Alternative magnesium sulfate regimens for women with pre-eclampsia and eclampsia

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Although there is strong evidence for the use of magnesium sulfate for the prevention and treatment of eclampsia and pre-eclampsia, available data on alternative treatment regimens are too limited to draw reliable conclusions. It is not advisable to make any changes to the current treatment regimens.

RHL Commentary by Soni BL

1. INTRODUCTION

Over half a million women die each year from pregnancy-related causes and 99% of these deaths occur in low- and middle-income countries (1). Hypertensive disorders of pregnancy (i.e. pre-eclampsia and eclampsia) are significant contributors to maternal and perinatal mortality and morbidity. Up to 10% of women have high blood pressure during pregnancy. Pre-eclampsia, defined as hypertension accompanied by proteinuria (2), usually occurs during the second half of pregnancy and causes complications in 2%–8% of pregnancies (3). Eclampsia accounts for more than 50 000 maternal deaths each year (4). Overall, 10%–15% of maternal deaths are associated directly with pre-eclampsia and eclampsia in low- and middle-income countries (4, 5). For the management of these disorders it is equally important to prevent and/or control the seizures. Owing to the wide experience of its use and its relative safety for both the mother and her infant, magnesium sulfate is the mainstay of pre-eclampsia and eclampsia treatment. Magnesium sulfate halves the risk of eclampsia (6). When magnesium sulfate is used to treat pre-eclampsia or eclampsia, the patient needs to be monitored regularly for urine output, respiratory rate and tendon reflexes, which can increase the cost of patient management. Moreover, there is a risk of toxicity with higher doses and there are disadvantages with the intramuscular route of administration (pain and infection at injection site) (7). These problems have spurred researchers to conduct trials to identify a lower dose and a shorter regimen than the standard regimen, especially for use in low-income settings where resources are lacking for administering the drug intravenously. The objective of the present Cochrane review (8) was to assess the comparative effects of alternative regimens for the administration of magnesium sulfate when used for the care of women with pre-eclampsia, eclampsia, or both.

2. METHODS OF THE REVIEW

The authors searched the Cochrane Pregnancy and Childbirth Group's Trials Register (June 2010). They sought to include randomized controlled trials comparing different regimens for administration of magnesium sulfate used in the care of women with pre-eclampsia or eclampsia, or both. Previous magnesium sulfate therapy was not an exclusion criterion.

Progression to eclampsia in pre-eclampsia, recurrence of seizures in eclampsia along with multi-organ involvement, side-effects and discontinuation of the therapy were the primary outcome measures for the woman, while death of baby before discharge from hospital, irrespective of fetal or neonatal age, was the
primary outcome measure for the baby.

Secondary outcomes for all women were maternal death, admission and length of stay in high-dependency unit, poor blood pressure control, administration of additional anticonvulsant and severe morbidity. The mode of delivery (cesarean section or vaginal), induction or augmentation of labour, prolonged labour, placental abruption, postpartum hemorrhage and retained placenta were the secondary outcomes for women randomized before delivery.

Secondary outcomes for the baby were admission to special care nursery or neonatal intensive care unit, neonatal morbidity (respiratory, neonatal enterocolitis, intra ventricular hemorrhage), side-effects such as hypotension, and development in childhood (cerebral palsy and neurodevelopmental delay).

The four authors assessed trial quality and extracted data independently. Statistical analyses was done appropriately, and the results are presented in the review as a summary risk ratio (RR) with 95% confidence intervals (CI). All other methods were also appropriate and the results are presented clearly in the review.

3. RESULTS OF THE REVIEW

Six trials involving 866 women met the inclusion criteria. These studies were conducted in both high- and low-income countries and all were hospital-based randomized controlled trials. In two trials, conducted in Bangladesh and India, 451 women were recruited before delivery, while in four trials conducted in India, South Africa, and the USA, 415 women were recruited after they had developed pre-eclampsia. In one small study (South Africa), the 17 women in the trial had severe pre-eclampsia or imminent eclampsia. Women in three studies (India and USA) were recruited post partum. Overall, the participants in these studies were pregnant woman with pre-eclampsia or eclampsia, irrespective of number of fetuses and period of pregnancy (i.e. antepartum, intrapartum or postpartum).

3.1 Types of intervention studied

3.1.1 For eclampsia

In one trial (Bangladesh), loading dose of 4 g intravenous (IV) plus 6 g intramuscular (IM) was compared with loading plus maintenance dose of 2.5 g IM every four hours. The former dose was the standard dose in Bangladesh (Dhaka regimen). In another trial (India), the Dhaka regimen (loading dose 4 g IV plus 6 g IM and maintenance dose 2.5 g IM every four hour) was compared with 4 gm IV plus 8 g IM as the loading dose and 4g IM every four hours as the maintenance dose.

3.1.2 For pre-eclampsia

In one small study (South Africa), women with severe pre-eclampsia or imminent eclampsia were included. The study compared a high-dose intravenous regimen (6 g IV loading dose followed by 2.5 g hourly by intravenous infusion) with the standard regimen (loading dose of 4 g IV plus 10 g IM followed by a maintenance dose of 5 g IM every four hours).

Three trials involving postpartum women (USA and India) compared alternative maintenance regimens. One trial compared stopping of maintenance therapy after the onset of diuresis with continued maintenance of therapy for 24 hours after delivery. Another Study (India) compared individual therapy based on clinical criteria with therapy continued for 24 hours. The third trial compared 12 hours of postpartum maintenance therapy with 24 hours of maintenance therapy (USA).

3.2 Effects of interventions
3.2.1 Comparison 1:

401 women with eclampsia: loading dose alone versus loading dose plus maintenance regimen for 24 hours.

In this comparison there were no clear differences between the two groups for recurrence of convulsions, maternal death, risk of cesarean section and stillbirth. No data were available for maternal morbidity.

3.2.2 Comparison 2:

50 women with eclampsia: lower-dose regimen (loading dose 4 g IV plus 6 g IM and maintenance dose 2.5 g IM every four hour) versus standard dose (loading dose 4 gm IV plus 8 g IM and maintenance dose 4g IM every four hours).

There were no clear differences between the two groups with regard to recurrence of convulsions, oliguria, absence of tendon reflexes and infant death. Data were insufficient for reliable conclusion on neonatal morbidity (admission to special care nursery, respiratory distress syndrome or neonatal respiratory depression).

3.2.3 Comparison 3:

Prevention of eclampsia (17 women): high dose IV versus standard IM maintenance regimen for 24 hours.

In this comparison no women developed eclampsia. There was less use of anti-hypertensive therapy in the standard IM regimen group (RR 3.94, 95% CI 1.13–13.74), although the confidence interval was very wide. The trial was too small (17 women) to obtain sufficiently reliable evidence about other indices of maternal morbidity (magnesium sulfate toxicity, renal failure, intra partum antihypertensive therapy and cesarean section) and the outcomes for the baby.

3.2.4 Comparison 4:

Duration of postpartum maintenance regimen (398 women): short versus standard (subgroups by severity of pre-eclampsia).

In these trials no women developed eclampsia. Women allocated to a short maintenance regimen were more likely to have their treatment regimen extended or restarted. However, this difference was not statistically significant (RR 5.41; 95% CI 0.96–30.37). Data were insufficient to draw meaningful conclusions about the effects on progression to more severe pre-eclampsia or antihypertensive therapy at discharge. Because of heterogeneity, data for the length of postpartum hospital stay were not totaled across the subgroups.

3.2.5 Comparison 5:

Duration of postpartum maintenance regimen: short versus standard regimen (subgroups by type of short regimen).

The trials included in this comparison were the same as those in comparison 4 and it is not possible to draw out separate results for this comparison.

DISCUSSION

4.1. APPLICABILITY OF THE RESULTS

The authors of the review conclude that, although there is strong evidence for the use of magnesium sulfate for the prevention and treatment of eclampsia and pre-eclampsia, available data on alternative treatment regimens are too limited to draw reliable conclusions. Small number of studies, with relatively small sample sizes and missing data for several important outcomes, are important limiting factors. There were also
problems with blinding in the available studies. For example, sequence generation and allocation of concealment were adequate in only two trials and not clear in the remaining four. Hence, it is not advisable to make any changes to the current regimens.

4.2. IMPLEMENTATION OF THE INTERVENTION

To administer magnesium sulfate treatment regimens effectively and safely, health-care facilities need sufficient numbers of trained staff who can undertake clinical monitoring of the patient effectively and manage the drug's toxicity or complications arising from the present regimen. In the absence of reliable data on reduced dosages and duration of treatment and the intramuscular route of administration, it will be wise to continue with existing protocols with which health-care workers are familiar.

4.3. IMPLICATIONS FOR RESEARCH

Further areas of research include the minimum effective dose, the best route of administration, and the duration of therapy, especially suited to under-resourced settings. There is a strong need to conduct large randomized multicentre trials on these topics in various settings. It is also be useful to assess the benefits and adverse effects of starting therapy before transfer to hospital.

Sources of support: none

References


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