Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis
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CRD summary
The review assessed the effectiveness of intravenous and nebulised magnesium sulphate in children and adults with acute asthma. It concluded that intravenous magnesium sulphate was effective in improving respiratory function and reducing hospital admissions in children, but the effectiveness of the treatment was uncertain in adults. Due to substantial variation in some analyses, the reliability of these conclusions is unclear.

Authors' objectives
To assess the effectiveness of intravenous and nebulised magnesium sulphate on hospital admissions and pulmonary function in adults and children with acute asthma

Searching
The Cochrane Airways Review Group Asthma Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to 2007), EMBASE (1988 to 2007), CINAHL (1982 to 2007) and AMED (1985 to 2007) were searched. Search terms were reported. Attempts were found to find other studies and grey literature by searching the MetaRegister of Current Controlled Trials, National Research Register, CenterWatch, Conference Papers Index, Web of Science, Dissertation Abstracts and the Internet using Google. The websites of a number of relevant journals, societies and colleges, plus conference proceedings for the previous five years, were also searched. References lists of retrieved articles were scanned. Clinicians and experts were contacted for additional potentially relevant studies.

Study selection
Studies were eligible if they were randomised or quasi-randomised trials of intravenous or nebulised magnesium sulphate in adults or children with acute asthma. Eligible trials had to report a measure of pulmonary function or hospital admission as an outcome.

Included trials had mixed samples of teenagers and adults, or focused solely on children or adults. Asthma severity ranged from mild to life-threatening. In a third of trials, participants had moderate to severe asthma. Asthma was mild to moderate in two trials and mild to severe in one trial. Participants had acute exacerbations, moderate, acute, severe or life threatening asthma in the remaining trials.

Intravenous magnesium was used bolus doses in included trials, ranging from 1.2 to 2g (25 to 100mg/kg for children). One trial followed the magnesium dose with an infusion. Nebulised magnesium had a large variation in the dose and number of nebulisations used. Nearly all trials were placebo controlled; two trials compared magnesium alone with a beta-agonist (salbutamol). Co-interventions were permitted. Pulmonary function was measured using peak expiratory flow rate, forced expiratory volume in one second (FEV₁), forced vital capacity and a few other index scores.

Two reviewers independently performed data selection, with differences resolved through discussion.

Assessment of study quality
Trials were assessed for quality with the 5 point Jadad scale.

Two reviewers independently performed the quality assessment, with differences resolved through discussion.

Data extraction
Data were extracted on characteristics of the trials and the two outcomes.

Two reviewers independently performed the data extraction, with differences resolved through discussion.
Methods of synthesis
Data were synthesized in meta-analyses using RevMan. Standardised mean differences (SMD) were calculated for pulmonary function and relative risks (RR) for hospital admissions, using a random-effects model.

Separate subgroup analyses were undertaken of the two different types of delivery of magnesium sulphate (intravenous versus nebulised) and for children versus adults, with estimates for subgroup and total analyses.

Results of the review
Of 27 eligible randomised controlled trials (RCTs), 24 were included in the review (n=1,699 patients); 15 trials of intravenous magnesium (n=1,137 patients) and nine trials of nebulised magnesium (n=532 patients). The reasons for exclusion of the three RCTs were: written in Chinese (one RCT), no reporting of eligible outcomes (one RCT) and inability to contact authors for clarification of abstract (one RCT). Sixteen out of 24 trials had a Jadad score of 4 or 5, four trials had a score of 3, two trials had a score of 2, one trial had a score of 1 and one trial had a score of 0.

Intravenous magnesium sulphate: In adults, intravenous magnesium was associated with a trend towards improved respiratory function (SMD 0.25, 95% confidence interval (CI) -0.01 to 0.51; nine RCTs), but there was no evidence of a significant reduction in the rate of hospital admission (RR 0.87, 95% CI 0.70 to 1.08; eight RCTs). In children, intravenous magnesium was associated with significantly improved respiratory function (SMD 1.94, 95% CI 0.80 to 3.08; four RCTs) and significantly reduced hospital admission (RR 0.70, 95% CI 0.54 to 0.90; three RCTs). There was substantial heterogeneity in the two subgroup analyses of respiratory function (I²=70.6% for adults and I²=84.4% for children).

Nebulised magnesium sulphate: In adults, there was a non significant trend (weak evidence) towards improved respiratory function (SMD 0.17, 95% CI -0.02 to 0.36; seven RCTs) and reduced hospital admissions (RR 0.68, 95% CI 0.46 to 1.02; six RCTs) with nebulised magnesium. In children, there was no evidence of an effect of nebulised magnesium on either respiratory function (SMD -0.26, 95% CI -1.49 to 0.98; two RCTs) or reduced hospital admissions (RR 2.0, 95% CI 0.19 to 20.93; one RCT). There was substantial heterogeneity in the subgroup analysis of children's respiratory function (I²=88.9%).

Authors' conclusions
The authors concluded that intravenous magnesium sulphate appeared to be an effective treatment for children, but effects of nebulised and intravenous magnesium sulphate on adults was unclear. Further trials are required.

CRD commentary
The review had a clear research question and inclusion criteria were appropriate. A wide variety of electronic databases and other sources were searched to find relevant trials; three unpublished trials were identified for inclusion in the review. The authors did not report whether language restriction was used in searching, but the exclusion of a potentially relevant trial written in Chinese indicated that language restriction was implicit. Therefore, language bias could not be ruled out. Methods used in the review process were appropriate.

The authors stated that the overall quality of the included trials was generally high. Most of the trials were small and did not have sufficient power to detect differences in hospital admission rates. Subgroup analysis, with separate analyses for children and adults, was undertaken, but heterogeneity for some analyses was substantial. There was variation in: the severity of asthma, the inclusion of participants with pulmonary pathology, the measures of respiratory function, and the doses of magnesium sulphate (particularly the nebulised form). Where heterogeneity was confirmed, the authors did not explore the reasons for this, except where the nature of the control group differed. In two of the trials, the control groups took active treatment (salbutamol); the remainder were placebo controlled. All studies were pooled, regardless of the nature of the control group. Sensitivity analysis was undertaken to explore the effects of trials where the control group took salbutamol.

The authors' conclusions reflected the evidence base and are appropriate, but substantial heterogeneity in some analyses means the reliability of the conclusions is unclear.
Implications of the review for practice and research

Practice: The authors stated that intravenous magnesium sulphate should be standard treatment for children with acute severe asthma that have not responded to initial treatment.

Research: The authors stated that a large randomised trial is required to compare nebulised and intravenous magnesium sulphate to each other and to placebo in adults with acute severe asthma. They also stated that the role of nebulised magnesium sulphate in children requires further investigation.

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