[Title] Use of magnesium sulfate in preterm deliveries for neuroprotection of the neonate

[Running title] Magnesium sulfate neuroprotection

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[Abstract]

Key Content

- The prevalence of preterm birth is increasing and, owing to advances in neonatal care, more infants are surviving. However, in parallel with this the incidence of cerebral palsy (CP) is also rising.
- Magnesium sulfate ($MgSO_4$) is currently recommended for use in women who are at risk of giving birth at less than 30–32 weeks of gestation for neuroprotection of their infants. The exact mechanism of action remains unclear.
- Meta-analyses report encouraging results that are consistent with a modest but tangible benefit for the use of $MgSO_4$ and suggest a number needed to treat (NNT) to prevent one case of CP in infants born preterm of 46 before 30 weeks of gestation and 63 before 34 weeks of gestation.

Learning Objectives

- To gain an understanding of the risk of neurodisability in infants delivered preterm.
- To become familiar with the main studies assessing the use of magnesium sulfate ($MgSO_4$) for neuroprotection in preterm deliveries.
- To become aware of the relevant international guidelines.

Ethical issues

- Concerns have been raised regarding the higher number of perinatal deaths reported with the use of $MgSO_4$ in the MagNET study. This was not substantiated in the Cochrane review.
- Given that $MgSO_4$ is a safe, readily available and inexpensive drug, even if there were only to be modest benefits from its use, the risk: benefit ratio would almost be in favour of its use.

Keywords: cerebral palsy / intrapartum / magnesium sulfate ($MgSO_4$) / neurodevelopment outcome / neuroprotection / preterm deliveries

[**Main Body of Text]**

[Heading1]Cerebral palsy in babies born preterm: causes and impact

The prevalence of preterm birth is increasing.[1] Every year, one in ten babies, equivalent to 15 million babies worldwide, will be born preterm. Of these, approximately one million will die and many more will suffer from lifelong disability, including neurodevelopmental impairment.[2]

Advances in neonatal care have improved the survival of infants born preterm, particularly those born at a very low birth weight or gestational age;[3] however, despite this improved survival rate, the prevalence of neurodisability, even in high income countries, remains static.[4] EPICure 2[5] highlighted the need for improved care, with particular consideration given to survival and long-term sequelae in these infants.

Cerebral palsy (CP) is a general term describing a range of non-progressive syndromes of posture and motor impairment that result from an insult to the developing central nervous system. It is the most common cause of severe

physical disability in childhood. The characteristic signs are spasticity, movement disorders, muscle weakness, ataxia and rigidity. Clinical patterns of involvement described in CP include: diplegia (significant leg involvement with little effect on the upper limbs); hemiplegia (involvement of ipsilateral arm and leg); and quadriplegia (involvement of all four limbs). Movement disorders can coexist with the clinical patterns of involvement, and there can be spasticity, rigidity, hypotonia, dystonia or a mixture of these. Diplegia is the commonest pattern seen in CP that has arisen secondary to prematurity.

The risk of CP increases the lower the gestational age at birth.[6] The prevalence of CP is highest in children born at less than 28 weeks of gestation (111.8/1000 neonatal survivors; 82.25/1000 live births) and declines with increasing gestational age, to 43.15/1000 live births between 28 and 31 weeks, 6.75/1000 between 32 and 36 weeks, and 1.35/1000 for those born later than 36 weeks of gestation.[7] CP results from a permanent static lesion of the cerebral motor cortex that occurs before, at, or within 2 years of birth. Although the lesion is non-progressive, the clinical manifestations of CP change as the child grows and develops. While there are several causes or associations for CP, including genetic mutations,[8] preterm delivery is a major risk factor and accounts for approximately 35% of all cases;[7] in 49% of these cases, CP is thought to be due to a perinatal insult.[9] For the purpose of this review, we briefly highlight perinatal neurological insults that can occur in association with preterm delivery and their neurodevelopmental sequelae. This review will also summarise current evidence for the use of $MgSO_4$ for neuroprotection in the antenatal period.

[Heading1]The link between preterm birth and perinatal fetal brain injury

Two identified patterns of central nervous system injury underlie the development of CP in the preterm infant: intraventricular/germinal matrix haemorrhage, typically initiating in the germinal matrix; and white matter injury, also known as periventricular leucomalacia (PVL). Severe intraventricular haemorrhage (grades III and IV) is reliably detected by

ultrasound, while PVL is best detected with MRI. Often the final diagnosis of CP takes a few years.

PVL is the predominant form of brain white matter lesion that affects preterm (23–32 gestational weeks) infants and is particularly associated with the subsequent development of CP in childhood.[10] PVL has been estimated to occur in 2–3% of infants born weighing less than 1500 g.[11] Approximately 10% of infants with PVL later exhibit CP and 50% show cognitive and behavioural deficits.[12] Pathology observed in PVL includes the development of lesions within the white matter as well as cerebral necrosis. These lesions can be diffuse or cystic. The areas of white matter peripheral to the lateral ventricles are predominantly affected and, less commonly, necrotic foci can also be detected within the corpus callosum, internal capsule and thalamus.[13] It is now believed that PVL is primarily caused by inflammatory cytokine production mediated by maternal and/or fetal infection (Figure 1).[14] It is characterised by a raised level of plasma interleukin 6 (IL-6) in the fetus; and an increase in IL-6 has been observed in the umbilical cord in association with PVL.[15]

Other neurodevelopmental consequences of prematurity may also be seen:

- Motor dysfunction can range from mild to gross dysfunction and may be asymmetrical. Impairment in fine motor skills is found in 40–60% and developmental coordination disorder, a milder motor disorder than CP, occurs in 18.3% of children who were born at less than 32 weeks of gestation.[16]
- Sensorineural impairment can also occur, with some evidence to suggest an inverse relationship between such impairment and both gestational age at birth and birthweight. An estimated 3% of infants born before 32 weeks of gestation have visual impairment,[17] with an incidence of 53% in those with known PVL.[18] Bilateral isolated hearing loss is reported at 2–3 years of age in 2.2% of children born before 28 weeks of gestation.[19] A study of 1384 children assessed at age 4–6 years and who had weighed less than 1250 g at birth found that those with PVL had the highest risk of visual impairment.[20]

- Epilepsy is more prevalent in babies born prematurely. This risk is increased with lower gestational age at birth, with an odds ratio (OR) of 4.98 for hospitalisation for epilepsy for those born between 23 and 31 weeks of gestation.[21]
- Cognitive impairment is most prevalent in children born prematurely. One study assessed developmental outcome at 2 years of age in children born earlier than 27 weeks of gestation and found that 40% had a developmental quotient (DQ) less than one standard deviation (SD), 6% had a DQ between 1 SD and 2 SD (mild delay), 35% had a DQ between 2 SD and 3 SD (moderate delay) and 19% had a DQ less than 3 SD (severe delay).[22]

[Heading1]Proposed mechanism of action of magnesium sulfate ($MgSO_4$) for neuroprotection

There remains a lack of understanding of how $MgSO_4$ may act as a neuroprotective agent. $MgSO_4$ freely crosses the placenta and takes part in many intracellular processes, resulting in effects including cerebral vasodilation, reduction in inflammatory cytokines and inhibition of calcium influx into cells.[23,24]

One widely cited theory for the possible neuroprotective effect of $MgSO_4$ is that, by blocking calcium processes and thus acting as a vasodilator, it may inhibit or delay ischaemic cell death during and after cerebral ischaemic events.[25] There is also evidence that $MgSO_4$ decreases the production of proinflammatory cytokines and free radicals during hypoxic-ischaemic reperfusion.[26,27] This theory is supported by several recent papers that demonstrate a suppression of cord blood cytokine production with $MgSO_4$ use.[28–30] In 2014, a randomised controlled trial in 72 women showed increased levels of brain-derived neurotrophic factor (BDNF) in cord blood of preterm babies (born before 34 weeks of gestation) where $MgSO_4$ (4 g loading dose and 1 g/h until delivery) had been given antenatally, compared with placebo.[31] BDNF is a neurotrophin shown to be protective against neonatal hypoxic-ischaemic brain injury in vivo.[32] In a recent study in which

$MgSO_4$ was given prior to preterm delivery at less than 32 weeks of gestation, there was an associated reduction in risk of developing echodensities and echolucencies associated with cystic PVL, as detected by cranial ultrasound performed in neonatal infants.[33]

[Heading1]Key studies on $MgSO_4$ use for neuroprotection in preterm deliveries

[Heading 2] Observational studies

The first observational study in 1988 by Leviton et al.[34] discovered that infants born preterm to women with pre-eclampsia toxaemia had a lower incidence of adverse central nervous system outcomes. Very low birthweight babies (weighing less than 1751 g) who had been exposed to $MgSO_4$ in utero were found to have fewer germinal matrix haemorrhages as a secondary benefit. Six years later, in a case–control study derived from the California Cerebral Palsy project, Nelson and Grether[35] reported an association between antenatal $MgSO_4$ administration and reduction of cerebral palsy in infants born weighing less than 1500 g.

[Heading 2]Randomised controlled trials

From 1997 to 2008, results from five randomised controlled trials (RCTs) were published that included data from 6145 babies.

In 1997, the MagNET trial, the first RCT, published interim safety data because an unexpectedly high number of adverse outcomes were found in fetuses exposed to $MgSO_4$.[36] This was a four-arm study of 149 women in preterm labour between 24 and 34 weeks of gestation. In the two unblinded tocolytic arms, women in preterm labour were randomised to receive $MgSO_4$ or an alternative tocolytic. In the other two double-blinded arms $MgSO_4$ was given to mothers in one group purely as a neuroprotective agent (and compared with normal saline). The study found ten intrauterine deaths in those receiving $MgSO_4$, compared with one death in those given saline, a significant difference. On further analysis, other causes of death such as congenital abnormality in one case and twin-to-twin transfusion in two cases were found in fetuses exposed to $MgSO_4$, leaving seven unexplained.

The Magpie trial, originally designed to assess maternal eclamptic outcomes in 33 countries,[37] reported a non-significantly lower risk of death or CP in children whose mothers had received $MgSO_4$ at 18 months of age (RR 0.83, 95% CI 0.66–1.03) as a secondary measure.[38] The main criticism of this study was the inconsistency of the paediatric follow-up.

Three large RCTs specific for neuroprotection in the preterm infant followed the Magpie trial (see Table 1 for comparison of the trials) between 2003 and 2008. No major maternal adverse effects were observed in the $MgSO_4$ group in any of these studies.

In ACTO$MgSO_4$, Crowther et al.[39] recruited 1062 women from Australia and New Zealand. The study reported a non-significant reduction in CP and death; however, a significant reduction in gross motor dysfunction was noted.

BEAM, a study involving 2241 women in the USA and using a different prescribing regimen (6 g loading dose and then 2 g/h for up to a further 12 h), found a significant difference in outcome between placebo and $MgSO_4$ for the occurrence of severe CP only.[40]

PREMAG**,** a French study of 688 infants whose mothers had been given a bolus 4 g dose of $MgSO_4$ perinatally, reported on data from 2006[41] with further 2-year follow-up data published in 2008.[42] Initially, the primary outcome of neonatal mortality before discharge was assessed and it was reported that total mortality, severe white matter injury, and the combination of these outcomes, were less frequent in babies exposed to $MgSO_4$, but these differences were not statistically significant. The complete 2-year follow-up data published in 2008 did not show a significant difference in rates of CP, gross motor dysfunction or combined death and CP between the control and treatment groups. However, a significant reduction was noted in the combined outcomes of death and gross motor dysfunction, as well as the composite outcomes of death, CP and cognitive dysfunction.

[Heading 2]Meta-analyses and Cochrane review

Meta-analyses of the RCTs are summarised in Table 2. These meta-analyses differed slightly in their methodology and inclusion criteria (gestation of inclusion and degree of CP) but primarily showed that, by combining the

numbers in the three RCTs and the Magpie and MagNET studies, a statistically significant difference could be demonstrated for reduction in CP when $MgSO_4$ had been administered. Doyle et al.[43] found a reduction in CP and motor dysfunction. No reduction was noted in the risk of intraventricular haemorrhage causing CP. This was also published as a Cochrane review,[44] which stated that there were insufficient data to recommend the optimal loading and maintenance doses of $MgSO_4$ for the best neuroprotective effect.

Costantine et al.[45] assessed the benefit of administering at different gestational ages, and found the benefit to be greater before 30 weeks, with an NNT of 46, versus an NNT of 56 between 32 and 34 weeks of gestation. Conde-Agudelo demonstrated similar results, with a reduction in CP and gross motor dysfunction in the infant when $MgSO_4$ had been administered.[46]

[Heading 2]International guidelines/scientific impact papers

The advice given in guidelines in various countries is summarised Table 3. In the UK, the RCOG[47] published a scientific paper in 2011 recommending a gestational age cut-off of less than 30 weeks for administering $MgSO_4$ for neuroprotection, which is similar to the Australian guidelines.[48] NICE recommends offering $MgSO_4$ to women at risk of giving birth before 30 weeks of gestation in their preterm labour and birth guidelines published in 2015.[49]

[Heading 2]Inconsistencies in recommendations for $MgSO_4$ treatment and dosage

$MgSO_4$ is currently recommended worldwide for women at risk of preterm birth before 30 to 32 weeks of gestation for neuroprotection of their infants, based on high quality evidence of benefit. Local trust guidelines on exact cut-off are currently being used. However, there remains uncertainty as to whether these benefits also apply at higher gestational ages. The MAGENTA trial[50] will assess the benefit of giving $MgSO_4$ between 30 and 34 weeks of gestation in a randomised controlled trial ($MgSO_4$ versus placebo), with a primary outcome examining the rate of death and CP at 2 years of age. Once reported, this will enable further evidence-based recommendations for the use of $MgSO_4$ in preterm deliveries occurring between 30 and 34 weeks.

[Heading 2]Long-term data

Recently the long-term school age data became available from two of the original RCT cohorts; ACTOMgSO_4 and PREMAG. The long-term data from PREMAG were published in 2014, reporting on 431 children with a mean age at follow-up of 11 years: no detrimental effects of prenatal $MgSO_4$ were reported. There was a trend for better long-term neurological and behavioural outcomes but these were not statistically significant.[51,52] Doyle et al.[53] followed up 867 children from the original ACTOMgSO_4 study, with a mean age of 8 years.[39] The paediatric mortality rate to school age was 14.0% in the $MgSO_4$ group, compared with 17.6% in the placebo group; this was not significantly different. The two groups were not different in the proportions with CP, nor its severity (8% vs 7%; OR 1.26, 95% confidence interval [CI], 0.84–1.91). No long-term difference in benefit or harm was found for the perinatal use of $MgSO_4$. The numbers in these two studies individually might be underpowered for CP, as was the case in the original RCTs. It wasn't until the original RCT data were pooled in meta-analyses that the size of the true effect became apparent.

[Heading 1]Concerns for fetal safety with perinatal $MgSO_4$ administration

Concerns were originally raised in 1997 in the MagNET trial following an interim safety report that described an increased rate of paediatric mortality in association with $MgSO_4$ use.[36] Composite findings of the MagNET trial published in 2002[54] suggested that greater antenatal use of $MgSO_4$ and higher umbilical cord $MgSO_4$ levels were associated with worse perinatal outcome.

Subsequent meta-analyses found no increase in the risk of adverse neonatal outcome or mortality[46] (Table 4).

[Heading 1]Limiting side effects in women receiving $MgSO_4$

$MgSO_4$ is widely regarded as a safe drug in pregnancy and is commonly used in obstetrics for the prevention and treatment of eclampsia. However, because of its narrow therapeutic range, caution is necessary when deciding on the

dose of administration. Conde-Agedulo's meta-analysis[46] published in 2009 did not show any evidence of an effect of $MgSO_4$ on serious maternal complications such as death (RR 0.32, 95% CI 0.01–7.92) or severe postpartum haemorrhage (RR 1.06, 95% CI 0.63–1.79). Women were more likely to experience minor side effects with $MgSO_4$, including flushing (RR 7.56, 95% CI 3.39–16.88) and nausea or vomiting (RR 4.60, 95% CI 1.54–13.75).

Serious, but rarer, side effects (usually associated with an overdose) include respiratory depression, pulmonary oedema and cardiac arrest. Women receiving $MgSO_4$ should therefore be closely monitored, with regular recordings of blood pressure and other maternal observations. Calcium gluconate should be available to give as an antidote if $MgSO_4$ toxicity is suspected. There is a risk of maternal hypotension, especially if $MgSO_4$ is used concurrently with nifidepine as a tocolytic drug.[55] There has also been a suggested risk of neuromuscular blockade with concomitant use of $MgSO_4$[55] and calcium channel blockers; however, a review did not support an increased risk.[56] A slower rate of administering the loading dose of $MgSO_4$ (over 60 minutes versus 20 minutes) significantly reduced the feeling of flushing and warmth at 20 minutes into the infusion. However, 71% of women experienced mild adverse effects (arm discomfort, flushing, warmth) from the infusion and administering a slower loading dose made no statistical difference to this incidence overall.[57]

[Heading 2]Optimal loading and maintenance dose

Most trials have used the existing pre-eclampsia regimen for $MgSO_4$ use; this is usually a 4 g bolus over 30 minutes given to women in whom delivery is felt to be imminent. After this and if delivery has not yet occurred, a 1 g/hour maintenance infusion is administered until birth, or up to a maximum of 24 hours. A single bolus of 4 g intravenously has been shown to improve outcome[43,58] and we recommend that it should be given even if delivery is imminent. In planned preterm deliveries, $MgSO_4$ should ideally be administered within 4 hours before the birth. The infusion should be discontinued once the baby is delivered. Where delivery is urgently mandated, it is important not to delay delivery in order to administer $MgSO_4$. In women

with renal impairment, the dose of $MgSO_4$ should be adjusted appropriately to avoid an overdose, with close monitoring of serum $MgSO_4$ levels.[38]

[Heading 1]Conclusion

$MgSO_4$ probably has a modest neuroprotective effect which is greater the earlier the gestational age of the infant at delivery. When administered at an appropriate dose and with proper monitoring, there is no evidence of harm to the fetus, neonate or mother. The optimum timing, dose and duration of its administration remains undefined by large studies; however, most guidelines recommend its use for 24 hours and within 4 hours of delivery using the standard pre-eclampsia toxaemia regimen. A study is underway in Australia to assess gestation-specific benefit between 30 and 34 weeks of gestation.

[heading 2] Disclosure of interests

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[Heading 2] Contribution to authorship

SU instigated, researched and edited the article. LF and JT contributed to the article; PRB and CL reviewed and edited the article. All authors approved the final version.

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Figure 1. Pathogenesis of periventricular leucomalacia.