WHO recommendation on magnesium sulfate for the prevention of eclampsia in women with severe pre-eclampsia

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Recommendation

Magnesium sulfate is recommended for the prevention of eclampsia in women with severe pre-eclampsia in preference to other anticonvulsants.

(high-quality evidence, strong recommendation)

Publication history

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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.

- Clinical evidence supports the use of magnesium sulfate in all pre-eclampsia patients. In settings where there are resource constraints to manage the administration of magnesium sulfate safely in all women with pre-eclampsia, there may be a need to accord greater priority to the more severe cases. Magnesium sulfate is effective in preventing seizures in both mild and severe pre-eclampsia. However, the guideline development group noted that a higher number of women need to be treated to prevent one seizure. The group agreed on the need to treat women with severe pre-eclampsia, but the group members were divided on the use of magnesium sulfate as a prophylaxis for mild pre-eclampsia.

- 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)

A Cochrane systematic review was conducted, on the use of magnesium sulfate and other anticonvulsants for women with pre-eclampsia.(6) 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 or 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 pre-eclampsia (P), does treatment with anticonvulsants (I) compared to other anticonvulsants, placebo or no treatment (C), improve maternal and perinatal outcomes (O)?
- If so, which drug/s and route of administration optimizes outcomes?

**Evidence Summary**
**Prevention of pre-eclampsia**

A Cochrane systematic review of 15 RCTs investigated the relative effects of magnesium sulfate and other anticonvulsants when used for prevention of eclampsia.\(^6\) Notable comparisons in this review were between magnesium sulfate and placebo or no anticonvulsants (six trials, 11 444 women); phenytoin (four trials, 2345 women); diazepam (two trials, 66 women); and nimodipine (one trial, 1750 women). One small trial (36 women) compared magnesium sulfate with isosorbide, and another trial (33 women) compared magnesium chloride with methyldopa.

**Magnesium sulfate versus placebo or no anticonvulsant**

Six RCTs (11 444 women), including the large multicentre Magpie Trial (7) involving 10 141 participants, provided the evidence for this comparison. About half of the women recruited into the trial had received the maintenance regimen of magnesium sulfate through the intravenous route (1 g/h) and the other half through the intramuscular route. The maintenance dose was administered strictly by the intravenous route in four trials and the intramuscular route in one trial. For most trials, clinical monitoring for potential adverse effects was reported and none of the six trials reported using serum monitoring of magnesium sulfate.

When compared with placebo or no anticonvulsant, magnesium sulfate was associated with statistically and clinically significant reduction in the risk of eclampsia by 59% (six trials, 11 444 women; RR 0.41, 95% CI 0.29–0.58). This effect was consistent for women who were antepartum at trial entry (six trials, 10 109 women; RR 0.40, 95% CI 0.27–0.57) but nonsignificant for those who were postpartum at trial entry (one trial, 1335, RR 0.54, 95% CI 0.16–1.80). The effect was also consistent and more pronounced among women who were 34 or more weeks pregnant (two trials, 6498 women; RR 0.37, 95% CI 0.24–0.59) and those who had received no anticonvulsants prior to trial entry (three trials, 10 086 women; RR 0.33, 95% CI 0.22–0.48). It was consistent regardless of the route of administration for the maintenance of magnesium sulfate (EB Table 36).

No statistically significant differences were observed between magnesium sulfate and placebo regarding the risks of maternal death (two trials, 10 795 women; RR 0.54, 95% CI 0.26–1.10), any serious maternal morbidity (two trials 10 332 women; RR 1.08, 95% CI 0.89–1.32), respiratory arrest (one trial, 10 110 women; RR 2.50, 95% CI 0.49–12.88) and toxicity as shown by respiratory depression and absent tendon reflexes (three trials, 10 899 women; RR 5.96, 95% CI 0.72–49.40) and calcium gluconate administration (two trials, 10 795 women; RR 1.35, 95% CI 0.63–2.88). Any reported side-effects were significantly more common among women treated with magnesium sulfate rather than placebo (one trial, 9992 women; RR 5.26, 95% CI 4.59–6.03).

For the baby, no clear difference were observed in the risks of stillbirth or neonatal death (three trials, 9961 babies; RR 1.04, 95% CI 0.93–1.15), admission to special care baby unit (RR 1.01, 95% CI 0.96–1.06) and Apgar score less than seven at 5 minutes (one trial, 8260 women; RR 1.02, 95% CI 0.85–1.22).

**Magnesium sulfate versus phenytoin**

Magnesium sulfate was compared with phenytoin for the prevention of eclampsia in four RCTs (2343 women). Compared with phenytoin, magnesium sulfate significantly reduced the risk of eclampsia (three trials, 2291 women; RR 0.08, 95% CI 0.01–0.60). No statistically significant differences were observed between the two groups in terms of stillbirth (RR 0.62, 95% CI 0.27–1.41), neonatal death (RR 0.26, 95% CI 0.03–2.31), Apgar score less than seven at 5 minutes (RR 0.58, 95% CI 0.26–1.30) and admission to neonatal care (RR 1.00, 95% CI 0.63–1.59) (EB Table 37).

**Magnesium sulfate versus diazepam**

A small trial involving 66 women compared magnesium sulfate and diazepam for the prevention of eclampsia. The sample size and the events recorded were too small to draw any reliable conclusions (EB
Magnesium sulfate was compared with nimodipine in one trial (1650 women). There were fewer cases of eclampsia among women allocated magnesium sulfate compared with nimodipine (RR 0.33, 95% CI 0.14–0.77) (EB Table 39).

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 36 to 39)
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 review:


References

Citation


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