Canadian Agency for Drugs and Technologies in Health

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HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: Intravenous Magnesium Sulfate Infusions for the Management of Pregnancy-Related Toxemia, Hypomagnesemia/Tetany, or Cardiac Dysrhythmias: Clinical Review of Safety and Effectiveness and Guidelines for Use

Date: 04 June 2008

Research questions:

1. What is the clinical safety and effectiveness of intravenous infusions of magnesium sulfate ($MgSO_4$) in adult patients for pregnancy-related toxemia, hypomagnesemia/tetany, and/or cardiac dysrhythmias?

2. What are the guidelines for use of intravenous infusions of $MgSO_4$ in adult patients?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 2, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and May 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

The summary of findings was prepared from the abstracts of the relevant information.

Results:

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews and meta-analyses are presented first. These are followed by randomized controlled trials, observational studies and evidence-based guidelines.

Overall summary of findings:

Pregnancy-related toxemia

No health technology assessments were identified for the infusion of $MgSO_4$ for pregnancy-related toxemia.

Two systematic reviews were identified. Duley *et al.* (2003)[1] assessed the effects of $MgSO_4$ on women with pre-eclampsia and their children. Six randomized controlled trials (n=11,444) comparing $MgSO_4$ with placebo or no anticonvulsant were included in the review. The authors concluded that magnesium sulfate more than halved the risk of eclampsia and appeared to reduce the risk of maternal death (although death reduction was not statistically significant), when compared with placebo or no anticonvulsant. Short term outcomes for babies did not change with $MgSO_4$ therapy. Side effects were present in 24% of women; the main effect was flushing.

In a second systematic review, Duley and Henderson-Smart (2003)[2] compared the effects of $MgSO_4$ with phenytoin, on women with eclampsia. Six trials (n=897) were included in the review. The authors concluded that $MgSO_4$ was significantly more effective than phenytoin for the reduction in recurrent convulsions in women with eclampsia. There appeared to be a statistically non-significant reduction in maternal death. Significant reductions in rates of pneumonia, ventilation, and admission to the intensive care unit were associated with the use of $MgSO_4$. Babies of mothers receiving $MgSO_4$ required fewer admissions to special care units. Adverse effects were not discussed in this review.

Three randomized controlled trials were identified. The Magpie Trial[3] (2002) compared $MgSO_4$ with placebo in 10,141 women with pre-eclampsia. $MgSO_4$ was given intravenously as a loading dose of 8 mL (4g $MgSO_4$), followed by 24 hours of 2 mL/hour (1 g/hour). $MgSO_4$ reduced the risk of eclampsia but did not significantly improve rates of maternal or infant death or serious maternal morbidities.

Belfort *et al.*[4] (2003) compared $MgSO_4$ (dosage not specified in abstract) with nimodipine for the prevention of eclampsia, in 1,650 women with severe pre-eclampsia. The authors concluded that $MgSO_4$ was more effective than nimodipine for prophylaxis against postpartum, but not antepartum seizures, in women with severe pre-eclampsia. Neonatal outcomes showed no significant difference. More women receiving $MgSO_4$ required hydralazine to control blood pressure.

Livingston *et al.*[5] (2003) compared intravenous $MgSO_4$ (dosage not specified in abstract) with placebo, for 222 women with mild pre-eclampsia. They concluded that $MgSO_4$ did not significantly improve disease progression in women with mild pre-eclampsia, nor did its use increase the rates of cesarean delivery, infectious morbidity, obstetric hemorrhage, or neonatal outcomes.

Two observational studies relating to safety and adverse events of $MgSO_4$ were identified. Omu *et al.*[6] (2008) evaluated the use of $MgSO_4$ in 450 women with pre-eclampsia and eclampsia. $MgSO_4$ was administered intravenously, 4g over 20 minutes, then continued at 1 g/hour for 24 hours postpartum. The perinatal mortality rate was 27 per 1,000. $MgSO_4$ toxicity was observed in 3.1% of patients as reduced tendon reflexes, and in 19.1% of patients as flushing, nausea and vomiting, and blocked nostrils. No maternal mortality was reported. The authors concluded that $MgSO_4$ was effective in the prevention of recurring eclamptic seizures and was safe for mother and fetus.

Magee *et al.*[7] (2005) performed a retrospective chart review of women with pre-eclampsia, admitted to a British Columbia women's hospital between 1997 and 2001 (total number of women not reported), who were given $MgSO_4$ (dosage not specified) for pre-eclampsia, either alone or in combination with nifedipine or another antihypertensive drug. The authors concluded that $MgSO_4$ in combination with nifedipine did not increase the risk of serious magnesium-related effects.

Brief summaries of five guidelines discussing $MgSO_4$ infusion for pre-eclampsia and eclampsia are presented in Table 1. Links to the full text are provided in the reference list.

Table 1: Guidelines and Recommendations for the Administration of $Mgso_4$ for Pre-Eclampsia and Eclampsia

Author/ Organization (Date)	Pre-Eclampsia Recommendations	Eclampsia Recommendations	Follow-Up Recommendations
von Dadelzen *et al.*[8] (2007)	$MgSO_4$ 4 g IV stat, then 1 g/h	$MgSO_4$ 2g IV stat, then increase to 1.5 g/h	Fluid intake should be ≤80 mL/h; urine outputs ≥10 mL/h.
Royal College of Obstetricians and Gynaecologists, UK[9] (2006)	$MgSO_4$ 4 g by infusion pump over 5 to 10 min, then 1 g/h	$MgSO_4$ 2 g by infusion pump over 5 to 10 min or increase infusion rate to 1.5 g/h or 2.0 g/h	Urine output should be ≥20 mL/h. Continue $MgSO_4$ for 24 h following delivery or following the last seizure, whichever is the later.
American Association of Clinical Endocrinologists[10] (2006)	$MgSO_4$ recommended for pre-eclampsia at high risk for seizures. No other details reported.	No details reported.	No details reported.
British Columbia Reproductive Care Program[11] (2006)	$MgSO_4$ 4 g IV stat, over 20 to 30 min, then 1 g/h	$MgSO_4$ 2 g IV stat, over 20 to 30 min, then 1.0 g/h to 1.5 g/h	Infusion should continue for 24 h or until 24 h after delivery, whichever is the later, if the following conditions are met after every 4 h period: biceps reflex present; respiratory rate >12/min; urinary output >100 mL in previous 4 h.
NSW Department of Health, Australia[12] (2005)	$MgSO_4$ 4 g IV, over 15 to 30 min, then 1 g/h	$MgSO_4$ 4 g IV, over 15 to 30 min, then 1 g/h	Care and observations during infusion: 1-2 h monitoring of blood pressure, respiratory rate (must be ≥10/min) and urine output (must be ≥30 mL for 3 consecutive h); patellar reflexes at completion of loading then at 2 h intervals; fetal heart rate monitoring; serum magnesium levels 60 min after commencing infusion, then as clinically indicated. Continue $MgSO_4$ maintenance dose for at least 24 h if these criteria are met.

g=grams; h=hours; mL=millilitres; min=minutes IV=intravenous

Hypomagnesemia / tetany

No health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, or guidelines were identified by the literature search.

One observational study, by Fakih *et al.*[13] retrospectively reviewed charts of 114 patients with colorectal cancer, treated with cetuximab. Thirteen patients had developed hypomagnesemia (a frequent side effect of cetuximab therapy), and were treated successfully with daily to 3-times-weekly intravenous $MgSO_4$ at 6 g to 10 g per dose. No further details were provided in the abstract.

Cardiac dysrhythmias

No health technology assessments, observational studies (focused on safety and adverse events), or guidelines were identified by the literature search.

Three systematic reviews/meta-analyses were identified. Li *et al.*[14] (2007) systematically reviewed the effect of intravenous magnesium (including $MgSO_4$) versus placebo, on early mortality and morbidity in acute myocardial infarction. The abstract does not indicate the number of randomized controlled trials or number of patients included in the review. The authors stated that, due to a high likelihood of publication bias and marked heterogeneity of treatment effects, the findings must be interpreted cautiously. They concluded that: "(1) it is unlikely that magnesium is beneficial in reducing mortality both in patients treated early and in patients treated late, and in patients already receiving thrombolytic therapy; (2) it is unlikely that magnesium will reduce mortality when used at high dose (>=75 mmol); (3) magnesium treatment may reduce the incidence of ventricular fibrillation, ventricular tachycardia, severe arrhythmia needing treatment or Lown 2-5, but it may increase the incidence of profound hypotension, bradycardia and flushing; and (4) the areas of uncertainty regarding the effect of magnesium on mortality remain the effect of low dose treatment (< 75 mmol) and in patients not treated with thrombolysis."[14]

Henyan *et al.*[15] (2005) performed a meta-analysis on the impact of intravenous magnesium on post-cardiothoracic surgery atrial fibrillation and length of hospital stay. Seven randomized trials (total number of patients not specified) were included in the analysis. Patients receiving prophylactic magnesium experienced significantly less postoperative atrial fibrillation and shorter hospital stays. Lower doses and pre-operative initiation of magnesium achieved the greatest reduction in postoperative atrial fibrillation.

Miller *et al.*[16] (2005) performed a meta-analysis to assess the effectiveness of magnesium (including $MgSO_4$) for preventing post cardiac surgery atrial fibrillation. The review included 20 randomized controlled trials, and a total of 2,490 patients. Treatment duration ranged from 10 to 144 hours, and the total amount of magnesium administered ranged from 7 to 110 mmol. Results showed that magnesium administration significantly decreased the percentage of patients developing postoperative atrial fibrillation. However, therapy with magnesium did not significantly affect length of hospital stay or in-hospital mortality rate. The authors concluded that administering magnesium effectively reduced post-operative atrial fibrillation, but they could not draw conclusions as to the optimal regimen of magnesium administration.

Six randomized controlled trials were identified and are summarized in Table 2.

Table 2: Randomized Controlled Trials of $Mgso_4$ for Cardiac Arrhythmias

First Author, Date	Objective	Number of Patients	Results
Cagli, 2006[17]	To determine if postoperative administration of intravenous low-dose amiodarone and $MgSO_4$ combination would reduce the incidence of atrial fibrillation following coronary artery bypass grafting in normomagnesemic high-risk patients	136	Postoperative atrial fibrillation occurred significantly less in patients randomized to receive a combination of amiodarone and $MgSO_4$ (1.5g) without a maintenance phase, compared with those receiving amiodarone alone or placebo.
Davey, 2005[18]	To examine the safety and efficacy of $MgSO_4$ in addition to usual care, for emergency department patients with atrial fibrillation and rapid ventricular response rate	199	Intervention patients receiving $MgSO_4$ (2.5g, 10 mmol intravenously over a 20 min period, followed by 2.5g, 10 mmol over a 2-h period) had improved ventricular response rate control and conversion to sinus rhythm compared with those receiving placebo. There was an increased risk of adverse events (mostly minor events such as flushing and nausea) in those receiving $MgSO_4$.
Zangrillo, 2005[19]	To evaluate the effectiveness of peri-operative magnesium for prophylaxis of atrial fibrillation following off-pump coronary artery surgery	160	Intra-operative infusion of $MgSO_4$ (2.5 g over 30 min) did not show an increased effect in preventing atrial fibrillation, compared with placebo.
bdel-Mageed, 2004[20]	To determine the optimal timing for magnesium supplementation and its impact on weaning and early postoperative course, following open-heart surgery	40	Patients were divided into 4 groups: no Mg, pre-operative Mg, Mg after initiation of cardiopulmonary bypass, and peri-operative Mg (dosages not specified in abstract). Administering Mg peri-operatively increased the incidence of spontaneous recovery of the heart, and reduced the incidence of peri-operative ventricular arrhythmias.
Hazelrigg, 2004[21]	To evaluate the effectiveness of pre-operative and postoperative $MgSO_4$ in preventing atrial and ventricular arrhythmias following coronary artery bypass surgery	202	Intervention patients received $MgSO_4$ infusion (80mg/kg over 30 min pre-operatively, then 8 mg/kg per h for >48 h). Atrial fibrillation and ventricular arrhythmias were not significantly reduced, except on the first postoperative day when compared with placebo.
Kaplan, 2003[22]	To investigate the effectiveness of $MgSO_4$ in the prophylaxis of atrial fibrillation following coronary artery bypass grafting surgery	200	Intervention patients received 3g $MgSO_4$ in 100 mL saline over 2 h (50 mL/h) pre-operatively, peri-operatively, and postoperatively at days 0, 1, 2, and 3. There was no improved effectiveness for the prevention of atrial fibrillation, compared to the placebo group.

g=grams; min=minutes; h=hours; mmol=millimoles; kg=kilogram; mL=millilitres

References summarized:

Pregnancy-related toxemia

Health technology assessments
No literature identified

Systematic reviews and meta-analyses

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Randomized controlled trials

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Note: Published results for this trial fall outside of our date limitations for this report.

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Observational studies (safety and adverse events)

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Guidelines and recommendations

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Hypomagnesemia / tetany

Health technology assessments
No literature identified

Systematic reviews and meta-analyses
No literature identified

Randomized controlled trials
No literature identified

Observational studies

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Guidelines and recommendations
No literature identified

Cardiac dysrhythmias

Health technology assessments
No literature identified

Systematic reviews and meta-analyses

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Randomized controlled trials

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Observational studies (safety and adverse events)
No literature identified

Guidelines and recommendations
No literature identified

Prepared by:

Karen Cimon, Research Assistant
Emmanuel Nkansah, MLS, MA, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439

Appendix – Further information:

Economic analyses and cost information

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Observational studies

24. Sleeswijk ME, Tulleken JE, Van NT, Meertens JH, Ligtenberg JJ, Zijlstra JG. Efficacy of magnesium-amiodarone step-up scheme in critically ill patients with new-onset atrial fibrillation: a prospective observational study. *J Intensive Care Med* 2008;23(1):61-6. PubMed: PM18320707

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