Can magnesium sulphate provide neuroprotection in preterm infants? A literature review

Abstract
The aim of this literature review is to determine if prenatal administration of magnesium sulphate (MgSO4) provides neuroprotection in preterm infants. Data was analysed from five randomised controlled trials (MagNET, ACTOMgSO4, MAGPIE, PREMAG and BEAM). The data from each trial supported a correlation between MgSO4 and neuroprotection; however, only one trial was statistically significant – BEAM. Previously conducted systematic reviews and meta-analyses combined data from the trials and produced statistically significant results in favour of MgSO4 for neuroprotection. Studies suggest that MgSO4 acts as an NMDA (N-Methyl-D-Aspartate) receptor antagonist, reducing the neuronal damage secondary to increased intracellular calcium. Other studies suggest that it prevents neuronal insult by decreasing intrauterine inflammation. The challenges of using MgSO4 are with determining the therapeutic window, appropriate timing of administration, re-treatment possibilities, bias in tocolytic choices, serious maternal side effects (hypotension, tachycardia), and neonatal side effects. Further research is needed to determine the neuroprotective mechanisms, specific indications for MgSO4, optimum gestational age, timing of administration, dosing, and need for re-treatment. Follow-up trials should assess the long-term effects of MgSO4 on preterm infants. In conclusion, MgSO4 provides neuroprotection in preterm infants and likely improves their quality of life.

Key words: Magnesium sulphate, neuroprotection, preterm infants, randomised controlled trials, systematic review, meta-analysis.
Introduction
Preterm birth and extremely low birth weight (less than 1,000g) are major risk factors for detrimental neurologic outcomes such as cerebral palsy.\textsuperscript{1-4} Cerebral palsy is a group of disorders of varying severity that results in abnormal movement and posture, which ultimately leads to limited activity.\textsuperscript{5,6} It is due to non-progressive brain damage that occurs \textit{in utero} or in infancy, with a multitude of consequences including chronic disability along with medical, emotional and economic burdens.\textsuperscript{7,8} Lifetime costs include direct costs such as physician visits, hospital stays, medications, and home/vehicle alterations, while indirect costs include productivity costs.\textsuperscript{7} The lifetime cost for an individual with cerebral palsy is approximately €860,000 for men and about €800,000 for women.\textsuperscript{10}

It is proven that the risk of neurological abnormalities increases with decreasing gestational age, and 25% of new cases of cerebral palsy occur in infants born at less than 34 weeks’ gestation.\textsuperscript{11-13} There has been an increase in survival rates among these preterm and low birth weight infants that can be attributed to improvements in perinatal and neonatal intensive care.\textsuperscript{4} Since these children have a much higher risk of neurological deficits like cerebral palsy, while also having a much higher rate of survival, it is of the utmost importance to explore preventive measures, such as magnesium sulphate (MgSO\textsubscript{4}), treatment that may improve their quality of life. MgSO\textsubscript{4} has two principal uses in obstetrics. First, it can be used as seizure prophylaxis in pre-eclampsia and treatment of eclampsia. Second, it is an agent of tocolysis, whereby it delays preterm labour to facilitate administration of corticosteroids to be given for foetal maturation, patient transport, or successful treatment of reversible aetiologies of preterm labour.\textsuperscript{23,24} It is believed that MgSO\textsubscript{4} also provides neuroprotection in preterm infants when given to mothers when labour is imminent. Observational studies by Nelson, Grether, and Schendel \textit{et al.} reported such findings, which were later supported by several randomised controlled trials.\textsuperscript{15,16} This report will discuss the findings of five randomised controlled trials pertaining to the correlation between antenatally administered MgSO\textsubscript{4} and subsequent neuroprotection in preterm infants, possible mechanisms that allow MgSO\textsubscript{4} to act as a neuroprotective agent, clinical challenges faced when using MgSO\textsubscript{4} for neuroprotection, and important research that needs to be done in the future.

Methods
A literature search was performed using Ovid/ Medline (1950 to February 2010) to identify randomised controlled trials and other published data associated with using MgSO\textsubscript{4} for neuroprotection in the foetus. A variety of key words were used including “magnesium sulphate”, “neuroprotection”, and “preterm”. The “AND” function was often used to combine these terms with each other or with the names of known authors. Bibliographies of significant studies, meta-analyses, and systematic reviews were assessed for additional relevant data. Google Scholar was used to obtain full text articles when only abstracts could be found in Medline. The Cochrane database was also searched. Further information and published data was retrieved from clinicians who had been to conferences where oral presentations relating to the subject were given and from those who had been involved in the development of hospital protocols to administer MgSO\textsubscript{4} to patients for the purpose of neuroprotection in preterm infants. The following principal outcome measures were extracted from the systematic reviews/meta-analyses: relative risk (cerebral palsy, gross motor dysfunction and paediatric mortality); absolute risk of cerebral palsy with MgSO\textsubscript{4}; and, number needed to treat. The relative risk is the ratio of the probability of developing cerebral palsy, gross motor dysfunction or paediatric death in the MgSO\textsubscript{4}-treated group versus a control group. When this ratio is less than 1, developing any of the previously listed adversities is less likely to occur in the treated group than in the control group. The opposite is true if the ratio is more than 1.

The absolute risk is the probability of developing cerebral palsy with MgSO\textsubscript{4} or with a control, and is calculated without comparing the two groups. The number needed to treat is the number of patients who need to be treated with MgSO\textsubscript{4} in order for just one patient to benefit. As the number needed to treat increases, the effectiveness of the MgSO\textsubscript{4} decreases.

Selection criteria
Systematic reviews/meta-analyses were included if they evaluated the following five randomised controlled trials: BEAM, MagNET, ACTOMgSO\textsubscript{4}, MAGPIE and PREMAG.\textsuperscript{5,17-21} The studies had to investigate any differences in relative or absolute risk of cerebral palsy compared with control groups and they also had to calculate number needed to treat with MgSO\textsubscript{4} in order to prevent one case of cerebral palsy. Only published studies were used to explain the possible neuroprotective mechanism of MgSO\textsubscript{4}, while published and non-published information was used to assess best practice measures. One reviewer evaluated and selected the literature reviews, meta-analyses and studies that would be included in this paper.

Statistical methods
The results from the reviews/meta-analyses calculated relative risk (cerebral palsy, gross motor dysfunction, paediatric mortality) and number needed to treat with confidence intervals, while the absolute risk was calculated in percentages. The reviews used a mixture of the following analytical tools to examine and combine the data from the various trials: Mantel-Haenszel chi-squared model, Wilcoxon rank-sum test, chi-square test, Fisher’s exact test, examining the symmetry of funnel plots, and statistically by using the Egger test, Review Manager software (RevMan 2008), MIX software version 1.7, and SAS software, version 8.2. In this literature review, these values were analysed and tabulated, allowing simple comparison of results.
Table 1: Characteristics of five randomised controlled trials analysed in the systematic reviews and meta-analyses.

<table>
<thead>
<tr>
<th>Name of trial, authors</th>
<th>Year</th>
<th>Number of centres</th>
<th>Number of participants</th>
<th>Control</th>
<th>Gestational age</th>
<th>Aim of study</th>
<th>MgSO₄ dose</th>
<th>Neuroprotective conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEAM, Rouse et al.</td>
<td>2008</td>
<td>20 (United States)</td>
<td>2,241 mothers</td>
<td>Placebo</td>
<td>24-31 weeks</td>
<td>Determine if foetal exposure to MgSO₄ before preterm birth might reduce the risk of cerebral palsy</td>
<td>Loading dose of 6g, maintenance dose of 2g/hr</td>
<td>Significant decrease in the risk of moderate or severe cerebral palsy among surviving children in the MgSO₄ group</td>
</tr>
<tr>
<td>MagNET, Mittendorf et al.</td>
<td>2002</td>
<td>1 (United States)</td>
<td>149 mothers</td>
<td>Placebo or, ‘Other’ tocolytic</td>
<td>25-33 weeks</td>
<td>Determine if using antenatal MgSO₄ prevents neonatal intraventricular haemorrhage, periventricular leukomalacia, death and cerebral palsy</td>
<td>Tocolytic arm: loading dose of 4g, maintenance dose of 2-3g/hr</td>
<td>Antenatal MgSO₄ was associated with worse, not better, perinatal outcome in a dose-response fashion</td>
</tr>
<tr>
<td>ACTOMgSO₄, Crowther et al.</td>
<td>2003</td>
<td>16 (Australia and New Zealand)</td>
<td>1,062 mothers</td>
<td>Placebo</td>
<td>&lt;30 weeks</td>
<td>Determine the effectiveness of magnesium sulphate given for neuroprotection to women at risk of preterm birth</td>
<td>Loading dose of 4g (8ml of 60ml bag), maintenance dose of 2ml/hour (of 60ml bag)</td>
<td>Total mortality, cerebral palsy and the combined outcome of mortality or cerebral palsy were all lower in the magnesium sulphate group, but differences were not statistically significant</td>
</tr>
<tr>
<td>Magpie Trial (follow-up), Magpie Trial Follow-Up Study Collaborative Group</td>
<td>2007</td>
<td>125 (19 countries, five continents)</td>
<td>3,375 mothers</td>
<td>Placebo</td>
<td>Not considered in the inclusion criteria</td>
<td>Assess the long-term effects of in utero exposure to MgSO₄ for children whose mothers had pre-eclampsia</td>
<td>Loading dose of 4g, maintenance dose of 1g/hr IV or, Loading dose of 4g IV + 10g IM, maintenance dose of 5g/4hrs IM</td>
<td>17 surviving children were identified as having cerebral palsy, 10 were among those whose mothers were allocated placebo, two arose during embryogenesis. This imbalance could have arisen by chance, but the trend shows a tendency to a lower risk of cerebral palsy</td>
</tr>
<tr>
<td>PreMAG Trial + Follow-up Trial, Marret et al.</td>
<td>2007 and 2008</td>
<td>18 (all in France)</td>
<td>573 (mothers in the original trial 472 (children followed up at two years)</td>
<td>Placebo</td>
<td>&lt;33 weeks</td>
<td>Determine if MgSO₄ given to women at risk of very preterm birth would be neuroprotective in preterm newborns and prevent neonatal mortality and severe white matter injury</td>
<td>Loading dose of 4g</td>
<td>Original trial: non-significant decrease in risks of short-term, severe white matter injury, mortality before hospital discharge Follow-up trial: prenatal low-dose MgSO₄ has beneficial neuroprotection effects, which approached significance and achieved significance when considering combined death and gross motor or cognitive dysfunction</td>
</tr>
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</table>
Results

Literature search

Three systematic reviews/meta-analyses met the inclusion criteria. These reviews analysed data from the following randomised controlled trials: BEAM, MagNET, ACTOMgSO4, MAGPIE, and PREMAG.5,17-21 The characteristics of these trials are outlined in Table 1 and the findings are summarised in Table 2. All of the randomised controlled trials compared MgSO4 with placebo/other treatment in patients at risk for preterm delivery (gestational age <37 weeks), were all performed in the last 10 years, had a large number of participants, and drew conclusions on MgSO4 and subsequent neuroprotection.

Analysis

There are five significant randomised controlled trials that could have a major impact on the use of MgSO4 for neuroprotection: the Magnesium and Neurologic Endpoints Trial [MagNET]; the Australasian Collaborative Trial of Magnesium Sulphate [ACTOMgSO4]; the Magnesium Sulphate for Prevention of Eclampsia [MAGPIE]; PREMAG; and, the Beneficial Effects of Antenatal Magnesium Sulphate [BEAM].5,17-21 Four of the trials revealed a trend of reduced rates in cerebral palsy in MgSO4-treated groups with no effect on total paediatric mortality.5,18-21 However, the results regarding decreased cerebral

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Table 2: Results from systematic reviews/meta-analyses.

<table>
<thead>
<tr>
<th>Author</th>
<th>Gestational age</th>
<th>Number of trials analysed and infants included</th>
<th>Reduced relative risk of CP</th>
<th>Absolute risk of CP with MgSO4 versus placebo</th>
<th>Number needed to treat</th>
<th>Reduced relative risk of gross motor dysfunction</th>
<th>Reduced relative risk of total paediatric mortality</th>
<th>Relative risk of total paediatric neurological outcomes in newborn or first years of life</th>
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<tr>
<td>Doyle et al.22</td>
<td>&lt;37 weeks</td>
<td>5 trials × 6,145 infants</td>
<td>0.69 (95% CI 0.54-0.87)</td>
<td>3.7% vs. 5.4%</td>
<td>63 (95% CI 43-155)</td>
<td>0.61 (95% CI 0.44-0.85; 5,980 infants considered)</td>
<td>1.01 (95% CI 0.82-1.23)</td>
<td>None</td>
</tr>
<tr>
<td>Conde-Aguadelo and Romero13</td>
<td>&lt;34 weeks</td>
<td>5 trials × 5,357 infants</td>
<td>0.69 (95% CI 0.55-0.88)</td>
<td>3.9% vs. 5.6%</td>
<td>52 (95% CI 31-154)</td>
<td>0.60 (95% CI 0.43-0.83; 4,387 infants considered)</td>
<td>1.01 (95% CI 0.89-1.14)</td>
<td>None</td>
</tr>
<tr>
<td>*Costantine et al.23</td>
<td>&lt;32-34 weeks</td>
<td>5 trials × 5,235 infants</td>
<td>0.70 (95% CI 0.55-0.89)</td>
<td>—</td>
<td>56 (95% CI 34-164)</td>
<td>—</td>
<td>1.01 (95% CI 0.89-1.14)</td>
<td>—</td>
</tr>
<tr>
<td>*Costantine et al.23</td>
<td>&lt;30 weeks</td>
<td>3 trials × 3,107 infants</td>
<td>0.69 (95% CI 0.52-0.92)</td>
<td>—</td>
<td>46 (95% CI 26-287)</td>
<td>—</td>
<td>1.00 (95% CI 0.87-1.15)</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: CP: cerebral palsy; MgSO4: magnesium sulphate; CI: confidence interval; —: not evaluated; None: no other neurological outcomes found.

*5 trials (all randomised controlled trials): BEAM,5 MagNET,17 ACTOMgSO4,18 MAGPIE19 and PREMAG20,21 (two-year follow-up)

*×3 trials (all randomised controlled trials): BEAM, ACTOMgSO4 and MAGPIE

*Costantine et al. separated the results of their meta-analysis based on two separate groups of gestational ages (<32-34 weeks and <30 weeks)
palsy were only statistically significant in the BEAM trial. The MagNET trial resulted in reduced rates of cerebral palsy in the magnesium-exposed group compared to the placebo group in its tocolytic arm, but its neuroprotective arm showed more cases of cerebral palsy in the magnesium group compared to the placebo group. However, according to Mittendorf et al.: “this study was too small and the complication of cerebral palsy was too uncommon for meaningful statistical analysis”. This trial also suggested a trend towards increased foetal/childhood death in MgSO4 groups; however, this was refuted in subsequent systematic reviews and meta-analyses. Another statistically significant result found in the individual trials was decreased substantial gross motor function in the BEAM and ACTOMgSO4 studies. When the data from these trials was combined through well conducted systematic reviews and meta-analyses, statistically significant results were attained that confirmed the neuroprotective role of MgSO4 therapy administered to women at risk of preterm delivery.

The following conclusions were made in the reviews/meta-analyses regarding MgSO4 administered to mothers at risk for preterm birth: it reduced the risk of cerebral palsy in their children; it decreased the absolute risk of cerebral palsy compared to placebo; on average, the number of people needed to treat to prevent one case of cerebral palsy was 54; on average, the number of people needed to treat to prevent one case of cerebral palsy was 54; and MgSO4 reduced the rate of substantial gross motor dysfunction in their children. MgSO4 administration also had no statistically significant effect on paediatric mortality, or other poor outcomes in the newborn period or in the first few years of life (e.g., blindness, deafness, developmental delay). The outcomes investigated in the newborn period were Apgar scores less than 7 at five minutes, ongoing respiratory support, intraventricular haemorrhage, periventricular leukomalacia, convulsions, and neonatal death.

Several studies and reviews suggest that high tocolytic doses of 50g or more increase paediatric mortality. Although the major randomised controlled trials used differing dosing regimens, total dose remained low. The median total exposure to MgSO4 in the ACTOMgSO4 trial was less than 10.5g (4g bolus infusion with 2g/hour maintenance) with a maximum allowable dose of 28g; the total exposure in the PREMAG trial was 4g (single bolus infusion) with a maximum allowable dose of 28g; total exposure in the PREMAG trial was 4g (single bolus infusion) with a maximum allowable dose of 28g;0 total exposure in the PREMAG trial was 4g (single bolus infusion). The low doses used in all of these trials showed a decrease in subsequent diagnosis of cerebral palsy. There may have been even more improvement in cerebral palsy outcome in the lower dose trials versus the higher dose BEAM trial. Determining the therapeutic window above which MgSO4 could be toxic to the foetus has proven difficult, since detecting magnesium levels in the infant can be unreliable. Babies delivered soon after magnesium infusions may have falsely high magnesium levels, whereas babies born after prolonged magnesium exposure may have falsely low magnesium levels.

Discussion
The exact mechanism by which MgSO4 provides neuroprotection is still unknown. Currently, there are two theories that describe how magnesium may inhibit neuronal damage, namely hypoxic-ischaemic damage and inflammatory damage. Cerebral palsy is thought to be a result of periventricular white matter damage that predominates in premature infants, especially those born before 32 weeks gestational age. Periventricular damage is illustrated by loss of oligodendrocytes (brain cells that myelinate or insulate nerves) and gain of astrocytes (cells involved in scarring). Hypoxic-ischaemic damage is a result of low oxygen and glucose supply, which ultimately leads to excessive glutamate release. Glutamate stimulates the N-methyl-D-aspartate (NMDA) receptor, allowing a large influx of sodium and calcium into the neuron. Intracellular calcium induces several enzymes that cause neuronal death, while reperfusion causes oxidative damage through free radicals. MgSO4 is an NMDA receptor antagonist and NMDA antagonists have proven to be strong neuroprotectants in various animal models. However, NMDA receptors are vital in certain aspects of brain development, which raises the issue that MgSO4 could have the potential to disrupt normal foetal brain development if given at specific stages in neurodevelopment. It is important to remember that there is a strong correlation between spontaneous preterm birth and intrauterine inflammation. The fact that preterm birth due to inflammation and cytokine production leads to neuronal insult has been shown in animal models. Burd et al. investigated the explicit mechanisms responsible for the injury and found that injured foetal neurons in mice are capable of damaging other normal neurons. They also found that foetal brains of mice exposed to lipopolysaccharide, a bacterial antigen that causes intrauterine inflammation, exhibited abnormal neuronal morphology with decreased dendritic processes, which can ultimately disrupt neuronal synaptic communication. A subsequent animal study demonstrated that foetal brains subjected to inflammation that were later treated with MgSO4 did not display neuronal injury associated with fewer dendritic processes. The medical community continues to face difficulties regarding best practice and antenatal use of MgSO4 despite years of its clinical use and significant findings from combined data. Concerns arise in the context of appropriate dosing and timing of administration, tocolytic choice, maternal side effects, and infant side effects. Several studies and reviews suggest that high tocolytic doses of 50g or more increase paediatric mortality. Although the major randomised controlled trials used differing dosing regimens, total dose remained low. The median total exposure to MgSO4 in the ACTOMgSO4 trial was less than 10.5g (4g bolus infusion with 2g/hour maintenance up to 24 hours) with a maximum allowable total dose of 28g; total exposure in the PREMAG trial was 4g (single bolus infusion) and, median total dose in the BEAM trial was 31.5g (6g bolus infusion with 2g/hour maintenance). The low doses used in all of these trials showed a decrease in subsequent diagnosis of cerebral palsy. There may have been even more improvement in cerebral palsy outcome in the lower dose trials versus the higher dose BEAM trial. Determining the therapeutic window above which MgSO4 could be toxic to the foetus has proven difficult, since detecting magnesium levels in the infant can be unreliable. Babies delivered soon after magnesium infusions may have falsely high magnesium levels, whereas babies born after prolonged magnesium exposure may have falsely low magnesium levels. Another clinical challenge arises when considering the optimum time to administer MgSO4 to mothers in preterm labour. The MagNET and BEAM trials used active preterm labour and cervical dilatation (>4cm and -8cm) as indications for treatment. Women were eligible for treatment in the BEAM, ACTOMgSO4 and
PREMAG trials if delivery was expected within 24 hours.\textsuperscript{3,18,20} The Brigham and Women's Hospital (BWH) in Boston, Massachusetts, has developed a new protocol regarding MgSO\textsubscript{4} for neuroprotection, and their goal for initiating infusion is set for four hours prior to delivery.\textsuperscript{25} However, there are difficulties in predicting when a woman will deliver, and the question of whether or not to re-treat (give another loading dose and maintenance infusions) emerges if the patient has not delivered within 24 hours of the original dose. Although the largest randomised controlled trial, the BEAM trial,\textsuperscript{5} would continue MgSO\textsubscript{4} infusion if six hours had passed since treatment stopped, there is not enough evidence to strongly support re-treatment.\textsuperscript{15}

There is controversy over the number of times a patient can be re-treated and the amount of magnesium to which a patient can safely be exposed.

Concern over biased use of MgSO\textsubscript{4} for tocolysis also arises given its neuroprotective quality. Clinicians are faced with the dilemma of administering magnesium as the primary tocolytic instead of what is currently used, or to use MgSO\textsubscript{4} simultaneously with the hospital's preferred tocolytic, such as indomethacin or nifedipine.\textsuperscript{36} Combining MgSO\textsubscript{4} and calcium channel blockers is especially challenging, as it may lead to serious maternal side effects such as hypotension.\textsuperscript{36} The BWH has dealt with this issue in their protocol by discontinuing nifedipine and beginning infusion with magnesium when delivery is believed to occur within four hours.\textsuperscript{35}

However, tocolysis and neuroprotection should be thought of separately, and all of the relevant data surrounding various tocolytics, along with individual patient traits, must be considered in order to choose the most suitable tocolytic.\textsuperscript{31} Maternal side effects are another important issue in antenatal MgSO\textsubscript{4} use. Both reviews and independent studies reported a greater number of adverse side effects in MgSO\textsubscript{4}-treated groups compared to placebo-treated groups.

Minor adverse effects included flushing, nausea, vomiting, sweating, problems at injection site, lethargy and blurred vision,\textsuperscript{5,14,18,31} and seemed to subside once treatment was finished.\textsuperscript{37} More serious side effects such as hypotension and tachycardia were also seen,\textsuperscript{14,18,37} and were increased by as much as 50\% in the MgSO\textsubscript{4} group compared to the placebo group.\textsuperscript{14} MgSO\textsubscript{4} therapy was rarely associated with severe side effects such as death,\textsuperscript{5,14,18,20,31,37} cardiac and respiratory arrest,\textsuperscript{5,14,18,20,31,37} pulmonary oedema,\textsuperscript{5,14} postpartum haemorrhage,\textsuperscript{14,18,20} and caesarean section.\textsuperscript{5,14,18,20} Clinicians must also be cautious of fluid overload, which can lead to severe cardiovascular complications.\textsuperscript{35} Infants exposed to MgSO\textsubscript{4} may also have side effects. Although these were not statistically significant in trials and reviews, they are a clinical reality. It has been noted by several clinicians at BWH that these infants often emerge less vigorous than those who have not been exposed to magnesium, but this is short-lived. However, if this is a known, transient effect, clinicians may be less concerned when it occurs and this could subsequently cause neglect of serious medical problems that warrant aggressive treatment. There is no evidence to support this finding, but it could be an interesting focus of research in the future. The issues associated with using MgSO\textsubscript{4} for neuroprotection are crucial in terms of best practice and should be carefully considered.

Supplementary studies must be performed to provide imperative information about antenatal use of MgSO\textsubscript{4} for neuroprotection in preterm birth. More randomised controlled trials are needed to determine the optimum gestational age, timing of administration, dosing, need for re-treatment,\textsuperscript{14,22,23} increased risk of NEC,\textsuperscript{14} and the immediate effects on the newborn infant. There is need for follow-up of the infants included in both new and previously performed trials into later childhood,\textsuperscript{14,22} since neurological outcomes such as cerebral palsy are sometimes not fully recognised until children are older.\textsuperscript{22}

Indications for MgSO\textsubscript{4} therapy must be further investigated,\textsuperscript{23,31} since there was a lack of consistency in patient characteristics among the five major trials.\textsuperscript{23} Various indications for treatment ranged from pre-eclampsia to preterm labour and preterm premature rupture of membranes, and MgSO\textsubscript{4} may affect these indications differently.\textsuperscript{23} The mechanism by which MgSO\textsubscript{4} provides neuroprotection\textsuperscript{24,31} to the human foetal brain must also be determined; however, this poses ethical, technical and financial difficulties.\textsuperscript{24} If the mechanisms at work in individual infants could be determined, this would provide the potential to develop treatments that matched specific patient needs.\textsuperscript{24} Finally, substantial information regarding serious maternal side effects should be obtained. For instance, only the BEAM trial looked into maternal pulmonary oedema, while the ACTOMgSO\textsubscript{4} was the only trial to explore maternal tachycardia.\textsuperscript{5,18}

Neuroprotection in preterm infants should be considered as a healthcare priority, since there has been an increase in the survival of preterm infants who have an increased risk of neurological injury leading to debilitating outcomes.

Neurological problems such as cerebral palsy result in serious burdens faced by the diagnosed individual, their carers, and the healthcare system. Antenatal use of MgSO\textsubscript{4} is a simple and economical way to relieve such burdens. Randomised controlled trials demonstrated a trend towards neuroprotection without subsequent neurological impairment or paediatric mortality when MgSO\textsubscript{4} was administered to mothers in preterm labour. These findings were verified by large-scale systematic reviews and meta-analyses. The neuroprotective mechanisms employed by magnesium have yet to be determined and clinical trials are warranted to resolve the challenges posed by antenatal use of MgSO\textsubscript{4}. Although some centres have begun using MgSO\textsubscript{4} for neuroprotection, future research is key to determine its optimal clinical use.

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References


