EFFICACY OF RIFAXIMIN VERSUS LACTULOSE FOR REDUCING THE RECURRENCE OF OVERT HEPATIC ENCEPHALOPATHY AND HOSPITALIZATIONS IN CIRRHOSIS

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EFFICACY OF RIFAXIMIN VERSUS LACTULOSE FOR REDUCING THE RECURRENCE OF OVERT HEPATIC ENCEPHALOPATHY AND HOSPITALIZATIONS IN CIRRHOSIS (Abstract): Both rifaximin and lactulose have been reported to be effective for maintenance of remission from hepatic encephalopathy (HE) in patients with cirrhosis. The aim of this study was to compare the efficacy of different treatment strategies for preventing recurrences and HE-related hospitalizations. Materials and methods: Seventy-eight cirrhotic patients who recovered from HE were grouped according to one of the following therapies: rifaximin intermittently 14 days/month (RI-group), rifaximin 400 mg three times daily (RD-group) and lactulose 30 to 60 ml in 2 or 3 divided doses daily (L-group) for a 6-month period. The follow-up lasted 12 months. A Kaplan-Meier analysis was performed to determine the probability of developing recurrent overt HE episodes. The frequencies of HE-related hospitalizations in the three groups were evaluated comparatively. Results: Over a 12-month follow-up period, 10 (26.31%) of 38 patients in the RI-group, 7 (25%) of 28 in the RD-group and 4 (33.33%) of 12 in the L-group experienced recurrent bouts of HE, the differences not being significant. More L-group patients experienced more severe episodes of overt HE in spite of mild or moderate disease. In the rifaximin groups overt HE episodes were similarly frequent, and the severity of bouts was associated with Child-Pugh score. Fewer hospitalizations were reported in the rifaximin groups. Conclusions: According to our data, rifaximin and lactulose are equally effective for the maintenance of remission from overt HE. However, rifaximin is superior for reducing the risk of HE-related hospitalization. Keywords: HEPATIC ENCEPHALOPATHY, LACTULOSE, RIFAXIMIN, HOSPITALIZATION.

Hepatic encephalopathy (HE) is a common complication of either acute or chronic liver disease, potentially reversible, or progressive. The annual risk of developing overt HE in cirrhotic patients is 20% (1). An estimated one-third to one-half of hospitalizations for cirrhosis are related to overt HE, and the frequency of hospitalization for overt HE has nearly doubled over the last decade.

HE is characterized by disturbances in consciousness and behavior, personality changes, fluctuating neurological signs, as-
The neuropsychiatric abnormalities range from cognitive deficits (referred to as subclinical HE, minimal HE, or more recently, covert HE), which can only be diagnosed by specialized testing to clinically apparent neuropsychiatric complications consisting of alterations in consciousness and motor disturbances (referred to as overt HE) (3, 4).

Gut-derived toxins such as ammonia are thought to play a central role in the pathogenesis of HE (5). Treatment strategies are based on the principle of reducing the production and absorption of ammonia in the gut.

The development of HE is considered a sign of a poor prognosis and patients should receive therapy for an indefinite period of time or until they undergo liver transplantation (6). Therefore, prevention of overt HE is warranted. The term secondary prophylaxis was proposed to define the therapy administered to prevent recurrence of overt HE in patients with a history of overt HE episodes (7). Currently, the options for a long-term treatment of HE are lactulose, a non-absorbable disaccharide, and rifaximin, a minimally absorbed oral antibiotic. Several studies have demonstrated the efficacy of rifaximin and lactulose for the maintenance of remission from HE and decrease in hospitalization requirement (7, 8).

In this prospective study conducted over a 12-month period we evaluated comparatively the efficacy of rifaximin and lactulose for prevention of overt HE recurrence and frequency of HE-related hospitalizations in patients with previous episodes of overt HE.

MATERIAL AND METHODS

Patients with cirrhosis who were followed up in our outpatient clinic or hospitalized between October 2010 and December 2011 were considered eligible. The study was performed in accordance with the ethical principles of the Declaration of Helsinki. The protocol was explained to at least one relative of each patient and written informed consent was obtained from all selected patients or their relatives.

Inclusion criteria were: patients with a definite diagnosis of cirrhosis, at least one episode of overt HE in the history (grade 2 or more according to West-Haven criteria) and remission at baseline (grade 0 or 1 according to West-Haven criteria), different grades of liver failure (Child-Pugh A-C, MELD 10-25), and a written informed consent to participate. Exclusion criteria were: gastrointestinal bleeding, spontaneous bacterial peritonitis or other conditions associated with HE precipitation within 3 months before the enrollment, diagnosis of a neurological or psychiatric disease, and current use of psychotropic medications, systemic uncontrolled disease (cardiac, respiratory, kidney failure), recent (< 3 months) active alcoholism, and absence of informed consent. Seventy-eight patients were evaluated. There were no significant differences in the distribution according to gender and etiology of the cirrhosis. Most patients had mild to moderate liver failure. Esophageal varices 2nd degree or more were detected in 54 of the 78 patients (tab. I).

Before enrollment, all patients had a score 0 or 1 according to West-Haven scale.

In order to evaluate the efficacy of different treatment strategies our patients were divided into three groups. RI Group = 38 patients (48.8%) was treated with rifaximin intermittently (14 days/month for 6 months), RD Group = 28 patients (35.9%) received rifaximin daily (400 mg three times daily), and L Group= 12 patients
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(15.3%) treated with lactulose 30 to 60 ml in 2 or 3 divided doses per day, for a 6-month period. No significant differences in terms of age, gender, etiology of cirrhosis and severity of liver disease were found in the three groups.

TABLE I
Patients characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>56.3 [41-75]</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>44/34</td>
</tr>
<tr>
<td>Etiology of cirrhosis:</td>
<td></td>
</tr>
<tr>
<td>Alcoholic</td>
<td>29</td>
</tr>
<tr>
<td>HCV/HBV/HBV+HDV</td>
<td>37/2/4</td>
</tr>
<tr>
<td>HCV+alcohol</td>
<td>6</td>
</tr>
<tr>
<td>MELD score</td>
<td>15.69 [10-25]</td>
</tr>
<tr>
<td>Child-Pugh class (A/B/C)</td>
<td>27/43/8</td>
</tr>
<tr>
<td>Esophageal varices (No/I/II/III/IV)</td>
<td>20/38/12/4</td>
</tr>
</tbody>
</table>

All patients were followed up every 3 months or at any presentation in outpatient clinic or hospital in a period of one year. Patients were monitored for occurrence of recurrent overt HE, the incidence and severity of episodes and number of hospitalizations involving any episode of overt HE being recorded.

HE was assessed using West-Haven mental status scale and asterixis grade. West-Haven criteria are defined as follows: grade 0: no detectable changes in behavior or personality; grade 1: trivial loss of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition; grade 2: lethargy or apathy, impaired performance of subtraction, minimal disorientation to time or place, subtle personality change, inappropriate behavior; grade 3: confusion, gross disorientation, somnolence to semi-stupor (may respond to verbal stimuli); and grade 4: coma (no response to verbal or noxious stimuli) (9). Asterixis was graded as follows: 0, no tremors; 1, few flapping motions; 2, occasional flapping motions; 3, frequent flapping motions; and 4, almost continuous flapping motions (10).

An episode of overt HE was defined as an increase from a baseline West-Haven score 0 or 1 to a score of 2 or more, or baseline West-Haven score and asterixis grade each increasing by 1 point. HE–related hospitalization was defined as hospitalization directly caused by HE or a hospitalization during which a HE event occurred.

RESULTS

Recurrence of overt HE

Of the 78 patients, overt HE episodes occurred in 21 (26.92%) during the 12-month study period. The distribution of total cases of overt HE was as follows: 10 of 38 patients in RI group, 7 of 28 patients in RD group and 4 of 12 patients in L group. Probability of developing recurrent overt HE, illustrated by a Kaplan-Meier analysis, was not significantly different in the three groups: 26.31% in RI group, 25% in RD group versus 33.33% in L group (fig. 1).

Severity of the overt HE episodes

Patients in L group experienced more
severe episodes of overt HE (grade 3/4) in spite of mild or moderate disease. In the rifaximin groups overt HE episodes were similarly frequent and associated with the severity of liver disease according to Child-Pugh score.

![Graph](image)

**Fig. 1.** Probability of developing recurrent overt HE in patients receiving therapy with lactulose following an episode of overt HE compared with patients receiving daily or intermittently rifaximin.

**Safety**

No serious adverse events related to either treatment were found during the study. There was no significant difference between rifaximin and lactulose on overall patient compliance (100% versus 92%). The most common adverse events with rifaximin were abdominal pain (5 patients - 7.57%) and dizziness (3 patients-) showing no consistent pattern or dose relationship. In the lactulose group, 2 patients (16.66%) complained of abdominal pain and 4 patients (33.33%) experienced diarrhea.

**TABLE II**

<table>
<thead>
<tr>
<th>Requirement for EH-related hospitalization</th>
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<tbody>
<tr>
<td>Number of EH-related hospitalizations</td>
</tr>
<tr>
<td>Rifaximin intermittently group (10 patients)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>One admission</td>
</tr>
<tr>
<td>Two admissions</td>
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</tbody>
</table>

**Hospitalizations**

A total number of 26 HE-related hospitalizations were recorded during follow-up. The 10 patients in RI group required 12 hospitalizations: two patients required two hospitalizations and eight patients one hospitalization. The 7 patients in RD group required 8 hospitalizations: one patient two admissions and six patients one. In the L group, the 4 patients experienced 10 hospi-
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talizations: two patients one admission and two patients two admissions (tab. II). The frequency of HE-related hospitalization was comparable between RI group and RD group (31.57% vs. 28.57%), but significantly lower than in L group (50%).

DISCUSSION

Recurrent bouts of HE that require evaluation and hospitalization cause a significant burden to patients, their families and caregivers as well as to the healthcare system.

Currently, lactulose and non-absorbable antibiotics such as rifaximin are the only two medications effective when used for secondary prophylaxis against recurrence of overt HE in patients who have recovered from an episode of overt HE (7, 8, 10).

Systematic reviews of randomized trials comparing disaccharides vs. antibiotics for the treatment of HE has shown contradictory results. Whilst Nielsen et al. found superior outcomes with the use of antibiotic therapy (11), a meta-analysis of seven randomized controlled trials concluded that rifaximin was not superior to non-absorbable disaccharides in the long-term or short-term treatment except that it was better tolerated (12). Recently, another meta-analysis found that rifaximin has similar effectiveness to other oral therapies with a better safety profile (13).

Both rifaximin and lactulose demonstrate superior efficacy versus placebo for maintenance of remission from HE and lowering the frequency of HE-related hospitalizations. Sharma et al.(7) published the results of a recent open-label study of lactulose versus placebo for preventing recurrence of overt HE in cirrhotic patients showing the utility of lactulose as a secondary prophylactic therapy. Over a median follow-up period of 14 months, the probability of developing recurrent overt HE in patients receiving lactulose was 19.6% compared with 46.8% in the placebo group. Bass et al.(10) found rifaximin 550 mg twice daily more effective than placebo for maintenance of remission from HE over a 6 month period (rifaximin 22% breakthrough HE episodes versus placebo 46%). Further evaluation in a 24 months open-label maintenance trial concluded that long term treatment with rifaximin provide continued protection from HE and reduce the hospitalization rate (8). One of the main limitations of the study was the lack of a real placebo group, concomitant administration of lactulose being permitted. Hence this limited the evaluation of the efficacy of rifaximin alone.

Our study confirmed the efficacy of the two drugs in the maintenance of remission from overt HE, in agreement with the published data (7, 8, 10). Lower frequencies of HE hospitalizations were observed in the rifaximin groups, in line with the results of retrospective chart reviews (14, 15), which have shown that rifaximin, as compared with lactulose, is associated with a significantly lower rate and duration of hospitalization and lower hospital costs. We found a better tolerability of rifaximin which coincides with previous data (14, 16). However, our results are in contradiction with a recent meta-analysis which reported no significant difference between rifaximin and lactulose on diarrhea, but a significant difference in favor of rifaximin on abdominal pain (12).

It appears that rifaximin monotherapy could be a suitable option for long term treatment. However, given the high treatment cost and the current available data, it may be prudent not to recommend rifaximin as long
term treatment in all cirrhotic patients. Our results could represent a starting point for evaluating in future studies the cost-effectiveness and budget impact of competing therapies in hepatic encephalopathy.

The current study differs from the previous randomized studies in that it compared rifaximin and lactulose in terms of prevention the recurrences of overt HE and HE-hospitalizations; we did not have a placebo group since the lack of the treatment in patients at high risk for hepatic encephalopathy was considered unethical. In addition, we evaluated two dosage regimens for rifaximin (daily/intermittent) which proved to be similar for secondary HE prophylaxis. As in a previous study, we chose to define remission as West-Haven grade 0 or 1 because of the difficulties and variability in diagnosing mild HE, in addition with a known fluctuating course between 0 and 1.

One limit of our study is related to the small number of enrolled patients. Also patients with highly advanced liver disease (MELD score >25) were not evaluated.

CONCLUSIONS

We demonstrated that over a 12-month period, rifaximin in daily or intermittently dosage and lactulose are effective in the prevention of overt HE recurrences. No marked difference between the three therapeutic regimens was found in terms of maintenance of remission from overt HE. However, rifaximin reduces the risk of hospitalization involving HE better than lactulose.

REFERENCES

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NEWS

EFFECT OF LAYERING METHODS, COMPOSITE TYPE, AND FLOWABLE LINER ON THE POLYMERIZATION SHRINKAGE STRESS OF LIGHT CURED COMPOSITES

The polymerization shrinkage and its associated stress still remain a major drawback of dental composite materials, resulting in bond failure, cuspal flexure, enamel microcracking and bacterial infiltration. Different materials and techniques have been suggested to minimize shrinkage stress of composite resins. The aim of this study was to investigate the effect of layering methods, flowable composite liner and use of low shrinkage silorane-based composite on the polymerization shrinkage stress of light cured composites. Aluminum blocks were used to prepare MOD cavities and divided into four groups. A universal hybrid methacrylate-based composite (Z250), a flowable composite (Z350 flowable), and a silorane-based composite (P90) were used to fill the cavities. Cavities were restored using the bulk technique with Z250, an increment technique with Z250, an increment technique with Z250 and a Z350 flowable lining, and an increment technique with P90. The axial shrinkage strain and flexural modulus of the three composites were determined, and cuspal deflection of each group was measured with linear variable differential transformer probes and compared among groups using ANOVA and Tukey's post hoc test (α = 0.05). The incremental filling technique yielded significantly lower cuspal deflection than the bulk filling technique. Flowable composite lining under universal composite (Z250) layering showed higher cuspal deflection than that without flowable composite lining. Silorane-based (P90) composite exhibited lower cuspal deflection than metacrylate based (Z250) composite. These results suggest that cuspal deflection resulting from polymerization shrinkage stress may be reduced by an incremental filling technique and by the use of low shrinking composite. On the other hand, flowable composite lining under conventional composite layering did not reduce the polymerization shrinkage stress in this study. The cuspal deflection of the first increment layered with a flowable composite liner (Z350 flowable) was considerably higher than the first increment layered with a conventional hybrid composite (Z250). However, the authors suggest that using flowable composite liners with different elastic modulus, shrinkage values, and varying thickness might produce different results (Kwon Y, Ferracane J. Effect of layering methods, composite type, and flowable liner on the polymerization shrinkage stress of light cured composites. Dental Materials 2012; 28(7): 801-809).

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