Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants: a meta-analysis

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CRD summary
This well-conducted review found that foetal exposure to magnesium sulphate in women at risk of preterm delivery significantly reduced the risk of cerebral palsy without increasing the risk of death. These conclusions were supported by the data and are likely to be reliable.

Authors' objectives
To review the evidence regarding neuroprotective effects of antenatal exposure to magnesium sulphate and to explore the findings at different gestational ages.

Searching
PubMed and Cochrane Database of Systematic reviews were searched to April 2008. Search terms were reported. No language restrictions were applied. Reference lists of relevant articles were screened. Trials register websites were searched to identify ongoing or completed studies.

Study selection
Randomised controlled trials (RCTs) that compared magnesium sulphate to placebo or alternative treatment in women at risk of preterm delivery were eligible for inclusion. Studies had to report data on long-term infant outcomes of cerebral palsy and perinatal/infant mortality. The primary outcome was the composite outcome of perinatal or infant death or cerebral palsy assessed at 18 to 24 months of age (corrected for prematurity). Secondary outcomes included death, cerebral palsy, moderate-severe cerebral palsy (inability to walk independently at age two years) and a combined outcome of death or moderate-severe cerebral palsy.

Three of the included studies administered magnesium sulphate with the aim of neuroprotection. One study consisted of two tandem trials in which magnesium sulfate was given for either neuroprotection or tocolysis. One trial administered magnesium sulphate for pre-eclampsia. Included studies enrolled women in preterm labour, with premature rupture of membranes or pre-eclampsia at 24 to 33 weeks gestation. Women with singleton, twin or triplet pregnancies were included. The magnesium regimen used and actual dosage received varied across studies and among women within the individual studies.

The authors did not state how studies were selected for inclusion in the review.

Assessment of study quality
Studies were assessed for methodological quality according to criteria of randomisation, allocation concealment, masking conditions and adequacy of follow-up.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted data to construct 2x2 contingency tables for each outcome and used these data to calculate relative risks (RR) and 95% confidence intervals (CIs). Where tables contained 0 cells, 0.5 was added to each cell. Additional data for one study was extracted from a Cochrane review that reported obtaining additional data from the study authors.

Methods of synthesis
Summary relative risks and 95% CIs were estimated using the Mantel-Haenszel fixed-effect model. Data were pooled separately for each outcome for different gestational ages (<32 to 34 weeks and <30 weeks of gestation) and according
to the intent of the study (primary aim of foetal neuroprotection). Heterogeneity was assessed, but details of the methods used were not reported. Publication bias was assessed using funnel plots and the Begg test.

**Results of the review**
Five RCTs (n=5,235) were included. Duration of follow-up ranged from 18 to 24 months. All trials were appropriately randomised, used an intention-to-treat analysis and masked the infant examiner to foetal exposure.

There was no difference between magnesium sulphate administered at <32 to 34 weeks gestation and control for the primary outcome of death or cerebral palsy or for death (five RCTs). Prenatal exposure was associated with a significant reduction in the combined outcome of death or moderate-severe cerebral palsy (RR 0.85, 95% CI 0.73 to 0.99; three RCTs), cerebral palsy of any severity (RR 0.70, 95% CI 0.55 to 0.89; five RCTs) and of moderate-severe cerebral palsy (RR 0.60, 95% CI 0.43 to 0.84; three RCTs). Results were similar when the analysis was restricted to women randomised at <30 weeks gestation (three RCTs). Restriction of the analysis to the three studies and one sub-trial that administered magnesium sulphate for neural protection showed a significant reduction in the primary outcome of combined death or cerebral palsy (RR 0.86, 95% CI 0.75 to 0.99), total cerebral palsy (RR 0.71, 95% CI 0.55 to 0.91), death or moderate-severe cerebral palsy (RR 0.85, 95% CI 0.73 to 0.99; three RCTs) and moderate-severe cerebral palsy (RR 0.60, 95% CI 0.43 to 0.84; three RCTs). There was no increase in the risk of death. There was no evidence of statistical heterogeneity for any analyses.

There was no evidence of publication bias for any of the outcomes (p-values ranged from 0.19 to 0.90) and funnel plots appeared symmetrical.

**Authors' conclusions**
Foetal exposure to magnesium sulphate in women at risk of preterm delivery significantly reduced the risk of cerebral palsy without increasing risk of death.

**CRD commentary**
The review addressed a focused question supported by clearly defined inclusion criteria. The literature search only involved one electronic database and so relevant studies may have been missed, but additional attempts made to locate unpublished data reduced the risk of publication bias. Appropriate steps were taken to minimise bias and errors during data extraction; it was unclear whether such steps were taken during study selection and study quality assessment. Appropriate criteria were used to assess study quality and the results of the assessment were summarised in a table. Methods used to pool data were appropriate and relevant sensitivity analyses were conducted; methods used to assess statistical heterogeneity were not reported.

The authors conclusions were supported by the data and are likely to be reliable.

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

**Research:** The authors stated that further research was required to identify the right patient candidate and ideal dosing regimen.

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