Naloxone in the management of hepatic encephalopathy

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CRD summary
This generally well-conducted review concluded that naloxone may improve hepatic encephalopathy, but that these results should be treated with caution as the published data were limited. Given the poor quality of the included trials, the authors’ cautious conclusions appear appropriate.

Authors' objectives
To assess the effectiveness and safety of naloxone in the management of hepatic encephalopathy.

Searching
MEDLINE, CBMdisc, the Cochrane Register of Controlled Trials (CENTRAL) and Science Citation Index were searched to April 2008 for articles in English or Chinese. Search terms were reported. Google was also searched. Reference lists of included trials and relevant reviews were scanned for additional studies.

Study selection
Randomised controlled trials (RCTs) of naloxone, in any dose or duration, in patients with any grade of acute or chronic hepatic encephalopathy were eligible for inclusion. Patients were allowed to receive additional interventions if both trial groups received them. Trials were excluded if they were published in abstract only form, or if they were duplicate reports.

The included trials evaluated naloxone (dose ranging from 0.4 to 4mg) compared with bedside routine, sodium chloride solution, potassium solution, glucose solution, and various other amino acid solutions. Included patients had hepatic encephalopathy, cirrhosis with hepatic encephalopathy, hepatitis B with hepatic encephalopathy, and liver cancer and cirrhosis. The outcomes reported included the number of improvements, adverse events, awakened time, fatality and other clinical measures.

Two reviewers independently selected studies and disagreements were resolved through discussion.

Assessment of study quality
All of the authors independently assessed trial quality according to the Cochrane Collaboration methodology and that of Kjaergard. Seven quality criteria were assessed: allocation concealment; blinding of participants, personnel and outcomes assessors; incomplete outcome data; selective outcome reporting; early stopping; baseline imbalance; and sequence generation. Each quality factor was graded as A (low risk of bias), B (uncertain risk of bias), or C (high risk of bias).

Data extraction
Two reviewers independently extracted data on clinical efficacy and used the data to calculate relative risks (RRs) or weighted mean differences (WMDs), together with 95% confidence intervals (CIs). Disagreements between reviewers were resolved through discussion. Authors of the included trials were contacted for missing data.

Methods of synthesis
The pooled relative risks or weighted mean differences, together with 95% confidence intervals, were calculated using a fixed-effect meta-analysis; where statistical heterogeneity was detected, a random-effects meta-analysis was undertaken. Statistical heterogeneity was assessed using the $X^2$ and $I^2$ statistic. Subgroup analysis was conducted grouping trials according to type of naloxone administration. Publication bias was assessed by funnel plot, Begg and Mazumdar test, and Egger's linear regression.

Results of the review
Seventeen trials (n=1,197 patients) were included in the review; the trial sample size ranged from 40 to 137 patients.
The quality of the included trials was generally poor, with few trials adequately concealing allocation or blinding patients.

Compared with control treatments, patients treated with naloxone had a statistically significant greater improvement in hepatic encephalopathy (RR 1.46, 95% CI 1.27 to 1.67; 15 trials; random-effects model).

Subgroup analysis revealed that compared with control treatments, naloxone delivered by both intermittent and continuous infusion was most effective (RR 1.34, 95% CI 1.17 to 1.53; I²=6%; five trials), as was naloxone delivered by infusion only (RR 1.42, 95% CI 1.19 to 1.69; I²=0%; three trials).

There was no evidence of publication bias.

**Authors' conclusions**
Naloxone may be a useful treatment for hepatic encephalopathy, but these results should be treated with caution as the published data were limited.

**CRD commentary**
Inclusion criteria for the review were clearly defined. Several relevant databases were searched. Publication bias was assessed and was not found to be present. However, there may be the potential for language bias as only studies in English or Chinese were included. The authors undertook each stage of the review in duplicate, reducing the potential for reviewer error and bias.

A standard checklist was used to assess included trial quality, which gave a reasonable estimation of trial quality. The included trials were generally poor quality, which the authors acknowledged. The trials were combined using a fixed-effect meta-analysis and subgroup analysis was undertaken, which appear appropriate. Heterogeneity was assessed using a standard method. Where heterogeneity was present, further random-effects analyses were conducted, which was fitting.

The review was generally well conducted. Given the poor quality of the included trials, the authors’ cautious conclusions appear appropriate.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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