Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomised trials

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Authors' objectives
To evaluate the effectiveness of magnesium sulphate in the treatment of eclampsia and pre-eclampsia by a systematic overview of controlled clinical trials.

Searching
MEDLINE was searched from 1966 to 1995 using a combination of the keywords 'magnesium sulphate' and 'pregnancy', the search being limited to 'humans'. Reference lists of all known primary research and review articles were examined and additional relevant citations were identified. Articles frequently cited were subsequently used (in the Science Citation Index) to identify additional studies that had cited these articles.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included if they fulfilled the following criteria: target population was women with eclampsia or pre-eclampsia, magnesium sulphate was compared with some other form of treatment, and seizure activity was used as the primary outcome measure.

Specific interventions included in the review
The interventions studied included intravenous and intramuscular magnesium sulphate, intravenous phenytoin, intravenous diazepam and a lytic cocktail composed of intramuscular pethidine, chlorpromazine and promethazine.

Participants included in the review
The participants included women with eclampsia or pre-eclampsia.

Outcomes assessed in the review
The main outcome assessed was seizure activity. Secondary outcomes assessed were maternal mortality, Caesarean section and perinatal deaths.

How were decisions on the relevance of primary studies made?
Two reviewers blinded to the author's name, institutional affiliation and journal independently reviewed the citation lists. The citations were categorised as relevant or irrelevant on the basis of whether or not the population, intervention, outcome measure and research design stated in the selection criteria were addressed in them. Complete manuscripts of citations considered relevant were subsequently reviewed for eligibility, if the paper was written in English, by two independent authors blinded to author's name, institutional affiliation, journal, date of publication and sources of financial support; papers not written in English were reviewed by a single reviewer who understood the language and was also trained in medicine. Any disagreements were resolved by consensus or arbitration by the third author.

Assessment of study quality
The methodological quality of the selected studies was assessed on the following items: concealment of randomisation, allocation sequence generation, blinding and description of follow-up. If the paper was written in English, two reviewers blinded to the author's name, institutional affiliation, journal, date of publication and sources of financial support independently assessed its validity; papers not written in English were reviewed by a single reviewer who understood the language and was also trained in medicine. Any disagreements were resolved by consensus or arbitration by the third author.
**Data extraction**
The following data were extracted independently by two authors: features of study design, population, interventions, outcome measures, seizure activity, maternal mortality, Caesarean section rates, perinatal mortality and a priori sample size calculations. Any disagreements were resolved by consensus or by arbitration by the third author. Where possible, data were abstracted to perform an intention to treat analysis. The treatment effect of magnesium compared with some other intervention was estimated for each study using the odds ratio (OR), and 95% confidence intervals (CIs) were calculated for various outcome measures.

**Methods of synthesis**

**How were the studies combined?**
The ORs were pooled and combined by a fixed-effect model using the Mantel-Haenszel method.

**How were differences between studies investigated?**
Heterogeneity was assessed using the Breslow-Day test. If heterogeneity was encountered, exploration of its sources was planned using stratified analysis based on variations in populations, interventions and study quality.

**Results of the review**

Nine RCTs (N=1,743) were used to evaluate the effects of magnesium sulphate.

Two RCTs were used to compare magnesium sulphate with phenytoin in the treatment of eclampsia: seizures and maternal deaths (N=797), Caesarean section and perinatal deaths (N=650).

Two RCTs were used to compare magnesium sulphate with diazepam in the treatment of eclampsia: seizures and maternal deaths (N=956) and perinatal deaths (N=690).

One RCT (N=633) was used to assess Caesarean section.

One RCT was used to compare magnesium sulphate with lytic cocktail in the treatment of eclampsia: seizures and maternal deaths (N=90), Caesarean section (N=75) and perinatal deaths (N=61).

Three RCTs were used to compare magnesium sulphate with phenytoin in the treatment of pre-eclampsia: seizures and Caesarean section (N=2,288); 2 of the RCTs were used to assess perinatal deaths (N=2,212).

One RCT (N=38) was used to compare magnesium sulphate with diazepam in the treatment of pre-eclampsia: seizures, Caesarean section and perinatal deaths.

One RCT (N=64) was used to compare magnesium sulphate with no anticonvulsant in the treatment of pre-eclampsia: seizures and maternal deaths.

Agreement concerning relevance was obtained for 98% of the citations reviewed with a kappa value of 0.72. Agreement concerning eligibility was 92% with kappa 0.83. Observer agreement regarding components of study quality was 88 to 100% with kappa levels of 1.0 for concealment of randomisation, 0.78 for sequence generation, 1.0 for double-blinding and 1.0 for drop-outs.

Eclampsia: magnesium sulphate versus phenytoin for seizures, OR 0.27 (95% CI: 0.17, 0.45, p=0.00; heterogeneity P=0.20); magnesium sulphate versus diazepam for seizures, OR 0.41 (95% CI: 0.30, 0.57, p=0.00; heterogeneity p=0.35); magnesium sulphate versus phenytoin for maternal mortality, OR 0.51 (95% CI: 0.24, 1.07); magnesium sulphate versus diazepam for maternal mortality, OR 0.78 (95% CI: 0.41, 1.45); magnesium sulphate versus lytic cocktail for maternal mortality, OR 0.19 (95% CI: 0.00, 9.88). The differences for secondary outcome measures were not statistically significant.

Pre-eclampsia: magnesium sulphate versus phenytoin for seizures, OR 0.15 (95% CI: 0.03, 0.72, p=0.01; heterogeneity p=0.28); magnesium sulphate versus phenytoin for Caesarean section, OR 1.27 (95% CI: 1.06, 1.54, p=0.01); magnesium sulphate versus phenytoin for perinatal mortality, OR 0.85 (95% CI: 0.41, 1.72, p=0.78).
Authors’ conclusions
Magnesium sulphate is a superior drug in preventing the recurrence of seizures in eclampsia and in seizure prophylaxis for pre-eclampsia.

CRD commentary
This is a well-written and clearly-presented review with methodologically-sound selection of studies based on inclusion criteria, quality assessment of primary studies and data extraction.

Comments made on problems encountered with the primary studies include inadequate concealment of randomisation and sequence generation, absence of double-blinding due to the mature of the interventions being compared, lack of sample size and power considerations, and the rarity of maternal mortality, making any adequately powered study assessing this outcome difficult to achieve.

The results of the trial quality assessment on randomisation concealment and sequence generation are included. Heterogeneity was statistically evaluated.

The literature search is stated to include 'all known primary research' but it is unclear what the source of this information was. Without details of this source it is not possible to determine whether some relevant studies may have been omitted. Entry criteria to three of the nine included trials are given, but definitions of the terms 'eclampsia' and 'pre-eclampsia' are not included in the criteria used to select studies for inclusion. Definition of the main outcome, i.e. seizure activity, is also lacking. Baseline comparisons of treatment groups would have been welcome to assess the effectiveness of randomisation. Whilst statistical tests showed no significant heterogeneity, examination of the ORs from individual studies shows some inconsistencies; a discussion of possible causes for this may have been helpful in indicating variables with potential influence on treatment effect. It is unclear whether the aim to abstract data for an intention to treat analysis was achieved.

Given the rarity of maternal death the selection of seizure activity would seem appropriate as a proxy measure. Without adequate definition of the entry criteria used for participants to all trials, and the main outcome assessed and details of the populations studied, it is not possible to comment on the generalisability of the results.

Implications of the review for practice and research
Further research is required to evaluate whether anticonvulsant therapy is necessary for women with pre-eclampsia, and to monitor maternal mortality and Caesarean section rates in women treated with magnesium sulphate.

Bibliographic details

PubMedID
8916993

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
AccessionNumber
11996001880

Date bibliographic record published
31/05/1998

Date abstract record published
31/05/1998

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.