Treatment with magnesium sulphate in pre-term birth: a systematic review and meta-analysis of observational studies

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CRD summary
The review of observational studies concluded that antenatal treatment with magnesium sulphate during premature delivery seemed to be associated with a reduced incidence of infant cerebral palsy and a decrease in the risk of infant mortality. Limitations of the included studies and in the review process mean that the reliability of these conclusions is uncertain.

Authors' objectives
To review the effect of magnesium sulphate on the risk of infant cerebral palsy and mortality in premature deliveries in observational studies.

Searching
PubMed, EMBASE and The Cochrane Library were searched from inception to October 1st 2010 for published studies. Search terms were reported. No language restrictions were applied. Reviews and studies with no abstract were excluded. Reference lists of identified papers were handsearched for additional studies.

Study selection
Observational studies of magnesium sulphate given to women in premature labour were eligible for inclusion. Eligible studies had to report either cerebral palsy or mortality as an outcome. The included studies defined premature labour on the basis of gestational age and/or birth weight. The reason for treatment with magnesium sulphate was tocolysis (inhibition of labour/premature birth), seizure prophylaxis in pre-eclampsia, or neuroprotection (where stated). Only two studies reported dosage details. Most studies excluded women with pre-eclampsia or babies with major abnormalities, although this was not defined. All studies defined cerebral palsy in the same way, although the age at diagnosis varied from two to three years. Infant mortality was defined differently between studies, ranging from seven-day mortality to mortality up to three years. All but one study were conducted in the USA.

Two reviewers independently selected the studies; discrepancies were resolved by consensus.

Assessment of study quality
Study quality was assessed using the Newcastle-Ottawa Scale, which assessed studies on selection, group comparability, and exposure/outcome assessment, giving scores from 0 to 9 points. High quality was defined as 6 points or more.

The authors did not state how many reviewers assessed the study quality.

Data extraction
Odds ratios (ORs) from case-control studies and relative risks (RRs) from cohort studies, with appropriate 95% confidence intervals (CIs), were extracted.

Two reviewers independently extracted the data onto predetermined abstraction forms. The authors did not state how discrepancies were resolved.

Methods of synthesis
Studies were combined in a narrative analysis and a fixed-effect meta-analysis, stratified by study design, to calculate pooled relative risks and odds ratios.

Statistical heterogeneity was investigated using $I^2$. If the $I^2$ value was 75% or more, meta-analysis was not reported. Heterogeneity was investigated using subgroup analyses, stratified by birthweight and study quality.
Results of the review
The review included 11 studies (16,804 participants). Of these, six were case-control studies (13,978 participants) and five were cohort studies (2,826 participants). The quality scores ranged from 2 to 9, with nine studies being classified as high quality.

**Mortality:** Five cohort studies (2,826 participants) showed a beneficial effect of magnesium sulphate on infant mortality (RR 0.73, 95% CI 0.61 to 0.89; I²=36%). No effect on the relative risk was found when one study of low quality was excluded (RR 0.73, 95% CI 0.66 to 0.88). Two case-control studies assessed the association between magnesium sulphate and mortality. One found a clear beneficial effect; the other found a non-significant detrimental effect. However, when the case-control studies were stratified by gestational age, a beneficial effect seen, but the authors reported that adjusted data could not be obtained. No meta-analysis was performed on the case-control studies.

**Cerebral palsy:** Five case-control studies (974 participants) showed a beneficial effect of magnesium sulphate on the incidence of cerebral palsy (OR 0.64, 95% CI 0.47 to 0.89), with evidence of heterogeneity (I²=70%). Stratification by birth weight found a stronger effect in infants born weighing under 1.750g (OR 0.39, 95% CI 0.20 to 0.77; I²=67%) than in heavier infants. One cohort study (1,097 participants) found a protective effect of magnesium sulphate treatment on cerebral palsy (OR 0.10, 95% CI 0.02 to 0.81).

Authors' conclusions
Antenatal treatment with magnesium sulphate during premature delivery seemed to be associated with a reduced incidence of infant cerebral palsy and a decrease in the risk of infant mortality.

CRD commentary
The review addressed a clear question, although the same question had already been addressed in a meta-analysis of randomised controlled trials; the authors did not suitably justify the need for a review of observational studies. Intervention and participant inclusion criteria were broad; outcome and study design criteria were clear. The search covered three main databases. No language restrictions were applied, so no language bias could have arisen. The authors did not report any attempts to identify unpublished studies; they noted that a funnel plot to investigate publication bias was not constructed because of the small number of included studies. The requirement that studies had to have an abstract meant that some publications may have been missed. Some efforts were made to reduce errors and bias during the review process, although the reporting was not clear at all stages of the review.

Combining the results in a meta-analysis was appropriate, but it was not clear why a random-effects model was not also used, since some degree of heterogeneity was detected. It was also unclear why results were stratified by study design, since similar results would be expected from case-control and cohort studies. Data on treatment doses of magnesium sulphate were not reported. The authors acknowledged that confounding affects all observational studies and discussed this in relation to corticosteroid use, which was likely to have had an effect on their results.

Given limitations of the included studies (inherent to all observational studies) and some limitations of the review process, the reliability of the authors' conclusions is uncertain.

Implications of the review for practice and research
**Practice:** The authors stated that treatment with magnesium sulphate during premature deliveries could produce a detectable decline on the incidence of pre-term cerebral palsy.

**Research:** The authors stated that a large, pragmatic clinical trial may be, to determine the effective dose and timing of treatment with magnesium sulphate may be needed.

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Bibliographic details
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.