REVIEW

Magnesium sulfate and fetal neuroprotection: overview of clinical evidence

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Abstract

Antenatal administration of magnesium sulfate is an important part of the neuroprotective strategy for preterm infants. Strong evidence from five randomized controlled trials and five meta-analyses has demonstrated that magnesium sulfate, when administered before preterm delivery, significantly reduces the risk of cerebral palsy at two years. Through secondary analyses of randomized controlled trials and other original clinical studies, this state-of-the-art review highlights the absence of serious adverse effects in both pregnant women and neonates, as well as the impact of maternal body mass index and preeclamptic status on the maternal and neonatal magnesium levels, which could influence the magnitude of the neuroprotective effect. Although antenatal magnesium sulfate is a cost-effective strategy, some practice surveys have demonstrated that the use of magnesium sulfate is not sufficient and that its use is heterogeneous, differing among different maternity wards. Since 2010, an increasing number of obstetrical societies have recommended its use to improve the neurological outcomes of preterm infants, especially the International Federation of Gynecology and Obstetrics and World Health Organization in 2015, and France in 2017. Considering the neuroprotective impact of magnesium sulfate when administered before delivery, postnatal administration should be considered, and its effects should be assessed using randomized controlled trials.

Key Words: *magnesium sulfate; preterm birth; neuroprotection; cerebral palsy; neurodevelopment; international recommendations; clinical studies; meta-analysis; preeclampsia; cost-effectiveness*

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Introduction

Improving the neurological outcomes of children born prematurely remains a crucial issue in perinatal medicine. Antenatal magnesium sulfate ($MgSO_4$) administration is a possible neuroprotective intervention that reduces the incidence of cerebral palsy (CP) at two years of age. Clinical evidence of the neuroprotective impact of $MgSO_4$ is based on five randomized controlled trials (RCTs), and five subsequent meta-analyses of these RCTs, including an individual patient data (IPD) meta-analysis. The purpose of this state-of-the-art review was to: 1) summarize the evidence for the neuroprotective effects of $MgSO_4$ on the immature brain obtained from the RCTs and meta-analyses; 2) resolve some issues through secondary analyses of the RCTs and/or other original clinical studies; 3) analyze the practical use of antenatal $MgSO_4$ in tertiary hospital maternity wards; 4) assess the cost-effectiveness of this intervention; and 5) highlight the increased rates of recommendation of antenatal $MgSO_4$ treatment for fetal neuroprotection since 2010 in many countries, which is key for optimizing individual $MgSO_4$ coverage.

Prevention of CP by Antenatal $MgSO_4$ Administration Before Preterm Delivery

Animal and human observational studies have suggested that $MgSO_4$ is neuroprotective for the immature brain (Marret et al., 1995; Wolf et al., 2012). The mechanisms underlying this neuroprotective effect are not well established; however, studies have indicated several hypotheses. Magnesium can prevent excitotoxicity *via* N-methyl-D-aspartic acid (NMDA) receptor antagonistic action and a reduction in extracellular glutamate (Nowak et al., 1984; Kang et al., 2011). Further, magnesium can exert anti-inflammatory effects by reducing oxidative stress and pro-inflammatory cytokines (Mazur et al., 2007; Burd et al., 2010; Rayssiguier et al., 2010). In the 2000s, five RCTs (MAGPIE, MAGNET, ACTOMgSO$_4$, PREMAG, and BEAM trials) assessed the impact of antenatal $MgSO_4$ infusion prior to preterm delivery on the incidence of CP at two years (Altman et al., 2002; Mittendorf et al., 2002; Crowther et al., 2003; Marret et al., 2007, 2008; Rouse et al., 2008). These have been described in detail in a previous review (Chollat et al., 2018). Briefly, the rate of motor dysfunction was lower in the $MgSO_4$ group when compared with the control group in the ACTOMgSO$_4$ trial (2.9% *versus* 5.4% in the placebo group, relative risk [*RR*]: 0.53, 95% confidence interval [*CI*]: 0.30–0.92); the rate of combined death or gross motor dysfunction was lower in the $MgSO_4$ group when compared with the control group in the PREMAG trial (25.6% *versus* 30.8%, odds ratio (*OR*): 0.62, 95% *CI*: 0.41–0.93); and the rate of moderate or severe CP was significantly reduced in the $MgSO_4$ group compared with the control group in the BEAM trial (1.9% *versus* 3.5%, *RR* 0.55, 95% *CI*: 0.32–0.95).

Five meta-analyses of these RCTs have demonstrated a

neuroprotective effect of antenatal $MgSO_4$ infusion on CP at two years of age (Conde-Agudelo and Romero, 2009; Costantine et al., 2009; Doyle et al., 2009; Zeng et al., 2016; Crowther et al., 2017). In the IPD meta-analysis, Crowther et al. (2017) demonstrated that $MgSO_4$ treatment significantly reduced CP in survivors (*RR* 0.68, 95% *CI*: 0.54–0.87, n = 4601 neonates, number of RCTs = 5, number of pregnant women who needed the treatment to avoid one CP = 46), regardless of the reason of preterm birth, gestational age at time of $MgSO_4$ treatment, or cumulative dose.

Despite this strong evidence, some questions have remained unaddressed by RCTs or meta-analyses. Some relevant clinical studies are seeking the resolution of these issues, as described in the following sections.

Fetal Neuroprotection by $MgSO_4$: Persisting Questions and Concerns

Minor maternal side effects

In a recent systematic review, maternal life-threatening side effects, such as death, cardiac or respiratory arrest, and intensive care admission were not associated with $MgSO_4$ treatment (Bain et al., 2013b). These data are consistent with the results of RCTs and meta-analyses. However, women receiving $MgSO_4$ had an increased risk of developing minor side effects. Specifically, they had double the risk of hypotension, tachycardia, respiratory depression, discomfort at the injection site, drowsiness, headache, dizziness, mouth dryness or thirst, and blurred vision; five times the risk of nausea and/or vomiting, flushing and warmth, and sweating; and 15 times the risk of itching, tingling, and muscle weakness. These adverse effects are transient and disappear with treatment cessation. A decrease in the dose administered could limit the occurrence of these side effects. One trial has shown that a lower dose regimen (2 g/3 hours) significantly reduced treatment cessation due to side effects when compared with a higher dose regimen (5 g/4 hours) (Malapaka and Ballal, 2011). In addition, extending the duration of the loading dose from 20 to 60 minutes reduces flushing and warmth, but has no impact on other side effects (Bain et al., 2014).

Low maternal body mass index (BMI) may also influence the occurrence of side effects. For example, more maternal adverse effects were observed in underweight women than in normal or overweight women (Vilchez et al., 2018).

Neonatal side effects

Results of the meta-analyses conducted on the RCTs did not show any adverse outcomes for neonates, including respiratory distress syndrome, need for mechanical ventilation, or necrotizing enterocolitis (Conde-Agudelo and Romero, 2009; Zeng et al., 2016). However, one trial showed a higher incidence of spontaneous intestinal perforation after antenatal $MgSO_4$ administration among extremely low birthweight infants (Rattray et al., 2014). In this monocentric retrospective study, spontaneous intestinal perforation and death among extremely low birthweight (ELBW) infants were evaluated before, during, and after the initiation of a neuroprotection protocol involving antenatal magnesium. One hundred and fifty-five ELBW infants were included: 81 before, 23 during, and 51 after establishing the $MgSO_4$ protocol. Overall, 78.3% of ELBW infants were exposed to $MgSO_4$ during the study, compared to 50.6% and 60.8% exposed before and after the protocol, respectively. The incidence of spontaneous intestinal perforation in the $MgSO_4$ protocol was 30.4% *versus* 12.9% in the group not receiving $MgSO_4$ (P = 0.03). The experimental design of this study makes these results difficult to interpret. First, the protocol used by Rattray et al. included a loading dose of 6 g and maintenance dose of 2 g per hour, whereas current protocols include a loading dose of 4 g and maintenance dose of 1 g per hour. Second, all groups were exposed to $MgSO_4$. Third, in the placebo group, the incidence of spontaneous intestinal perforation was higher (12.9%) than usual (< 1%) (Suply et al., 2015). Finally, the sample size was small. In addition, this adverse effect was not reported in other RCTs or meta-analyses. Therefore, this effect may be influenced by local or study design factors and may not be representative of current $MgSO_4$ treatment practices.

Antenatal $MgSO_4$ administration did not influence neonatal vital parameters, such as heart and respiratory rates, temperature, oxygen saturation, and glycemia (Nunes et al., 2017). The assessment of hemodynamic parameters by echocardiography one day after antenatal $MgSO_4$ infusion showed lower systemic vascular resistance and higher myocardial function in preterm infants born before 29 weeks of gestation (WG) (James et al., 2015).

Two meta-analyses have shown that antenatal $MgSO_4$ exposure does not improve 5-minute Apgar scores that are < 7 (Doyle et al., 2009; Zeng et al., 2016). A secondary analysis of the BEAM cohort did not show any difference in rates of intubation, chest compressions, hypotension, or mechanical ventilation between the $MgSO_4$ and placebo groups (Drassinower et al., 2015). These findings support the safety of antenatal $MgSO_4$ exposure on short-term neonatal outcomes.

The incidence of side effects due to hypermagnesemia is anecdotal and often secondary to administration errors (Rigo et al., 2017). Some case reports have reported an association between major side effects, including hypotension, QT interval prolongation, intraventricular conduction delay, respiratory distress, apnea, lethargy hypotonia, neuromuscular blockade, and coma, and severe hypermagnesemia (18–22 mM) (Huey et al., 1995; Ali et al., 2003; Hyun et al., 2011). In these case reports, neonates were not exposed to $MgSO_4$ before delivery, and the etiology of hypermagnesemia was unknown or caused by a malfunction of an automated parenteral nutrition-mixing device. Therefore, an appropriate administration protocol for $MgSO_4$ is essential to limit $MgSO_4$ administration errors.

Dosage, duration of infusion, and serum levels of magnesium: what is the impact on the neuroprotective effect of $MgSO_4$?

Serum magnesium levels decrease in women during pregnancy from 0.75–0.95 mM, which is the range found in healthy adults (Costello et al., 2016), to 0.59–0.95 mM during gestation and 0.54 to 0.90 mM (mean 0.74 mM, 95% *CI*: 0.43–1.04) at delivery (Rigo et al., 2017). In a prospective pharmacokinetic cohort of 111 pregnant women, the steady state level of magnesium before birth ranged from 2.0 in non-preeclamptic women to 3.5 mM in preeclamptic women after $MgSO_4$ administration. The placental transfer of $MgSO_4$ was excellent and resulted in a ratio of the mean magnesium levels of the neonate to the mother at delivery of 0.94 ± 0.15 mM (Brookfield et al., 2016). A meta-analysis has found that neonatal magnesium levels at birth are estimated to be 0.76 mM (95% *CI*: 0.52–0.99) or 1.29 mM (95% *CI*: 0.50–2.08) with or without maternal magnesium supplementation, respectively (Rigo et al., 2017).

Several factors affect maternal and neonatal $MgSO_4$ levels. These include:

-A decrease in $MgSO_4$ clearance in preeclamptic women (3.98 L/h *versus* 5.88 L/h for non-preeclamptic women), which directly affects magnesium levels (3 mM in preeclamptic women *versus* 2.1 mM in non-preeclamptic women).

-The linear relationship between maternal weight and the time required to reach a steady state. BMI has a significant effect on magnesium levels, and obese women (in particular, those with BMI > 30 kg/m^2) could be subject to subtherapeutic magnesium levels (Tudela et al., 2013).

-A significant correlation between neonatal magnesium levels in the first 24 hours of life and the total dose of $MgSO_4$ received by the mother (Borja-Del-Rosario et al., 2014; García Alonso et al., 2018).

Considering these findings, questions arise regarding the impact of the mother's weight (especially if the mother is obese) on the neurological outcome of the infant. A secondary analysis of the BEAM trial showed that $MgSO_4$ significantly reduced CP, but only in non-obese women (Vilchez et al., 2018). This finding suggests that a dosage adjustment based on maternal weight is required. More studies are required to explore this association.

Similarly, a retrospective study on 304 mother-baby dyads found a correlation between neurological outcomes and serum magnesium levels. Neonates with low (< 1.0 mM) or high (> 1.9 mM) serum magnesium levels had a higher OR for grade 3 or 4 intraventricular hemorrhage than neonates with magnesium levels between 1 and 1.9 mM (Narasimhulu et al., 2017). In this study, the neonatal magnesium levels were dependent on the maternal magnesium dose, maternal serum concentration, and duration of therapy. In a retrospective study with 88 infants exposed to $MgSO_4$, elevated magnesium levels (> 1.5 mM) were associated with lower locomotor scores in the first year of life (Morag et al., 2017). Conversely, another retrospective cohort that included 75 preterm infants exposed to $MgSO_4$ revealed that higher levels of $MgSO_4$ (> 1 mM) were associated with a significantly decreased risk of abnormal motor examination findings between 20 and 36 months of age (Doll et al., 2014).

The relationship between neonatal magnesium levels and neurological outcomes is unclear. There may be a range of serum magnesium levels that elicit the neuroprotective effects of $MgSO_4$ therapy. The recommended dose of $MgSO_4$ used for fetal neuroprotection was obtained based on the dose used for tocolysis or prevention of preeclampsia, as a preliminary consensus based on previous clinical trials is lacking. Studies assessing the optimal target level of magnesium are necessary to optimize the neuroprotective effects of $MgSO_4$ and limit any possible side effects.

The duration of $MgSO_4$ infusion does not affect its neuroprotective effects. A secondary analysis of the BEAM trial found no change in neurological outcomes when comparing the administration durations of < 12 hours, between 12 and 18 hours, or > 18 hours (McPherson et al., 2014). These findings are consistent with the IPD AMICABLE meta-analysis that showed a neuroprotective effect against CP regardless of the total dose received (Crowther et al., 2017). However, the proximity of magnesium exposure to delivery could be crucial. A final $MgSO_4$ exposure < 12 hours before delivery was associated with significantly reduced odds of CP compared with exposure > 12 hours before delivery (Turitz et al., 2016).

Use of $MgSO_4$: Terms of Use, Feasibility, and Safety of Therapeutic Protocols

No studies have compared the neurological effects of different $MgSO_4$ regimens. All currently published RCTs report a loading dose range of 4–6 g over 15–30 minutes (Bain et al., 2012). Maintenance doses of 1–2 g per hour until birth or for up to 12–24 hours have been used in all trials, except the PREMAG trial. Re-treatment was considered only in the BEAM trial. Furthermore, the IPD meta-analysis found no significant difference in the incidence of CP among different $MgSO_4$ regimens (Crowther et al., 2017).

Two national surveys have shown heterogeneous clinical practices regarding the maintenance dose (1 or 2 g/h), duration of treatment (until delivery, or for a maximum of 12 or 24 hours), consideration of re-treatment, and minimal interval between the two treatments (De Silva et al., 2015; Chollat et al., 2017). This heterogeneity is likely to be a result of differences in the regimens that are reported in the literature.

Consequently, the use of $MgSO_4$ for fetal neuroprotection must be optimized. In Europe, only 7.6% of all maternity units reported the use of $MgSO_4$ in 2012, resulting in only 14.3% of eligible women receiving $MgSO_4$ for fetal neuroprotection (Wolf et al., 2017). Individual $MgSO_4$ coverage improves following the implementation of a standard protocol. In Australia and New Zealand, the proportion of eligible women who did not receive antenatal

$MgSO_4$ decreased from 69.7% in 2011 to 22.5% in 2013 after the development of a standard protocol (Siwicki et al., 2015). A French study showed that 68% of eligible women received $MgSO_4$ before delivery during the first year of implementing a protocol in a tertiary obstetric unit (Bouet et al., 2015). A similar study in an Australian maternity unit showed that 74% of preterm infants born at < 32 WG were antenatally exposed to $MgSO_4$ in the first 12 months following the implementation of a national guideline (Ow et al., 2012). A qualitative study highlighted that information dissemination was a key enabler for increasing the knowledge of and skills for the use of $MgSO_4$ in order to optimize $MgSO_4$ administration. Forgetting to prescribe $MgSO_4$, difficulty in predicting preterm birth, and complex administration processes were the most significant barriers perceived by health professionals precluding the use of $MgSO_4$ (Bain et al., 2015). In Canada, a multifaceted knowledge translation strategy was implemented to improve $MgSO_4$ administration for eligible women. This program included national clinical guidelines and online e-learning modules, educational rounds, focus group discussions, and surveys focused on barriers and facilitators. This intervention was associated with an improvement of 84% in the odds of optimal use in 10 years (Teela et al., 2015; De Silva et al., 2018). Many audits have shown that the implementation of an administration protocol for $MgSO_4$ for fetal neuroprotection is safe and feasible (Ow et al., 2012; Bain et al., 2013a; Bouet et al., 2015; Tan and Groom, 2015).

Economic Analysis: Is the $MgSO_4$ Strategy Cost-Effective?

CP is a life-long condition that deeply affects infants and their families, and generates costs for both the healthcare system and society. A recent systematic review provided information on the economic aspects of CP, including interventions for its prevention. The authors concluded that the "administration of magnesium sulfate for imminent preterm birth is a dominant strategy resulting in less cost and more benefit compared with no treatment" (Shih et al., 2018). In addition, two studies have analyzed the cost-effectiveness of $MgSO_4$ treatment (Cahill et al., 2011; Bickford et al., 2013). Cahill et al. demonstrated that for every 10,000 women at risk for preterm birth treated with $MgSO_4$, $1.8 million was saved and 52 quality-adjusted life years (QALY) were gained. Bickford et al. (2013), moreover, showed that $MgSO_4$ treatment allowed for savings of $112,602 for each QALY gained and $1,554,198 for each case of CP prevented. In light of these analyses, $MgSO_4$ intervention seems highly cost-effective.

International Recommendations

Since 2010, many national obstetrical societies have recommended the use of $MgSO_4$ before preterm birth as a means of providing neuroprotection to preterm neonates (**Table 1**). $MgSO_4$ use, in terms of the maximum term of administration (from 29 + 6 WG to 33 + 6 WG), duration of the maintenance dose (from 12–24 hours), and possibility of re-treatment (mentioned in the Australian, New Zealand, Irish, and FIGO recommendations) (**Table 1**), varies among countries. Finally, because preterm birth is a major health issue, the World Health Organization strongly recommends the use of $MgSO_4$ for fetal protection against neurological complications before 32 WG.

Conclusions

Antenatal $MgSO_4$ administration is a key intervention for preventing CP in preterm neonates. $MgSO_4$ infusion is associated with minor transient maternal side effects and but is well tolerated by neonates. Maternal weight and pre-eclamptic status affect maternal and neonatal magnesium levels, which could in turn influence the neuroprotective effects of $MgSO_4$. The standardization of an acceptable range of maternal magnesium levels that elicit neuropro-

Table 1 Protocols for the administration of $MgSO_4$ for neuroprotection according to international recommendations

	Publication date	Maximum Gestational age (weeks of gestation + day)	Loading dose (gram)	Maintenance dose	Re-treatment
Australia and New Zealand	2010	29+6	4	1 g/h until birth, max 24 hours	Possible
USA	2010	"Physicians … should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials". Details are not specified (American College of Obstetricians and Gynecologists Committee on Obstetric Practice and Society for Maternal-Fetal Medicine, 2010).			
Canada	2011	31+6	4	1 g/h until birth, max 24 hours	Not specified
Ireland	2013	31+6	4	1 g/h until birth, max 24 hours	Possible
Belgium	2014	31+6	4	1 g/h until birth, max 24 hours	Not specified
United Kingdom	2015	29+6 and even 33+6	4	1 g/h until birth, max 12 hours	Not specified
FIGO	2015	31+6	4	1 g/h until birth, max 24 hours	Not possible
WHO	2015	31+6	Not specified	1 g/h until birth, max 12 hours	Not specified
France	2017	31+6	4	1 g/h until birth, max 12 hours	Not specified

$MgSO_4$: Magnesium sulfate; FIGO: International Federation of Gynecology and Obstetrics; USA: United States of America; WHO: World Health Organization.

tective effects may optimize the beneficial impact of $MgSO_4$ on neonatal neurological outcomes. This strategy would require monitoring of the maternal magnesium level and, if necessary, dose adjustments.

Considering the beneficial effects of antenatal $MgSO_4$ administration on CP, postnatal administration of $MgSO_4$ in preterm infants should be considered and its effects should be assessed *via* RCTs to obtain the optimal magnesium serum levels for neuroprotection.

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