Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis


CRD summary
The authors concluded that rifaximin was not superior to non-absorbable disaccharides for acute or chronic hepatic encephalopathy in the long-term or short-term treatment, except that it may be better tolerated. Given the lack of reporting on methodological processes and the small number of included participants, this conclusion should be interpreted with caution.

Authors' objectives
To evaluate the effectiveness of rifaximin compared with non-absorbable disaccharides in the treatment of hepatic encephalopathy (or portosystemic encephalopathy).

Searching
Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Science Citation Index and China Biological Medicine Database (CBMdisc) were searched to October 2007. There were no language or publication status restrictions. Search terms were reported. References lists of relevant articles were also searched.

Study selection
Eligible for inclusion in the review were randomised controlled clinical trials (RCTs) that compared rifaximin with non-absorbable disaccharides, in patients with signs and symptoms of acute, chronic or minimal hepatic encephalopathy (according to Conn's modification of Parsons Smith Classification). Eligible trials had to include patient populations aged 18 years and over, with serum ammonia levels greater than 75 μmol/L. The following were excluded from the review: non-controlled clinical trials; studies with patients with certain concomitant conditions; pregnant or lactating women; patients who did not fulfil protocol requirements; and results published in abstract form and where raw data was not completed.

The primary outcome was clinical efficacy, which was defined as an improvement in hepatic encephalopathy clinical syndrome, or a significant decrease in the portosystemic encephalopathy index. Secondary outcomes were blood ammonia concentration and adverse reports of diarrhoea and abdominal pain.

Included trials were performed in Spain, Italy and Korea. Type of hepatic encephalopathy in the included trials varied in terms of grade and chronic or acute status. A range of evaluation criteria for hepatic encephalopathy were used.

Two reviewers independently selected the studies for inclusion in the review. It was not reported how disagreements were resolved.

Assessment of study quality
Trial quality was assessed using the Jadad scale, which assesses the descriptions of randomisation, blinding and withdrawals. A maximum score of 5 points was achievable. Trials were deemed to be of high quality if they scored 3 or more points.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Data was extracted in order to calculate relative risk (RR) and 95% confidence intervals (CI) for dichotomous outcomes and weighted mean differences (WMD) and 95% confidence intervals for continuous outcomes.

Methods of synthesis
Relative risks or weighted mean differences were combined in a meta-analysis using the fixed-effect model. It appears that low quality trials were excluded from the analysis. Heterogeneity was assessed using the Q test and $I^2$ test. If heterogeneity was present, the relative risks or weighted mean differences were then combined in a random-effects (DerSimonian and Laird) model. Publication bias was assessed using the Begg's and Egger's tests. Sensitivity analysis was performed according to ethnic group, by the removal of the Korean study from the analysis, and also by chronic versus acute hepatic encephalopathy.

**Results of the review**

Five RCTs were included in the review (264 patients). Sample sizes ranged from 22 to 103. It was noted that there was a discrepancy in the number of patients reported to be randomised for one trial. The range of trial quality was 3 to 5 points. There was no evidence of publication bias.

There was no statistically significant difference between rifaximin and non-absorbable disaccharides in terms of clinical efficacy or diarrhoea. There was a statistically significant association between the use of rifaximin and the decreased risk of abdominal pain (RR: 0.28, 95% CI 0.08 to 0.95), but statistically significant heterogeneity was reported ($I^2=62.7\%$). Blood ammonia concentrations were not analysed due to large differences in baseline concentrations.

Sensitivity analysis also revealed that there was no statistically significant difference between rifaximin and non-absorbable disaccharides in the treatment of hepatic encephalopathy according to ethnicity or chronic versus acute state of hepatic encephalopathy. However, no data on the presence or absence of heterogeneity was reported for the sensitivity analysis.

**Authors' conclusions**

Rifaximin was not superior to non-absorbable disaccharides for acute or chronic hepatic encephalopathy in long-term or short-term treatment except that it may be better tolerated.

**CRD commentary**

The review addressed a clear research question and was supported by appropriate inclusion criteria. The search strategy was adequate and had no language or publication status restrictions. There was no evidence of publication bias. The study quality assessment tool was appropriate for the included study designs. However, it was not reported how the study quality assessment or data extraction was performed, so these review processes may have been subject to reviewer error or bias. Synthesis methods were appropriate. However, the use of heterogeneity to determine the employment of a fixed-effect or random-effects model may not be reliable. Given the lack of reporting on methodological processes and the small number of included participants, the authors' conclusion should be interpreted with caution.

**Implications of the review for practice and research**

*Practice:* The authors did not state any implications for practice.

*Research:* The authors stated that further studies on larger populations of patients are necessary to obtain more sufficient evidence for the evaluation of rifaximin versus non-absorbable disaccharides for hepatic encephalopathy.

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