alcohol intake	0	0	
Child's Score	13	13	0.91
HE Grade*	3	2.6	0.21
PSE Score†	12.5	11.2	0.19
PSE Index‡	7	6.7	0.20

*West Haven hepatic encephalopathy grade
† Portal systemic encephalopathy score
‡ Portal systemic encephalopathy index

Table 2. Comparison of changes in clinical measures of hepatic encephalopathy at entry, at 48 hours and at the end of therapy.

	Entry	48 hours	*P* value	Entry	End of Treatment	*P* value
Lactulose Enema + Oral Lactulose						
PSE score*	12.53	9.38	0.001	12.53	7.08	0.001
Grading †	3.07	1.53	0.001	3.07	1.07	0.001
PSE index ‡				7.07	3.77	0.0001
Plain Enema + Oral Lactulose						
PSE score *	11.38	9.92	0.089	11.38	7.92	0.039
Grading†	2.61	2.23	0.137	3.07	1.46	0.025
PSE index‡				6.23	4.14	0.027

* Portal systemic encephalopathy score
† West Haven encephalopathy grading
‡ Portal systemic encephalopathy index

Table 3. Change in clinical measures of hepatic encephalopathy at start, at 48 hours and in the end.

	Oral lactulose + plain enema	Oral lactulose + lactulose enema	*P* Value
Grade* shift at 48 hours	0.38	1.46	0.018
Grade* shift at end	1.15	1.92	0.229
PSE score† improvement at 48 hours	1.46	3.92	0.034
PSE score improvement at end	3.46	5.54	0.309
PSE index‡ improvement at end	2.09	3.30	0.091

*West Haven encephalopathy grading
† Portal systemic encephalopathy score
‡ Portal systemic encephalopathy index

Discussion

Lactulose (or other non-absorbable disaccharide) administration has become a standard practice in episodic hepatic encephalopathy in advanced liver cirrhosis.[5] Based on its mechanism of action in the large intestine, we thought that a retention enema might shorten the time to improvement in hepatic encephalopathy.

With standard oral treatment, lactulose is administered in sufficient quantities to produce 2 to 3 semisolid stools per day. It may take 48 to 72 hours before any appreciable improvement in hepatic encephalopathy is noted.[6] Moreover, there is individual variability in tolerance and response to lactulose and dose titration itself may require additional time.[1,2] In situations of deep hepatic encephalopathy (grade III and IV), it may be desirable to shorten this time to initial improvement. To our knowledge, this study is the first randomized, controlled study to evaluate rapidity of recovery from hepatic coma. In most cases of hepatic coma, a precipitating event can be identified and correction of the precipating factor takes precedence over other measures to treat encephalopathy.[1] Correction of such contributing factors can complicate evaluation of an intervention. We, therefore, excluded patients with a clear precipitating event. Many previous studies comparing lactulose with other modalities of treatment did not exclude such patients.[11,12]

In deep hepatic coma (grade II to IV), hepatic encephalopathy grading alone has been agreed upon as the best outcome measure in clinical trials.[7] We, therefore, used the West Haven hepatic encephalopathy grading as our primary outcome measure.[7] As there can be an overlap in grades, especially between grades II and III, we also applied the clinical portal systemic encephalopathy score described by Jones and Gammal.[8] Blood ammonia has been extensively employed as a proxy measure of hepatic encephalopathy, but its correlation with clinical outcome is at the best poor. [7] We took ammonia levels in the beginning and at the end and interpreted them according to the portal systemic encephalopathy (PSE) index.[9]

We noted that there was an impressive improvement in encephalopathy at the end of 48 hours in patients administered lactulose enema (average of 1.54). Such an improvement is often clinically appreciable. At the same time

interval, patients given oral lactulose improved by 0.33. At the end of the study period, however, both groups had a comparable improvement in encephalopathy. The slight remaining difference is likely to have been equal if the study had been extended for more than an average of 4.5 days. After searching Medline, indices of related journals and other sources, we were unable to find studies which included time to improvement of encephalopathy as primary end point.

In 1987, Uribe et al compared acidifying versus non-acidifying enemas in hepatic coma of grade II-IV.[12] The study targeted the final outcome of coma, in which acidifying enemas proved superior to tap water. The time to improvement was not compared in that study. Many studies have compared the efficacy of oral lactulose and lactitol. Some studies have reported a time to improvement in favor of lactitol as a secondary end point, but did not exclude patients with precipitating factors, or compared improvement in encephalopathy at the end of five days.[12-14]

It is well known that cirrhotic patients progressing to deep hepatic coma (grade II-IV) carry a high mortality, due to both underlying liver disease and associated precipitating factors, e.g. hemorrhage. It is not known if deep encephalopathy itself contributes to the outcome, but it is certainly desirable that the duration of the coma be minimized. Flumazenil-like substances acting as GABA receptor antagonists have not been found useful in hepatic coma; only a subset of patients have derived marginal benefit.[3] In our study, earlier improvement in coma with lactulose enema was noted in patients with both deep (grade III and IV) and lighter grades (grade II) of encephalopathy. Therefore, we concluded that duration, but not the ultimate outcome, of hepatic coma can be minimized with simultaneous administration of lactulose through oral and retention enema. Whether this shortening in duration of coma has any effect on immediate or subsequent mortality remains to be seen, as deaths in both the groups could not be compared because of the rather small sample size.

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