WHO recommendation on magnesium sulfate as the first line anticonvulsant in women with eclampsia

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Recommendation

Magnesium sulfate is recommended for the treatment of women with eclampsia in preference to other anticonvulsants.

(moderate evidence, strong recommendation)

Publication history

First published: October 2011

Updated: no update planned

Assessed as up-to-date: October 2011

Remarks

- Magnesium sulfate is a lifesaving drug and should be available in all health-care facilities throughout the health system. The guideline development group believed that capacity for clinical surveillance of women and administration of calcium gluconate were essential components of the package of services for the delivery of magnesium sulfate.
- Large trials have evaluated and demonstrated the effectiveness of full regimens of magnesium sulfate, which include a loading dose followed by 24-hour maintenance therapy. Specific guidance on how to administer magnesium sulfate can be found in the WHO manual entitled Managing complications in pregnancy and childbirth: a guide for midwives and doctors.(1)
- The guideline development group deliberated on the best course of action in settings in which it is not possible to administer the full magnesium sulfate regimen. The group debated the possible (but yet unproven) benefits of administering only the loading dose versus transferring women with severe preeclampsia and eclampsia without any magnesium sulfate. The group felt that that, even in cases where immediate transfer of the woman to a higher-level facility was not possible, the patient was likely to be better off with only the loading dose than without it. The group felt that since this was a common scenario in many low-income countries, it should be given high priority for further research.

Background

Hypertensive disorders of pregnancy are an important cause of severe morbidity, long-term disability and
death among both mothers and their babies. Worldwide, they account for approximately 14% of all maternal deaths, whereas in Latin America and the Caribbean, they contribute to approximately 22% of all maternal deaths.(2)

Among the hypertensive disorders that complicate pregnancy, pre-eclampsia and eclampsia stand out as major causes of maternal and perinatal mortality and morbidity. The majority of deaths due to pre-eclampsia and eclampsia are avoidable through the provision of timely and effective care to the women presenting with these complications.

Methods

The recommendation was developed using standardized operating procedures in accordance with the process described in the “WHO handbook for guideline development”, guided by the GRADE approach.(3, 4) Outcomes used for this recommendation were aligned with the prioritized outcomes from the WHO recommendations on prevention and treatment of pre-eclampsia eclampsia (2011).(5)

Cochrane systematic reviews were conducted, on the use of magnesium sulfate and other anticonvulsants for women with eclampsia. (6-8) In the review, randomized controlled trials relevant to the key question were screened by review authors, and data on relevant outcomes and comparisons were extracted. Evidence profiles (in the form of GRADE tables) were prepared for comparisons of interest, including the assessment and judgments for each outcome, and the estimated risks.

WHO convened a Guideline Development Group (GDG) meeting on recommendations for prevention and treatment of pre-eclampsia eclampsia in April 2011, where this recommendation was developed. The GDG comprised of a group of independent experts, who used the evidence profiles to assess evidence on effects on the pre-specified outcomes. GDG members discussed the balance between desirable and undesirable effects, overall quality of supporting evidence, values and preferences of stakeholders, resource requirements, cost-effectiveness, acceptability, feasibility and equity, to formulate the recommendation. Remarks were added to clarify the recommendation, and aid implementation.

Recommendation question

For this recommendation, we aimed to answer the following question/s:

- in women with eclampsia (P), does treatment with magnesium sulfate (I) compared to other anticonvulsants, placebo or no treatment (C), improve maternal and perinatal outcomes (O)?

Evidence Summary

**Magnesium sulfate versus diazepam for women with eclampsia**

A Cochrane systematic review of seven RCTs involving 1396 women provided the evidence on the differential effects of magnesium sulfate when compared with diazepam for the care of women with eclampsia.(8) Most women in the trials had eclampsia either before or after delivery and about half of them received an anticonvulsant before trial entry. All regimens used in the trials for both magnesium sulfate and diazepam included loading and maintenance doses.

Magnesium sulfate fared better than diazepam regarding critical maternal outcomes of death (seven trials; 1396 women; RR 0.59, 95% CI 0.38–0.92) and recurrence of convulsions (seven trials; 1390 women; RR
There were no statistical differences between the two drugs for any serious maternal morbidity (two trials, 956 women; RR 0.88, 95% CI 0.64–1.19) or any of its proxies addressed in this comparison. Regarding fetal outcomes, no clear difference was demonstrated between the comparison groups for perinatal death (four trials, 788 infants; RR 1.04, 95% CI 0.81–1.34) and admission to intensive care unit (three trials, 634 infants; RR 0.92, 95% CI 0.79–1.06). Magnesium sulfate was associated with fewer cases of babies born with Apgar scores lower than seven at 5 minutes (three trials, 643 infants; RR 0.70, 95% CI 0.54–0.90) (EB Table 40).

Comparison of the two treatment groups according to route of administration of magnesium sulfate maintenance showed that intramuscular maintenance significantly reduced the risks of maternal respiratory depression (two trials, 120 women; RR 0.30, 95% CI 0.10–0.93) and maternal ventilation (two trials, 120 women; RR 0.20, 95% CI 0.05–0.88), but there was no statistically significant difference for maternal cardiac arrest (two trials, 120 women; RR 0.52, 95% CI 0.10–2.66) (EB Table 41). The two trials from which these findings were derived had a moderate risk of bias, small sample sizes and few events, resulting in inadequate quality of data.

**Magnesium sulfate versus phenytoin for women with eclampsia**

Evidence related to the effects of magnesium sulfate compared with phenytoin for the care of women with eclampsia came from a Cochrane systematic review of six RCTs involving a total of 972 women (22). Most of the women had eclampsia before delivery and had received anticonvulsants prior to trial entry. Eighty percent of the women in the review had participated in the relatively large Collaborative Eclampsia Trial,(9) which had a low risk of bias. The other five trials were all small and at a moderate risk of bias.

Compared with those treated with phenytoin, women treated with magnesium sulfate were at reduced risk of recurrence of convulsions (six trials, 972 women; RR 0.34, 95% CI 0.24–0.49), admission to intensive care unit (one trial, 775 women; RR 0.67, 95% CI 0.50–0.89) and need for ventilatory support (two trials, 825 women; RR 0.68, 95% CI 0.50–0.91). There were no statistically significant differences between the two treatment groups for maternal death (three trials, 847 women; RR 0.50, 95% CI 0.24–1.05), any serious maternal morbidity (one trial, 775 women; RR 0.94, 95% CI 0.73–1.20) and the reported proxy outcomes for severe maternal morbidity (EB Table 42).

Babies born to women treated with magnesium sulfate, rather than phenytoin, were less likely to be admitted for special care (one trial, 518 infants, RR 0.73, 95% CI 0.58–0.91) but no clear differences were observed between the two treatment groups with regard to the risks of perinatal death (two trials, 665 infants; RR 0.85, 95% CI 0.67–1.09) and Apgar score less than seven at 5 minutes (one trial, 518 infants; RR 0.86, 95% CI 0.52–1.43).

**Magnesium sulfate versus lytic cocktail for women with eclampsia**

The evidence on the differential effects of magnesium sulfate compared with the so-called “lytic cocktail” (usually a combination of chlorpromazine, promethazine and pethidine) was derived from a Cochrane systematic review of three small trials involving a total of 397 women.(7) Compared with lytic cocktail, magnesium sulfate was associated with significantly fewer cases of maternal death (three trials, 397 women; RR 0.14, 95% CI 0.03–0.59), recurrence of convulsions (three trials, 397 women; RR 0.06, 95% CI 0.03–0.12), coma for more than 24 hours (one trial, 108 women; RR 0.04, 95% CI 0.00–0.74) and respiratory depression (two trials, 198 women; RR 0.12, 95% CI 0.02–0.91). No clear differences were observed between the two treatment groups for any other proxy outcome for severe maternal morbidity. The risks of stillbirth and neonatal mortality were also similar between the two treatment groups (EB Table 43).

**Implementation considerations**
The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation.

The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.

A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations (including, for example, the availability of low-dose aspirin in antenatal care settings), and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.

In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.

Research implications

The 2011 GDG identified that further research on the following high-priority questions is needed:

- There is a need to assess the safety and efficacy of the loading dose magnesium sulfate at the primary care level flowed by transfer to higher level facility.
- Implementation research is needed to increase utilization of magnesium sulfate therapy.

Related Links

WHO recommendations on prevention and treatment of pre-eclampsia and eclampsia (2011) - full document and evidence tables (EB Tables 40 to 43)

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors

Supporting systematic reviews:


Duley L, Gülmezoglu AM, Chou D. Magnesium sulfate versus lytic cocktail for eclampsia. Cochrane Database of Systematic Reviews, 2010 (9):CD002960.

References


Citation


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