Therapy of shock with naloxone: a meta-analysis
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Authors' objectives
To evaluate the effectiveness of naloxone in human shock; and to estimate the methodologic quality of the clinical trials.

Searching
All studies concerning the treatment of shock with naloxone that were published after January 1979 and before July 1996 were retrieved, using the following procedure. First, a primary search of English and French literature published from 1979 onward was performed on MEDLINE (keywords used were: clinical trials, critical care, intensive care unit, meta-analysis, naloxone, prospective studies, sepsis, septic shock, shock). Second, a manual search was done scrutinising the reference lists of the papers found during the first step. Third, the primary investigators of eligible studies were contacted by mail and asked if they knew of any other study or meta-analysis on the same topics. This process was repeated until no new paper was found.

Study selection
Study designs of evaluations included in the review
Randomised controlled, double blind trials, published as either an article or an abstract in a peer-reviewed journal.

Specific interventions included in the review
Bolus of 30 mcg/kg naloxone followed by continuous infusion of 30-60 mcg/kg/hr for 1 or 8-16hrs or bolus of 0.4 mg every 5 mins x 3 doses versus placebo.

Participants included in the review
Adult patients with septic shock.

Outcomes assessed in the review
Hemodynamic improvement (increase in blood pressure, a decrease in the amount of vasopressor and/or inotrope) or a change in case fatality rate.

How were decisions on the relevance of primary studies made?
The literature was independently reviewed by three readers. Disagreement regarding inclusion was resolved by a consensus of at least 2 readers. Agreement on the decision to include a study was assessed by the percentage of concordance and the Kappa-score. Overall agreement on the selection of studies was perfect (concordance: 100%).

Assessment of study quality
Quality criteria according to Chalmers et al. (see Other Publications of Related Interest no.1) were used. Quality was assessed independently by the same 3 readers for all studies included in the review. Disagreements were settled by consensus, which was defined as agreement by at least 2 readers. Agreement was evaluated by the intraclass correlation coefficient (ICC). Overall agreement for the evaluation of the quality of each study was good (ICC=0.71).

Data extraction
Data on the effectiveness of naloxone to treat shock were extracted from the included studies and were displayed in 2 (hemodynamic improvement and death) two-by-two contingency tables. Thereafter, the 2 tables were mailed to each primary investigator with the request to verify the data.

Methods of synthesis
How were the studies combined?
Data were combined to estimate a typical odds ratio (OR) and its 95% confidence interval (CI) for all the studies using a fixed-effect model. The cumulative evidence of the pooled studies was evaluated by the method suggested by Collins & Langman (see Other Publications of Related Interest no.2). A correction factor of 0.5 was attributed to zero cells. An overall effect size, weighted according to sample size, was estimated. To analyse the 'file-drawer effect', a 'fail-safe number' (N-fs) was calculated. This number estimates how many additional studies without treatment effect would have to be found to render the overall effect size not significant.

How were differences between studies investigated?
The heterogeneity of treatment effects across the studies was ascertained by a chi-squared analysis.

Results of the review
Three double-blind randomised trials including 61 adult patients with septic shock: 29 patients treated with naloxone and 32 controls.

Naloxone therapy was associated with a statistically significant hemodynamic improvement (OR=0.24; 95% CI: 0.08,0.68). The overall effect size was 0.89. However, publication bias is possible. The case fatality rate was not decreased by naloxone (OR=0.60; 95% CI: 0.21,1.67); a chi-square analysis detected significant heterogeneity for this outcome (p<0.05).

Authors’ conclusions
The results of this meta-analysis suggest that naloxone is an effective treatment for shock, but the power for these results is weak, due to insufficient data in the primary trials.

CRD commentary
This is a well-performed review on the use of naloxone in the treatment of shock.

The review question was clear and the inclusion criteria explicit. The search strategy was limited as only MEDLINE was used and only English and French studies were included. As acknowledged by the author publication bias may be present due to exclusion of grey literature. Inclusion and exclusion of studies, methodological quality assessment and data extraction were performed in an acceptable way.

A summary estimate of effect across studies was generated and the method was clearly described. Differences between studies were investigated by means of a chi-square analysis. The conclusions of the review seem to follow from the evidence presented, however as the authors acknowledged the evidence is weak and might be explained by a publication and selection bias.

Implications of the review for practice and research
Research: More clinical trials are needed to assess the usefulness of naloxone, in the treatment of shock.

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