CrossMark

Probiotics for secondary prevention of hepatic encephalopathy

doi:10.1136/flgastro-2014-100534

Philip Hendy, Nik Ding

Probiotic therapy: a promising addition to the therapeutic armamentarium of prophylactic therapies for patients with cirrhosis and previous hepatic encephalopathy

- Dhiman RK, Rana B, Agrawal S, *et al.* Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. *Gastroenterology* 2014;147:1327–37.

This randomised controlled trial reports that daily VSL#3 monotherapy reduces hospitalisation rates for hepatic encephalopathy in patients, with established cirrhosis, who have recently been discharged following an episode hepatic encephalopathy.

Hepatic encephalopathy (HE) causes significant disability in patients with hepatic cirrhosis, occurring in up to 50% and being associated with a 1-year survival rate of <50%. The aetiology is incompletely understood, but is known to be related to portal hypertension, hyperammonaemia and an intestinal microbial dysbiosis. There is considerable interest in modulating the gut microbiota to correct the dysbiosis and reduce the volume of ammonia-producing organisms. Diet, antibiotics, correction of micronutrients and probiotics have all been studied. Randomised controlled trial (RCT) data and subsequent meta-analyses have shown the benefit of rifaximin in the secondary prevention of breakthrough HE, but the National Institute for Health and Care Excellence has not recommended its use for this indication.

A number of studies have shown a benefit of probiotic supplementation for this indication.¹ Meta-analysis data are also positive for the use of probiotics. It is important to consider, though, that probiotics are heterogeneous containing a range of

different organisms and at different concentrations, and thus meta-analyses should be interrogated thoroughly before their verdicts are accepted.

Patients with hepatic cirrhosis, of any aetiology, and a resolved episode of HE in the preceding month at a tertiary care hospital in India were assigned to a 6-month regimen of once daily VSL#3 or placebo, in this double-blind RCT. For those patients already taking lactulose or rifaximin, both were stopped 1 week prior to randomisation, with sodium picosulfate given in place and dose titrated to achieve 2–3 semisoft stools per day. The primary endpoint was occurrence of a breakthrough HE episode. Secondary endpoints included: time to hospitalisation; development of a significant complication of liver disease (gastrointestinal haemorrhage, spontaneous bacterial peritonitis, other sepsis); change in severity of liver disease as measured by Child–Pugh (CP) score or the model for end-stage liver disease (MELD). Patients who reached an endpoint were withdrawn from the study and had the study drug/placebo stopped, but were still followed up for outcome.

In all, 221 patients with hepatic cirrhosis and at least one episode of HE were screened and 130 patients met the eligibility criteria and recruited into the study. There was a non-significant reduction in the primary outcome, breakthrough HE (34.8% in the probiotic group vs 51.6% in the placebo group, $p=0.12$). Of the breakthrough HE events, the grade of HE was significantly lower in the probiotic group ($p=0.01$). There was also a significant reduction in the number of hospitalisations with probiotics ($p=0.034$), probably as a

result of the HE episodes being less severe. CP and MELD scores were both significantly improved in the probiotic group. There was no significant difference in the time to overt HE ($p=0.10$), and no difference in serum ammonium levels between the groups.

The paper concludes that VSL#3, when used for 6 months as secondary HE prophylaxis, results in significant reductions in hospitalisation and severity of breakthrough HE.

Comment

This study adds further data supporting the importance of therapeutic microbiota modulation to prevent HE and demonstrates the superiority of VSL#3 probiotic over placebo in the setting of secondary prophylaxis of HE in hepatic cirrhosis. In a previous open label trial, lactulose and probiotic were found to have equivalent efficacy in HE secondary prophylaxis. Since lactulose is cheaper, it would seem reasonable to use this as the first line, and it has the additional benefit of regulating bowel habit. Probiotic could be used as a monotherapy for microbiota modulation for those who do not tolerate lactulose although it is still mandatory to ensure that 2–3 semisoft stools are passed per day. It is important to note that the standard therapies, lactulose and rifaximin, were stopped for the course of the trial in order to avoid confounding the results. This study, therefore, does not give any evidence for the benefit of adding probiotic as an additional therapy to the usual first line standard of lactulose therapy. A further double-blind RCT would be needed to address this question. The study was funded by the manufacturer.

The study adds to our tools for managing HE, in particular for preventing the severity of further episodes. That said, it would be important to study probiotics as an addition to the proven standard therapies, rifaximin and/or lactulose, to really understand the full benefit

of this therapy in patients with cirrhosis and HE.

Contributors PH wrote the article. ND contributed to the writing of the article.

Competing interests None.

Provenance and peer review Not commissioned; internally peer reviewed.

Reference

- 1 Agrawal A, Sharma BC, Sharma P, *et al.* Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy. *Am J Gastroenterol* 2012; 107:1043–50.