Evidence for magnesium sulfate as a tocolytic agent

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Authors' objectives
To assess the efficacy and side-effects of magnesium sulfate for acute tocolysis, compared with both placebo and beta-agonists.

Searching
Two authors independently searched MEDLINE from 1966 to 1996 for RCTs published in the English language, using the keywords 'magnesium sulfate', 'premature labor' and 'tocolysis'. The bibliographies of the retrieved articles and obstetrical texts were also examined for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), which compared the use of magnesium sulfate with placebo, ritodrine or ritodrine plus other beta-agonists, to prevent pre-term birth.

Specific interventions included in the review
Magnesium sulfate (4 g loading dose, followed by 3 to 5 g/hour or as determined by magnesium levels). This was compared with placebo, intravenous ritodrine, and ritodrine plus other beta-agonists (intravenous or subcutaneous terbutalene).

Participants included in the review
Women in pre-term labour, defined by cervical change or regularity of contractions, were included.

Outcomes assessed in the review
The assessed outcomes were: a delivery delay of greater than 48 hours; a delivery delay of greater than 7 days; the frequency of delivery after 37 weeks; the frequency of major drug events (pulmonary oedema, myocardial ischaemia, serious cardiac arrhythmia); the frequency of medication discontinuation because of side-effects; and the mean latency period (interval from randomisation until delivery).

How were decisions on the relevance of primary studies made?
The literature was assessed independently by two investigators who were blinded to specific details of the papers, i.e. the authors, institution, date and journal of publication.

Assessment of study quality
The studies were evaluated in terms of the following: their descriptions of patient selection and therapeutic regimens; blinding and randomisation; blinding of observers; the comparability of the groups assessed; and intention to treat analysis. This approach was adapted from the method developed by Chalmers et al. (see Other Publications of Related Interest no.1). The trials were evaluated independently by two reviewers using an approach adapted from the method of Chalmers et al. (see Other Publications of Related Interest no.1). Any disagreements were resolved by a third reviewer. Kappa-statistics were calculated to assess inter-observer agreement for the evaluation of trial quality.

Data extraction
The data were abstracted by two independent, blinded reviewers. Any differences between the reviewers in terms of the recorded clinical trial characteristics or data points were settled by joint review of these specific elements by the two primary reviewers.
Methods of synthesis
How were the studies combined?
The pooled odds ratios and 95% confidence intervals (CIs) were calculated using a random-effects model, as described by DerSimonian and Laird (see Other Publications of Related Interest no.2). These calculations were confirmed using exact stratified analysis because of the small number of participants in some of the trials.

Data on latency were pooled using a simple inverse variance-weighted average of the within-study differences in means.

How were differences between studies investigated?
Inter-study heterogeneity was assessed by means of a Q statistic, using a p-value of less than 0.10 as the significance level.

Results of the review
Eight RCTs were included in the review. Several trials compared magnesium sulfate with more than one other treatment. Two trials compared magnesium sulfate with placebo (92 in the magnesium sulfate group and 99 in the untreated group). Four trials compared magnesium sulfate with ritodrine (182 in the magnesium sulfate group and 166 in the ritodrine group). Six trials compared magnesium sulfate with a beta-agonist agent including ritodrine (222 in the magnesium sulfate group and 261 in the beta-agonist group).

The primary reviewers initially agreed on 78.5% of the items in the trial evaluation. The kappa-statistics ranged from 0.13 to 1.0 for the various items assessed, with the lowest scores observed for ‘intention to treat analysis’ and ‘blinded randomisation’.

In the 2 trials of magnesium sulfate versus placebo, the results were not significant for either the delay of delivery (greater than 48 hours and greater than 7 days) or delivery after 37 weeks; inter-study heterogeneity was also insignificant.

In the trials of magnesium sulfate versus ritodrine, there was no significant difference between treatments for either the delay of delivery (greater than 48 hours and greater than 7 days) or delivery after 37 weeks; inter-study heterogeneity was also insignificant. Major adverse drug effects were uncommon and the treatments did not differ in terms of the occurrence of these events. The mean latency between treatment groups was 0.2 days (95% CI: -4.86, 5.26), showing no substantial difference.

In the trials of magnesium sulfate versus beta-agonists, there was no significant difference between treatments for either the delay of delivery (greater than 48 hours and greater than 7 days) or delivery after 37 weeks. There was a significant improvement in the mean latency in the beta-agonist group relative to magnesium sulfate, but there was considerable heterogeneity between 3 of the 6 trials for this outcome. Major adverse drug effects were uncommon and the treatments did not differ in terms of the occurrence of these events. However, compared with beta-agonists, there was a significant reduction in the odds of magnesium sulfate being discontinued because of side-effects.

Authors' conclusions
Magnesium sulfate seemed comparable to ritodrine and beta-agonists, although the available data were insufficient for a rational choice between these agents.

CRD commentary
The authors made a wide and high-quality review of the literature, and addressed possible bias in the selection of the trials. The authors also performed a quality review of the selected trials and took measures to mitigate against investigator bias when extracting the data from the trials. The inclusion criteria were stated and details of the studies were provided. The studies were pooled appropriately.

The review was flawed only by limiting the literature search to English language studies identified in MEDLINE, since relevant studies could have been missed. No attempt was made to identify unpublished articles or to contact researchers in this field.
The authors reasoned from the results that magnesium sulfate is of similar efficacy to ritodrine and beta-agonists. These results, however, should be viewed with caution for several reasons. First, the authors calculated that the number of trials included in the study was limited, and that the number of participants in the individual trials was less than the sample size necessary to detect a significant difference. Second, the authors found wide CIs around the results of the review for each treatment comparison, again raising concern that additional participants should have been included in the trials. Finally, the authors found several instances of missing data in the original trials, and agreement between the two initial reviewers was poor on three of the six trial evaluation categories; this raises concerns about the reliability and validity of the data gathered from the initial trials.

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

Practice: There were no further implications for practice.

Research: The authors believe that additional data is needed if a rational choice is to be made between magnesium sulfate and ritodrine or other beta-agonists. They state that they evaluated only intermediate outcomes, and that the research question remains as to whether magnesium sulfate can reduce neonatal complications and death, and whether individual tocolytes increase the risk of adverse outcomes.

**Bibliographic details**


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**Other publications of related interest**


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Subject indexing assigned by NLM

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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.