



CLINICAL PRACTICE GUIDELINE

**ANTENATAL MAGNESIUM SULPHATE FOR
FETAL NEUROPROTECTION**

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Royal College of Physicians of Ireland
And
Directorate of Strategy and Clinical Care
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Key Recommendations	3
1.0 Purpose and Scope.....	4
2.0 Background and Introduction.....	4
3.0 Methodology	4
4.0 Clinical Guideline	5
4.1 Magnesium Sulphate: Mechanisms of Action.....	5
4.2 Evidence for benefit	5
4.3 Eligible patients	9
4.4 Gestational age	9
4.5 Dosing Schedule	10
4.6 Timing of Administration	10
4.7 Adverse effects.....	11
4.8 Monitoring.....	12
4.8.1 Maternal Monitoring.....	12
4.8.2 Fetal Monitoring	12
4.9 Contraindications to Use of Magnesium Sulphate	12
5.0 References/Recommended Reading.....	14
6.0 Implementation Strategy	16
7.0 Key Performance Indicators.....	16
8.0 Qualifying Statement.....	16

Key Recommendations

1. Data from several large randomized controlled trials and a Cochrane meta-analysis give evidence for a beneficial effect for magnesium sulphate in reducing the risk of cerebral palsy in infants delivered at preterm gestations. Thus administration of magnesium sulphate should be considered in all cases of planned or anticipated preterm delivery
2. Use of magnesium sulphate should be considered in all patients at risk of imminent preterm delivery before 32 weeks. However, in situations of limited resources, emphasis should be placed on ensuring that women delivering at 28 weeks or less, when the greatest benefit has been shown, receive antenatal magnesium sulphate.
3. Optimal benefit is seen with use of a loading dose of magnesium sulphate followed by an infusion. The recommended dosing regimen is 4g loading dose followed by an infusion of 1g/hr continued until delivery or for 24 hours, whichever occurs sooner.
4. In cases of limited resources for maternal monitoring, or limited time, it is reasonable to administer a 4g loading dose only, without a subsequent infusion.
5. Aim to commence magnesium sulphate approximately 4 hours prior to delivery. If it is not possible to achieve a 4 hour window prior to delivery, magnesium sulphate should still be administered, as it is likely that some benefit will be seen when administered within this time
6. No evidence available at present to guide management regarding repeated doses of magnesium sulphate in those patients that do not deliver and have magnesium sulphate discontinued. It is reasonable to consider giving a repeat dose in the event of imminent preterm delivery if 24 hours have elapsed since discontinuing the magnesium sulphate.
7. Given the potential for adverse maternal and fetal effects of magnesium sulphate both maternal and fetal monitoring must be employed during magnesium sulphate administration.

1.0 Purpose and Scope

The purpose of this clinical guideline is to assist healthcare professionals in decision-making regarding the use of magnesium sulphate to reduce the risk of cerebral palsy in babies born at preterm gestations.

2.0 Background and Introduction

Cerebral Palsy (CP), a group of non-progressive disorders of movement with or without cognitive impairment, is a potentially devastating complication of preterm delivery. Rates of CP are inversely proportional to gestational age at delivery, with up to 15% of babies born before 27 weeks gestation affected, in contrast to rates of CP of just 0.1% in infants born at term.

Studies have identified maternal administration of magnesium sulphate prior to delivery as an effective strategy in reducing the incidence of CP.

This guideline evaluates the current available evidence and provides recommendations for the use of magnesium sulphate in mothers at imminent risk of preterm delivery.

3.0 Methodology

The literature was reviewed to identify all randomized controlled trials published evaluating magnesium sulphate administration to prevent cerebral palsy. Meta-analyses, including Cochrane and non Cochrane systematic reviews on this subject, were also reviewed. In addition, international guidelines published from Australia, Canada, United States and a scientific opinion paper from the Royal College of Obstetricians and Gynaecologists were evaluated.

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4.0 Clinical Guideline

4.1 Magnesium Sulphate: Mechanisms of Action

The exact mechanism by which magnesium sulphate exerts a protective role in the prevention of neuronal injury in the fetal brain has not been elucidated. However there is evidence for various effects of magnesium sulphate, some or all of which likely play a role in the neuroprotective effect observed (Marret et al, 2007).

Magnesium ions are involved in the maintenance of cell membrane integrity and also various intracellular processes including glycolysis, oxidative phosphorylation and protein synthesis (Mildvan 1987).

There is evidence that magnesium decreases the production of pro-inflammatory cytokines and free radicals produced during hypoxic-ischaemic reperfusion and also prevents calcium-induced injury (Hoffman et al, 1994; Shogi et al, 2003). This is due to inhibition of the N-methyl-D-aspartate receptor to glutamate, leading to reduced calcium entry into cells (Nowak et al, 1984).

Beneficial haemodynamic effects of magnesium sulphate have also been postulated, with potential increased cerebral perfusion and a stabilizing effect on neonatal blood pressure variability reported (Macdonald et al, 2004; Rantone et al, 2002).

4.2 Evidence for benefit

The first reported association between in-utero exposure to magnesium sulphate and a reduction in perinatal morbidity was by Kuban and colleagues in 1992 (Kuban et al, 1992). They conducted a prospective study of 449 babies delivered at birth weight less than 1501g and found that maternal receipt of magnesium sulphate was associated with a decreased incidence of intraventricular haemorrhage.

This association was again reported in 1995 when Nelson et al (Nelson and Grether, 1995) published a case-control study investigating the effect of in utero exposure to magnesium sulphate on the subsequent development of cerebral palsy (CP). They compared a group of very low birth weight infants (VLBW, <1500g) surviving to 3 years with moderate to severe CP with a control group of VLBW infants without CP. There was a significantly higher rate of intrapartum exposure to magnesium sulphate among the control group suggesting a neuro-protective effect for magnesium sulphate.

Conflicting results from subsequent studies (Kimberlin et al, 1998; Paneth et al, 1997; Boyle et al, 2000) underscored the need for large randomized controlled trials (RCT) to definitively investigate this potential intervention. To date there have been three large RCTs performed, all of which have

confirmed a benefit for magnesium sulphate in the prevention of cerebral palsy and/or gross motor dysfunction in the preterm infant. There were differences between these studies in inclusion criteria and also in magnesium sulphate dosing regimens.

Crowther et al, 2003 published the first of these studies in 2003. This multicenter RCT was performed at 16 tertiary hospitals in Australia and New Zealand between 1996 and 2000. Recruitment criteria were women less than 30 weeks gestation, in whom delivery was planned or anticipated within 24 hours. They were randomized to receive magnesium sulphate 4g loading dose over 20 minutes, followed by an infusion of 1g per hour or a placebo. The infusion was continued for 24 hours or until delivery, whichever occurred sooner.

The primary outcomes in the Crowther trial were total paediatric mortality up to 2 years of age, cerebral palsy at 2 years of age or the combined outcome of death or cerebral palsy at 2 years. Of 1255 live infants recruited to the study outcome, data at 2 years was obtained on 99% of children (n= 1047). When the primary outcome measures were compared between the two groups, there were lower rates of death (RR 0.83, 95% CI 0.64 – 1.09), cerebral palsy (RR 0.83, 95% CI 0.54 – 1.27) and the combination of death or cerebral palsy RR 0.83, 95% CI 0.66 – 1.03) among infants exposed to magnesium sulphate. However none of these differences achieved statistical significance.

In 2007 the results of the PREMAG trial were published (Marret et al, 2007). This was a RCT performed in 18 tertiary hospitals in France, evaluating the effect of magnesium sulphate on the preterm brain. Women were eligible for entry to the study if delivery at 33 weeks or less was planned or anticipated within the next 24 hours. The dosing regimen for magnesium sulphate used in this trial consisted of a 4g loading dose of magnesium sulphate administered over 30 mins. No subsequent infusion was administered.

The primary endpoints of the PREMAG trial were neonatal mortality before hospital discharge, severe white matter injury (WMI) detected on cranial ultrasound, or a combination of mortality or severe WMI. Cranial ultrasound was carried out at intervals up to 6 weeks following delivery on all participating infants.

The trial was stopped prior to achieving their target sample size due to low rates of recruitment. In total data was analysed on 668 infants of 564 mothers. In similar findings to the study by Crowther et al, lower rates of all primary outcome measures were observed on the group receiving antenatal magnesium sulphate when compared with placebo. However, none of the findings were statistically significant. The adjusted odds ratios for total mortality, severe WMI and the combination of death or severe WMI were 0.79 (95% CI 0.44 – 1.44), 0.78 (95% CI 0.47 – 1.31) and 0.86 (95% CI 0.55 – 1.34) respectively.

In 2008 Marret et al published the 2-year follow up of the PREMAG cohort (Marret et al, 2008). The following outcomes were evaluated at this time

point: death, motor dysfunction, cerebral palsy, cognitive dysfunction and their combined outcomes. Reduced rates of all secondary endpoints were noted in the group receiving magnesium sulphate. Only the combined outcome of death or gross motor dysfunction showed a statistically significant reduction (OR 0.62; 0.41 – 0.93).

Between 1997 and 2004 the NICHD carried out the largest RCT to date evaluating magnesium sulphate in the prevention of cerebral palsy (Rouse et al, 2008). The BEAM (Beneficial Effects of Antenatal Magnesium Sulphate) Trial was carried out at 20 centers in the United States. Women with planned or anticipated delivery within 24 hours at gestations up to 31 weeks were eligible for recruitment. Women were excluded if delivery was anticipated within 2 hours.

The regimen of magnesium sulphate used was a 6g loading dose, infused over 20 – 30 minutes, followed by 2g per hour maintenance. The cohort was randomized to receive this regimen or a placebo. This was continued for up to 12 hrs.

The primary outcome of the BEAM Trial was the composite outcome of stillbirth or death by 1 year of age or moderate or severe cerebral palsy beyond 2 years of age.

Of 2241 women recruited to the study complete outcome data was evaluated on 95.6% of babies. Although no significant difference was found between the two groups in the primary outcome of death or cerebral palsy (RR 0.97, 95% CI 0.77 – 1.23), children exposed to magnesium sulphate had significantly lower rates of moderate to severe cerebral palsy at 2 years (RR 0.55, 95% CI 0.32 – 0.95, p=0.03).

In 2009 a Cochrane review was published which combined the results of these 3 RCTs (Doyle et al, 2009). Also included in the Cochrane meta-analysis were the results a small RCT by Mittendorf et al, 2002 and a secondary analysis of the MAGPIE Trial, which evaluated the use of magnesium sulphate in the prevention of eclampsia. Table 1 summarizes the key characteristics and findings of the studies included in the Cochrane review.

Table 1: Studies included in Cochrane Review

Study	Gestational Age	MgSO4 Dosing Regimen	Number of women enrolled	Results
Crowther et al¹³	< 30 weeks	4g loading dose, 1g/hr infusion	1062	Lower rates of death (RR 0.83, 95% CI 0.64 – 1.09), cerebral palsy (RR 0.83, 95% CI 0.54 – 1.27) and the combination of death or cerebral palsy RR 0.83, 95% CI 0.66 – 1.03) among infants exposed to magnesium sulphate
Marret et al¹⁴	<33 weeks	4g loading dose	573	No difference in rates of total mortality, severe WMI and the combination of death or severe WMI at discharge. 2 year follow up: Significant reduction in combined outcome of death or gross motor dysfunction (OR 0.62; 0.41 – 0.93).
Rouse et al¹⁶	<31 weeks	6g loading dose, 2g/hr infusion	2241	Exposure to magnesium sulphate associated with significantly lower rates of moderate to severe cerebral palsy at 2 years (RR 0.55, 95% CI 0.32 – 0.95, p=0.03). No difference in combined outcome of death or cerebral palsy.
Mittendorf et al¹⁸	25-33 weeks	4g loading dose	149	Antenatal exposure to magnesium sulphate associated with an increased risk of adverse neonatal outcome (OR 3.7; 95% CI, 1.1-11.9)
Duley et al	All gestations	4g loading dose, 1g/hr infusion	1544	Non-significant reduction in cerebral palsy among infants exposed to magnesium sulphate (RR 0.4, 95% CI 0.08 – 2.05)

The Cochrane review concluded that antenatal administration of magnesium sulphate with neuroprotective intent to women at risk of preterm delivery reduced the risk of death or cerebral palsy (RR 0.85, 95% CI 0.74 – 0.98), cerebral palsy (RR 0.71, 95% CI 0.55 – 0.91) and substantial gross motor dysfunction (RR 0.60, 95% CI 0.43 – 0.83). It did not suggest any effect of magnesium sulphate on fetal or infant death (RR 0.95, 95% CI 0.80 – 1.12).

4.3 Eligible patients

Administration of magnesium sulphate should be considered for all patients with anticipated preterm delivery less than 32 weeks gestation within the subsequent 12 hours.

Consideration for use should be given in the following clinical scenarios:

- 1) Preterm labour with evidence of cervical dilatation
- 2) Preterm prelabour rupture of the membranes with regular uterine contractions
- 3) Severe preeclampsia/HELLP with planned delivery within the subsequent 12 hours
- 4) Severe intrauterine growth restriction with planned delivery with the subsequent 12 hours
- 5) Any other medical or obstetric condition necessitating preterm delivery.

4.4 Gestational age

As cerebral palsy is more common following delivery at earlier gestations and also is more likely to have a perinatal origin, any intervention to reduce this risk will have a greater magnitude of effect at these earlier gestations. This is reflected in an increase in the number needed to treat (NNT) to prevent 1 case of cerebral palsy as gestation advances.

Gestational age at administration varied among the RCTs, as outlined above See Table 1. All patients were less than 34 weeks with the majority recruited at gestational age of 32 weeks or less. A sub analysis of patients recruited to the BEAM study showed the reduction in cerebral palsy following antenatal administration of magnesium sulphate was greatest in those delivering before 28 weeks gestation (RR 0.45, 95% CI 0.23 – 0.87) (Rouse et al, 2008).

A meta-analysis by Conde-Agudelo et al, 2009, concluded that the NNT at before 34 weeks was 52 to prevent one case of cerebral palsy. Another meta-analysis by Costantine et al, 2009, subdivided the results of the trials by gestation and determined that the NNT at 30 weeks gestation or less was 46, increasing to 56 at 32 – 34 weeks gestation.

With evidence of benefit for magnesium sulphate in the prevention of cerebral palsy at 32 weeks or less its use should be considered in all patients at risk of imminent preterm delivery before 32 weeks. However, in situations of limited resources, emphasis should be placed on ensuring that women delivering at 28 weeks or less, when the greatest benefit has been shown, receive antenatal magnesium sulphate.

4.5 Dosing Schedule

The magnesium sulphate regimen used was different in each of the RCTs designed with neuroprotective intent (Crowther et al, 2003; Marret et al, 2007; Rouse et al, 2008; Mittendorf et al, 2002). All gave a bolus dose of 4g or 6g but not all gave a subsequent infusion. Among those that administered an infusion this was either 1g/hr (Marret et al, 2007) or 2g/hr (Rouse et al, 2008). Benefit in terms of reduction in the rates of cerebral palsy was shown with each of these regimens. It remains to be determined what the minimum effective dose of magnesium sulphate is.

A recent Cochrane review addressed the issue of different regimens of magnesium sulphate for fetal neuroprotection and concluded that further research is required to define the optimal dosing schedule (Bain et al, 2012).

However, it is noteworthy that the only trial in which there was a statistically significant reduction in cerebral palsy was the trial by Rouse et al, 2008 in which the dosing regimen was a 6g loading dose followed by an infusion of 1g/hr. As the largest study included in the Cochrane meta-analysis this study also significantly contributed to the overall finding of a 40% reduction in cerebral palsy with antenatal magnesium sulphate.

Within the Cochrane review, when the analysis was limited to only the 2 trials using a loading dose and subsequent infusion of magnesium sulphate the evidence for benefit in reduction in rates of cerebral palsy persisted. (RR 0.68, 95% CI 0.52 – 0.91).

Given these findings consideration should be given to administering both a loading dose and an infusion of magnesium sulphate to women deemed eligible. There is considerable experience among Obstetricians with use of a 4g loading dose, administered over 20-30 minutes followed by an infusion of 1g/hr, the regimen commonly used in the setting of eclampsia prophylaxis. This is the currently recommended dosing schedule in the setting of fetal neuroprotection.

In cases of limited resources for maternal monitoring, or limited time, it is reasonable to administer a 4g loading dose only, without a subsequent infusion.

4.6 Timing of Administration

The presumed mechanism of action of magnesium sulphate in the prevention of fetal neuronal injury is contingent on adequate fetal levels of magnesium sulphate at the time of delivery. Studies evaluating placental transfer of magnesium sulphate in animals (Hallak and Cotton, 1993) have shown that within 2 hours of a sustained maternal infusion of magnesium sulphate it crosses the fetal blood-brain barrier, with concentrations increased in the fetal forebrain after 4 hours of sustained treatment.

A study evaluating fetal serum concentrations of magnesium sulphate in patients undergoing fetal blood sampling (Hallak et al, 1993) showed elevated levels of magnesium sulphate in the fetal serum at 1 hour and 3 hours post administration. Levels increased between 1 and 3 hours. Fetal serum magnesium concentrations correlated with maternal magnesium concentrations.

An analysis of placental transfer of magnesium sulphate in patients within the Crowther study showed prompt transfer of magnesium sulphate from mother to fetus after commencing the infusion with neonatal magnesium levels remaining elevated for up to 24 hours.

Further research is necessary to determine the optimum timing of administration of antenatal magnesium sulphate for fetal neuroprotection. However the current evidence suggests that benefit may be seen quickly after administration. With evidence for increased fetal levels 3-4 hours after commencing magnesium sulphate in cases of planned preterm delivery, one should aim to commence magnesium sulphate approximately 4 hours prior to delivery. If it is not possible to achieve a 4 hour window prior to delivery, magnesium sulphate should still be administered, as it is likely that some benefit will be seen when administered within this time.

There is no evidence available at present to guide management regarding repeated doses of magnesium sulphate in those patients that do not deliver and have magnesium sulphate discontinued. It is reasonable to consider giving a repeat dose in the event of imminent preterm delivery if 24 hours have elapsed since discontinuing the magnesium sulphate.

4.7 Adverse effects

Intravenous infusion of magnesium sulphate causes maternal side effects due to its' vasodilatory action. It is common to experience flushing and sweating when receiving magnesium sulphate. Less commonly patients experience vomiting, headaches and palpitations. More serious adverse effects, related to toxic maternal levels of magnesium, include respiratory depression, respiratory or cardiac arrest and death.

In a meta- analysis by Conde-Agudelo et al of 6 trials evaluating use of magnesium sulphate for the prevention of cerebral palsy, 70.7% of patients reported minor adverse effects. There were no cases of serious adverse effects including death, cardiac arrest, respiratory depression/arrest or severe postpartum haemorrhage.

4.8 Monitoring

4.8.1 Maternal Monitoring

Due to the potential for adverse maternal effects all women receiving magnesium sulphate treatment require careful monitoring. However, with the doses of magnesium sulphate being administered in this setting, serious adverse events are unlikely.

The location of the patient while antenatal magnesium sulphate is administered should be determined by each individual clinical facility and will depend on the clinical situation.

While receiving magnesium sulphate patients require the following observations:

- Assessment of maternal pulse rate, blood pressure, respiratory rate and deep tendon reflexes prior to commencement
- Hourly assessment of maternal pulse, blood pressure, respiratory rate, deep tendon reflexes
- Hourly urine output monitoring

Discontinue magnesium sulphate if:

- Respiratory rate drops to less than 12 breaths per minute
- Diastolic BP drops more than 15mmHg below baseline
- Deep tendon reflexes are absent
- Urine output decreases to less than 100mls over 4 hours

Monitoring of serum magnesium levels is only necessary if there is maternal renal compromise.

Calcium Gluconate 1g IV over 10 mins may be administered as an antidote to magnesium sulphate if there is significant maternal toxicity.

4.8.2 Fetal Monitoring

Continuous fetal heart rate monitoring with cardiotocography should be employed when maternal magnesium sulphate is being administered.

4.9 Contraindications to Use of Magnesium Sulphate

Absolute:

- Maternal Myasthenia Gravis

Relative:

- Non reassuring fetal heart rate tracing: Delivery should not be delayed to facilitate administration of magnesium sulphate. It is

reasonable to consider administration of the bolus dose of magnesium sulphate in these situations.

- Use of calcium channel blockers: The potential interaction between calcium channel blockers, such as nifedipine, and magnesium sulphate leading to hypotension and neuromuscular blockade mandates more intensive monitoring of maternal haemodynamic status.
- Renal Insufficiency: Monitoring of maternal serum levels of magnesium with appropriate dose adjustment of rate of magnesium sulphate infusion is necessary in cases of impaired renal function.

5.0 References/Recommended Reading

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6.0 Implementation Strategy

- Distribution of guideline to all members of the Institute and to all maternity hospitals.
- Implementation through HSE Obstetrics and Gynaecology programme local implementation boards.
- Distribution to other interested parties and professional bodies.

7.0 Key Performance Indicators

To be developed.

8.0 Qualifying Statement

This guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. Clinical material offered in this guideline does not replace or remove clinical judgement or the professional care and duty necessary for each pregnant woman. Clinical care carried out in accordance with this guideline should be provided within the context of locally available resources and expertise.

This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible for:

- Discussing care with women in an environment that is appropriate and which enables respectful confidential discussion.
- Advising women of their choices and ensure informed consent is obtained.
- Meeting all legislative requirements and maintaining standards of professional conduct.
- Applying standard precautions and additional precautions, as necessary, when delivering care
- Documenting all care in accordance with local and mandatory requirements.

