

The Collaborative Eclampsia Trial (1991-1992)¹

Purpose

- Primary research questions:
 - Which of three standard anticonvulsant regimens works best to prevent recurrence of eclamptic seizures?
 - Which of the standard anticonvulsant regimens works best to prevent maternal morbidity and mortality in eclamptic women?
- Primary outcomes:
 - Rate of recurrence of convulsions
 - Maternal mortality rates
 - Serious perinatal morbidity or mortality, among women who entered the trial before the time of delivery.
- Perceived clinical importance: Death during pregnancy can be caused by eclampsia, the occurrence of convulsions (fits) during pre-eclampsia, a multi-system disorder associated with increased blood pressure and proteinuria. Definitive evidence through a randomized trial would dispel controversial and untested beliefs of the best therapy to prevent eclampsia.

Background and Context

- Eclampsia occurs in 1 to 100/1700 deliveries in developing countries, leading to some 50,000 maternal deaths every year worldwide. In Europe, the US, and other developed countries it is a complication of childbirth in 1/2000 deliveries and in the UK, at least, it is a contributing factor in 10% of maternal deaths.^{2; 3}
- Magnesium sulphate, diazepam, and phenytoin were the anticonvulsants most commonly used to treat seizures in eclamptic women. Which to use, however, was the subject of "vociferous, if not vitriolic" debate.^{4; 5} This debate crossed geographical boundaries (the US versus UK schools of thought) and specialties (obstetrics versus neurologists) because of the differing traditions in practice and various beliefs in eclampsia etiology.
 - Those who were reluctant to use magnesium sulphate (most obstetricians in the UK) argued that its proponents (mainly in the US) did not understand its mechanism of action, whereas diazepam was widely used, and had a long record of use for

- other types of seizures.
- Critics of magnesium sulphate said that it was inappropriate relied upon by obstetricians while it was neither an effective antihypertensive nor effective anticonvulsant.
- There was sparse RCT evidence, and although MgSO₄ appeared to be favored, results were inconclusive. Only two studies, with a total of 73 participants, had been published before this trial.

Date and Place Conducted

- International, multicenter.
 - 27 centers in 9 countries (South Africa, Argentina, Columbia, Zimbabwe, India, Venezuela, Ghana, Uganda, Brazil)

Principal Investigators

- Eclampsia Trial Collaborative Group, L Duley.

Sponsored by/Source of funding

- Overseas Development Administration (UK) and the World Health Organization, with support from the Wellcome Trust.
 - Coordinating centers: Centro Rosarino de Estudios Perinatales, Rosario, Argentina, National Perinatal Epidemiology Unit, Oxford, UK.

Size and Design

- Number of participants: 905 (Diazepam vs. MgSO₄), 775 (Phenytoin vs. magnesium sulphate). Total 1680.
- Type of participants: All women with eclampsia except those with any contraindication to any of the study drugs
 - mean age 22
 - ~65% primiparous
 - just over 50% in each group had a diastolic BP > 110 mmHg
- Design: Multi-center, blinded, randomized-controlled trial
- The trial examined two separate comparisons:
 - magnesium sulphate versus diazepam: 1991 (23 centers).
 - magnesium sulphate versus phenytoin: 1992 (4 centers)
 - Local investigators chose which contrast would be tested at their site.
 - Randomly assigned 453 women to magnesium sulphate and 452 to diazepam

- The two groups were well-balanced in prognostic factors of interest.
 - Of the women allocated to magnesium sulphate 99% received it (9% received another anticonvulsant) and of those allocated to diazepam 98% received it (14% had another anticonvulsant).
- Four centers in 2 countries compared magnesium sulphate versus phenytoin.
 - Randomly assigned 388 women to magnesium sulphate and 387 to phenytoin.
 - The two groups were well-balanced in prognostic factors of interest.
 - Of the women allocated to magnesium sulphate 99% received it (9% received another anticonvulsant) and of those allocated to diazepam 99% received it (12% also received diazepam)
 - Follow-up was until the first of: death, discharge, or 6 weeks after entry into the trial.
 - If a woman was discharged undelivered, data were obtained later.

Issues Encountered During the Trial

- Trial implementation called for the importation of magnesium sulfate into some countries for which it had not previously been available.⁶
- Independent review of interim data twice in 1993 found no methodological reason to recommend modification of the trial.¹
- A commentary noted the ethical difficulties (particularly obtaining informed consent) in conducting a trial of eclampsia in a developing country setting where many women were illiterate, over a third had received no antenatal care, and ~50% were unconscious or semi-conscious at the time of entry.
 - Exclusion of these cases would have omitted the group who would have benefited the most.
 - Non-participation would have meant withholding internationally widely used treatments.
 - Given these issues, while the WHO Committee on Research Involving Human Subjects initially deferred the award of funding upon the insistence of informed consent, this was reversed as local ethics/research committees felt it was

unnecessary.⁷

Findings

- Primary Outcomes:
 - Magnesium sulphate-diazepam:
 - Women on magnesium sulphate had a risk of recurrent convulsions that was 52% lower (CI 37%-64% reduction) of the risk of women on diazepam.
 - Among those who did have recurrent convulsions, those on magnesium sulphate had fewer.
 - Maternal mortality was lower (3.8% vs. 5.1%, RR= 0.74, CI 0.4-1.4)) among women on magnesium sulphate.
 - Magnesium sulphate-phenytoin:
 - Women on magnesium sulphate had a risk of recurrent convulsions 67% lower (CI 47% - 79%) of that observed among women assigned phenytoin.
 - Maternal mortality was lower on magnesium sulphate, (2.6% vs. 5.2%, RR=0.5, CI 0.24-2.0).
 - For both comparisons to magnesium sulphate the trends were similar regardless of whether the drug was given before or after delivery, as well as whether or not a prior anticonvulsant was given.
- Secondary Outcomes:
 - Magnesium sulphate-diazepam:
 - No significant differences were observed in measures of serious maternal morbidity.
 - No significant differences were observed in perinatal morbidity or mortality (22.4% vs. 24.8%).
 - Magnesium sulphate-phenytoin:
 - Women on magnesium sulphate were less likely to require ventilation, develop pneumonia, or be admitted to intensive care facilities than those on phenytoin.
 - Neonates of the magnesium sulphate group fared significantly better than those of the phenytoin group:
 - They were less likely to be intubated (13% vs. 24%, $p<0.001$), and
 - They were less likely to require special care (32% vs. 44%, $p<0.001$).
- Adverse events

- Phenytoin not only appeared less effective than magnesium sulphate, it may have been associated with poorer outcome among newborns (intubation, requiring special care).

Impact

- The authors concluded that the evidence of magnesium sulphate's superior effect was "compelling" and it was received as such by the medical community, and this was called the "most important randomized trial ever performed in obstetrics."⁹ Practice shifted to favor magnesium sulphate^{6; 8} The results further fueled hypotheses to the debates over the physiological mechanisms behind eclampsia.
- Both the results of the trial were heralded as significant as were the fact that a study of this size could be implemented successfully in nine developing countries.⁷ The trial authors noted the fact that it could be implemented could be considered "a model for tackling some of the major problems in women's health in developing countries".
- The relatively low cost and ease of use of magnesium sulphate should, in principle, make it possible for all countries (both developed and developing) to adopt it as standard practice in preventing recurrence of eclamptic seizures.
 - The treatment packs had considerable practical implications for both developing and developed countries.⁶
 - The high levels of recruitment (97%) and treatment allocation (99%) was described as a positive reflection of the effectiveness of the treatment packs and the fact that the care provided for some of the women was better than the care received had they not entered the trial.⁷
 - The possibility that the trial itself effected the case fatality rate (Hawthorne effect) was one potential explanation why there was insufficient power to detect any statistically significant difference in mortality between treatments.⁷
- (ISI citations 247 as of May 10, 2006)

Unresolved issues

- Several questions remained that could not be answered from the design of the study:

- The optimal dose of magnesium sulphate remained to be determined.⁹
 - The trial did not demonstrate conclusively that magnesium sulphate reduces maternal mortality and some investigators felt a larger trial might do so; however it was considered clinically significant.
 - The better secondary outcomes with magnesium sulphate vs. phenytoin may, the investigators note, have been due "to complications of phenytoin rather than benefits of magnesium sulphate."
 - Due to the design, diazepam could not be compared directly to phenytoin.
- The practice of undertaking future clinical research in developing countries was considered for both the benefit of carrying out a study where there may be higher prevalence of disease, but the implications of their generalizability back to the developed world.¹⁰

Summary

This trial was the largest that had ever been conducted to compare the effectiveness of different anticonvulsants for eclamptic seizures and the feasibility of implementation in wide variety of countries and settings, including those in the developing world. The results regarding recurrent seizure prevention were strongly in favor of magnesium sulphate, as were endpoints related to maternal and child morbidity in the phenytoin comparison. The treatment did not clearly improve mortality, a primary outcome, although the trial was underpowered to detect this. The trial served as a model for large-scale evaluation of questions relevant to developing world settings, and showed the efficacy of a simple, safe, inexpensive treatment with a great potential to decrease maternal and infant morbidity related to eclamptic seizures, and raised the possibility of saving lives as well.

References

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