Aminoglycosides and Metronidazole for the Prevention and Treatment of Hepatic Encephalopathy in Adults with Cirrhosis

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Background and Aims

The EASL/AASLD guidelines stipulate that both neomycin and metronidazole may be used as alternatives for the treatment of overt HE, whereas the Italian guidelines state that these antibiotics are currently not recommended, mainly because of their potential systemic toxicity. This study aims to evaluate the utility of aminoglycosides and metronidazole *vs.* placebo, non-absorbable disaccharides (NAD) and other active treatment, for the management of HE in adults with cirrhosis

Methods

Electronic/manual searches of the literature were undertaken for relevant RCTs. The results of the meta-analyses are presented as risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CIs). Bias control was assessed using the CHBG domains and the certainty of the evidence using GRADE.

Results

Twenty RCTs evaluated aminoglycosides including neomycin (n=15) paromomycin (n=4), and ribostamycin (n=1). Treatment periods ranged from 3 to 168 days. Comparators included: placebo (n=2), NADs (n=7), other antibiotics *viz.* rifaximin, erythromycin and ciproxin (n=9) and BCAAs (n=2). All but one trial was at 'high risk of bias'; the certainty of the evidence was low or very low for all outcomes.

Twenty trials, with 1110 participants, reported mortality data, although there were no events in 12 trials. No differential beneficial or harmful effects were found in any of the trials (RR 1.10, 95% CI 0.89 to 1.42, I^2 6%, p=0.39). Seventeen trials, with 1025 participants reported data on HE. No differential beneficial or harmful effects were found in any of the trials (RR 0.89, 95% CI 0.57 to 1.39, I^2 69%, p=0.62). Twenty trials, with 1110 participants, reported 778 serious adverse events (SAEs), although there were no events in eight trials. Use of the aminoglycosides was associated with more SAEs including pneumonia and renal failure (RR 1.46, 95% CI 0.99 to 2.16, I^2 0%, p=0.06) (Figure 1).

One RCT evaluated metronidazole *vs.* rifaximin. Treatment was administered for three days as an adjunct to oral lactulose, LOLA and thrice daily enemata. Both regimens were equally as effective; no adverse events were reported

Conclusion

Although no significant differences were observed between the effects of aminoglycosides and other interventions, in relation to death and HE, in patients with cirrhosis, their use may be associated with an increased risk of serous adverse events. The utility of metronidazole for the management of HE can not be evaluated on the basis of the available literature. Neither drug should be used routinely in this setting.

Figure 1: Serious adverse events and aminoglycosides in patients with hepatic encephalopathy