Rifaximin versus Lactulose in Treatment of Hepatic Encephalopathy: Evidence Based Case Report

Author
dr. Anindia Larasati
NPM: 1206234540

Division of Hepatology
Department of Internal Medicine
Faculty of Medicine University of Indonesia
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INTRODUCTION

Approximately 5.5 million persons in the United States have hepatic cirrhosis, a major cause of complications and death. Hepatic encephalopathy, a complication of hepatic cirrhosis, imposes a burden on patients, their families, and health care provider. Overt episodes of hepatic encephalopathy are debilitating, can occur without warning, and frequently result in hospitalization. In 2003, more than 40,000 patients were hospitalized with hepatic encephalopathy, a number that increased to over 50,000 in 2004. Hepatic encephalopathy is a neuropsychiatric syndrome for which symptoms, manifested on a continuum, are deterioration in mental status, with psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration, disorientation, and — in severe forms — coma. The clinical diagnosis of overt hepatic encephalopathy is based on two concurrent types of symptoms: impaired mental status, as defined by the Conn score (also called West Haven criteria) (on a scale from 0 to 4, with higher scores indicating more severe impairment). 1

Most therapies for hepatic encephalopathy focus on treating episodes as they occur and are directed at reducing the nitrogenous load in the gut, an approach that is consistent with the hypothesis that this disorder results from the systemic accumulation of gut-derived neurotoxins, especially ammonia, in patients with impaired liver function and portosystemic shunting. Current treatment strategies include measures aimed at reducing the serum level of ammonia, providing specialized nursing care as well as correcting precipitating factors such as gastrointestinal hemorrhage, infection, constipation, and electrolyte disturbances. Lactulose ($\beta$-galactoside fructose) and lactitol ($\beta$-galactoside sorbitol) have been the first-line drug for the treatment of HE. They are directed at reducing the serum level of ammonia, since they decrease the absorption of ammonia through cathartic effects and by altering the colonic pH. The side effects of nonabsorbable disaccharides include abdominal pain, flatulence, and severe diarrhea, which may lead to the cessation of therapy. Antibiotics such as neomycin, vancomycin, metronidazole, and rifaximin were shown to be effective in the treatment of both acute and chronic encephalopathy.1,2,3

Antibiotics reduce bacterial production of ammonia through suppression of intestinal flora. Due to serious side effects such as ototoxicity and nephrotoxicity, most antibiotics
exception of rifaximin are not suitable for longterm use for the treatment of HE. Rifaximin is a minimally absorbed oral gastrointestinal selective antibiotic, with very few systemic side effects and has a low risk of inducing bacterial resistance. Various studies, such as cases study, observational, longitudinal design (case control and cohort), and also clinical trials, had been conducted to search a new evidence of rifaximin and lactulose use in HE. Every research resulted into different conclusions, therefore, we think it would be very useful if we made evidence-based case report (EBCR) comparing rifaximin to nonabsorbable disaccharides for the treatment of patients with HE.1,2,3

Clinical Question

In patient with minimal hepatic encephalopathy, is rifaximin more effective than lactulose in treating patient with minimal hepatic encephalopathy?

Searching the evidence

In order to answer the question above, we conduct a searching in PubMed site by using keywords, they are “rifaximin” AND “nonabsorbable disaccharides” OR “lactulose” on February 18th 2014. We found 13 articles, and then to attain the best evidence, we limit our search only on articles that were published in the last 5 years. Based on this strategy there were 9 articles remained. Then we excluded 6 articles which lacking abstract, not available in full text, not written in English, and articles which did not answer the clinical question. Based on this strategy the searching were narrowed down to 2 articles. Of all the 2 articles, 1 of them were randomized controlled trial and 1 of them was meta analysis. To attain the best evidence, we limit our search on RCT and meta analysis (the highest level in the evidence based medicine pyramid). Thus, from the searching step, there were 3 articles that go to the next process.

The next process was selection by reading those 2 articles. The articles included in this EBCR were articles that reviewing the use of rifaximin and lactulose in hepatic encephalopathy patient.

The first article written by Wu Dong et al. Reviewed Rifaximin versus nonabsorbable disaccharides for the treatment of hepatic encephalopathy. The study was a meta analysis of controlled trial which was published in 2013.4

The second article written by Sharma, et al. Comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. The study was a randomized, double blind controlled trial which published in 2013.5
Thus, in this ebcr, those 2 articles were included. One article written by Wu Dong et al, and 1 article by Sharma et al. The following figure is regarding the method use to select the article that becomes the reference in this EBCR.

Results

A randomized, double blind, controlled trial comparing rifaximin plus lactulose with lactulosa alone in treatment of overt hepatic encephalopathy

Sharma et al conducted the study which was published in 2013 to evaluate the efficacy and safety of rifaximin plus lactulose versus lactulose alone for treatment of overt HE. Group A patients were treated with rifaximin, one 400 mg capsule three times a day, and lactulose, 30 – 60 ml / three times a day, so that patient passes two to three semisoft stools in a day. Group B patients were treated with lactulose 30 – 60 ml / three times a day so that patient passes two to three semisoft stools in a day and one placebo capsule (sugar) three times a day. A total of 120 patients (mean age 39.4 ± 9.6 years; male / female ratio 89:31) were included in the study. 37 (30.8 % ) patients were in Child – Turcotte – Pugh (CTP) class B and 83 (69.2 % ) were in CTP class C. Mean CTP score was 9.7 ± 2.8 and the MELD (model for end-stage liver disease) score was 24.6 ± 4.2. At the time of admission, 22 patients (18.3 % ) had grade 2, 40 (33.3 % ) had grade 3, and 58 (48.3 % ) had grade 4 HE. Of the patients, 48 (76 % ) in group A compared with 29 (50.8 % ) in group B had complete reversal of HE ( \( P < 0.004 \)).
The primary end point of the study was complete reversal of HE as per West Haven criteria. The secondary end points were mortality and hospital stay. There was a significant decrease in mortality after treatment with lactulose plus rifaximin vs. lactulose and placebo (23.8 % vs. 49.1 %, \( P < 0.05 \)). There were significantly more deaths in group B because of sepsis (group A vs. group B: 7:17, \( P = 0.01 \)), whereas there were no differences because of gastrointestinal bleed (group A vs. group B: 4:4, \( P = \) nonsignificant (NS)) and hepatorenal syndrome (group A vs. group B: 4:7, \( P = \) NS). Patients in the lactulose plus rifaximin group had shorter hospital stay (5.8 ± 3.4 vs. 8.2 ± 4.6 days, \( P = 0.001 \)). There were no serious side effects related to lactulose and placebo or lactulose and rifaximin therapy. The highlight of this study would be the combination therapy of lactulose and rifaximin is decrease hospital mortality mainly by decreasing sepsis-relapsed death thus it is more effective in the treatment of HE and the combination therapy should be the standard care for the treatment of hepatic encephalopathy. 

Rifaximin versus nonabsorbable disaccharides for the treatment of hepatic encephalopathy: A meta-analysis

Wu et al conducted a meta-analysis which was published in 2013 evaluate all RCT’s comparing rifaximin to nonabsorbable disaccharides for the treatment of patients with HE. Some studies showed that rifaximin is superior to lactulose and antimicrobials in patients with mild to moderate severe HE, but previous studies have reached different conclusions. Wu performed a meta-analysis through electronic searches to evaluate the efficacy and safety of rifaximin in comparison with nonabsorbable disaccharides. A total of 8 randomized controlled trials including 407 patients were included. The efficacy of rifaximin was equivalent to nonabsorbable disaccharides according to the statistical data (risk ratio (RR): 1.06, 95% CI: 0.94–1.19; \( P = 0.34 \)). Analysis showed that patients treated with rifaximin had better results in serum ammonia levels (weighted mean difference (WMD): –10.63, 95% CI: –30.63–9.38; \( P = 0.30 \)), mental status (WMD: –0.32, 95% CI: –0.67–0.03; \( P = 0.07 \)), asterixis (WMD: –0.12, 95% CI: –0.31–0.08; \( P = 0.23 \)), electroencephalogram response (WMD: –0.21, 95% CI: –0.34–0.09; \( P = 0.0007 \)), and grades of portosystemic encephalopathy (WMD: –2.30, 95% CI: –2.78–1.82; \( P < 0.00001 \)), but only the last ones had statistical significance. The safety of rifaximin was better than nonabsorbable disaccharides (RR: 0.19, 95% CI: 0.10–0.34; \( P < 0.00001 \)).
### Inclusion Criteria

- **Sharma et al. (2013)**
  - Patient aged 18-80 years with liver cirrhosis and overt HE

- **Wu et al. (2013)**
  - Patient over 18 years

### Intervention

- **Sharma et al. (2013)**
  - Treatment group (A): Rifaximin 3x400mg per day and lactulose 30-60 ml 3x/day
  - Control group (B): Lactulose 30-60 ml/day and placebo 3x/day

- **Wu et al. (2013)**
  - Treatment group (A): Rifaximin 1200 mg/day
  - Control group (B): Lactulose 45-120 ml/day

### Outcome

- **Sharma et al. (2013)**
  - Complete reversal of HE
  - Mortality and hospital stay

- **Wu et al. (2013)**
  - Efficacy
  - Safety or Adverse event
  - Secondary outcomes: Psychometric parameters, blood ammonia level

### Study Design

- **Sharma et al. (2013)**
  - Prospective double blind randomized controlled trial

- **Wu et al. (2013)**
  - Meta analysis

## Internal Validity

### Table 2. Internal validity

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Baseline characteristics</th>
<th>Equal treatment</th>
<th>Outcome</th>
<th>Blinding</th>
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<td>Sharma et al. (2013)</td>
<td>Yes</td>
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<tr>
<td>Wu et al. (2013)</td>
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## Discussion

Hepatic encephalopathy (HE) is the second most common major complication in cirrhotics, following ascites. It is a complex neuropsychiatric syndrome characterized by a general depression of the central nervous system, with clinical manifestations ranging from only minor signs of altered brain function, overt psychiatric and/or neurological symptoms to deep coma, commonly reversible after therapy. Although different factors have been implicated in HE pathogenesis, however plasma ammonia certainly remains the key factor. Ammonia is mainly produced in the gut by glutamine metabolism in the small bowel and by bacterial flora in the large bowel. Different precipitating factors of HE onset in cirrhotics have been
identified. Protein overload (dietary intake or gastrointestinal bleeding), constipation, catabolism status (infections, starvation) and diuretics are well-known risk factors for HE. Of note, all these conditions lead to an ammonia increase. Therefore, current therapeutic approaches for HE treatment and prevention mainly rely on ammonia lowering strategies. Diagnosis of overt hepatic encephalopathy should be made after the exclusion of other brain disorders and based on two types of symptoms. Impaired mental status, as defined by the Conn score, with higher scores indicating more severe impairment, and impaired neuromotor function includes hyperreflexia, rigidity, myoclonus, and asterixis. Elevated serum ammonia level is an effective index of HE and is detected in 60%–80% of affected patients, but a single ammonia level in the diagnosis of HE is uncertain given the substantial overlap of ammonia levels in both patients with and without encephalopathy.

The prevention of episodes of hepatic encephalopathy is an important goal in the treatment of patients with liver disease, especially since symptoms of overt encephalopathy are debilitating and decrease the ability for self-care, leading to improper nutrition and nonadherence to a therapeutic regimen, which in turn leads to severe symptoms, frequent hospitalizations, and a poor quality of life. Study conducted by Bass et al (2010) showed that the use of rifaximin reduced the risk of a breakthrough episode of hepatic encephalopathy during a 6-month period among patients in remission who had a recent history of recurrent overt hepatic encephalopathy (≥2 episodes within the previous 6 months) before enrollment. The reduced risk was seen across subgroups, further showing the consistency of the results, which expand previously reported findings of the efficacy of rifaximin in the treatment of overt hepatic encephalopathy.

Treatment of an acute episode of HE consists of both the removal of any precipitating event, such gastrointestinal bleeding, constipation, electrolyte imbalance and infection, and in lowering ammonia production in the bowel, by using cathartic procedures and nutritional support. Unfortunately, recurrence of HE is not a rare event in these patients, even in the absence of any identifiable precipitating factor. Different therapeutic approaches have been attempted to prevent HE recurrence, such as branched-chain amino acids supplementation, acetyl-l-carnitine. In clinical practice, administration of non-absorbable disaccharides is commonly applied to both treat and prevent HE in patients with advanced disease or in cirrhotics at increased risk, such as those with transjugular intrahepatic portosystemic shunt (TIPS). Indeed, both lactulose and lactitol administered per os (or by enema when patient is
in coma) are able to reduce both the production and absorption of ammonia through different mechanisms. At the standard doses used (30-60 mg/d), non-absorbable disaccharides therapy is safe, generally well tolerated, effective in both treating and preventing an overt HE episode, including the minimal HE, and cheap. Therefore, this cornerstone therapy is generally considered as the current golden standard for comparison with all other therapeutic strategies.6,7

Rifaximin is a poorly absorbed, oral antibiotic. It is derived from rifamycin and has a broad spectrum of activity against Gram-positive and Gram-negative, aerobic and anaerobic, enteric bacteria. It is thought to diminish deaminating enteric bacteria to decrease production of nitrogenous compounds that are subsequently absorbed and cause HE. The number and length of hospitalizations for acute HE were significantly reduced in patients treated with rifaximin in comparison to lactulose. Since rifaximin has efficacy in the treatment of acute HE and has a favorable side-effect profile that lends itself to long-term therapy, a trial was undertaken to examine the effect of rifaximin on the reduction of risk of recurrence of HE in a group of patients at high risk. The efficacy and safety of rifaximin in maintaining remission of HE over 6 months in patients at high risk were assessed within the context of a phase 3, randomized, double-blind, placebo-controlled, multicenter, ultinational trial. Study conducted by Wu et al (2013) showed that rifaximin was as effective as nonabsorbable disaccharides but with fewer adverse events. A randomized, double-blind, placebo-controlled trial showed that rifaximin was effective in preventing hepatic encephalopathy. Over a 6-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than placebo. Rifaximin treatment also significantly reduced the risk of hospitalization involving hepatic encephalopathy. So, rifaximin is effective in the treatment and prevention of hepatic encephalopathy, but more studies are needed to assess its safety, including tolerance, toxicity, bacterial resistance, and mycotic infection.4,8

Study conducted by Sharma et al (2013) showed that a combination of rifaximin plus lactulose was more effective than lactulose alone for improvement of HE and reduction in mortality. Rifaximin offers an attractive choice as the risk of bacterial resistance appears to be lower with rifaximin than with systemic antibiotics. Plasma levels of rifaximin are negligible; therefore, bacteria outside the gastrointestinal tract are not exposed to appreciable selective pressure. Both rifaximin and lactulose have exclusive mechanisms of action. Lactulose lowers the colonic pH that favors formation of insoluble ammonium from soluble
ammonia, resulting in reduced systemic absorption. In addition, lactulose causes a fourfold increase in fecal nitrogen excretion because of its cathartic effects. Small intestinal bacterial overgrowth in cirrhotic patients is common and is associated with systemic endotoxemia. Rifaximin contributes to restore gut microflora imbalance and is an important therapeutic agent in small intestinal bacterial overgrowth.5

**Conclusion**

In summary, we conclude that these study shows that rifaximin is as effective as nonabsorbable disaccharides, maybe better in some psychometric outcomes, with fewer adverse events. Sensitivity analysis showed significant difference in the treatment of acute HE, favoring the use of rifaximin, but the result may be not credible because of small samples. We suggest that rifaximin should be used as second-line, because of its expensive price and safety in long-term use. Patients who have severe adverse events in disaccharides therapy could use rifaximin instead. Combination of rifaximin and lactulose is more effective than lactulose alone for treatment of overt HE in patients with cirrhosis.

**References**