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The Society for Maternal Fetal Medicine

Magnesium Sulfate Before Anticipated Preterm Birth for Neuroprotection

Abstract: Numerous large clinical studies have evaluated the evidence regarding magnesium sulfate, neuroprotection, and preterm births. The Committee on Obstetric Practice and the Society for Maternal-Fetal Medicine recognize that none of the individual studies found a benefit with regard to their primary outcome. However, the available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials.

In the 1990s, observational studies suggested an association between prenatal exposure to magnesium sulfate and less frequent subsequent neurologic morbidities (1–3). Subsequently, several large randomized prospective clinical trials have been performed to evaluate the utility of magnesium sulfate for fetal and neonatal neuroprotection (4–9).

In 1997, researchers reported on an interim analysis of 134 women participating in a four-arm single center trial of magnesium sulfate for prevention of cerebral palsy (4, 5). The incidence of infant death was not greater in the neuroprotection arm, in which 57 women (59 infants) in preterm labor before 34 weeks of gestation and with cervical dilatation greater than 4 cm were randomized to magnesium sulfate treatment or placebo treatment. However, total infant death was more common when this group was combined with the unblinded cohort in which magnesium sulfate tocolysis was compared with other tocolytic agents. Recruitment to the study was discontinued because of these results.

In 2003, researchers reported the results of a multicenter placebo-controlled study of 1,062 women (1,255 infants) in whom delivery was planned or expected within 24 hours at less than 30 weeks of gestation (see Table 1) (6). Primary outcomes included infant death or cerebral palsy or both by 2 years corrected age. No significant reductions in the occurrences of infant death or cerebral palsy or both were seen with magnesium sulfate treatment. In a secondary analysis, the researchers demonstrated significantly less frequent "substantial gross motor dysfunction" or death or both in the infants exposed to magnesium sulfate. *Substantial gross motor dysfunction* is defined as inability to walk without assistance.

One study reported the results of a randomized clinical trial that enrolled 564 gravid women (688 infants) before 33 weeks of gestation with planned or expected delivery within 24 hours (see Table 1) (7). Women were randomized to magnesium sulfate treatment or placebo treatment. The primary outcome for this study was infant death or severe white matter injury. The study evaluated infant outcomes before hospital discharge and found no significant differences in total infant death or severe white matter injury or both between magnesium sulfate treatment and placebo treatment groups (7). In a 2-year follow-up evaluation, these investigators did not find statistically significant reductions in cerebral palsy or death or both, but did demonstrate significant reductions in death or "gross motor dysfunction" or both and death or "motor or cognitive dysfunction" or both with magnesium sulfate treatment (9).

Researchers published results from a multicenter trial of 2,241 women at imminent risk for delivery before 32 weeks of gestation in which women were randomized to magnesium sulfate treatment or placebo treatment groups (see Table 1) (8). The primary outcome was a total of stillbirth or infant death by 1 year or moderate to severe

cerebral palsy at or beyond 2 years. There was no significant reduction in the primary outcome with magnesium sulfate treatment. There was a reduction in moderate to severe cerebral palsy in the magnesium sulfate treatment group, and in a secondary analysis, less frequent overall cerebral palsy in the magnesium sulfate treatment group (4.2% compared with 7.3%, P=0.004).

A recent meta-analysis synthesized the results of the clinical trials of magnesium sulfate for neuroprotection (10). Pooling the results of the available clinical trials of magnesium sulfate for neuroprotection suggests that prenatal administration of magnesium sulfate reduces the occurrence of cerebral palsy when given with neuroprotective intent (relative risk [RR], 0.71; 95% confidence interval [CI], 0.55–0.91). Likewise, the meta-analysis suggested that magnesium sulfate given with neuroprotective intent reduced the total occurrences of death and cerebral palsy (summary RR, 0.85; 95% CI, 0.74–0.98). The results of this meta-analysis did not suggest any effect on fetal or infant death with magnesium sulfate therapy (summary RR, 0.95; 95% CI, 0.80–1.12). Two subsequent meta-analyses of similar design have confirmed these results (11, 12).

None of the aforementioned trials demonstrated significant pregnancy prolongation when magnesium sulfate was given for neuroprotection. Although minor maternal complications were more common with magnesium sulfate in the three major trials, serious maternal complications (eg, death, cardiac arrest, and respiratory failure) were not more frequent in these studies or on meta-analysis (6–8, 10).

Although the goal of each of the three major randomized clinical trials was to evaluate the effect of magnesium sulfate treatment on neurodevelopmental outcomes and death, comparison is made difficult by differences in inclusion and exclusion criteria, populations studied, magnesium sulfate regimens, gestational age with treatment, and outcomes studied between the trials.

The Committee on Obstetric Practice and the Society for Maternal-Fetal Medicine recognize that none of the individual studies found a benefit with regard to their primary outcome. However, the available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials (see Table 1) (6–8).

Table 1. Inclusion Criteria, Treatment Regimens, and Concurrent Tocolysis of Large Trials

Study	Total Number of Participants	Inclusions	Dose	Duration	Death and Cerebral Palsy	Death	Cerebral Palsy
Crowther	1,255	Less than 30 weeks of gestation; likely delivery within 24 hours	4 g load 1 g/hr	Up to 24 hours	RR, 0.83; 95% CI, 0.66–1.03	RR,0.83; 95 % CI, 0.64–1.09	RR, 0.83; 95% CI, 0.54–1.27
Marret	688	Less than 33 weeks of gestation	4 g load only	Loading dose only	OR, 0.80; 95% CI, 0.58–1.10	OR, 0.85; 95% CI, 0.55–1.32	OR, 0.70; 95% CI, 0.41–1.19
Rouse	2,241	24–31 weeks of gestation; at high risk of spontaneous birth	6 g load 2 g/hr	Up to 12 hours; treatment resumed when delivery imminent	RR, 0.97; 95% CI, 0.77–1.23	RR, 1.12; 95% CI, 0.85–1.47	RR, 0.55; 95% CI, 0.32–0.95

CI, confidence interval; RR, relative risk; OR, odds ratio.

Data from Crowther CA, Hiller JE, Doyle LW, Haslam RR. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. JAMA 2003;290:2669–76; Marret S, Marpeau L, Zupan-Simunek V, Eurin D, Leveque C, Hellot MF, et al. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial. PREMAG trial group. BJOG 2007;114:310–8; *and* Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. N Engl J Med 2008;359:895–905.

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