Comparison of Rifaximin Plus Lactulose with the Lactulose Alone for the Treatment of Hepatic Encephalopathy

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Abstract
Hepatic encephalopathy is a challenging complication of liver dysfunction. Therapeutic treatment options for hepatic encephalopathy are currently limited and have appreciable risks and benefits associated with their use. Rifaximin is a novel anti-microbiological agent with wide spectrum of activity that has shown promise as an alternative option for hepatic encephalopathy.

Aims and Objectives: The present study was undertaken to compare the effectiveness of Rifaximin and Lactulose as a combination vs Lactulose alone, to compare the adverse effects and to study the rapidity of therapeutic effects of Rifaximin and Lactulose.

Methods: It was a prospective observational study. 60 patients suffering from hepatic encephalopathy (HE) were studied. Patients were investigated and treated as per treating physician’s decision. At the time of analysis, patients were divided into 2 groups, Rifaximin group who received Rifaximin + Lactulose (R+L) and Lactulose group (L), who received Lactulose only. Parameters such as mental status grade, Asterixis grade, Serum Ammonia grade, Number Connection Test grade (NCT grade), Hepatic Encephalopathy Index (HE index) were evaluated and compared in both groups. Clinical efficacy was determined using HE index improvement. Primary end points were decrease in HE index and reversal of HE grades. Secondary end points were mortality from HE or any other cause, decrease in mental status grade, asterixis grade, serum Ammonia grade, NCT grade.

Results: Out of 60 patients, 32 received Rifaximin + Lactulose combination and 28 patients received Lactulose alone. Mean Child-Turcotte-Pugh score (CTP score) was 10.6 in R+L group and 10.32 in L group. There was statistically significant improvement in mental status grade, Asterixis grade, Serum Ammonia grade, Number Connection Test grade (NCT grade), Hepatic Encephalopathy Index (HE index) in both groups, p value <0.05 but no statistically significant difference between improvement in mental status grade, Asterixis grade, Serum Ammonia grade, NCT grade, HE index between the two groups. Rifaximin + Lactulose combination was effective in 31 out of 32 i.e. 96.87% and Lactulose alone in 24 out of 28 patients, i.e. in 85.71%, which is not statistically different, p=0.3251.

Discussion: Rifaximin + Lactulose combination is not superior to Lactulose alone in treatment of refractory hepatic encephalopathy. Addition of Rifaximin may help in the treatment of refractory hepatic encephalopathy.
**Conclusion:** Rifaxmin + Lactulose combination is effective, but not superior to Lactulose alone in treatment of hepatic encephalopathy.

Most therapies for hepatic encephalopathy focus on treating episodes as they occur and are directed at treatment of precipitating factors, reducing the nitrogenous load in the gut. In general, the oral antibiotics neomycin, paromomycin, vancomycin, and metronidazole have been effectively used, with or without lactulose, to reduce ammonia-producing enteric bacteria in patients with hepatic encephalopathy.

Treatment with nonabsorbable disaccharides lactitol or lactulose is the current standard of care for patients with hepatic encephalopathy, which decreases the absorption of ammonia through cathartic effects and by altering colonic pH. Gastrointestinal acidification ultimately inhibits the production of ammonia by coliform bacteria. An analysis of Cochrane Hepato-Biliary Group data demonstrated efficacy of lactulose over placebo, but showed no benefit in survival.

Rifaximin is a semisynthetic, nonsystemic antibiotic that is almost exclusively and completely excreted in the feces as unchanged drug. It was approved in late March 2010 by the FDA for the treatment of overt hepatic encephalopathy. It is believed that by altering the flora in the gastrointestinal tract, rifaximin decreases intestinal production and absorption of ammonia. Rifaximin has a broad spectrum of antibacterial activity and thus may be an appropriate agent for eliminating both the anaerobic and aerobic colonic bacteria that are capable of producing ammonia but with low risk of inducing bacterial resistance. Rifaximin is well tolerated in nearly all patient populations, including young children. No dosage adjustment is needed in patients with hepatic encephalopathy or renal insufficiency. With minimal systemic bioavailability, rifaximin may be more conducive to long-term use than other, more bioavailable antibiotics with detrimental side effects. It has been proven to prevent the episode of HE and decrease the risk of hospitalization. In randomized studies, rifaximin was more effective than nonabsorbable disaccharides and had efficacy that was equivalent to or greater than that of other antibiotics used in the treatment of acute HE.

In recent meta-analysis of 12 randomized controlled trials, Eltawil et al. reported that rifaximin is as effective as other conventional oral agents for the treatment of HE with a better safety profile. But studies comparing the efficacy of combination of Rifaximin and Lactulose are limited. Hence current study is undertaken to compare the efficacy and safety profile of combination of Rifaximin and Lactulose vs Lactulose alone in treatment of HE.

**Methods**

This was a prospective observational nonrandomized study conducted from January 2011 to July 2012 at tertiary care institute. After obtaining Ethics committee permission from institution, 60 patients suffering from overt HE, fulfilling inclusion and exclusion criteria were enrolled. All patients were investigated and treated as per treating physician. Duration of treatment varied from 7-15 days till discharge from the hospital or death. Any adverse event was recorded specifying the time of onset, duration and severity.

**Study Design**

The severity of HE was graded according to West Haven criteria. Severity of cirrhosis was graded by CHILD-PUGH-TURCOTTE (CPT) score. Detailed history, clinical, neurological examination was carried out in every patient. Routine investigations like complete blood count, liver function test, renal function test, serum electrolytes, blood sugar, Prothrombin time and International normalized ratio were recorded. Details of special investigations like USG Abdomen, Sr. Ammonia, CT brain, CXR, viral markers, ascitic fluid analysis, hepatoportal Doppler were recorded. The blood investigations were done on the day of admission (Day-1) and were subsequently repeated serially from the day of admission till the final outcome. At the time of analysis patients were divided into two groups:

Rifaximin+Lactulose, (R+L) group who received Rifaximin 1200 mg / day in 3 divided doses and Lactulose, 30–60 ml/three times a day, so that patient passes two to three semisoft stools in a day. Lactulose Group (L) in which patients who received lactulose 30–60 ml/three times a day so that patient passes two to three semisoft stools in a day.

Parameters like mental status grade, Asterixis grade, Sr. Ammonia grade, number connection grade (NCT grade), hepatic encephalopathy index (HE index) were estimated on Day 1, Day 3, and Day (5-8) in both groups.

**Grade of Mental State**

This was examined semi-quantitatively using Conn’s modification of the Parsons-Smith classification. Grade 0: no abnormality; Grade 1: trivial loss of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction performance; Grade 2: lethargy, disorientation with respect to time, obvious personality...
HE index was calculated by (Grade of mental state) X 3 + Grade of Flapping tremor + Grade of Serum ammonia. Requirement of renal replacement therapy and inotropic support, Upper GI scopy, Fresh Frozen Plasma support was also looked for in both groups. Patient outcome and response to treatment was assessed using these parameters, with respect to demographic factors, which drug they received, and adverse effects if any. Efficacy was graded as improved, unchanged or worsened.

A decrease in HE index by at least 1 point was defined as improved and increment of HE index by one point or more was defined as worsened. The treatment duration was 7-15 days depending on the course and outcome.

Primary end points were decrease in HE index and reversal of HE grades. Secondary end points were mortality from HE or any other cause, decrease in mental status grade, asterixis grade, serum ammonia grade and NCT grade.

### Statistical Analysis

Mean of mental status grades, Serum ammonia grades, NCT grade, flapping tremor grades, HE grade and HE index were calculated. To compare the change in grades post treatment, independent paired T test was used. To compare the change in mental status grade, Serum Ammonia grades, NCT grade, flapping tremor grades, HE index post-treatment in both the groups, multivariate analysis of variance test was applied. Fisher exact test was used to know the improvement in HE grades and HE index.

### Results

A total of 74 patients, suffering from cirrhosis of liver and hepatic encephalopathy (HE) were screened. Of these 14 were excluded not fulfilling inclusion criteria. 60 patients were included.

Mean age was 50.8 yrs and S.D of 10.07. Male to female ratio was 28/5.

### Blood Ammonia Levels

Blood ammonia was measured before and after the treatment using Cobas Integra 800 (Roche, Basel, Switzerland). Grade 0: < 75 µM/L; Grade 1: 76-150 µM/L; Grade 2: 151-200 µM/L; Grade 3: 201-250 µM/L; and Grade 4: > 251 µM/L.

### HE Index

HE index was calculated by

\( HE \) index = (Grade of mental state) X 3 + Grade of Number connection test + Grade of Flapping tremor + Grade of Serum ammonia.

### Change, inappropriate behavior; Grade 3: somnolence to semi-stupor, responsive to stimuli, confusion, gross disorientation, bizarre behavior; and Grade 4: coma, unable to test mental function.

### The Severity of Flapping Tremor

Severity was determined by extending the patients’ arms and forearms with the wrists dorsiflexed for at least 30 seconds. We adopted a simplified grading system to minimize inter-observer variance. Grade 0: no flapping motion; Grade 1: infrequent flapping motion; Grade 2: continual flapping motion; and Grade 3: unable to test.

### Number Connection Test (NCT)

The time taken to connect 25 progressive numbers, i.e. part A of the number connection test. Grade 0: < 30 sec (normal); Grade 1: 31-50 sec; Grade 2: 51-80 sec; Grade 3: 81-120 sec; and Grade 4: > 120 sec.

### Recovery of HE

HE grades improved in 31 out of 32 i.e. 96.87% in R+L group. In Lactulose group, it improved in 28 out of 28 patients, i.e. in 85.71%, p value 0.3251, which is (Table 3) not statistically significant. In our study, mental status grade improved from 1.81 to 0.22 (p=<0.05) in R+L group and from 1.57 to 0.43 (p=<0.05) in L group (Table 2); using independent paired t test. Asterixis grade improved from (Table 2) 2.13 to 0.16 (p=<0.05) in R+L group and
from 2.18 to 0.39 (p<0.05) in L group after treatment. In our study, after applying independent t test, it showed that; NCT grade improved from 3.84 to 1.75 (p<0.05) in R+L group and from 3.75 to 2.07 (p<0.05) (Table 2) in L group after treatment. Serum Ammonia grade improved from 2 to 0.81 (p<0.05) in R+L group and from 2.36 to 1.11 (p<0.05) in L (Table 2) group after treatment. In our study, after applying independent t test, it showed that; HE index pretreatment was 13.31 and 12.96 in R+L group and 8.79 in L group. P value being <0.05 in both groups after treatment, P value was 13.31 and 12.96 in R+L group and 4.86 in L group; using independent paired t test (Table 2).

Table 3: Changes in HE index and related parameters post-treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rifaximin + Lactulose</th>
<th>Lactulose</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood ammonia level (mmol/L)</td>
<td>172.53</td>
<td>191.75</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ammonia grade</td>
<td>2.0</td>
<td>2.36</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mental status grade</td>
<td>1.81±0.64</td>
<td>1.57±0.69</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Grade of flapping tremor</td>
<td>2.12</td>
<td>2.18</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Grade of NCT</td>
<td>3.84</td>
<td>3.75</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HE index</td>
<td>13.31</td>
<td>12.96</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Worsened</td>
<td>24</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>24</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>24</td>
<td>2</td>
<td></td>
</tr>
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</table>

In our study, hepatic encephalopathy index improved in 31 out of 32 i.e.96.87% in R+L group. In Lactulose group, it improved in 24 out of 28 patients, i.e. in 85.71%. After applying fisher exact test, it showed that there was no statistically significant difference in improvement of HE index in both groups after treatment, P value (2-tail) 0.3251 (Table 3). 6 patients expired and 54 patients survived. 2 deaths occurred in Rifaximin+ Lactulose group and 4 in Lactulose group.

Major causes of deaths were progressive hepatic encephalopathy, acute renal failure, hepatorenal syndrome, shock. Progressive hepatic encephalopathy accounted for 2 (33.33%) of deaths, hepatic encephalopathy + acute renal failure accounted for 1 (16.66%), hepatic encephalopathy +hepatorenal syndrome accounted for 2 (33.33%) of deaths, hepatic encephalopathy + shock due to hematemesis accounted for 1(16.66%) of deaths.

Adverse Effects
In Rifaximin + Lactulose combination group, loose motions occurred in 3(9.3%) patients, pain in abdomen in 2(6.2) patients. No serious adverse effects occurred in Rifaximin +Lactulose group. 27(84.5%) patients were free of any side effects. In Lactulose alone group, loose motions occurred in 4 (14.3%) patients, pain in abdomen in 1(3.6%) patient. No serious adverse effects occurred in this group. 23(82.1%) patients were free of any side effects. No patient withdrawn from the study due to an undue adverse effect. Frequency of adverse effects was same in both the groups.

Discussion
Rifaximin is an effective treatment of reversing HE. Several randomized controlled trails found Rifaximin to be at least as effective as current first line therapy in improving HE grades at a dose of 400 mg tds. A meta-analysis by Karim M Eltawil published in World J Gastroenterol 2012, performed a systematic review and random effects meta-analysis of all eligible trials identified through electronic and manual searches. 7 studies that investigated the efficacy of rifaximin (n = 184) vs non-absorbable disaccharides (n = 165) revealed that both groups experienced either full resolution of HE or clinical improvement that was considered significant by the primary investigators without reaching statistical significance (OR = 1.92, 95% CI: 0.79-4.68, P = 0.15). Bucci et al also showed equal efficacy of rifaximin and lactulose, with better tolerability and lack of side effects with rifaximin. Paik et al reported that both rifaximin and lactulose were effective in the majority of patients (84.4% and 95.4%, respectively) with significant improvement in blood NH3, flapping tremor, mental status, and psychometric test. In a randomized trial by Sharma et al. Comparing Rifaximin Plus Lactulose vs Lactulose Alone in treatment of Overt Hepatic Encephalopathy, 48 (76%) patients in group Rifaximin plus Lactulose compared with 25 (44%) patients in group who received Lactulose alone had complete reversal of HE (P=0.004) within 10 days. There was a significant decrease in mortality in the lactulose plus rifaximin group (15(24%) vs. lactulose alone (28 (49.1%), P<0.05).

In our study, mental status grade improved from 1.81 to 0.22 (p<0.05) in R+L group and from 1.57 to 0.43 (p<0.05) in L group; using independent paired t test (Table 2). But after applying multivariate analysis of variance test to compare the mental status grade between...
two groups on day 1, 3, 5-8, we found that the difference in the improvement in mental status in the two groups was not statistically significant; (p=0.191). In our study, Asterixis grade improved from 3.84 to 1.75 (p=<0.05) in R+L group and from 3.75 to 2.07 (p=<0.05) in L group after treatment. But after applying multivariate analysis of variance test to compare the Asterixis grade between two groups on day 1, 3, 5-8, we found that the difference in the improvement in Asterixis grade in the two groups was not statistically significant; (p=0.465). In our study, after applying independent t test, it showed that; NCT grade improved from 2.36 to 1.11 (p=<0.05) in R+L group and from 2.18 to 0.39 (p=<0.05) in L group after treatment. But after applying multivariate analysis of variance test to compare the NCT grade between two groups after treatment. P value (2 tail) 0.3251 Clinical efficacy was determined using HE index improvement (Table 3).

## Conclusion

The drug groups, Rifaximin + Lactulose combination and Lactulose are equally effective in treatment of hepatic encephalopathy. But the combination of Rifaximin + Lactulose is not superior to Lactulose alone in improving HE grades, HE index, Serum Ammonia and in treatment of hepatic encephalopathy. As adverse effects included pain in abdomen, diarrhea in few patients. Limitations of study is its non-randomized study, small sample size. Further such studies are required in future.

## References

2. Gastroenterology and Hepatology Volume 7, Issue 4 April 2011 R. Todd Frederick, MD