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Magnesium Sulphate to Prevent Cerebral Palsy following Preterm Birth

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1. Background

The prevalence of preterm birth is increasing.¹ While the survival of infants born preterm has improved,² the prevalence of cerebral palsy has risen.³ The incidence of cerebral palsy decreases significantly with increasing gestational age: 14.6% at 22–27 weeks of gestation, 6.2% at 28–31 weeks, 0.7% at 32–36 weeks and 0.1% in term infants.⁴ Twenty-five percent of all cases of cerebral palsy are in infants born at less than 34 weeks of gestation.⁵ In children born preterm the proportion whose cerebral palsy is considered to have a perinatal origin (49%) is greater than in those born at term (35%).^{6,7} Strategies to reduce cerebral palsy in these infants should be considered and implemented if shown to be effective in order to reduce the effects of this disabling condition on individuals, families, health care and society.

2. Neuroprotection

In the late 1990s studies of infants born to mothers given magnesium sulphate to prevent eclamptic seizures or as tocolysis showed a reduction in rates of cystic periventricular leucomalacia (PVL) and cerebral palsy. In those babies born preterm and exposed to magnesium sulphate⁸ the odds ratio for cerebral palsy was 0.14 (95% CI 0.05–0.51).⁹ Although the exact mechanism of action of magnesium as a neuroprotective agent is unknown, it has a number of biologically plausible actions which may contribute to a protective effect on the preterm neonatal brain.

The most common pathological lesion associated with cerebral palsy in preterm infants is periventricular white matter injury.⁵ Oligodendrocytes constitute a major glial population in the white matter. N-methyl-D-aspartic acid (NMDA) receptors on oligodendrocytes are thought to be important in the glial injury process. NMDA receptor antagonists are potent neuroprotective agents in several animal models of perinatal brain injury. Magnesium sulphate may reverse the harmful effects of hypoxic/ischaemic brain injury by blocking NMDA receptors, acting as a calcium antagonist and reducing calcium influx into the cells.^{10,11} Magnesium sulphate is also implicated in tissue protection against free radical activity,¹¹ has been shown to act as a vasodilator,³ reduces vascular instability, prevents hypoxic damage,¹² attenuates cytokine or excitatory amino acid induced cell damage¹² and has anti-apoptotic actions.¹³ Magnesium complexed with adenosine triphosphate is required for the activity of many functional proteins, including membrane transporters, ion pumps and a broad array of other enzymes.¹¹

Five randomised controlled trials,^{12,14–18} three subsequent meta-analyses^{5,19,20} and a Cochrane review²¹ followed. On the basis of these studies, the University of Adelaide issued, in March 2010, a guideline on best practice for clinical care in the use of antenatal magnesium sulphate prior to preterm birth for the neuroprotection of the fetus, infant and child.²² The guideline was developed according to the requirements of the Australian National Health and Medical Research Council and the New Zealand Guidelines Group. It was authored by a panel of experts in the field including maternal and fetal subspecialists, neonatologists, midwives, pharmacists, epidemiologists, statisticians and consumers. The authors concluded that in women at risk of early preterm imminent birth, magnesium sulphate should be used for neuroprotection of the fetus, infant and child.²²

2.1 Effect on cerebral palsy

In 2002 Mittendorf et al. conducted a randomised trial in which 149 women in preterm labour, between 24 and 34 weeks of gestation, received magnesium sulphate, another tocolytic or placebo. They reported an excess of adverse outcomes (a composite of neonatal intraventricular haemorrhage, PVL, cerebral palsy or death) in fetuses exposed to magnesium sulphate when followed up to 18

months of age.¹⁴ These study findings are in contrast to other larger studies. Reasons for the difference are unclear. The study assessed a bolus of magnesium sulphate in those at risk of imminent delivery and a bolus/infusion regimen in those requiring tocolysis. There was no significant difference in neonatal outcomes between control and treatment groups in either arm of the study, or even when they were combined. However, multivariable analyses, modelled to control for confounding by other maternal or obstetric risk factors, suggested that clinical evidence of chorioamnionitis as well as ionised magnesium levels in the cord blood were associated with adverse outcomes. Differences with other studies include:

- Size: this was a small study with only 29 mothers in the neuroprotective arm and 46 in the tocolysis arm receiving magnesium sulphate.
- Outcomes: the main outcomes contributing to the composite score were intraventricular haemorrhage and death (not altered by magnesium sulphate in the meta-analyses) rather than cerebral palsy, for which the study was underpowered.

In 2003 Crowther et al. conducted a randomised trial of 1062 women at less than 30 weeks of gestation in a study designed to address neuroprotection. They noted that the number of children with cerebral palsy at a corrected age of 2 years was lower in the magnesium sulphate group (36 [6.8%] versus 42 [8.2%]), although this was not a statistically significant difference (RR 0.83; 95% CI 0.54–1.27). The combined outcome of death or cerebral palsy was also lower for children in the magnesium sulphate group (123 [19.8%] versus 149 [24.0%]), although again this was not statistically significant (RR 0.83; 95% CI 0.66–1.03).¹⁵

The Magpie trial was primarily designed to determine the maternal neurological effects of magnesium, but also reported on neonatal outcomes.¹⁸ The study included women giving birth at all gestations, 80% of whom were recruited from developing countries. Paediatric follow-up was not consistent but the study was large (1544 women) and, although not significant, suggested a lower risk of death or cerebral palsy in children at 2 years of age if the mothers were allocated magnesium sulphate rather than placebo (RR 0.83; 95% CI 0.66–1.03). There was no increase in death or sensory disability in the magnesium sulphate group, providing reassurance on long-term safety to children born after maternal administration of magnesium sulphate.

In the two remaining 2007–2008 studies designed to investigate the neonatal neuroprotective role of magnesium, both demonstrated a benefit in children whose mothers received magnesium sulphate.^{12,16} In the largest of the randomised controlled trials primarily addressing neuroprotection, Rouse et al. studied 2241 women delivering between 24 and 31 weeks of gestation and noted that moderate or severe cerebral palsy, assessed at or beyond 2 years of age, occurred less frequently in the magnesium sulphate group (1.9% versus 3.5%; RR 0.55; 95% CI 0.32–0.95). The risk of death was not different between the groups.¹² Marrett et al. conducted a randomised trial of 564 women at less than 33 weeks of gestation and noted a reduction in neonatal mortality (OR 0.79; 95% CI 0.44–1.44), severe neonatal white matter injury (OR 0.78; 95% CI 0.47–1.31) and combined severe white matter injury and/or mortality (OR 0.86; 95% CI 0.55–1.34) at discharge in the magnesium sulphate arm. These results were not, however, statistically significant.¹⁶

Conde-Agudelo et al. conducted a systematic review and meta-analysis of the literature in women delivering before 34 weeks of gestation.⁵ Their review included the Mittendorf study reporting adverse outcomes associated with magnesium sulphate. The authors concluded that in women at risk of preterm delivery before 34 weeks of gestation, the number of mothers needed to treat to prevent one case of cerebral palsy in their child was 52 (95% CI 31–154). In the three studies reporting cerebral palsy severity,^{12,15,16} benefit was observed in both moderate and severe groups, but not mild. There was no effect on mortality.⁵

The Cochrane review of trials concluded that antenatal magnesium sulphate therapy given to women at risk of preterm birth substantially reduced the risk of cerebral palsy in their children with a relative risk of 0.68 (95% CI 0.54–0.87). There was also a significant reduction in the rate of substantial gross motor dysfunction (RR 0.61; 95% CI 0.44–0.85).²¹ When only those trials using magnesium sulphate

for neuroprotection^{12,14-16} (Duley¹⁸ and a subset of the cases in Mittendorf et al¹⁴ excluded) were analysed as a subgroup, a similar magnitude of reduction was seen (RR 0.71; 95%CI 0.55-0.91).²¹

3. Gestation at administration

The gestational age at which magnesium sulphate administration has its greatest effect has been debated.⁷ As perinatal and neonatal factors are more prominent in the aetiology of cerebral palsy in less mature infants, an intervention immediately pre-delivery is more likely to be effective at earlier gestations. Thus the number needed to treat will increase significantly with advancing gestational age.⁷ This concept is supported by data from Rouse et al. showing a significant reduction in moderate or severe cerebral palsy in babies of women recruited at less than 28 weeks of gestation (RR 0.45; 95% CI 0.23–0.87), but not in those between 28 and 31 weeks of gestation.¹² Knight⁷ combined Rouse et al. data from the less than 28 week subgroup with Crowther et al.¹⁴ data on 29 week or lower pregnancies, and showed a significant reduction in moderate or severe cerebral palsy (RR 0.55; 95% CI 0.35–0.88). Costantine et al. looked at those trials addressing outcome at less than 34 weeks of gestation and concluded that the number needed to treat at less than 30 weeks of gestation was 46 (95% CI 26–187) and rose to 56 (95% CI 34–164) before 32–34 weeks of gestation.¹⁹

In the clinical practice guidelines issued by the University of Adelaide the panel conclude that magnesium sulphate should be considered in women at less than 30 weeks of gestation.²² In the discussion they argue that while benefit has been observed at more advanced gestations, the magnitude of effect is likely to be largest at earliest gestations and limitation of resources makes an upper limit of 30 weeks a pragmatic choice.

3.1 Dose and timing of administration

All studies^{12,14-18} described included multiple pregnancies, those where delivery was expected within 24 hours and those with premature rupture of membranes. Rouse et al.¹² excluded women with hypertension or pre-eclampsia. This suggests that irrespective of the indication any infant delivering preterm might be expected to benefit from the observed reduction in cerebral palsy risk. The dose of magnesium sulphate administered varied between studies. All used a loading dose of magnesium sulphate that varied between 4 and 6 g. Not all trials administered a maintenance infusion and in those that did, the dose varied: 1 g/hr, 2 g/hr or 2–3 g/hr. Mittendorf¹⁴ reported different doses in two arms of the study: neuroprotection (4 g loading dose only) and tocolysis (4 g bolus and maintenance 2–3 g/hr). Rouse et al. administered a 6 g bolus over 20–30 minutes followed by 2 g/hr (discontinued if not delivered by 12 hours).¹² However, the Conde-Agudelo meta-analysis confirmed that the beneficial effect of magnesium sulphate on cerebral palsy persisted in those studies using lower doses of magnesium.⁵ The University of Adelaide guideline panel concluded that an intravenous 4 g loading dose over 20–30 minutes should be given followed by a 1 g/hr maintenance regime to continue for 24 hours or until birth, whichever occurred soonest.²² However, there are insufficient data to define a minimum effective dose of magnesium sulphate.

For those women in advanced labour or those failing to deliver when a delivery was anticipated, Rouse et al.¹² suggested discontinuing therapy if birth was not achieved within 12 hours. They excluded women who were more than 8 cm cervical dilation or less than 2 hours from delivery.¹² If women were deemed to be at risk of delivery more than 6 hours after stopping then a further bolus was given.¹² In animal studies subcutaneous magnesium given to rats crosses the placenta within 2 hours of sustained maternal magnesium levels, enters the fetal blood–brain barrier and concentrates in the forebrain.²³ This suggests that any effect might be seen early. The Australian guideline suggests that ideally infusion should be commenced at least 4 hours before birth but agrees that there may still be a benefit if given less than 4 hours before delivery.²² Data on the latest that magnesium sulphate can be given before delivery in order to be of benefit are not available.

Given the time needed to draw up an infusion, magnesium sulphate administration is likely to be impractical where delivery is imminent and may distract caregivers from providing appropriate

obstetric care. In time-critical situations where delivery needs to be expedited for reasons of maternal or fetal wellbeing then delivery should not be delayed solely for magnesium sulphate administration. Magnesium sulphate when given solely for protection against cerebral palsy is discontinued after delivery.

3.2 Side effects

Intravenous magnesium sulphate is associated with maternal side effects such as facial flushing and rarely, in those with neuromuscular disorders, can result in muscle weakness and paralysis.²⁴ When given in conjunction with calcium channel antagonists, cardiovascular and neuromuscular effects may be exaggerated.²⁴ Conde-Agudelo et al.⁵ addressed maternal outcomes and suggested there was no evidence of an effect on maternal death, cardiac respiratory arrest, pulmonary oedema, respiratory depression, severe postpartum haemorrhage or caesarean section rates. However, a 50% increase in hypotension and tachycardia was observed with a number needed to treat for harm of 30 (95% CI 17–156) and 28 (95% CI 14–379) respectively. Seventy percent reported side effects such as flushing, nausea and vomiting, sweating and injection site problems with a number needed to treat for harm of 2 (95% CI 2–2). These adverse effects were not considered to be of clinical significance by the authors and are the same as those observed in routine clinical practice when magnesium sulphate is used in similar doses to prevent or treat eclamptic seizures.

4. Opinion

Magnesium sulphate given to mothers shortly before delivery reduces the risk of cerebral palsy and protects gross motor function in those infants born preterm. The effect may be greatest at early gestations and is not associated with adverse long-term fetal or maternal outcome.¹⁷ Women should be advised of an increase in minor adverse effects associated with the medication.

This evidence is not new. However, the data have not led to a widespread change in clinical practice within the UK, and a recent opinion paper from the American College of Obstetricians and Gynecologists²⁵ supports the use of magnesium sulphate but does not provide a ringing endorsement. There are a number of possible factors for this reluctance to change practice including: data from one study showing adverse neonatal outcomes following magnesium sulphate; the lack of a statistically significant difference in primary outcome measures from all the randomised controlled trials; and the large number needed to treat for benefit, compared with maternal administration of steroids to improve neonatal lung function. Balanced against these concerns are a number of reasons that should convince clinicians that magnesium sulphate is an important component of a care package to improve neonatal outcome following preterm birth. First, the meta-analyses clearly show that magnesium reduces cerebral palsy and motor deficits, no matter what the original indication for magnesium sulphate administration. As it is highly unlikely that anyone will embark on another randomised controlled trial of this topic the data will not change, although a meta-analysis of individual case data might be of interest (but would be difficult to conduct). Second, unlike steroids that need to be administered up to 24 hours before preterm birth to have their optimal effect, it appears that magnesium has a much more rapid neuroprotective effect, making it more widely relevant. Finally, obstetricians are already familiar with giving a similar magnesium sulphate regime to women at risk of pre-eclampsia and know that major maternal adverse effects are uncommon. The recent Australian guideline from the Adelaide group provides a well-reasoned, practical guide on which to base local clinical guidelines.²²

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