Obstetrical and Pediatric Anesthesia

Best evidence in anesthetic practice

Prevention: Magnesium sulfate reduces the risk of eclampsia in women with pre-eclampsia

Article #1 appraised

The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002; 359: 1877–90.

Structured abstract

Question: In women with pre-eclampsia, does peripartum administration of magnesium sulfate decrease the risk of eclampsia, maternal morbidity, or neonatal morbidity compared to placebo?

Design: Multicentre, randomized, double-blind, placebo-controlled trial.

Setting: One hundred and seventy-five secondary and tertiary level hospitals in 33 countries.

Patients: Ten thousand one hundred and forty-one women who were pregnant or ≤ 24 hr postpartum, with at least two blood pressure readings of ≥ 90 mmHg diastolic blood pressure or ≥ 140 mmHg systolic blood pressure, proteinuria of 1 + or more, and clinical uncertainty of the benefit of the use of magnesium sulfate. Exclusion criteria were hypersensitivity to magnesium, hepatic coma with risk of renal failure, or myasthenia gravis.

Intervention: Five thousand and seventy-one women were allocated to magnesium 4 g *iv* (loading dose) followed by a maintenance regimen of either 1 $g \cdot hr^{-1}$ *iv* infusion for 24 hr or 2.5 to 5 g *im* every four hours for 24 hr; 5,070 women were allocated to equivalent volumes of placebo (normal saline) for loading and maintenance.

Main outcomes: The primary outcome was eclampsia. Secondary outcomes included maternal mortality, serious maternal morbidity, and side effects and toxicity from the study drug. For women randomized before delivery, in-hospital death was also a primary outcome and complications of labour and delivery and neonatal morbidity were additional secondary outcomes. Patients and their babies were followed until hospital discharge.

Main results: Analysis was intention-to-treat. Clinical characteristics were similar between both groups. Eclampsia occurred less frequently in the magnesium sulfate group (0.8%) than in the placebo group (1.9%). There were no differences in in-hospital baby death; maternal mortality or morbidity; neonatal morbidity; or outcomes related to pregnancy, labour, or delivery except for fewer placental abruptions in the magnesium group (2.0%) than in the placebo group (3.2%; Table).

Conclusion: Compared to placebo, magnesium sulfate decreases the risk of eclampsia in women with pre-eclampsia.

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Article #2 appraised

Belfort MA, Anthony J, Saade GR, Allen JC Jr, for the Nimodipine Study Group. A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med 2003; 348: 304–11.

Structured abstract

Question: In women with severe pre-eclampsia undergoing labour and delivery, does nimodipine decrease the risk of seizures compared to magnesium sulfate?

Design: Multicentre, randomized, unblinded, controlled trial.

Setting: Fourteen hospitals in eight countries.

Patients: One thousand seven hundred and fifty women, who had severe pre-eclampsia, were undergoing labour and delivery, had not received magnesium

TABLE Results from randomized controlled trials of magnesium sulfate for the prevention of eclampsia in women with pre-eclampsia

Outcome	*Magnesium sulfate*	*Control**	*Relative risk (95% confidence intervals)†*	*Number-needed-to-prevent or harm‡*	*P value*
Magpie Trial					
Eclampsia	40/5055	96/5055	0.42 (0.29; 0.60)	NNP 91	< 0.0001
Maternal mortality	11/5055	20/5055	0.55 (0.26; 1.15)		0.15
Baby mortality	576/4538	558/4486	1.02 (0.92; 1.14)		0.74
Severe maternal morbidity	196/5055	183/5055	1.07 (0.88; 1.30)		0.53
Placental abruption	90/4415	141/4359	0.63 (0.48; 0.82)	NNP 84	0.001
Nimodipine Study					
Eclampsia	7/831	21/819	0.33 (0.14; 0.77)	NNP 34	0.01
Need for hydralazine	451/831	374/819	1.19 (1.08; 1.31)	NNH 12	< 0.001
Flushing	59/831	13/819	4.47 (2.47; 8.09)	NNH 18	< 0.001
Postpartum hemorrhage	20/831	8/819	2.46 (1.09; 5.56)	NNH 70	

NNH = number-needed-to-harm; NNP = number-needed-to-prevent. *The control group was placebo in the Magpie Trial and nimodipine in the Nimodipine Study. †A relative risk less than one favours magnesium sulfate; a relative risk greater than one favours placebo or nimodipine. Relative risks were calculated based on the data from the original studies. ‡NNP and NNH have been calculated for differences between groups that were statistically significant.

sulfate, and did not have a pre-existing seizure disorder. One hundred patients did not complete the study.

Intervention: Eight hundred and nineteen patients were allocated to nimodipine 60 mg orally every four hours for 24 hr; 831 patients were allocated to magnesium sulfate 6 g *iv* (loading dose) followed by 1 $g \cdot hr^{-1}$ *iv* for 24 hr.

Main outcomes: The primary outcome was eclampsia up to 24 hr postpartum. Secondary outcomes included blood pressure control, side effects and adverse effects from the study drug, complications of labour and delivery, and fetal and neonatal morbidity.

Main results: Analysis was per protocol. The study was terminated early based on results from a planned interim analysis. Clinical characteristics were similar between both groups. Eclampsia occurred more frequently in the nimodipine group (2.6%) than in the magnesium group (0.8%); however, antihypertensive therapy with hydralazine, postpartum hemorrhage, and flushing were significantly increased in the magnesium group (Table). The incidences of complications of labour and delivery and fetal and neonatal morbidity did not differ significantly between the two groups.

Conclusion: Compared to nimodipine, magnesium sulfate decreases the risk of eclampsia in women with severe pre-eclampsia.

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Commentary by M.J. Douglas

Eclampsia is the occurrence of convulsions in a pre-eclamptic patient without a pre-existing seizure disorder. Some authors suggest that cerebral vasoconstriction leads to ischemia and seizure, although others postulate that elevated cerebral perfusion pressure is the underlying mechanism for seizure.[1] A well-designed study has confirmed that magnesium sulfate (*vs* phenytoin and diazepam) is the best anticonvulsant for eclampsia;[2] but until now studies confirming the benefit of prophylactic magnesium have been lacking. Both abstracted studies are well designed, well written and the results are significant.[3,4]

The Magpie Trial examined the effectiveness of magnesium in preventing seizures in women with mild or severe pre-eclampsia.[3] The study was conducted in 33 countries with varying perinatal mortality rates making its results impressive and generalizable. Magnesium was better than placebo in preventing convulsions but this was associated with more side effects (25% *vs* 5% for placebo). However, few were life-threatening and maternal morbidity was similar. There was an anesthetic-related maternal death in the magnesium group but no details were provided.

Belfort *et al.* hypothesized that nimodipine would be more effective in preventing eclampsia in women with severe pre-eclampsia, because of its effects on the cerebral circulation.[4] In contrast to their hypothesis, magnesium was more effective than nimodipine in preventing seizures, particularly postpartum, lending credence to elevated cerebral perfusion pressure as the underlying cause of eclampsia.

In the Nimodipine Study there was an association between postpartum seizure and anesthesia in the nimodipine group ($P < 0.01$).[4] Nine women who received general or regional anesthesia had a postpartum seizure compared to none who received no anesthesia or local anesthesia for delivery. Because of the small numbers this association is interesting but other factors such as length of labour, operative delivery, or an interaction between nimodipine and the anesthetic agents may be responsible.

The Magpie Trial found that 91 women had to receive magnesium to prevent one case of eclampsia. In those with severe pre-eclampsia the number-needed-to-prevent is 63.[3] Should all women with pre-eclampsia receive magnesium or only those with severe pre-eclampsia? In the Magpie Trial there was a 55% reduction in maternal mortality in the magnesium group (0.2% *vs* 0.4% for placebo) that was not statistically significant.[3] No deaths were reported in the Nimodipine Trial but independent risk factors for seizure were identified.[4] Those at the highest risk had a history of hypertension treated with medication [relative risk (RR) 4.3] or an age less than 18 yr (RR 4.2). The two studies confirm the benefits of magnesium prophylaxis in all women with severe pre-eclampsia, especially in those at highest risk. Whether the side effects of magnesium sulfate outweigh the benefits in women with mild pre-eclampsia (number-needed-to-prevent 109)[3] is less certain.

In summary, both studies clearly show that magnesium is the best agent to prevent eclampsia. Magnesium prophylaxis is unlikely to be problematic for Canadian anesthesiologists as it is already used extensively for this purpose. However, as general anesthesia is used less frequently there is a risk that the interaction between magnesium and non-depolarizing muscle relaxants may be forgotten, particularly in an emergency.

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3 *The Magpie Trial Collaborative Group.* Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002; 359: 1877–90.

4 *Belfort MA, Anthony J, Saade GR, Allen JC Jr, for the Nimodipine Study Group.* A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. N Engl J Med 2003; 348: 304–11.

Commentary by A. Macarthur

I am delighted to comment on two outstanding obstetric studies evaluating the association between magnesium sulfate and eclampsia.[1,2] The use of magnesium sulfate is well known in Canada, influenced by American practice. Since the 1930's, Americans have believed in the anecdotal evidence for magnesium. However, the rest of the world has remained undecided or in a position of "clinical equipoise" (the genuine uncertainty on the part of the expert medical community about the comparative merits of two or more regimens). Therefore, these two clinical trials represent powerful tools to investigate the effectiveness of magnesium in preventing eclampsia.

Before accepting the results or conclusions of any randomized controlled trial (RCT) I first assess its quality using a simple three-item, five-point scale.[3] Points are awarded on the basis of randomization (two points), double-blinding (two points), and the description of study withdrawals or dropouts (one point).[3] Studies with higher points are of superior quality, and likely contribute to increasing our objective knowledge on the intervention.

Both RCTs utilized objective randomization schedules (two points). Randomization reduces bias (a systematic error in quantifying the association between intervention and outcome) that arises from selection, measurement, or confounding errors. Only the Magpie Trial incorporated double-blinding into the study design (two points), a feature that has been demonstrated to minimize exaggeration of an intervention's effectiveness. In the Nimodipine Study, patients, physicians, and evaluators could identify those receiving oral nimodipine or *iv* magnesium (zero point). The authors defended the lack of blinding with the argument that the outcome, occurrence of a peripartum seizure, was "objective and not subject to observer or measurement bias." Knowledge of a patient's allocated drug regimen could influence the likelihood of withdrawal from the study; therefore, all patients entering the study would have to be rigorously accounted for and reported. The last criterion required a description of any patients who consented to the study but did not receive the randomized intervention, did not complete the observation period, or were not included in the analysis. Both studies report this information. Thus, the Magpie Trial has a quality score of 5 while the Nimodipine Study receives a rat-

ing of 3. Both scores indicate the manuscripts are worth reading.

My last comment is a request. When reading the articles I encourage clinical researchers to acknowledge the effort involved in recruiting women into these studies while at the end of a complicated pregnancy. Your appreciation will also be increased by the study investigators who enrolled over 59% of the participants in the Magpie Trial despite few national health resources (in Bangladesh, Egypt, India, Malawi, Nigeria, Pakistan, Sierre Leone, South Africa, Sri Lanka, Uganda, Yemen and Zimbabwe).

The two studies results are generalizable to women with pre-eclampsia in developed and developing nations. The Nimodipine Study contributed to improved understanding of the intracranial pathophysiology of pre-eclampsia. Abnormal cerebral perfusion pressure may be as relevant as cerebral vasoconstriction.[4] Anesthesiologists in the future may need to categorize a patient's intracranial pathophysiology before choosing the appropriate anesthetic agents.

While preparing this commentary I searched the term "magnesium sulfate and anesthesia" and was struck by the many new indications for magnesium in anesthesia. For many reasons, such as reduction in anesthetic requirements by NMDA receptor antagonism[5] to treatment of autonomic hyper-reflexia[6] to its use in pre-eclampsia, magnesium sulfate will become an increasingly familiar medication to anesthesiologists.[7]

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