Anticonvulsant therapy for eclampsia

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Magnesium sulfate is the drug of choice for the treatment of women with eclampsia. The duration of treatment should normally not exceed 24 hours beyond delivery or the last convulsion, whichever occurs last. Either intravenous or intramuscular route can be used for maintenance therapy. Clinical monitoring of respiration, urine output and tendon reflexes is essential, while serum monitoring is unnecessary and should not be used.

RHL Commentary by Atallah AN Torloni MR

1. INTRODUCTION

Eclampsia is an avoidable cause of maternal death that continues to be a major health problem in many parts of the world. The incidence of eclampsia is higher in developing countries (1 in 100–1700 deliveries) than in developed countries (1 in 2000 deliveries). This disparity is due to barriers in access to medication and health services in under-resourced settings. It is estimated that worldwide approximately 63 000 women die each year as a consequence of severe pre-eclampsia and eclampsia (1) and over 90% of these deaths occur in developing countries (2).

A large number of studies carried out over the last two decades indicate that magnesium sulfate (MgSO4) is effective in reducing the recurrence of convulsions and maternal deaths. Although its mechanism of action remains unclear, it is probably multi-factorial, including both vascular and neurological effects (3). Three recently updated Cochrane systematic reviews compared MgSO4 with diazepam (4), phenytoin (5) and lytic cocktail (a mixture of chlorpromazine, promethazine and pethidine) (6) for the treatment of antepartum, intrapartum and postpartum eclampsia.

2. METHODS OF THE REVIEW

The methodology of the three reviews was sound. The authors of each review searched all key databases for appropriate trials without any language restrictions. All adequately controlled trials that could be identified were included and appropriately analysed for quality. The date and the findings are presented clearly in the three review.

3. RESULTS OF THE REVIEW

Compared with diazepam, phenytoin and lytic cocktail, the use of MgSO4 significantly reduced the recurrence of convulsions as follows, respectively: by 57% [relative risk (RR) 0.43, 95% confidence interval
(CI) 0.33–0.55, seven trials, 3096 patients]; by 66% (RR 0.34, 95% CI 0.24–0.49; six trials, 972 women); and by 94% (RR 0.06, 95% CI 0.03–0.12; three trials, 397 women).

Treatment of eclampsia with MgSO4 resulted in 41% fewer maternal deaths than when diazepam was used (RR 0.59, 95% CI 0.38–0.92, seven trials, 3096 patients). The trend in maternal mortality also favours MgSO4 when compared to phenytoin (RR 0.50, 95% CI 0.24–1.05; three trials, 847 women). There were 86% fewer deaths when women were treated with MgSO4 versus lytic cocktail (RR 0.14, 95% CI 0.03–0.59; three trials, 397 women). Additionally, women with eclampsia treated with MgSO4 instead of lytic cocktail had less respiratory depression (RR 0.12, 95% CI 0.02–0.91; two trials, 198 women), less coma (RR 0.04, 95% CI 0.00–0.74; one trial, 108 women), and less pneumonia (RR 0.20, 95% CI 0.06–0.67; two trials, 307 women).

MgSO4 also had beneficial effects for the baby, reducing the risk of low Apgar scores at one minute by 25% (RR 0.75, 95% CI 0.65–0.87; two trials, 597 infants) and at five minutes by 30% (RR 0.70, 95% CI 0.54–0.90; three trials, 643 infants) as well as the need for intubation by 33% (RR 0.67, 95% CI 0.45–1.00; two trials, 591 infants) when compared with diazepam (4). Infants born to women who received MgSO4 instead of phenytoin were less likely to be admitted to a special care unit (RR 0.73, 95% CI 0.58–0.91; one trial, 518 infants), and less likely to stay in the special care unit for more than 7 days (RR 0.53, 95% CI 0.33–0.86; one trial, 518 infants) (5).

In all trials, MgSO4 levels were monitored exclusively through clinical examination, without any laboratory assessments of plasma levels. Intramuscular and intravenous MgSO4 maintenance protocols were equally effective in achieving the main outcomes (reduction of seizure recurrence and maternal mortality) and no adverse neonatal effects were detected in any of the trials.

DISCUSSION

4.1. APPLICABILITY OF THE RESULTS

The results of these three reviews clearly indicate that MgSO4 is the drug of choice for the treatment of women with eclampsia. The duration of treatment should not normally exceed 24 hours. Either intravenous or intramuscular route can be used for maintenance therapy. Clinical monitoring of respiration, urine output and tendon reflexes is essential, whereas serum monitoring is unnecessary and should not be used. Since this drug is inexpensive and easy to use, it is especially suitable for low- and middle-income settings. Almost all the trials were conducted in developing countries.

4.2. IMPLEMENTATION OF THE INTERVENTION

The publication of clinical trials on MgSO4 versus other anticonvulsants was followed by a spontaneous and rapid increase in its use in developed countries (7). For example, 60% of European providers surveyed indicated they would use MgSO4 for eclampsia in 1998, up from only 2% in 1992 (7, 8). In developing nations, despite some progress, the use of MgSO4 is not universal and the implementation of this life-saving intervention still remains a challenge. Universal implementation of MgSO4 for the treatment of eclampsia should be a public health priority.

The main barriers to the use of MgSO4 in developing countries include: lack of national guidelines mandating its use for all women with eclampsia; financial and logistic problems related to drug availability in all settings that care for pregnant women; lack of training of health-care professionals on how to administer the medication; and exaggerated concerns about possible toxicity of the drug and administration errors (9). Since eclampsia and severe pre-eclampsia affect a relatively small number of patients compared with other health problems, and because MgSO4 is inexpensive and not patent-protected, pharmaceutical companies have no incentive to market the drug.
Potential facilitating factors include appropriate training of all health-care professionals (including midwives, nurses, family physicians, emergency-room personnel, anesthetists and pharmacists) in the use of MgSO4 for the treatment of all women with eclampsia. Widespread availability and appropriate use of affordable, ready-to-use “eclampsia treatment packs” can also facilitate the use of the drug. For example, in a trial (10) carried out in 25 centers in India, Latin America and sub-Saharan Africa, sealed treatment packs were used successfully and made recruitment to the trial easier. Such packs are now widely used in high-income countries, and some low- and middle-income countries. They include the loading dose of MgSO4, maintenance therapy, and calcium gluconate for use in the event of toxicity, plus everything needed to initiate treatment as well as instructions for administration and clinical monitoring, which can be carried out by appropriately trained medical, midwifery or nursing staff.

Additionally, campaigns could be conducted to dispel common myths and fears that deter health-care professionals from using MgSO4. Morbidity and mortality arising from MgSO4 administration errors and toxicity have been widely publicized and this has led to the erroneous conclusion that this medication is dangerous and should be used only by highly trained professionals in tertiary facilities. In some countries, the use of MgSO4 is viewed as being appropriate only in intensive care units, where patients can be closely monitored and magnesium serum levels can be periodically assessed. This is completely erroneous and non-evidence based. Due to this misconception, many health-care workers have not been trained to administer MgSO4 and their confidence in using the drug remains low.

4.3. IMPLICATIONS FOR RESEARCH

There is compelling and irrefutable evidence indicating that MgSO4 is currently the drug of choice for women with eclampsia. However, there is still need for further research in such areas as the minimum effective dose, the optimal mode of administration, and duration of treatment. Also, further research should focus on identifying country-specific barriers and potential facilitating factors related to the availability and use of MgSO4. The decision-making mechanisms related to scaling up the use of MgSO4 could be another potential area of research.

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