REVIEW ARTICLE

Magnesium and the obstetric anaesthetist

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ABSTRACT
Magnesium is one of the most abundant cations in the human body. It is utilised extensively within the medical world and its role in the treatment of various conditions in both mother and fetus is increasing. This review focuses on the importance of magnesium for the obstetric anaesthetist and looks at the most recent evidence surrounding its use in hypertensive disorders of pregnancy, neuroprotection of the premature infant and the expanding role of magnesium as an analgesic and adjunct to anaesthesia.

Introduction
Magnesium is found in abundance within the earth’s crust as deposits of magnesite and dolomite. It was first isolated in 1808 by the English chemist Sir Humphrey Davy using electrolysis of a mixture of magnesia and mercury oxide. Over the last century its medicinal uses have increased considerably (Table 1). Magnesium is integral to many of the body’s basic functions and has an increasing role in the world of anaesthesics and obstetrics. Some uses remain controversial, prompting further trials and study. This review focuses on the obstetric and anaesthetic implications of magnesium, including the uses, indications and recent developments in research for both mother and neonate. The authors reviewed articles related to magnesium and, where significant, to the practice of obstetric anaesthesia, published in the last 20 years in the Medline and Cochrane libraries. Studies published earlier than 1991 were also included if considered vital to the discussion. Throughout this review, levels of evidence refer to the U.S. Preventive Services Task Force system. Grades A, B, C, D and I refer to the recommendation and suggestion for practice, whereas the level of certainty (High, Moderate or Low) refers to the level of certainty regarding net benefit.

Physiology of Magnesium
Magnesium is the fourth most abundant cation in the human body (after sodium, potassium and calcium) with 60% contained in bone and 39% in the intracellular compartment of muscle and soft tissue. Within the extracellular fluid, magnesium is present in both an ionised and unionised form, the ionised form being the active element. Serum levels reflect a small proportion of the body’s total 24 g of magnesium since only 1% is maintained in the blood.10

The body relies on nutrition to maintain adequate magnesium levels. Significant sources of magnesium include green vegetables, cereal grains and meats. Recommended daily intake for an adult female is approximately 320 mg.11 However, a national USA survey demonstrated that a large proportion of American adults fail to consume their recommended daily dose.12 Dietary magnesium is absorbed in the small intestine via an active transport system. Passive absorption maintains a constant baseline uptake of magnesium. Absorption is inversely proportional to the amount consumed and the majority is absorbed in the distal small bowel.13 Efficient processes both in the gastrointestinal tract and kidneys maintain plasma magnesium concentrations. The underlying mechanism for this tight homeostatic control is poorly understood, although postulated to be related to levels of parathyroid hormone.14 The kidneys regulate magnesium by excreting excess amounts above a specific threshold and actively conserving when the body’s magnesium is low. As a consequence, magnesium surplus to the body’s requirements, either dietary or given parenterally, may be almost entirely excreted.15

Magnesium is critical for many cellular processes, such as the formation of biological compounds for energy utilisation and protein synthesis. Over 300 enzymatic processes, including nucleic acid synthesis...
and virtually all hormonal reactions, are reliant on magnesium. Free magnesium in the intracellular space activates important secondary messenger systems, such as phospholipase C, and enables active transport of potassium and calcium across the plasma membrane. Magnesium is an important structural element in DNA and cell membranes. Additionally, magnesium is a physiological calcium antagonist and actively contributes to the maintenance of neuronal activity, control of vasomotor tone, glycolysis and cardiac excitability (Fig. 1).

Magnesium, however, is not a benign drug. Reaching toxic levels via excess dietary uptake is unusual, and usually occurs only in the context of renal failure. The most common cause of hypermagnesaemia is iatrogenic, from intravenous (i.v.) administration. Overdose can have catastrophic consequences on obstetric and fetal outcomes. Toxic effects include changes in mental status, gastrointestinal disturbances, muscle weakness, respiratory distress, severe hypotension, and arrhythmias. As serum levels of magnesium increase, the clinical symptoms and outcomes worsen (Table 2).

Magnesium as a therapeutic intervention was first recognised in the early 1900s as a novel treatment for tetanus. Over the following decades its use in obstetrics increased; the role of magnesium in obstetrics and anaesthesia are now established and further interest continues into its wide range of uses.

### Hypertensive diseases of pregnancy

Preeclampsia affects up to 7% of all pregnancies in the USA. The disease remains a significant cause of maternal and fetal morbidity and mortality, and there still is no known preventative treatment. In the USA, preeclampsia is the third leading cause of maternal death after thromboembolism and haemorrhage: 64 of the 548 maternal deaths reported in the USA in 2007 were due to preeclampsia or eclampsia. Similarly, preeclampsia remained in the top three direct causes of maternal death in the 2006–08 UK Centre for Maternal and Child Enquiries (CMACE) Report, with 19 of 261 deaths being directly related to preeclampsia.

Magnesium has been used to treat acute hypertensive crises, especially in the context of pheochromocytoma management and treatment of pregnancy-related hypertension with magnesium sulphate was considered as early as 1906. However, magnesium has taken on an increasing role in obstetrics, replacing diazepam and phenytoin for the treatment of eclampsia.

The use of magnesium in both mild and severe preeclampsia (Table 3) is now widespread, however, its mechanism of action remains unclear. Magnesium is a calcium antagonist which acts at the majority of calcium channels, including those in vascular smooth muscle, and inhibits the release of calcium from the sarcoplasmic reticulum.

### Table 1 Medical uses of magnesium

<table>
<thead>
<tr>
<th>System</th>
<th>Use</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Acute exacerbation of asthma</td>
<td>Bronchial smooth muscle relaxation</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Digoxin induced ventricular arrhythmias</td>
<td>Calcium antagonist</td>
</tr>
<tr>
<td></td>
<td>VT/VF/Torsades de Pointes refractory to</td>
<td>Activation of adenylate cyclase</td>
</tr>
<tr>
<td></td>
<td>other treatment</td>
<td>↓ neurotransmitter release at motor nerve terminal</td>
</tr>
<tr>
<td>Neurological</td>
<td>Spinal cord injury</td>
<td>Calcium antagonist</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Antacid</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Resection of pheochromocytoma</td>
<td>Suppression of catecholamine release</td>
</tr>
<tr>
<td>Obstetric</td>
<td>Preeclampsia</td>
<td>Calcium antagonist</td>
</tr>
<tr>
<td></td>
<td>Preterm fetal neuroprotection</td>
<td>NMDA antagonist</td>
</tr>
<tr>
<td>Anaesthesia</td>
<td>Analgesia</td>
<td>NMDA antagonist</td>
</tr>
<tr>
<td>Other</td>
<td>Tetanus</td>
<td>Calcium antagonist</td>
</tr>
<tr>
<td></td>
<td>Noise-related hearing loss prevention</td>
<td>NMDA antagonist</td>
</tr>
</tbody>
</table>

ACh: acetylcholine; NMJ: neuromuscular junction; ACE: angiotension converting enzyme; NMDA: N-methyl-D-aspartate; SA: sinoatrial; AV: atrioventricular; VT: ventricular tachycardia; VF: ventricular fibrillation.
The anticonvulsant action of magnesium is considered to be due to antagonism at the N-methyl-D-aspartate (NMDA) receptor centrally. Receptor antagonism increases seizure threshold and leads to seizure prevention.33

Mild Preeclampsia
The quoted incidence of eclamptic seizures in women with mild preeclampsia is <1%.29 Two randomised, double-blind, placebo-controlled trials have looked at parturients with mild preeclampsia, and management with magnesium.34,35 The first study specifically focused on magnesium administered to parturients with mild preeclampsia.34 The primary outcome was the number with evidence of disease progression, defined as the presence of end-organ involvement e.g. headache, visual disturbance, nausea and vomiting or epigastric pain, or the presence of laboratory abnormalities consistent with a diagnosis of haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. Following recruitment of 222 women, it was concluded that magnesium did not have a statistically significant effect on progression of mild preeclampsia ($P = 0.41$, RR 0.8). There was no increase in caesarean delivery, infection, maternal haemorrhage or neonatal respiratory morbidity.34

The second study focused on duration of labour and the rate of preeclampsia disease progression as a secondary outcome when magnesium was used to treat mild preeclampsia.35 One hundred and thirty-five patients were studied and there were no seizures in either the magnesium or placebo arm. There were no differences in any important clinical outcomes including caesarean delivery, uterine atony, blood loss, chorioamnionitis and Apgar scores. A criticism of both studies was the...
Table 2  Magnesium levels and toxicity

<table>
<thead>
<tr>
<th>Serum magnesium level (mmol/L)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal plasma level</td>
</tr>
<tr>
<td>2-3</td>
<td>Therapeutic level</td>
</tr>
<tr>
<td>5</td>
<td>Loss of deep tendon reflexes (used as a clinical sign of adequate administration), facial paraesthesia, drowsiness, nausea</td>
</tr>
<tr>
<td>6-8</td>
<td>Severe muscle weakness, respiratory depression, CNS depression</td>
</tr>
<tr>
<td>7</td>
<td>Cardiac conduction abnormalities (including bradycardia, widening QRS complex, complete heart block)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>Cardiac arrest</td>
</tr>
</tbody>
</table>

CNS: central nervous system.

Potential for a type II error with the low number of patients recruited: 357 in the two studies. These small but rigorous trials led Alexander et al. to conduct a large, prospective, observational study of more than 72,000 women over four and a half years. Before starting the study, their clinical practice had changed from administering intramuscular (i.m.) magnesium to all women with gestational hypertension (including mild and severe preeclampsia), to a more selective approach giving i.v. magnesium solely to those women with evidence of severe gestational hypertension (severe preeclampsia). In their large study cohort, 6431 women had gestational hypertension, with 3935 meeting their criteria for severe preeclampsia (Table 4). In total, 87 women developed eclampsia, equating to one in 828 deliveries. Of these, 39 women were considered normotensive (BP <140/90 mmHg) or had mild gestational hypertension and did not receive magnesium prophylaxis, according to department protocol. The incidence of eclampsia with the selective regimen was 50% greater compared to the more general administration of magnesium to all women with gestational hypertension (historical control). This increase was a result of more seizures in the group not receiving magnesium. The authors commented that despite this observed rise, there was no statistically significant evidence to support the use of magnesium in mild gestational hypertension. A subsequent study, using a decision model, suggested there was insufficient evidence to support or not support the prophylactic use of magnesium in mild preeclampsia.

In the parturient with mild preeclampsia, magnesium can be administered either prophylactically or with evidence of disease progression. Both strategies are clinically valid, and therefore the decision to use magnesium rests with the physician (evidence, Grade B: level of certainty, Moderate).

Severe Preeclampsia

Moodley initially highlighted the need for a large trial to examine the role of anticonvulsants in the prophylaxis and treatment of convulsions in hypertensive diseases in pregnancy. They performed a small unblinded randomised study, administering antihypertensive agents to 228 parturients, and additional magnesium sulphate to just under half of these patients. One patient had a convulsion; she had been assigned to receive magnesium prophylaxis. The authors concluded that whilst it may be the case that severe preeclampsia could be solely managed with aggressive antihypertensive therapy alone, there was a need for larger trials to establish the role of prophylactic anticonvulsants.

Subsequently, several larger studies have focused on the use of magnesium in parturients with severe preeclampsia, the most notable study being the Magnesium Sulphate for Prevention of Eclampsia (Magpie) Trial. This multi-centre, international study was carried out in 175 hospitals, and randomised over 10,000 women with blood pressure >140/90 mmHg and proteinuria 30 mg/dL, to receive either magnesium or placebo.

Table 3  Definition of mild and severe preeclampsia

<table>
<thead>
<tr>
<th></th>
<th>Mild Preeclampsia</th>
<th>Severe preeclampsia *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>&gt;140 mmHg</td>
<td>&gt;160 mmHg</td>
</tr>
<tr>
<td>Diastolic</td>
<td>&gt;90 mmHg</td>
<td>&gt;110 mmHg</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>&gt;300 mg/24 h</td>
<td>&gt;5 g/24 h</td>
</tr>
<tr>
<td>Neurology</td>
<td>Nil</td>
<td>Visual disturbance, headache, hyper-reflexia</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nil</td>
<td>Epigastric/RUQ pain</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Nil</td>
<td>Pulmonary oedema, cyanosis</td>
</tr>
<tr>
<td>Haematological</td>
<td>Nil</td>
<td>Thrombocytopenia &lt;100 × 10⁹/L</td>
</tr>
<tr>
<td>Fetus</td>
<td>Nil</td>
<td>Fetal growth restriction</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Nil</td>
<td>Liver dysfunction</td>
</tr>
</tbody>
</table>

RUQ: right upper quadrant; *One or more of the following features must be present.
two groups and aspects of clinical care which varied greatly between participating hospitals, the study demonstrated a significant risk reduction (58%) for seizures in women receiving magnesium \( (P < 0.001) \).\(^{41}\)

Several years before the Magpie study, a study published in 1998 also highlighted the beneficial role of magnesium for the prevention of eclampsia. Six hundred and eighty-five women were studied, and 0.3% of those receiving magnesium developed eclampsia as opposed to 3.2% of those receiving placebo (saline).\(^{42}\)

A review by Sibai\(^ {41}\) and a Cochrane review\(^ {43}\) support the Magpie Trial findings of a significantly lower incidence of eclampsia in women receiving magnesium. A subsequent meta-analysis of these trials confirmed the compelling evidence that magnesium provided significant seizure prophylaxis in parturients with severe preeclampsia (Table 5).\(^ {44}\)

The incidence of side effects varied in different trials; in the Magpie trial approximately 25% of those women receiving magnesium complained of adverse side effects compared with 5% of the placebo group.\(^ {39}\) Side effects were also higher with i.m. rather than i.v. administration. Flushing was the most common side effect and occurred in 25% of women receiving i.m. magnesium. Respiratory muscle weakness is the most concerning potential side effect of magnesium. While there was a greater frequency in the magnesium group throughout the studies, the number of cases remained very small and there was no overall statistically significant difference between groups in terms of serious maternal morbidity or neonatal requirement for ventilation.

Further large studies have compared magnesium and other pharmacological agents, or placebo, for the treatment of severe preeclampsia, and prevention of eclamptic seizures. In 2003, Belfort et al. compared nimodipine and magnesium in 1650 parturients. There was a significant decrease in the incidence of seizures within the magnesium group (0.8% vs. 2.6%, \( P = 0.01 \)), most notably in the postpartum period. Of note, hydralazine was required to control blood pressure more often in the magnesium group than in those receiving nimodipine.\(^ {45}\)

There is Grade A evidence (level of certainty, High) to support the use of magnesium in the parturient with severe preeclampsia to prevent eclampsia.

### Eclampsia

The prominent Collaborative Eclampsia Trial, published in the Lancet in 1995, demonstrated the role of magnesium in managing convulsions in 1680 eclamptic women.\(^ {46}\) The study focused on establishing the anticonvulsant agent of choice for the management of eclampsia. This was a multi-centre, randomised trial, the primary outcome being recurrence of convulsions and/or maternal death. Participating centres compared either phenytoin or diazepam to magnesium using the following regimens:

1. Diazepam: i.v. diazepam 10 mg over 2 min (repeated if required), followed by i.v. diazepam 40 mg over 24 h
2. Phenytoin: i.v. diazepam 10 mg to control seizure, followed by i.v. phenytoin 1 g over 20 min and 100 mg every 6 h for 24 h
3. Magnesium sulphate: i.v. magnesium 4 g over 5 min followed by i.v. magnesium 1 g/h OR i.v. magnesium 4 g followed by i.m. magnesium 5 g every 4 h

The study showed a statistically significant decrease in the risk of recurrent convulsions in women receiving magnesium. Compared with diazepam 15 per 100 fewer women had further convulsions, and with phenytoin there were 11 per 100 fewer recurrent seizures. Women in the magnesium group had fewer detrimental outcomes, such as the requirement for ventilation, pneumonia and intensive care unit admission. There was also a non-statistically significant reduction in maternal mortality noted within both magnesium groups.

There is Grade A evidence (level of certainty, High) to support the use of magnesium in the parturient with eclampsia to prevent recurrent seizures, and it has superior actions to diazepam and phenytoin.

### Tocolysis

Magnesium has been used worldwide as a tocolytic agent; however, the supporting evidence for this role is controversial. The mechanism of action is thought to be calcium antagonism, leading to a decrease in intracellular calcium, decrease in myosin activity and thus relaxation of the uterine muscle.

In 1959, Hall et al. first reported prolonged labour in preeclamptic women treated with magnesium.\(^ {47}\) This was confirmed in 1993 when Friedman et al. reported a significantly slower rate of cervical dilation in preeclamptic women treated with magnesium compared with phenytoin.\(^ {48}\) Atkinson et al. looked at the effect of magnesium when given as seizure prophylaxis in women undergoing induction of labour for preeclampsia.\(^ {49}\) Their hypothesis was that induction would be prolonged in this group of women; however, when compared to phenytoin, the induction-to-delivery time was similar.

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**Table 4 Criteria for magnesium sulphate prophylaxis**\(^ {37}\)

- Blood pressure of 140/90 mmHg or greater after 20 weeks gestation in a woman not known to be chronically hypertensive
- Proteinuria of 2+ or greater as measured by dipstick in a catheterized urine specimen
- Serum creatinine more than 1.2 mg/dL
- Platelets less than 100 x 10\(^{9}\)/L
- Aspartate transaminase elevated two times above upper limit of normal range
- Persistent headache or scotomata
- Persistent mid-epigastric or right-upper quadrant pain
Their study also showed magnesium did not increase the rate of caesarean delivery. A subsequent Cochrane meta-analysis of 23 trials failed to demonstrate a benefit of magnesium as a tocolytic agent, compared to placebo or nifedipine. In addition, the risk of both fetal and neonatal death was higher when the mothers had received magnesium.

There is no evidence to support the use of magnesium as a tocolytic agent. Magnesium does not prolong labour when administered as seizure prophylaxis (evidence, Grade D: level of certainty, High).

### Fetal neuroprotection

Preterm birth (<37 weeks of gestation) is associated with significant neonatal morbidity and mortality, including an increased risk of neurological deficits and cerebral palsy. Cerebral palsy is defined as non-progressive brain injury resulting in permanent motor dysfunction. Evidence in the 1990s indicated a link between the use of i.v. magnesium in the parturient and reduction in the incidence of moderate to severe cerebral palsy in surviving preterm infants. Following these findings, several large multi-centre trials were performed to confirm this link (Table 6).

Mittendorf et al. carried out a randomised, placebo controlled trial aimed at determining whether the use of antenatal magnesium sulphate affected the incidence of adverse outcomes in the neonate (MagNET Trial). In total 149 women with a diagnosis of preterm labour (<34 weeks of gestation) were enrolled. From this group, 75 parturients (85 newborns) were randomised to receive magnesium sulphate, either for tocolysis (cervical dilatation ≤4 cm) or for neuroprotection (cervical dilatation >4 cm). The dosage of magnesium administered was greater within the tocolytic group (4 g bolus, 2–3 g/h infusion) as opposed to the smaller dose for the neuroprotective cohort (4 g bolus only). In total, 165 infants were studied. Within the non-magnesium group, 15 adverse events occurred in 80 infants, as opposed to 27 adverse events noted in the 85 infants receiving antenatal magnesium. These composite comparisons approached significance, and with secondary analysis it was noted that this was probably a dose-related phenomenon. Those infants with “extremely adverse outcomes” had a significantly higher exposure to magnesium in utero. In conclusion, the MagNET Trial did not support the use of magnesium within the context of preterm labour tocolysis for neuroprotection.

Subsequently, the ACTOMgSO4 group in New Zealand and Australia published data from a multicentre randomised controlled trial. The group focused on determining the effectiveness of magnesium in the prevention of paediatric mortality and/or cerebral palsy in preterm labour (defined as <30 weeks of gestation). The follow-up period was to a corrected age of two years. The group reported a lower incidence of mortality and cerebral palsy within the cohort receiving magnesium; however, this was not statistically significant. They did find a significant reduction in the incidence in moderate to severe cerebral palsy, resulting in substantial motor dysfunction, amongst survivors (incidence of 3.4% vs. 6.6%). This result was supported by the PREMAG group, a randomised placebo-controlled study of 688 infants. A non-significant reduction in both mortality and severe white matter injury was noted.

Finally, a study by Rouse et al. published in 2008 randomised over 2000 women to receive magnesium or placebo during preterm labour (24–31 weeks of gestation). The primary outcome was the composites of stillbirth or infant mortality by one year of corrected age or moderate or severe cerebral palsy. There was no significant difference in the primary outcome between the magnesium group and those receiving placebo. However, on secondary analysis it was noted that there was a significantly lower rate of cerebral palsy in the magnesium group.

These studies were followed by a meta-analysis that confirmed that magnesium administration is linked with a significant reduction in the incidence of moderate and severe infant motor dysfunction. It should be noted that magnesium did not affect infant mortality. The authors recommended the use of magnesium for neuroprotection in preterm labour <32–34 weeks of gestation.

### Table 5 Major trials of severe preeclampsia and magnesium

<table>
<thead>
<tr>
<th>Trial design</th>
<th>n</th>
<th>Mg dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAGPIE30</td>
<td>9992</td>
<td>i.v.: 4 g bolus; 1 g/h</td>
<td>Fewer seizures in Mg group</td>
</tr>
<tr>
<td>Coetzee42</td>
<td>685</td>
<td>4 g bolus; 1 g/h</td>
<td>Fewer seizures in Mg group</td>
</tr>
<tr>
<td>Moodley39</td>
<td>228</td>
<td>i.v. 4 g bolus; 10 g i.m.; 5 g/4 h</td>
<td>One seizure in Mg group</td>
</tr>
</tbody>
</table>

i.v.: intravenous; i.m.: intramuscular; Mg: magnesium.
leased by the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine.58

There is now Grade A evidence (level of certainty, High) to support the use of magnesium for fetal neuroprotection in preterm labouring women. There is a clear reduction in the incidence of moderate and severe cerebral palsy, but no statistically significant decrease in the incidence of fetal mortality.

**Magnesium and Anaesthesia**

Anaesthetists are now involved in the management of over 60% of obstetric patients,59 and in the 2006–08 UK CMACE report, an anaesthetist was involved in the care of 49% of those mothers who died.26 Seven of the 261 deaths were directly attributed to anaesthesia. Interest in the use of magnesium by the anaesthetist was raised initially by James in 1985 when he used magnesium for perioperative stabilisation of patients with phaeochromocytoma.27 Additional roles have subsequently been investigated.

**Hypertension at tracheal intubation**

Laryngoscopy and tracheal intubation cause release of endogenous catecholamines, increasing both blood pressure and heart rate, with possible serious sequelae such as intracranial bleeding and myocardial ischaemia.60 Different techniques have been studied to obtund this response, including topicalisation of the airway with loc

cal anaesthetic or administration of opioids, beta receptor antagonists, lidocaine, direct acting vasodilators or a combination. Magnesium can contribute to stabilisation of cardiovascular parameters, and prevent hypertension at intubation. This effect can be especially valuable in the context of the hypertensive diseases of pregnancy.

In 1989 James et al. published data from a randomised, controlled trial of i.v. magnesium 60 mg/kg vs. 0.9% saline administered pre-intubation.61 Catecholamine levels were measured post-intubation and the impact of intubation on heart rate and blood pressure were recorded. Noradrenaline levels were significantly higher in the control group compared to those receiving magnesium (\(P \leq 0.01\)), and this increased level persisted for 5 min post-intubation. Heart rate increased slightly on administration of magnesium (13±3.9 beats/min) but then remained stable throughout intubation. In contrast, the control group showed significant increases in heart rate to 121 beats/min as opposed to 107 beats/min (\(P = 0.05\)) at intubation. Blood pressure changes followed similar trends. The authors concluded that magnesium may be a useful alternative to opioids, especially in the hypertensive parturient.

Subsequently, two studies focused on the use of magnesium at caesarean delivery performed under general anaesthesia.52,60 The first study demonstrated the superiority of magnesium over lidocaine in controlling maternal haemodynamics, and a less detrimental effect on the fetus than alfentanil in the preeclamptic patient.62 A follow-up study was undertaken using a combination of alfentanil and magnesium.63 A dose of magnesium

<table>
<thead>
<tr>
<th>Trial design</th>
<th>n</th>
<th>Mg dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>MagNET53</td>
<td>149 (165 infants) PTL &lt; 34/40</td>
<td>Bolus: 4 g Mg Infusion: 2–3 g/h Mg or other tocolytic</td>
<td>No significant difference in IVH, PVL, CP, fetal death (1-sided Fisher’s exact test, (P = 0.04)); 2-sided Fisher’s exact test, (P = 0.07).</td>
</tr>
<tr>
<td>ACTOMgSO454</td>
<td>1062 (infants) PTL &lt; 30/40</td>
<td>Bolus: 4 g Mg Infusion: 1 g/h Mg</td>
<td>No significant difference in death (up to 2 y) and/or CP ((P = 0.19) for total deaths, (P = 0.38) for CP, (P = 0.09) for death or CP) ↓ substantial motor dysfunction in Mg group (3.4% vs. 6.6%, RR 0.51, CI 0.29–0.91, (P = 0.02))</td>
</tr>
<tr>
<td>PREMAG trial55</td>
<td>564 (688 infants) PTL &lt; 33/40</td>
<td>Bolus: 4 g Mg</td>
<td>No significant difference in death, severe CUS abnormalities, severe WMI</td>
</tr>
<tr>
<td>Rouse56</td>
<td>2241 (infants) PTL 24-31/40</td>
<td>Bolus: 6 g Mg Infusion: 2 g/h</td>
<td>No significant difference in stillbirth/infant death rate (9.5% vs. 8.5%, RR 1.12, CI 0.85–1.47, (P = 0.41)) ↓ moderate and severe CP in Mg group (1.9% vs. 3.5%, RR 0.55, CI 0.32–0.95, (P = 0.03))</td>
</tr>
</tbody>
</table>

IVH: intraventricular haemorrhage; PVL: periventricular leucomalacia; CP: cerebral palsy; PTL: preterm labour; PPH: postpartum haemorrhage; CUS: cranial ultrasound; WMI: white matter injury; Mg: magnesium; RCT: randomised controlled trial; RR: relative risk; CI: confidence interval.*Other tocolytic agents: ritodrine, terbutaline, nifedipine, indomethacin: decision dependant on physician’s choice.
30 mg/kg plus alfentanil 7.5 μg/kg, resulted in significantly more stable cardiac parameters than alfentanil alone. There was no detrimental impact on the fetus noted following administration of magnesium.

There is Grade B evidence (level of certainty, Moderate) that the use of magnesium, either alone or with an opioid, can lead to attenuation of the hypertensive response to tracheal intubation.

**Adjunct to general anaesthesia**

When general anaesthesia is required for caesarean delivery, a balance has to be achieved between the desired effect of the anaesthetic and potential adverse haemodynamic and obstetric concerns such as uterine atony. Intraoperative awareness due to inadequate doses of anaesthetics has fortunately become less common although it may still occur.64 In 2002, magnesium was reported as a potential adjunct to anaesthesia in non-pregnant patients. In a randomised, placebo-controlled trial, Telci et al. observed that magnesium, given as a pre-induction bolus, significantly reduced requirements for propofol and remifentanil, based on changes in arterial blood pressure and heart rate, in 81 patients undergoing elective spinal surgery.65 A subsequent study, in 60 patients also undergoing spinal surgery, confirmed these findings.66 In addition, postoperative recovery, defined as a bispectral index (BIS) >80, was delayed if magnesium was administered (P < 0.0001) compared to clonidine or placebo.

Durmus et al. studied the effects of magnesium on the minimum alveolar concentration (MAC), as determined by patient movement, of sevoflurane for both tracheal intubation and surgical incision in 60 patients.67 This prospective, randomised, placebo-controlled trial evaluated the effect of a bolus plus infusion of magnesium pre-induction. They compared a 30 mg/kg bolus plus a 10 mg/kg/h infusion with 50 mg/kg plus infusion of 10 mg/kg/h on the concentration of sevoflurane required to prevent patient movement using an up-down sequential allocation method. They found that administration of magnesium pre-induction increased the MAC of sevoflurane by up to 15% for both intubation and incision.

These findings were confirmed in a study by Lee and Kwon looking at caesarean delivery under general anaesthesia.68 They found that i.v. administration of magnesium 45 mg/kg before induction of anaesthesia led to greater haemodynamically stability (P < 0.05) and lower BIS numbers (P < 0.001), implying less risk of awareness.

Magnesium can be used as an adjuvant for general anaesthesia and there is Grade B evidence (level of certainty, Moderate) to support this. Of note, magnesium resulted in a significant increase in anaesthesia recovery time.

**Muscle relaxants**

With the increasing use of magnesium in the obstetric population, a parturient has a greater likelihood of hypermagnesaemia. Magnesium suppresses acetylcholine transmission by blocking the calcium channel at the motor endplate, and by decreasing pre-synaptic release of acetylcholine. As a result, motor blockade and train-of-four are prolonged when magnesium is combined with non-depolarizing muscle relaxants.69 Magnesium alone can produce neuromuscular blockade at serum levels above 5 mmol/L, hence the use of loss of patellar reflexes as a clinical monitor for magnesium toxicity.70

| Table 7 Analgesia and magnesium |
|---|---|---|
| Trial design | n | Dose/Route | Outcome |
| Buvanendran77 | Prospective, double blind, placebo randomised trial | 50 | IT Mg 50 mg | Duration of analgesia prolonged in Mg group |
| Malleeswaran78 | Prospective, double blind, placebo controlled trial | 60 | IT Mg 50 mg | Onset of sensory and motor block slower in Mg group |
| Sun79 | Prospective, double blind, placebo randomised trial | 200 | Epidural Mg 500 mg ± morphine | Duration of spinal anaesthesia longer in Mg group |
| Yousef80 | Prospective, double blind, placebo controlled trial | 90 | Epidural Mg 500 mg | Diclofenac requirement lower in Mg group |
| Sullivan81 | Prospective, placebo controlled trial | 68 | i.v. Mg infusion for preeclampsia vs. placebo following spinal with IT fentanyl | Lower post-operative pain scores in group receiving Mg and morphine |
| | | | | No difference in time of onset or height of block |
| | | | | Better motor block and muscle relaxation in Mg group |
| | | | | Later onset of postoperative pain in Mg group |
| | | | | Duration of analgesia unaffected by administration of Mg |

IT: intrathecal; Mg: magnesium.
Several case reports have highlighted the potential for clinical difficulties with non-depolarizing muscle relaxants in obstetric patients with therapeutic hypermagnesaemia. A group from Japan reported prolonged ventilatory support in two parturients receiving vecuronium following administration of magnesium for pre-eclampsia and tocolysis. 71

The neuromuscular blockade produced by suxamethonium is not potentiated in hypermagnesaemic states. Onset and duration of the depolarising muscle relaxant remain unchanged. However, if a Phase II block is produced by repeated doses of suxamethonium, magnesium can prolong neuromuscular blockade. In addition, it has been demonstrated that magnesium may reduce the fasciculations seen on induction of the neuromuscular block. 72

There is Grade C evidence (level of certainty, Moderate) that magnesium hastens the onset time of neuromuscular blockade and prolongs recovery with non-depolarising muscle relaxants.

### Analgesia

Magnesium has anti-nociceptive properties due to antagonism at the NMDA receptor. This antagonism within the dorsal horn of the spinal cord may reduce the risk of chronic pain by preventing central sensitisation. 73 Additionally, magnesium reduces calcium influx and may augment opioid analgesia and subsequently decrease morphine requirement. 74,75

Various studies have focused on magnesium as a potential adjunct for labour analgesia or postoperative pain relief, and it has been administered via a number of different routes including i.v., intrathecal and directly into the epidural space (Table 7).

In 2007, Lysakowski et al. conducted a systematic review of randomised trials looking at i.v. magnesium as an analgesic adjunct. 76 The authors concluded that “the beneficial effects of magnesium were not unequivocal”. Some trials demonstrated a highly significant reduction in analgesic requirements and less discomfort, but this result was not universal. These findings may be due to the wide variation in dosage and timing of magnesium administration, as well as varied anaesthetic techniques and assessment of pain. The most pronounced result was the effect of magnesium in reducing postoperative analgesia requirements. There was up to a 28% reduction in morphine requirements in some of the trials, which may translate to a reduction in morphine-related side effects although the authors were unable to confirm this. 76

Evidence has emerged over the last decade suggesting that intrathecal administration of magnesium during caesarean delivery decreases postoperative pain. In 2002, Buvanendran et al. published work from a prospective randomised controlled trial looking at the effect of adding magnesium 50 mg to the intrathecal component of combined spinal-epidural (CSE) analgesia in labouring parturients. 77 They enrolled 50 women into the study, and concluded that there was significantly longer duration of analgesia in the group receiving a combination of fentanyl and magnesium as opposed to fentanyl alone (75 vs. 60 min). They also commented that there was no increase in adverse effects in the group receiving magnesium.

More recently Malleeswaran et al. conducted a randomised study looking at 60 women with mild pre-eclampsia undergoing caesarean delivery under spinal anaesthesia. 78 They administered either intrathecal magnesium 50 mg or saline and found a significant decrease in postoperative pain scores at 4 h (P < 0.001), and an overall decrease in postoperative analgesic requirements (P = 0.02).

An observational study by Sun et al. concentrated on efficacy of labour analgesia in women receiving i.v. magnesium infusions for pre-eclampsia. 79 They observed 68 nulliparous parturients undergoing induction of labour, half of whom were receiving continuous i.v. magnesium infusion for pre-eclampsia. Intrathecal fentanyl 25 μg was injected and an epidural catheter inserted but no analgesia administered into the epidural space until requested. There was no significant difference in duration of analgesia in those women receiving seizure prophylaxis magnesium compared to the control group. This was, however, a small study and the authors point out that it may have been underpowered to detect a difference. 79

Administration of epidural magnesium also shows promising results. In a randomised trial of 90 women undergoing caesarean delivery using a CSE technique, intrathecal 0.5% hyperbaric bupivacaine 2 mL was injected before threading the epidural catheter. 80 The patient was moved to the supine position, with left uterine displacement, and either 0.25% bupivacaine 10 mL with 0.9% saline 10 mL and fentanyl 100 μg or 0.25% bupivacaine 10 mL with 5% magnesium 10 mL and fentanyl 100 μg. In the magnesium group, the onset of postoperative pain was delayed (P < 0.05), and operative conditions (greater motor block and muscle relaxation) were improved (P < 0.05). All patients receiving magnesium developed complete anaesthesia, whereas almost a quarter of those solely receiving epidural bupivacaine and fentanyl required intraoperative analgesic supplementation for pain and discomfort (visual analogue scale >4). The incidence of shivering also was decreased in the magnesium group (P < 0.05). There were no significant differences in the incidence of hypotension, nausea, vomiting, pruritus and dizziness between the two groups. 80

There is varied evidence supporting the use of i.v. magnesium for enhancing analgesia, and Grade B evidence (level of certainty, Moderate) to suggest a positive...
benefit of intrathecal or epidural administered magnesium. Further large-scale trials are required to establish the role magnesium has as an analgesic adjunct within the obstetric setting.

Summary

Magnesium has an increasing role in the treatment of the parturient, with important implications for the obstetric anaesthetist. It is now established in the management of severe pre eclampsia and prevention/treatment of eclamptic seizures where it is considered as standard therapy. The use of magnesium for neuroprotection of the preterm fetus, preventing disabling cerebral palsy in the newborn, will undoubtedly continue to increase. Further studies are required to establish magnesium’s role as an analgesic; however, research is promising for its use as a second line agent. Magnesium has an established safety profile in parturients; however, caution should always be taken when it is administered.

Disclosure

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