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Magnesium Sulphate for Fetal Neuroprotection

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Key Words: Magnesium sulphate, preterm birth, cerebral palsy, death, neuroprotection

Abstract

Objective: To provide guidelines for the use of antenatal magnesium sulphate ($MgSO_4$) for fetal neuroprotection of the preterm infant.

Options: Antenatal $MgSO_4$ administration should be considered for fetal neuroprotection when women present at ≤ 31+6 weeks with imminent preterm birth, defined as a high likelihood of birth because of active labour with cervical dilatation ≥ 4 cm, with or without preterm pre-labour rupture of membranes, and/or planned preterm birth for fetal or maternal indications.

There are no other known fetal neuroprotective agents.

Outcomes: The outcomes measured are the incidence of cerebral palsy (CP) and neonatal death.

Evidence: Published literature was retrieved through searches of PubMed or Medline, CINAHL, and the Cochrane Library in May 2010, using appropriate controlled vocabulary and key words (magnesium sulphate, cerebral palsy, preterm birth). Results were restricted to systematic reviews, randomized controlled

trials, and relevant observational studies. There were no date or language restrictions. Searches were updated on a regular basis and incorporated in the guideline to August 2010. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Benefits, harms, and costs: Antenatal magnesium sulphate for fetal neuroprotection reduces the risk of "death or CP" (RR 0.85; 95% CI 0.74 to 0.98; 4 trials, 4446 infants), "death or moderate-severe CP" (RR 0.85; 95% CI 0.73 to 0.99; 3 trials, 4250 infants), "any CP" (RR 0.71; 95% CI 0.55 to 0.91; 4, trials, 4446 infants), "moderate-to-severe CP" (RR 0.60; 95% CI 0.43 to 0.84; 3 trials, 4250 infants), and "substantial gross motor dysfunction" (inability to walk without assistance) (RR 0.60; 95% CI 0.43 to 0.83; 3 trials, 4287 women) at 2 years of age. Results were consistent between trials and across the meta-analyses. There is no anticipated significant increase in health care-related costs, because women eligible to receive antenatal $MgSO_4$ will be judged to have imminent preterm birth.

Validation: Australian National Clinical Practice Guidelines were published in March 2010 by the Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel. Antenatal $MgSO_4$ was recommended for fetal neuroprotection in the same dosage as recommended in these guidelines. However, $MgSO_4$ was recommended only at < 30 weeks' gestation, based on 2 considerations. First, no one gestational age subgroup was considered to show a clear benefit. Second, in the face of uncertainty, the committee felt it was prudent to limit the impact of their clinical practice guidelines on resource allocation. Also in March 2010, the American College of Obstetricians and Gynecologists issued a Committee Opinion on $MgSO_4$ for fetal neuroprotection. It stated that, "the available evidence suggests that magnesium sulphate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants." No official opinion was given on a gestational age cut-off, but it was recommended that physicians develop specific guidelines around the issues of inclusion criteria, dosage, concurrent tocolysis, and monitoring in accordance with one of the larger trials.

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Summary Statement

1. "Imminent preterm birth" is defined as a high likelihood of birth due to one or both of the following conditions (II-2):
   - Active labour with ≥ 4 cm of cervical dilation, with or without PPROM.
   - Planned preterm birth for fetal or maternal indications.

Recommendations

1. For women with imminent preterm birth (≤ 31+6 weeks), antenatal magnesium sulphate administration should be considered for fetal neuroprotection. (I-A)
2. Although there is controversy about upper gestational age, antenatal magnesium sulphate for fetal neuroprotection should be considered from viability to ≤ 31+6 weeks. (II-1B)
3. If antenatal magnesium sulphate has been started for fetal neuroprotection, tocolysis should be discontinued. (III-A)
4. Magnesium sulphate should be discontinued if delivery is no longer imminent or a maximum of 24 hours of therapy has been administered. (II-2B)
5. For women with imminent preterm birth, antenatal magnesium sulphate for fetal neuroprotection should be administered as a 4g IV loading dose, over 30 minutes, followed by a 1g/hr maintenance infusion until birth. (II-2B)
6. For planned preterm birth for fetal or maternal indications, magnesium sulphate should be started, ideally within 4 hours before birth, as a 4g IV loading dose, over 30 minutes, followed by a 1g/hr maintenance infusion until birth. (II-2B)
7. There is insufficient evidence that a repeat course of antenatal magnesium sulphate for fetal neuroprotection should be administered. (III-L)
8. Delivery should not be delayed in order to administer antenatal magnesium sulphate for fetal neuroprotection if there are maternal and/or fetal indications for emergency delivery. (III-E)
9. When magnesium sulphate is given for fetal neuroprotection, maternity care providers should use existing protocols to monitor women who are receiving magnesium sulphate for preeclampsia/eclampsia. (III-A)
10. Indications for fetal heart rate monitoring in women receiving antenatal magnesium sulphate for neuroprotection should follow the fetal surveillance recommendations of the SOGC 2007 Fetal Health Surveillance: Antepartum and Intrapartum Consensus Guideline. (III-A)
11. Since magnesium sulphate has the potential to alter the neonate's neurological evaluation, causing hypotonia or apnea, health care providers caring for the neonate should have an increased awareness of this effect. (III-C)

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ABBREVIATIONS

APH	antepartum hemorrhage
CP	cerebral palsy
IQR	interquartile range
IUGR	intrauterine growth restriction
NNT	number needed to treat
PPROM	preterm pre-labour rupture of membranes
PTL	preterm labour

BACKGROUND

The Importance of Preterm Birth

The Canadian preterm birth rate overall reached 8.2% of live births in 2004, with births at < 32 weeks representing 1.2% of live births in Canada.[1] The survival of infants born preterm has improved with interventions such as antenatal corticosteroids and surfactant. However, survival has been associated with substantial risk of medical and neurodevelopmental impairment.

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well–designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

* The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[47]

† Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[47]

Two identified patterns of injury appear to underlie the central nervous system complications of preterm infants: (1) intraventricular hemorrhage and (2) white matter injury. Severe intraventricular hemorrhage (grades 3 and 4) is reliably detected by ultrasound and occurs primarily among babies who are born at or before 28 weeks' gestation. Although the incidence of severe intraventricular hemorrhage is highest at 24 to 25 weeks, severe intraventricular hemorrhage is still a relevant problem up to 28 weeks, because there are more births at 26 to 28 weeks than at 24 to 25 weeks. MRI is required for reliable detection of white matter injury, which has a peak prevalence at 28 weeks. Its severity is associated with adverse motor and cognitive outcomes.[2]

Clinically, the most frequent adverse neurological outcomes associated with preterm birth are cerebral palsy and cognitive impairment. Other adverse outcomes include blindness, deafness, developmental delay, and/or other neurological impairment. More than 50% of very preterm babies suffer from learning or motor disabilities or school difficulties, compared with about 20% of normal birthweight controls.[3]

The Importance of Cerebral Palsy

Cerebral palsy is a symptom complex of non-progressive motor impairment syndromes secondary to brain injury or anomalies arising in early development.[4] The typical signs of CP include spasticity, movement disorders, muscle weakness, ataxia, and rigidity. There are 4 main types of cerebral palsy:

1. Spastic (increased muscle tone)
2. Athetoid or dyskinetic (slow, uncontrolled movements)
3. Ataxic (problems with balance and depth perception)
4. Mixed

The most common pattern is spasticity plus athetoid movements.[5] CP can be reliably diagnosed by the age of 2 years.

The prevalence of CP is 2 to 2.5 per 1000 live births.[6] The risk of CP is highest at earlier gestational ages. Compared with infants born at term, infants born preterm have a CP risk that is approximately 3-fold higher at 34 to 36 weeks,[7] 8-fold[7] to 14-fold[8] higher at 30 to 33 weeks, 46-fold higher at 28 to 30 weeks,[8] and as high as 30-fold[4] to 80-fold[8] higher at < 28 weeks.[9] The gestational age-related risk is associated, in part, with very low birth weight (i.e., < 1500 g) and intraventricular hemorrhage.[10–12] Multiples are also at heightened CP risk.[13]

Temporal trends in the prevalence of CP among infants born very preterm are a matter of controversy. Rates have been reported to be both falling[14,15] and rising,[10,16] possibly because perinatal mortality rates are decreasing, so that the rate of "death or CP" among infants born at < 30 weeks has appeared to be stable.[6]

What is agreed upon, however, is that the economic burden associated with CP is enormous. The US Centers for Disease Control and Prevention estimate that lifetime health care, productivity, and social costs for a person with CP are US$921 000 (2003).[17]

There is no known cure for CP, which makes effective preventive measures of primary importance. To date, no

Table 2. Inclusion criteria in the randomized controlled trials of magnesium sulphate for fetal neuroprotection

Study	Women, n	Multiple pregnancy, %	Inclusion criteria*							
			Gestational age, weeks	Delivery likely within 24 hours	PTL, %	PPROM	Chorioamnionitis	Pre-eclampsia	Severe IUGR	APH
Neuroprotective intent										
ACTOMgSO$_4$ Crowther et al. 2003[35]	1062	17	< 30	Yes	63	9%	14%	15%	9%	14%
PREMAG Marrett et al. 2006[36]	564	22	< 33	Yes	85	61%	11%	Excluded	Excluded	19%
MAGnet Mittendorf et al. 2002—neuroprotective intent arm[37]	57	4	25 to 33+6	NA	100†	If associated with PTL	Excluded	Excluded	NA	NA
BEAM Rouse et al. 2008[38]	2241	9	24 to 31+6	NA	10	87%	NA	Excluded	Included by % NA	NA
Other primary intent										
MAGnet Mittendorf et al. 2002, tocolytic arm[37]	92	15	25to 33+6	NA	100	If associated with PTL	Yes‡	Excluded	NA	Yes‡
MAGPIE 2006[41]	10 141	4	< 37 (but subgroup analyses were possible for lower gestational age categories)	NA	NA	NA	NA	100%	NA	NA

LD: loading dose; NA: not available

* indications for at least 90% of study population listed.

† With cervical dilatation > 4 cm and therefore not eligible for tocolysis.

‡ 71.1% had PPROM and 50.8% had chorioamnionitis, but the results were not presented according to whether women were in the tocolytic or neuroprotective intent arms.

antenatal interventions have been identified that effectively decrease CP risk among preterm infants.

Magnesium Sulphate for Neuroprotection

In two studies published in the 1980s, preterm infants born to women with preeclampsia had a lower incidence of adverse CNS outcomes than gestational age-matched neonates born to mothers without preeclampsia.[18,19] In 1995, a seminal case–control study[20] was conducted with data derived from the California Cerebral Palsy project.[21] It demonstrated an association between antenatal magnesium sulphate administration prior to preterm birth and fewer cases of CP among infants born < 1500 g.[20] It has been proposed that use of magnesium sulphate for eclampsia treatment and prophylaxis may underlie the potential association between antenatal administration of magnesium sulphate and CP,[20,22] but the findings of subsequent observational studies investigating the association have been inconsistent.[23–25] Although the effectiveness of magnesium sulphate for prevention and treatment of maternal eclampsia is well proven, there remains a lack of understanding of how it may act as a neuroprotective agent.[26,27] Magnesium acts in many intracellular processes, and its actions include cerebral vasodilation, reduction in inflammatory cytokines and/or oxygen free radicals, and/or inhibition of calcium influx into cells.[28,29] Animal studies have shown a neuroprotective effect.[30,31]

From 2002 to 2008, 5 randomized controlled trials (6145 babies) studied magnesium sulphate for fetal neuroprotection (Table 2). In 2009, a milestone was reached with the publication of 3 meta-analyses, all of which concluded that magnesium sulphate for fetal neuroprotection decreases the risk of childhood CP.[32–34] Four trials used magnesium sulphate specifically for fetal neuroprotection among women likely to deliver within 24 hours.[35–38] The fifth trial[26] evaluated the effectiveness of magnesium sulphate for eclampsia prevention in women with preeclampsia. Of the 4 trials with neuroprotective intent, one also included a tocolytic arm.[37] Three of these 4 trials enrolled primarily women with preterm labour (with or without PPROM),[35–37] whereas the fourth focused on women with PPROM.[38] Children were followed-up to the age of 2 years for CP assessment, and 3 trials undertook cognitive testing.[26,35,38]

Study quality was good.[32] Importantly, 4 of the 5 trials (and all neuroprotective intent trials) described an adequate

Table 3a. Magnesium sulphate versus placebo: perinatal outcomes in neuroprotection trials only

	RR (95%CI)			Trials, n, Infants, n		
	Doyle et al.[34]	Costantine and Weiner[33]	Conde-Agudelo and Romero[32]	Doyle et al.[34]	Costantine and Weiner[33]	Conde-Agudelo and Romero[32]
			Primary outcomes			
Death or CP	0.85 (0.74 to 0.98)	0.86 (0.75 to 0.99)	Not presented	4 trials, 4446 infants	4 trials, 4314 infants	Not presented
Death or moderate-severe CP		0.85 (0.73 to 0.99)	Not presented	Not presented	3 trials, 4250 infants	Not presented
Death or substantial gross motor dysfunction	0.84 (0.71 to 1.00)	Not presented	Not presented	3 trials, 4387 infants	Not presented	Not presented
Death	0.95 (0.80 to 1.12)	0.95 (0.80 to 1.13)	0.95 (0.80 to 1.12)	4 trials, 4446 infants	4 trials, 4324 infants	4 trials, 4446 infants
CP	0.71 (0.55 to 0.91)	0.71 (0.55 to 0.91)	0.71 (0.55 to 0.91)	4 trials, 4446 infants	4 trials, 4314 infants	4 trials, 4446 infants
Moderate-severe CP	Not presented	0.60 (0.43 to 0.84)	Not presented	Not presented	3 trials, 4250 infants	Not presented
Substantial gross motor dysfunction	0.60 (0.43 to 0.83)	Not presented	Not presented	3 trials; 4387 infants	Not presented	Not presented
Any neurological impairment	1.03 (0.87 to 1.21)	Not presented	Not presented	1 trial, 1255 infants	Not presented	Not presented
			Other neonatal CNS outcomes			
IVH	0.96 (0.86 to 1.07)	Not presented	Not presented	4 trials to 4446 infants	Not presented	Not presented
Severe IVH (grade 3 or 4)	0.83 (0.62 to 1.13)	Not presented	Not presented	2 trials; 3699 infants	Not presented	Not presented
PVL	0.93 (0.68 to 1.28)	Not presented	Not presented	4 trials to 4446 infants	Not presented	Not presented
			Other infant/child neurodevelopmental outcomes			
Developmental delay or intellectual impairment	1.00 (0.91 to 1.09)	Not presented	Not presented	3 trials, 4387 infants	Not presented	Not presented
Major neurological disability	1.14 (0.86 to 1.51)	Not presented	1.09 (0.83 to 1.43)	1 trial, 1255 infants	Not presented	2 trials, 2060 infants
Blindness	0.97 (0.14 to 6.90)	Not presented	0.97 (0.14 to 6.90)	2 trials, 1943 infants	Not presented	2 trials, 1943 infants
Deafness	0.51 (0.05 to 4.96)	Not presented	0.51 (0.05 to 4.96)	2 trials, 1943 infants	Not presented	2 trials, 1943 infants

CNS: central nervous system; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia.

method of allocation concealment.[26,35,36,38] All but the tocolytic arm of Mittendorf et al.[37] described double-masking of outcome assessment.

Magnesium Sulphate Use in Obstetrics

Magnesium sulphate is widely available and commonly used in Canadian obstetric practice for eclampsia prophylaxis and treatment.[26,27,39] Magnesium sulphate is no longer recommended for tocolysis, because it is ineffective.[34]

This document summarizes the relevant evidence and provides practice recommendations related to the use of antenatal magnesium sulphate for fetal neuroprotection among women with imminent preterm birth.

Summary Statement

1. "Imminent preterm birth" is defined as a high likelihood of birth due to one or both of the following conditions (II-2):
   - Active labour with ≥ 4 cm of cervical dilation, with or without PPROM.
   - Planned preterm birth for fetal or maternal indications.

Recommendation

1. For women with imminent preterm birth (≤ 31+6 weeks), antenatal magnesium sulphate administration should be considered for fetal neuroprotection. (I-A)

Table 3a presents the results of the 3 relevant meta-analyses of neuroprotective trials,[32–34] and shows that antenatal magnesi um sulphate reduced the risk of "death or CP," "death or moderate-severe CP," "any CP,"

Table 3b. Magnesium sulphate versus placebo: perinatal outcomes in all trials of antenatal magnesium sulphate

	Doyle et al.[34]		Costantine and Weiner[33]		Conde-Agudelo and Romero[32]	
	RR (95% CI)	Trials, n Infants, n	RR (95% CI)	Trials, n Infants n	RR (95% CI)	Trials, n Infants n
Primary outcomes						
Death or CP	0.94 (0.78 to 1.12)	5 trials, 6145 infants	0.92 (0.83 to 1.03)	5 trials, 5225 infants	0.92 (0.83 to 1.02)	5 trials, 5357 infants
Death or moderate-severe CP	Not presented	Not presented	0.85 (0.73 to 0.99)	3 trials, 4250 infants	Not presented	Not presented
Death or substantial gross motor dysfunction	0.92 (0.75 to 1.12)	4 trials, 5980 infants	Not presented	Not presented	Not presented	Not presented
Death	1.01 (0.82 to 1.23)	5 trials, 6145 infants	0.95 (0.80 to 1.13)	4 trials, 4324 infants	1.01 (0.89 to 1.14)	5 trials, 5357 infants
CP	0.69 (0.54 to 0.87)	5 trials, 6145 infants	0.71 (0.55 to 0.91)	4 trials, 4314 infants	0.69 (0.55 to 0.88)	5 trials, 5357 infants
Moderate-severe CP	Not presented	Not presented	0.60 (0.43 to 0.84)	3 trials, 4250 infants	0.64 (0.44 to 0.92)	3 trials, 4387 infants
Substantial gross motor dysfunction	0.60 (0.43 to 0.83)	4 trials, 4387 infants	Not presented	Not presented	0.60 (0.43 to 0.83)	3 trials, 4387 infants
Any neurological impairment	1.01 (0.86 to 1.19)	2 trials, 2848 infants	Not presented	Not presented	1.02 (0.86 to 1.20)	2 trials, 2060 infants
Other neonatal CNS outcomes						
IVH	0.96 (0.86 to 1.08)	4 trials, 4552 infants	Not presented	Not presented	0.96 (0.86 to 1.08))	5 trials, 4552 infants
Severe IVH (grade 3/4)	0.83 (0.62 to 1.13)	2 trials, 3699 infants	Not presented	Not presented	0.83 (0.61 to 1.11)	4 trials, 3864 infants
PVL	0.93 (0.68 to 1.28)	4 trials, 4552 infants	Not presented	Not presented	0.93 (0.68 to 1.28)	5 trials, 4552 infants
Other infant/child neurodevelopmental outcomes						
Developmental delay or intellectual impairment	0.99 (0.91 to 1.09)	4 trials, 5980 infants	Not presented	Not presented	Not presented	Not presented
Major neurological disability	1.07 (0.82 to 1.40)	2 trials, 2848 infants	Not presented	Not presented	1.09 (0.83 to 1.43)	2 trials, 2060 infants
Blindness	0.74 (0.17 to 3.30)	3 trials, 3536 infants	Not presented	Not presented	0.97 (0.14 to 6.90)	2 trials, 1943 infants
Deafness	0.79 (0.24 to 2.56)	3 trials, 3536 infants	Not presented	Not presented	0.51 (0.05 to 4.96)	2 trials, 1943 infants

CNS: central nervous system; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia.

"moderate-severe CP," and "substantial gross motor dysfunction" (inability to walk without assistance) at 2 years of age. The direction of effect was the same for death or substantial gross motor dysfunction, but this did not reach statistical significance. Results were consistent between trials and across the meta-analyses. Use of magnesium sulphate was not associated with an increase in pediatric death. The tocolytic arm of one study[37] was stopped early because of an increase in pediatric mortality; although this is consistent with the effects of magnesium sulphate administered as a tocolytic in other studies,[34] there were other quality issues with the Mittendorf et al. tocolytic arm. These included the confounding effect of multiple births (i.e., more in the magnesium sulphate arm), the low quality score (Jahad score of 2/8 when the other neuroprotective intent trials scored 7–8/8), the lack of a placebo arm, that crossover was allowed, and that 3 of the 8 neonatal deaths in the magnesium sulphate arm were related to congenital anomalies (n = 1) or twin-to-twin transfusion (n = 2).

When the tocolytic arm of the MAGnet Trial[40] and results of the preeclampsia prophylaxis trial (MAGPIE)[41] were included in the meta-analyses, antenatal magnesium sulphate was shown to reduce the risk of death or moderate-severe CP, any CP, moderate-severe CP, and substantial gross motor dysfunction; the outcome of death or CP no longer reached statistical significance (Table 3b). Although such analyses support the use of magnesium sulphate to decrease CP, the results of the neuroprotective intent trials suggest a change in clinical practice.

For antenatal magnesium sulphate given specifically for fetal neuroprotection, the NNT to prevent one case of death or CP is 43 (based on an event rate of 14.9% overall in the magnesium arm of trials and 17.2% among placebo-treated controls). The NNT to prevent one case of CP is 63 (based on an event rate of 3.4% overall in the magnesium arm of the trials and 5.0% among placebo-treated controls). These compare favourably with other established obstetric interventions, such as the NNT of 50 (95% CI 34 to 100) for use of magnesium sulphate to prevent eclampsia among women with severe preeclampsia.[26]

While the 3 meta-analyses demonstrate significant results for antenatal magnesium sulphate reducing the risk of death or CP, death or moderate-severe CP, any CP, moderate-severe CP, and substantial gross motor dysfunction at 2 years of age, it is important to note that no single trial demonstrated a statistically significant decrease in the combined outcome of death or CP.

Despite these favourable results, strong evidence is lacking with respect to 4 clinical issues:

1. The gestational age below which this therapy should be offered.
2. The optimal loading and maintenance doses.
3. Antenatal magnesium sulphate has not been associated with a decrease in central nervous system pathology associated with CP, cognitive impairment (i.e., intraventricular hemorrhage or white matter injury measured as cystic periventricular leukomalacia), and other adverse developmental outcomes associated with preterm birth (e.g., developmental delay, neurological impairment, blindness, or deafness). However, confidence intervals in these trials[35–38] were reasonably wide and compatible with any of the following: a protective effect (38% reduction), harmful effect (13% increase), or no effect at all. Further evidence is needed to determine whether there is an association between magnesium sulphate and decreased CNS pathology.
4. There is no information on the effect of magnesium sulphate on learning disabilities, school difficulties, or other common school-age disabilities, because none of the trials reported on outcomes beyond 2 years of age; follow-up to school-age is planned for 2 of the trials.[35,36] Neurological follow-up was conducted to the age of 2 years in 3 trials, 2 of which undertook detailed neurocognitive testing.[35,38] However, learning disabilities and developmental coordination disorder, which are prevalent among extremely low birth weight babies born preterm, cannot be reliably detected until school age.

Recommendations

2. Although there is controversy about upper gestational age, antenatal magnesium sulphate for fetal neuroprotection should be considered from viability to ≤ 31+6 weeks. (II-1B)
3. If antenatal magnesium sulphate has been started for fetal neuroprotection, tocolysis should be discontinued. (III-A)

There is some uncertainty about the gestational age at which magnesium sulphate should be administered. A lower gestational age limit for viability has not been specified in these studies[35,37] so that clinical decisions can take into consideration both parental preference and institutionally defined thresholds. Each of the trials in the meta-analyses[32–34] had a different upper gestational age limit for study eligibility, ranging from < 30 weeks[35] to ≤ 33+6,[37] making it challenging to recommend an upper age limit.

It is uncertain whether the neuroprotective effect of magnesium sulphate depends on gestational age at birth. Table 4a presents the results of trials with neuroprotective intent. The outcome of death or CP was significantly decreased by magnesium sulphate when therapy was administered at < 34 weeks. The outcome of CP was significantly decreased at all gestational ages. Results for all trials are shown in Table 4b; the < 30 week and < 28 week analyses include post hoc analyses of the MAGPIE and BEAM trials, as randomization was not stratified by these gestational age groupings. No effect of magnesium sulphate was seen on the outcome of death or CP, but CP was significantly decreased at all gestational ages.

There are 2 key considerations when determining a gestational cut-off: (1) the potential for effect modification by gestational age (i.e., the potential for magnesium sulphate to have a different effect at different gestational ages), and (2) the baseline prevalence of CP at different gestational ages (since the NNT will be lower with a higher baseline prevalence of a disease). Table 4a (neuroprotective intent trials) and Table 4b (all relevant trials) both show that the point estimate for the effect of magnesium sulphate on CP risk reduction appears to be lower at < 28 weeks. Since the prevalence of CP is also higher at < 28 weeks, the NNT to prevent one case of CP is lowest at < 28 weeks. The NNT appears to fall for administration of magnesium at earlier gestational ages, with a more obvious trend among all trials rather than among only neuroprotective trials. Regardless, the NNT to prevent one case of CP is low at all gestational ages at < 34 weeks.

Table 4a. Subgroup analyses by gestational age at randomization: neuroprotective trials only[35–38]

	RR (95% CI)		NNT to prevent harm		
Weeks	Death or CP	CP	Death or CP	CP	Trials, n, infants, n
< 34	0.85 (0.74 to 0.98)	0.71 (0.55 to 0.91)	43	53	5 trials, 6145 infants
< 32	0.86 (0.74 to 1.00)	0.68 (0.52 to 0.91)	43	50	3 trials, 3981 infants
< 30*	0.87 (0.74 to 1.03)	0.69 (0.48 to 0.99)	36	53†	3 trials, 2475 infants
< 28*	0.95 (0.74 to 1.22)	0.45 (0.23 to 0.87)	91	30	1 trial, 938 infants

* Includes the < 28 week subgroup of Rouse et al.[38] which had women as the denominator.

† Inclusion of only the Crowther et al.[35] trial and exclusion of the BEAM data (Rouse et al.[38]) give an NNT of 24.

Table 4b. Subgroup analyses by gestational age at randomization: all trials[26,35-38,41]

	RR (95% CI)		NNT to prevent harm		
Weeks	Death or CP	CP	Death or CP	CP	Trials, n, infants, n
< 34	0.94 (0.78 to 1.12)	0.68 (0.54 to 0.87)	105	63	5 trials, 6145 infants
< 32	0.95 (0.76 to 1.18)	0.69 (0.52 to 0.91)	71	56	3 trials, 3981 infants
< 30*	0.97 (0.78 to 1.21)	0.70 (0.49 to 0.99)	71	56†	3 trials, 2475 infants
< 28*	0.95 (0.74 to 1.22)	0.45 (0.23 to 0.87)	91	30	1 trial, 938 infants

* Includes the < 28 week subgroup of Rouse et al.,[38] which had women as the denominator.

This also includes the < 30 week subgroup data provided by the MAGPIE trial.

† In the Cochrane review,[34] the < 30 week subgroup did not include the BEAM trial data for < 28 week[38] and the NNT was 50.

A more useful post hoc analysis would be to examine CP risk reduction within gestational age strata (32 to 33 weeks, 30 to 31 weeks, 28 to 29 weeks, and < 28 weeks) to identify the gestational age at which babies may be most likely to benefit. In the BEAM trial,[38] analyses were stratified by gestational age (< 28 vs. 28 to 31 weeks). Although it appeared as if the decrease in CP was confined to the < 28-week subgroup, the test for interaction by gestational age was actually not significant. This should be interpreted as revealing no difference in magnesium effect on CP rate by gestational age up to 31+6 weeks. In MAGPIE,[41] which was not a neuroprotective intent trial and which underreported CP, CP risk was similar at < 30 weeks (RR 1.04; 95% CI 0.06 to 16.06) and at 30 to 33 weeks (RR 0.95; 95% CI 0.71 to 1.27).

In summary, CP risk is highest at earlier gestational ages, but these very preterm infants are fewer in number. Use of magnesium sulphate at gestational ages closer to 34 weeks has the potential to substantially increase overuse of magnesium sulphate for women with threatened preterm birth who do not deliver in the subsequent 24 to 48 hours. Therefore, consensus was reached to recommend an upper gestational age cut-off of < 32 weeks (i.e., ≤ 31+6 weeks) to strike a balance between appropriate use of magnesium sulphate at earlier gestational ages and potential overuse of magnesium sulphate at later gestational ages, when neurological morbidity is lower. Institutions may choose different thresholds (< 34 weeks) according to other considerations, including the accuracy of gestational age determination and resource allocation.

Table 2 presents the baseline characteristics of women who were enrolled in the relevant randomized controlled trials. In 3 of the 4 neuroprotective intent trials, most women had preterm labour with anticipated delivery within 24 hours. This is not equivalent to threatened preterm labour for which tocolysis is an option in the hope/expectation of being able to arrest labour; this must be emphasized to prevent potential overuse of magnesium sulphate for neuroprotection in patients who are not truly in labour. The other major indications for very preterm delivery (APH or IUGR) were present in a minority of women enrolled in the relevant trials. Although many women also had PPROM, only the BEAM trial[38] enrolled women with PPROM without associated preterm labour. In this guideline, these women are not included as eligible for magnesium sulphate for neuroprotection. First, in the BEAM trial, re-treatment with magnesium was administered for 59.1% of women. Second, women with PPROM who are not in labour are not necessarily in a delivery suite and receiving one-to-one nursing care; administration of magnesium for neuroprotective intent could have significant hospital resource implications for these women.

All trials excluded women with the usual contraindications to magnesium sulphate (i.e., hypersensitivity to the drug, hepatic

Table 5. Inclusion and exclusion criteria for antenatal magnesium sulphate administration in randomized controlled trials

Inclusion criteria	Exclusion criteria
Singleton and multiple pregnancies	Magnesium sulphate already administered for preeclampsia/ eclampsia
Nulliparous and parous	< 12 hours since discontinuation of previous magnesium sulphate infusion
Anticipated vaginal or Caesarean delivery	Magnesium sulphate contraindicated
Any reason for anticipated preterm birth	Fetus unlikely to benefit

coma, myasthenia gravis) and those whose fetus was unlikely to benefit from potential neuroprotection (i.e., severe fetal malformations or chromosomal abnormalities). Antenatal magnesium sulphate for fetal neuroprotection should be used with caution in women who have renal impairment, and serum magnesium levels should be monitored.

Magnesium sulphate for neuroprotection should be administered regardless of singleton or multiple gestation, as women with multiple pregnancies were enrolled in all trials.

The inclusion and exclusion criteria from the published trials are summarized in Table 5.

Recommendations

4. Magnesium sulphate should be discontinued if delivery is no longer imminent or a maximum of 24 hours of therapy has been administered. (II-2B)
5. For women with imminent preterm birth, antenatal magnesium sulphate for fetal neuroprotection should be administered as a 4g IV loading dose, over 30 minutes, followed by a 1g/hr maintenance infusion until birth. (II-2B)
6. For planned preterm birth for fetal or maternal indications, magnesium sulphate should be started, ideally within 4 hours before birth, as a 4g IV loading dose, over 30 minutes, followed by a 1g/hr maintenance infusion until birth. (II-2B)

As shown in Table 6, 4 trials of magnesium sulphate administered a 4 g IV loading dose over 20 to 30 min[35–37,41] Maintenance dosing varied from none[36,37] to 1 g/hr[35,41] or 2 g/hr[38] for 12 hr[38] or 24 hr.[35,41] The median dose received was as high as 31.5 g (IQR of 29.0 to 44.6), but this was the trial primarily of women who had PPROM without labour, and 59.1% of women were re-treated when delivery was again considered to be imminent.[38] The median dose was much lower, at 6.5 g (IQR of 4.5 to 14.0 g),[35] when women were enrolled primarily for preterm labour, reflecting a very short median time from enrolment to delivery.

There have been no direct comparisons of different dosing regimens of magnesium sulphate for neuroprotection. A loading dose of 4 g IV with a maintenance infusion of 1 g/hr has been recommended to (1) resemble current clinical practice and hospital protocols for magnesium sulphate for eclampsia prophylaxis and treatment, and (2) minimize concerns about maternal safety, particularly as higher dosing regimens have not been associated with greater neuroprotection. Trials that administered maintenance infusions treated for a maximum of 24 hours antenatally.

For women with planned preterm birth, for fetal or maternal indications, it is recommended that magnesium sulphate be started as close as possible to 4 hours before birth, as this was the mean time from randomization to birth in subgroup analysis.[35] No trials randomized women with planned preterm birth to different durations of magnesium sulphate therapy.

Risk of medication errors may be decreased if magnesium sulphate is prepared in the central pharmacy rather than in the labour and delivery suite.

Magnesium sulphate for fetal neuroprotection should be discontinued at delivery.

The one trial (Rouse et al.[38]) in which re-treatment was performed enrolled primarily women who had PPROM without labour, and 59.1% of women were re-treated when delivery was again considered to be imminent.[38]

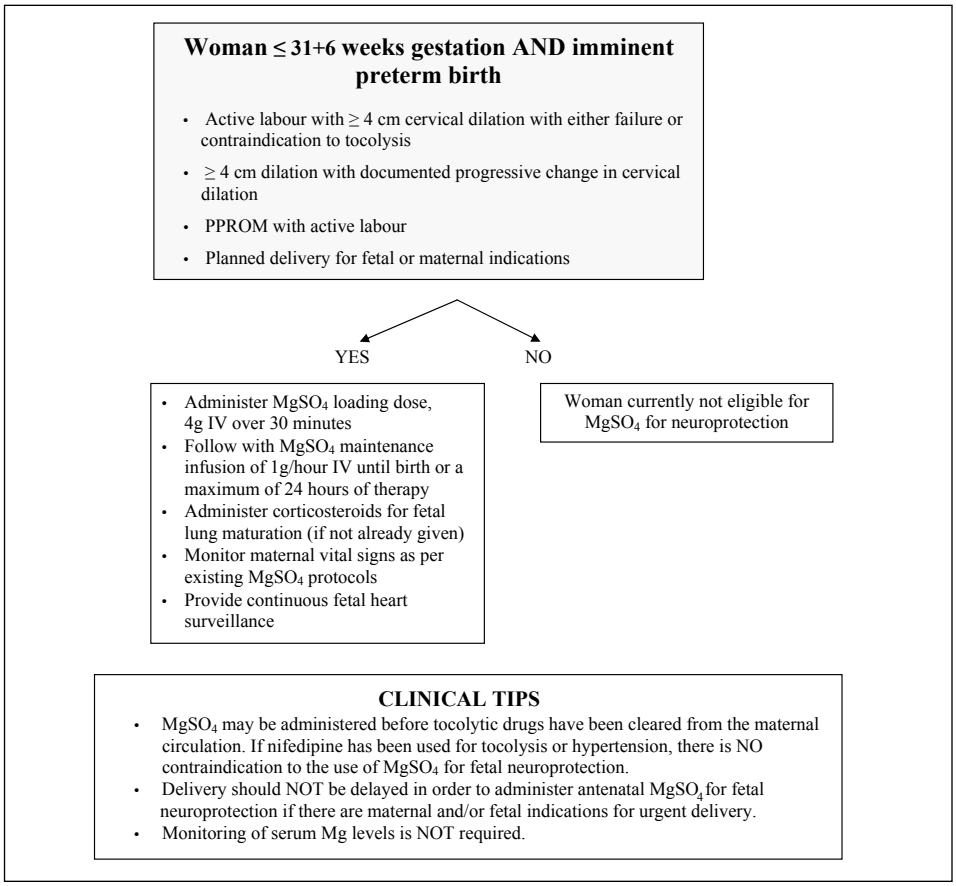
Magnesium sulphate was infused for neuroprotective intent as quickly as 20 minutes before delivery.

Recommendations

7. There is insufficient evidence that a repeat course of antenatal magnesium sulphate for fetal neuroprotection should be administered. (III-L)
8. Delivery should not be delayed in order to administer antenatal magnesium sulphate for fetal neuroprotection if there are maternal and/or fetal indications for emergency delivery. (III-E)
9. When magnesium sulphate is given for fetal neuroprotection, maternity care providers should use existing protocols to monitor women who are receiving magnesium sulphate for preeclampsia/ eclampsia. (III-A)

Existing protocols developed for eclampsia prophylaxis and treatment may be used for women given magnesium sulphate for fetal neuroprotection. Close monitoring of

Magnesium sulphate for fetal neuroprotection in imminent preterm birth (≤ 31+6 weeks)



"Imminent preterm birth" is defined as a high likelihood of birth, due to one or both of the following conditions: active labour with ≥4 cm of cervical dilation, with or without PPROM; planned preterm birth for fetal or maternal indications.

maternal urine output should not be required to the same degree (i.e., no requirement for Foley catheter) when magnesium sulphate is given with neuroprotective intent.

Magnesium sulphate produces peripheral vasodilation when infused intravenously. In neuroprotective intent trials, dose-related effects were common, particularly flushing, problems at the injection site, sweating, and nausea and vomiting (Table 7). Serious maternal side effects were uncommon, with only maternal hypotension and tachycardia reaching statistical significance. Few women discontinued magnesium sulphate because of side effects. Neither maternal death nor cardiorespiratory arrest was reported in the magnesium sulphate arm of these trials.

Monitoring of maternal serum magnesium levels is not required when magnesium sulphate is administered solely for fetal neuroprotection. Maternal adverse effects are dose-related, with respiratory or cardiac arrest associated with levels in excess of 5 mmol/L. Levels of this magnitude are not anticipated when magnesium contraindications are observed but are more frequent when magnesium sulphate is prepared in the delivery suite rather than by a central pharmacy.

Because of their underlying condition, women with imminent preterm birth require continuous fetal heart rate monitoring, in accordance with the SOGC fetal health surveillance guidelines.[42]

Recommendations

10. Indications for fetal heart rate monitoring in women receiving antenatal magnesium sulphate for neuroprotection should follow the fetal surveillance recommendations of the SOGC's 2007 Fetal Health Surveillance: Antepartum and Intrapartum Consensus Guideline. (III-A)
11. Since magnesium sulphate has the potential to alter the neonate's neurological evaluation, causing hypotonia or apnea, health care providers caring for the neonate should have an increased awareness of this effect. (III-C)

Table 6. Magnesium sulphate dosing in the randomized controlled trials of magnesium sulphate for fetal neuroprotection

Study	Women, n	Intervention: $MgSO_4$ Loading dose	Women who received the LD, %	Maintenance dose	Median (IQR) dose received (g)
Neuroprotective intent					
ACTOMgSO_4 Crowther et al. 2003[35]	1062	4g IV over 20 mins	90%	1g/hr IV for 24 hr or until delivery, whichever comes first	6.5 (4.5, 14)
PREMAG Marrett et al. 2006[36]	564	4g IV over 30 mins	99%	None given	4 g IV over 30 mins
MAGnet Mittendorf et al. 2002—neuroprotective intent arm[37]	57	4g IV bolus	Not reported	Neuroprotective arm: none (Tocolysis arm: 2–3g/hr)	Not reported
BEAM Rouse et al. 2008[38]	2241	6g IV over 20–30 mins*	>90%†	2 g/hr IV for a maximum of 12 hr or until delivery†	31.5 (29.0, 44.6)
Other primary intent					
MAGnet Mittendorf et al. 2002—tocolytic arm[37]	92	4g IV "bolus"	Not known	2–3 g/hr	Not reported
MAGPIE 2006[41]	10 141	4g IV over 10 to15 mins	96%	1g/hr IV (or 5g/4hrs IM) for 24 hours	18 (9, 29)‡

LD: loading dose; NA: not available.

* 71.5% of women were eligible for re-treatment. 59.1% of women were re-treated and were on magnesium sulphate at delivery.

† Based on the fact that 91% of women were on magnesium sulphate for at least three hours.

‡ Estimated as value uncertain from published data.[33]

The relevant randomized controlled trials[34] raise no concerns about short-term neonatal adverse effects of antenatal exposure, and no additional neonatal assessment or care is required. Neonates with hypermagnesemia may present with symptoms of apnea or hypoventilation, weakness, hypotonia, absent or reduced deep tendon reflexes, and stupor or coma. This symptom complex has been described in the neonates of mothers administered large doses of IV magnesium sulphate for eclampsia with neonatal serum levels >4.5 mEq/L.[43] However, antenatal magnesium sulphate administered specifically for fetal neuroprotection did not affect the incidence of Apgar score <7 at 5 minutes (RR 1.03; 95% CI 0.90 to 1.18; 3 trials, 4387 infants), neonatal hypotonia (RR 1.02; 95% CI 0.77 to 1.36; 1 trial, 2444 infants), or the need for ongoing ventilatory support (RR 0.94; 95% CI 0.89 to 1.00; 3 trials; 4387 women). None of the main trial publications reported on the need for active resuscitation at birth,[34] but a subanalysis of the BEAM trial found no correlation between cord blood magnesium levels and the need for bag-mask ventilation, intubation, or chest compressions.[44] It is unknown whether magnesium sulphate exposure would affect the need for ventilation in neonatal intensive care units using protocols to minimize ventilation.

The relevant randomized controlled trials[35–38] demonstrated no other differences in neonatal morbidity, including seizures, respiratory distress syndrome, bronchopulmonary dysplasia, or necrotizing enterocolitis.

Few newborn subjects with in utero exposure to magnesium sulphate remote from delivery were included in the relevant trials. There is no clear rationale for any additional assessment of these newborns.

There should be an ongoing registry of children exposed to antenatal magnesium sulphate for neuroprotection. This would allow evaluation of the following:

1. Effects on delivery room resuscitation, especially in units with ventilation-avoidance protocols
2. Anticipated reduction in CP
3. Effect on the high prevalence of school age morbidities among infants born preterm.

SPECIAL CONSIDERATIONS REGARDING THE USE OF MAGNESIUM SULPHATE FOR FETAL NEUROPROTECTION

Transport

When maternal transport is being considered, magnesium administration should be decided on in consultation with the receiving centre, on a case-by-case basis.

Drug Interactions

Antenatal corticosteroids should be administered for fetal lung maturation.

When tocolysis has been employed to attempt to arrest preterm labour, magnesium sulphate can be used once

Table 7. Maternal outcomes in trials of magnesium sulphate for fetal neuroprotection in neuroprotective intent trials (adapted from Conde-Agudelo and Romero[32])

	$MgSO_4$ n (%)	Placebo n (%)	RR (95% CI)	Trials n
Clinical and self-assessed maternal side effects				
Any side effect	1356/1917 (70.7)	343/1950 (17.6)	5.05 (2.06 to 12.39)	3
Minor side effects				
Flushing	1119/1917 (58.4)	162/1950 (8.3)	7.56 (3.39 to 16.88)	3
Problems at injection site	614/1631 (37.6)	68/1672 (4.1)	9.12 (7.19 to 11.57)	2
Sweating	411/1631 (25.2)	57/1672 (3.4)	6.37 (1.96 to 20.68)	2
Nausea or vomiting	312/1917 (16.3)	76/1950 (3.9)	4.60 (1.54 to 13.75)	3
Serious side effects				
Hypotension	80/821 (9.7)	52/805 (6.5)	1.51 (1.09 to 2.09)	2
Tachycardia	56/535 (10.5)	36/527 (6.8)	1.53 (1.03 to 2.29)	1
Respiratory depression	41/1631 (2.5)	31/1672 (1.9)	1.31 (0.83 to 2.07)	2
Pulmonary edema	8/1096 (0.7)	3/1145 (0.3)	2.79 (0.74 to 10.47)	1
Infusion stopped due to adverse effects	123/1631 (7.5)	44/1672 (2.6)	2.81 (2.01 to 3.93)	2
Serious maternal adverse effects				
Death	0/1917	1/1950	0.32 (0.01 to 7.92)	3
Cardiac or respiratory arrest	0/1917	0/1950	—*	3

* Not estimable.

tocolysis has been discontinued because delivery is considered imminent. If nifedipine has been used for tocolysis or hypertension, there is no contraindication to the use of magnesium sulphate for fetal neuroprotection. Although case reports have described neuromuscular blockade with concomitant use of magnesium sulphate and nifedipine or other calcium channel blockers, a controlled study and synthesis of the literature failed to demonstrate an increased risk.[42]

Potential Obstetrical Adverse Outcomes

In the Conde-Agudelo and Romero meta-analysis,[32] magnesium sulphate given with neuroprotective intent was not associated with a difference in Caesarean section (822 [42.9%] in the magnesium arm vs. 834 [42.8%] for placebo; RR 1.0; 95% CI 0.9 to 1.1; 3 trials, 3867 women) or severe postpartum hemorrhage (28 [3.4%] in the magnesium arm vs. 26 [3.2%] for placebo; RR 1.1; 95% CI 0.6 to 1.8; 2 trials, 1626 women). None of the trials reported on length of labour or augmentation of labour.

CLINICAL PRACTICE GUIDELINES AND COMMITTEE OPINION

Australian National Clinical Practice Guidelines[45] were published in March 2010 by the Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel. They recommended antenatal magnesium sulphate for fetal neuroprotection (excellent evidence) in the same dosage as recommended in these guidelines. However, magnesium was recommended only at < 30 weeks' gestation (good evidence) on the basis of two considerations. First, no one gestational age subgroup (of the < 34, < 33, < 32, and < 30 week categories considered) was considered to show a clear benefit, although the < 28 week subgroup of Rouse et al.[38] was not included, because the committee felt that the predominance of PPROM in that study population limited generalizability to the target population of women with imminent preterm labour (which the committee defined as planned or definitely expected within 24 hours). Second, in the face of uncertainty, the committee felt it was prudent to limit the impact of their clinical practice guidelines on resource allocation.

Also in March 2010, the American College of Obstetricians and Gynecologists issued a committee opinion on magnesium sulphate for fetal neuroprotection. It stated that "the available evidence suggests that magnesium sulphate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants." No official opinion was given on a gestational age cut-off, but it was recommended that physicians develop specific guidelines around the issues of inclusion criteria, dosage, concurrent tocolysis, and monitoring in accordance with one of the larger trials.[46]

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