Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis

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CRD summary
This well-conducted review concluded that magnesium sulphate administered to women at risk of delivery before 34 weeks of gestation reduced the risk of cerebral palsy in their children. The authors' conclusions are likely to be reliable.

Authors' objectives
To determine the efficacy and safety of antenatal magnesium sulphate administered to women at risk of pre-term delivery before 34 weeks of gestational age for the prevention of cerebral palsy in their children.

Searching
PubMed, EMBASE, CINAHL, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science were searched, without language restrictions, to March 2009. Search terms were reported. Several online trial registries and conference proceedings were also searched. Further relevant studies were sought from reference lists of identified studies, textbooks and reviews.

Study selection
Randomised controlled trials (RCTs) of magnesium sulphate versus placebo, or no magnesium sulphate, in women at risk of pre-term birth before 34 weeks of gestation, whose primary aim was to prevent cerebral palsy and other neurologic abnormalities in unborn infants, were eligible for inclusion. Trials with other primary aims, but which reported infant cerebral palsy data, were also eligible. Quasi-randomised trials were excluded.

The primary outcomes were cerebral palsy and total paediatric mortality (foetal death and any mortality of live births that occurred during the two years of corrected age after the birth). Pre-specified secondary outcomes were also reported.

Most included trials were of magnesium sulphate as an infant neuroprotective agent. Most trials used a loading dose of 4g, but the maintenance doses varied. Median total doses ranged from 4 to 49.8g. All but one trial used a placebo control treatment. Women at a range of gestational ages were included. Diagnoses of cerebral palsy were made (using varying criteria) by a paediatrician at a corrected age of at least 18 or 24 months. The number of trial centres ranged from one to 125.

Two reviewers independently assessed studies for inclusion, with disagreements resolved though consensus.

Assessment of study quality
Trial quality was assessed using a modified Jadad scale (which examines randomisation, allocation concealment, and drop-outs/withdrawals), with trials receiving a score between 0 (lowest quality) and 8 (highest quality).

Two reviewers independently made the assessments, with disagreements resolved though consensus.

Data extraction
Data were extracted in order to calculate relative risks (RR) and 95% confidence intervals (CI). Authors were contacted for additional data when necessary.

Two reviewers independently extracted data, with disagreements resolved by discussion.

Methods of synthesis
Meta-analyses were used to pool relative risks using a fixed-effect model or a random-effects model if heterogeneity -
which was assessed using the I² statistic - was substantial (I²≥50%). The number needed-to-treat (NNT) with 95% confidence intervals, for beneficial or harmful outcomes, was calculated for outcomes significant at the 5% level. Outcomes were analysed using intention-to-treat data.

Sensitivity analyses examined the impact of type of statistical model, modified Jadad score, and completeness of follow up. Pre-specified subgroup analyses were also described. Publication bias was assessed using funnel plots and the Egger test.

**Results of the review**

Five studies (counted as six trials) were included in the review (n=5,357 infants), with sample sizes ranging from 165 to 2,444 infants. The overall quality of trials was deemed to be relatively good. All trials used computer-generated randomisation. Five trials were doubled-blinded. Modified Jadad scores ranged from 2 to 8 (out of 8), with three studies scoring 8.

Antenatal magnesium sulphate was associated with a reduced risk of: cerebral palsy (RR 0.69, 95% CI 0.55 to 0.88; I²=4%; NNT=52; six trials); moderate or severe cerebral palsy (RR 0.64, 95% CI 0.44 to 0.92; I²=0%; NNT=74; three trials); mild cerebral palsy (RR 0.74, 95% CI 0.52 to 1.04; I²=0%; three trials); and substantial gross motor dysfunction (RR 0.60, 95% CI 0.43 to 0.83; I²=0%; NNT=53; three trials). Sensitivity analyses indicated that pooled effects were of similar magnitude when considering just the better quality trials. There was no significant difference in the risk of total paediatric mortality.

Hypotension (two trials) and tachycardia (one trial), as well as minor side effects such as flushing, and nausea and vomiting (three trials), were more common in women receiving magnesium sulphate. There was no evidence of publication bias. Further results were reported.

**Cost information**

If magnesium sulphate was given to all women at risk of pre-term delivery before 34 weeks of gestation, the incremental cost of preventing one case of cerebral palsy would be $10,291 (95% CI 6,135 to 30,477).

**Authors' conclusions**

Magnesium sulphate administered to women at risk of delivery before 34 weeks of gestation reduced the risk of cerebral palsy in their children.

**CRD commentary**

The review addressed a clear question, supported by appropriate inclusion criteria. Database searches, supplemented by numerous other methods, were used to identify all eligible studies. For all relevant review processes, the authors used methods to minimise the risks of reviewer error and bias.

Trial details were tabulated (although population-based details such as mean ages and ethnicity were not provided) and an adequate quality assessment of the trials was made; this was used in interpreting the results of the review. Appropriate methods were used to pool data and assess heterogeneity. Potential limitations in interpreting the results were also discussed by the authors.

This was a well-conducted review and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that antenatal magnesium sulphate should be considered for use in women at high risk of delivery before 34 weeks of gestation, mainly in those with premature rupture of membranes, labour in active phase, and planned delivery within 24 hours.

**Research:** The authors stated that further studies (or individual patient data meta-analyses) are required to assess: the minimum effective dose of magnesium sulphate; the optimal time to administer it; the need for re-treatment; the efficacy in singleton and multiple pregnancies; the effect on the risk of necrotising enterocolitis; and the long-term
consequences of exposure for the women and their children.

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