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

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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 ($MgSO_4$) provides neuroprotection in preterm infants. Data was analysed from five randomised controlled trials (MagNET, ACTOMgSO_4, MAGPIE, PREMAG and BEAM). The data from each trial supported a correlation between $MgSO_4$ 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 $MgSO_4$ for neuroprotection. Studies suggest that $MgSO_4$ 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 $MgSO_4$ 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 $MgSO_4$, optimum gestational age, timing of administration, dosing, and need for re-treatment. Follow-up trials should assess the long-term effects of $MgSO_4$ on preterm infants. In conclusion, $MgSO_4$ 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.

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Introduction

Preterm birth and extremely low birth weight (less than 1,000g) are major risk factors for detrimental neurologic outcomes such as cerebral palsy.[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.[5,6] It is due to non-progressive brain damage that occurs *in utero* or in infancy, with a multitude of consequences including chronic disability along with medical, emotional and economic burdens.[7,8] Lifetime costs include direct costs such as physician visits, hospital stays, medications, and home/vehicle alterations, while indirect costs include productivity costs.[9] The lifetime cost for an individual with cerebral palsy is approximately €860,000 for men and about €800,000 for women.[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.[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.[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 ($MgSO_4$), treatment that may improve their quality of life.

$MgSO_4$ 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.[23,24] It is believed that $MgSO_4$ also provides neuroprotection in preterm infants when given to mothers when labour is imminent. Observational studies by Nelson, Grether, and Schendel *et al.* reported such findings, which were later supported by several randomised controlled trials.[15,16] This report will discuss the findings of five randomised controlled trials pertaining to the correlation between antenatally administered $MgSO_4$ and subsequent neuroprotection in preterm infants, possible mechanisms that allow $MgSO_4$ to act as a neuroprotective agent, clinical challenges faced when using $MgSO_4$ 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 $MgSO_4$ 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 $MgSO_4$ 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 $MgSO_4$; 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 $MgSO_4$-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 $MgSO_4$ 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 $MgSO_4$ in order for just one patient to benefit. As the number needed to treat increases, the effectiveness of the $MgSO_4$ decreases.

Selection criteria

Systematic reviews/meta-analyses were included if they evaluated the following five randomised controlled trials: BEAM, MagNET, ACTOMgSO_4, MAGPIE and PREMAG.[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 $MgSO_4$ in order to prevent one case of cerebral palsy. Only published studies were used to explain the possible neuroprotective mechanism of $MgSO_4$, 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.

Name of trial, authors	Year	Number of centres	Number of participants	Control	Gestational age	Aim of study	$MgSO_4$ dose	Neuroprotective conclusions
BEAM, Rouse *et al.*	2008	20 (United States)	2,241 mothers	Placebo	24-31 weeks	Determine if foetal exposure to $MgSO_4$ before preterm birth might reduce the risk of cerebral palsy	Loading dose of 6g, maintenance dose of 2g/hr	Significant decrease in the risk of moderate or severe cerebral palsy among surviving children in the $MgSO_4$ group
MagNET, Mittendorf *et al.*	2002	1 (United States)	149 mothers	Placebo or, 'Other' tocolytic	25-33 weeks	Determine if using antenatal $MgSO_4$ prevents neonatal intraventricular haemorrhage, periventricular leucomalacia, death and cerebral palsy	Tocolytic arm: loading dose of 4g, maintenance dose of 2-3g/hr Neuroprotective arm: loading dose of 4g	Antenatal $MgSO_4$ was associated with worse, not better, perinatal outcome in a dose-response fashion
ACTOMgSO_4, Crowther *et al.*	2003	16 (Australia and New Zealand)	1,062 mothers	Placebo	<30 weeks	Determine the effectiveness of magnesium sulphate given for neuroprotection to women at risk of preterm birth	Loading dose of 4g (8ml of 60ml bag), maintenance dose of 2ml/hour (of 60ml bag)	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
Magpie Trial (follow-up), Magpie Trial Follow-Up Study Collaborative Group	2007	125 (19 countries, five continents)	3,375 mothers	Placebo	Not considered in the inclusion criteria	Assess the long-term effects of *in utero* exposure to $MgSO_4$ for children whose mothers had pre-eclampsia	Loading dose of 4g, maintenance dose of 1g/hr IV or, Loading dose of 4g IV + 10g IM, maintenance dose of 5g/4hrs IM	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
PreMAG Trial + Follow-up Trial, Marret *et al.*	2007 and 2008	18 (all in France)	573 (mothers in the original trial) 472 (children followed up at two years)	Placebo	<33 weeks	Determine if $MgSO_4$ given to women at risk of very preterm birth would be neuroprotective in preterm newborns and prevent neonatal mortality and severe white matter injury	Loading dose of 4g	Original trial: non-significant decrease in risks of short-term, severe white matter injury, mortality before hospital discharge Follow-up trial: prenatal low-dose $MgSO_4$ has beneficial neuroprotection effects, which approached significance and achieved significance when considering combined death and gross motor or cognitive dysfunction

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

Author	Gestational age	Number of trials analysed and infants included	Reduced relative risk of CP	Absolute risk of CP with $MgSO_4$ versus placebo	Number needed to treat	Reduced relative risk of gross motor dysfunction	Relative risk of total paediatric mortality	Other neurological outcomes in newborn or first years of life
Doyle *et al.*[22]	<37 weeks	5 trials× 6,145 infants	0.69 (95% CI 0.54-0.87)	3.7% vs. 5.4%	63 (95% CI 43-155)	0.61 (95% CI 0.44-0.85; 5,980 infants considered)	1.01 (95% CI 0.82-1.23)	None
Conde-Agudelo and Romero[13]	<34 weeks	5 trials× 5,357 infants	0.69 (95% CI 0.55-0.88)	3.9% vs. 5.6%	52 (95% CI 31-154)	0.60 (95% CI 0.43-0.83; 4,387 infants considered)	1.01 (95% CI 0.89-1.14)	None
*Costantine *et al.*[23]	<32-34 weeks	5 trials× 5,235 infants	0.70 (95% CI 0.55-0.89)	—	56 (95% CI 34-164)	—	1.01 (95% CI 0.89-1.14)	—
*Costantine *et al.*[23]	<30 weeks	3 trials×× 3,107 infants	0.69 (95% CI 0.52-0.92)	—	46 (95% CI 26-287)	—	1.00 (95% CI 0.87-1.15)	—

Abbreviations: CP: cerebral palsy; $MgSO_4$: magnesium sulphate; CI: confidence interval; —: not evaluated; None: no other neurological outcomes found.
×5 trials (all randomised controlled trials): BEAM,[5] MagNET,[17] ACTOMgSO$_4$,[18] MAGPIE[19] and PREMAG[20,21] (two-year follow-up)
××3 trials (all randomised controlled trials): BEAM, ACTOMgSO$_4$ 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)*

Results

Literature search

Three systematic reviews/meta-analyses met the inclusion criteria. These reviews analysed data from the following randomised controlled trials: BEAM, MagNET, ACTOMgS0$_4$, 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 $MgSO_4$ 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 $MgSO_4$ and subsequent neuroprotection.

Analysis

There are five significant randomised controlled trials that could have a major impact on the use of $MgSO_4$ for neuroprotection: the Magnesium and Neurologic Endpoints Trial [MagNET]; the Australasian Collaborative Trial of Magnesium Sulphate [ACTOMgSO$_4$]; 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 $MgSO_4$-treated groups with no effect on total paediatric mortality.[5,18-21] However, the results regarding decreased cerebral

palsy were only statistically significant in the BEAM trial.[5] 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.[17] However, according to Mittendorf *et al.*: "this study was too small and the complication of cerebral palsy was too uncommon for meaningful statistical analysis".[17] This trial also suggested a trend towards increased foetal/childhood death in $MgSO_4$ groups; however, this was refuted in subsequent systematic reviews and meta-analyses.[14,22,23,30] Another statistically significant result found in the individual trials was decreased substantial gross motor function in the BEAM and ACTO$MgSO_4$ studies.[5,18] 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 $MgSO_4$ therapy administered to women at risk of preterm delivery.[14,22,23] The following conclusions were made in the reviews/meta-analyses regarding $MgSO_4$ administered to mothers at risk for preterm birth: it reduced the risk of cerebral palsy in their children;[14,22,23] it decreased the absolute risk of cerebral palsy compared to placebo;[22,14] on average, the number of people needed to treat to prevent one case of cerebral palsy was 54;[14,22,23] and $MgSO_4$ reduced the rate of substantial gross motor dysfunction in their children.[14,22] $MgSO_4$ administration also had no statistically significant effect on paediatric mortality,[14,22,23] or other poor outcomes in the newborn period or in the first few years of life (e.g., blindness, deafness, developmental delay).[14,22] The outcomes investigated in the newborn period were Apgar scores less than 7 at five minutes, ongoing respiratory support, intraventricular haemorrhage, periventricular leukomalacia, convulsions,[14,22] respiratory distress syndrome, bronchopulmonary dysplasia, mechanical ventilation, and necrotising entercolitis (NEC), even though a drift toward increased NEC was found.[14] All of the reviews also found that the studies giving $MgSO_4$ exclusively for neuroproection provided the most compelling evidence for reduced risk of cerebral palsy. While the major randomised controlled trials did not independently exhibit significant results, collectively they produced strong evidence that may persuade clinicians to use $MgSO_4$ as a neuroprotective agent.

Discussion

The exact mechanism by which $MgSO_4$ 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.[24,25] Periventricular damage is illustrated by loss of oligodendrocytes (brain cells that myelinate or insulate nerves) and gain of astrocytes (cells involved in scarring).[25] Hypoxic-ischaemic damage is a result of low oxygen and glucose supply, which ultimately leads to excessive glutamate release.[24] Glutamate stimulates the N-methyl-D-aspartate (NMDA) receptor, allowing a large influx of sodium and calcium into the neuron.[24] Intracellular calcium induces several enzymes that cause neuronal death, while reperfusion causes oxidative damage through free radicals.[24] $MgSO_4$ is an NMDA receptor antagonist[24,31] and NMDA antagonists have proven to be strong neuroprotectants in various animal models.[26] However, NMDA receptors are vital in certain aspects of brain development, which raises the issue that $MgSO_4$ could have the potential to disrupt normal foetal brain development if given at specific stages in neurodevelopment.[24]

It is important to remember that there is a strong correlation between spontaneous preterm birth and intrauterine inflammation.[27] The fact that preterm birth due to inflammation and cytokine production leads to neuronal insult has been shown in animal models.[28,29] 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.[25] 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.[25] A subsequent animal study demonstrated that foetal brains subjected to inflammation that were later treated with $MgSO_4$ did not display neuronal injury associated with fewer dendritic processes.[27]

The medical community continues to face difficulties regarding best practice and antenatal use of $MgSO_4$ despite years of its clinical use and significant findings from combined data.[30] 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[30] increase paediatric mortality.[31-34] Although the major randomised controlled trials used differing dosing regimens, total dose remained low. The median total exposure to $MgSO_4$ in the ACTO$MgSO_4$ 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;[30] total exposure in the PREMAG trial was 4g (single bolus infusion);[20] and, median total dose in the BEAM trial was 31.5g (6g bolus infusion with 2g/hour maintenance).[31] The low doses used in all of these trials showed a decrease in a 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.[30] Determining the therapeutic window above which $MgSO_4$ 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 $MgSO_4$ to mothers in preterm labour. The MagNET and BEAM trials used active preterm labour and cervical dilatation (>4cm and 4-8cm) as indications for treatment.[5,17] Women were eligible for treatment in the BEAM, ACTO$MgSO_4$ and

PREMAG trials if delivery was expected within 24 hours.[5,18,20] The Brigham and Women's Hospital (BWH) in Boston, Massachusetts, has developed a new protocol regarding $MgSO_4$ for neuroprotection, and their goal for initiating infusion is set for four hours prior to delivery.[35] 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,[5] would continue $MgSO_4$ infusion if six hours had passed since treatment stopped, there is not enough evidence to strongly support re-treatment.[35]

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 $MgSO_4$ 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 $MgSO_4$ simultaneously with the hospital's preferred tocolytic, such as indomethacin or nifedipine.[36] Combining $MgSO_4$ and calcium channel blockers is especially challenging, as it may lead to serious maternal side effects such as hypotension.[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.[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.[31]

Maternal side effects are another important issue in antenatal $MgSO_4$ use. Both reviews and independent studies reported a greater number of adverse side effects in $MgSO_4$-treated groups compared to placebo-treated groups.

Minor adverse effects included flushing, nausea, vomiting, sweating, problems at injection site, lethargy and blurred vision,[5,14,18,31] and seemed to subside once treatment was finished.[37] More serious side effects such as hypotension and tachycardia were also seen,[14,18,37] and were increased by as much as 50% in the $MgSO_4$ group compared to the placebo group.[14] $MgSO_4$ therapy was rarely associated with severe side effects such as death,[5,14,18,20,31,37] cardiac and respiratory arrest,[5,14,18,20,31,37] pulmonary oedema,[5,14] postpartum haemorrhage,[14,18,20] and caesarean section.[5,14,18,20] Clinicians must also be cautious of fluid overload, which can lead to severe cardiovascular complications.[35]

Infants exposed to $MgSO_4$ 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 $MgSO_4$ 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 $MgSO_4$ 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,[14,22,23] increased risk of NEC,[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,[14,22] since neurological outcomes such as cerebral palsy are sometimes not fully recognised until children are older.[22]

Indications for $MgSO_4$ therapy must be further investigated,[23,31] since there was a lack of consistency in patient characteristics among the five major trials.[23] Various indications for treatment ranged from pre-eclampsia to preterm labour and preterm premature rupture of membranes, and $MgSO_4$ may affect these indications differently.[23] The mechanism by which $MgSO_4$ provides neuroprotection[24,31] to the human foetal brain must also be determined; however, this poses ethical, technical and financial difficulties.[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.[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 ACTO$MgSO_4$ was the only trial to explore maternal tachycardia.[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 $MgSO_4$ 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 $MgSO_4$ 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 $MgSO_4$. Although some centres have begun using $MgSO_4$ for neuroprotection, future research is key to determine its optimal clinical use.

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