Magnesium sulfate, a biologically potent compound, given sometimes in extraordinarily high doses, is among the most commonly used pharmaceuticals in American obstetric practice. Although most clinicians are in accord regarding its value for seizure prophylaxis in the setting of preeclampsia, such unanimity is not the case regarding its role in preterm labor. Credible scientific data indicate not only a lack of efficacy, but also toxicity to susceptible fetuses when magnesium sulfate is used in the high dosages found in tocolysis. In apparent contrast, three recent clinical trials, although individually inconclusive, provide data from which a very recent meta-analysis affirms a potential role for magnesium sulfate in prophylaxis against fetal neurologic injury. Comparing outcomes from these trials, with attention to dosage, relationships are revealed that unify observations previously regarded as conflicting: Magnesium sulfate indeed may have both neuroprotective and fetal toxic effects. The better, and safer, neuroprotection seems to occur at comparatively low antenatal doses (perhaps in a range between 4 g and 10.5 g), whereas increasing dosages exceed a “therapeutic window” whereby, as with most drugs, toxic sequelae begin to accrue.

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Disappointingly, for the primary composite variable of infant death or cerebral palsy, the long-awaited findings from the MFMU Network trial of magnesium neuroprophylaxis revealed no significant benefit. This inconclusive report, however, is not the final word regarding a putative beneficial fetal effect. Two other trials of “neuroprotective” magnesium sulfate (Australasian Collaborative Trial of Magnesium Sulphate [ACTOMgSO4] from Australia and New Zealand and PREMAG4 from France) have also been published. Both of these studies, using relevantly lower antenatal dosages of magnesium, had more encouraging results (albeit without statistical significance due, probably, to small sample size). Indeed, when evaluated together,5 the three trials do reveal a clinically relevant and statistically significant neuroprotective effect from antenatal magnesium. However, the therapeutic relationship is not likely so simple as the formerly hypothesized “yes or no” magnesium sulfate exposure.

MAGNESIUM SULFATE SEIZURE PROPHYLAXIS IN PREECLAMPSIA

Because of high-quality data and consistency of findings, the use of magnesium sulfate for maternal pre-eclamptic seizure prophylaxis is its best-established obstetric indication. For example, a recent systematic meta-analysis6 of six well-designed randomized clinical trials (n=11,444 preeclamptic women) revealed a marked reduction in the occurrence of eclampsia (relative risk [RR] 0.41, 95% Confidence Interval [CI] 0.29–0.58) among treated women compared with placebo controls. Importantly, no differences in the risk of fetal and neonatal death (RR 1.04, 95% CI 0.93–1.15) were detected. Regarding clinical trials comparing magnesium sulfate with other anticonvulsants, magnesium was found significantly more efficacious for seizure prophylaxis than phenytoin (two trials, 2,241 women; RR 0.05, 95% CI 0.00–0.84). Likewise, magnesium sulfate performed superiorly to nimodipine (one trial, 1,650 women; RR 0.33, 95% CI 0.14–0.77).

MAGNESIUM SULFATE AS TOCOLYTIC

In 2006, Grimes and Nanda authored a Current Commentary in this journal, “Magnesium Sulfate Tocolysis: Time to Quit,”7 in which they firmly recommended abandoning magnesium sulfate as a tocolytic. To date, as documented then, there has never been evidence that magnesium sulfate is more effective than placebo for stopping preterm labor. More importantly, there remains no evidence that its use for tocolysis leads to any measure of improvement in perinatal outcome. Contrarily, there is credible evidence from 1) the first, and only, placebo-controlled randomized clinical trial of tocolytic magnesium sulfate conducted at Parkland Memorial Hospital,8 2) the Magnesium and Neurologic Endpoints Trial (MagNET), a neuropreventive study from the University of Chicago using either high-dose tocolytic or low-dose (4 g) prophylactic magnesium sulfate,9 and 3) a meta-analysis from the Cochrane Database of Systematic Reviews,10 that magnesium sulfate, in tocolytic doses (typically totaling at least 50 g, if not more), is associated with increased total pediatric (fetal plus infant) mortality (RR 2.8, 95% CI 1.2–6.6). Even so, probably due to a long-standing and widely disseminated misperception that it is “safe and effective,” high-dose magnesium sulfate continues to be used inappropriately with the anecdotal hope of tocolysis.

MAGNESIUM SULFATE NEUROPROTECTION STUDIES

In 1995, epidemiologists Nelson and Grether11 published a compelling retrospective case–control study generating the original hypothesis of fetal neuroprotection from antenatal magnesium exposure. Analyzing data on more than 150,000 children, followed through at least 3 years of age, they reported that only 7% of very low birth weight children exposed antenatally to magnesium sulfate developed cerebral palsy, as compared with 36% of randomly selected gestational age–matched, but unexposed, children (OR 0.14, 95% CI 0.05–0.51). Naturally, this report generated enormous interest, particularly because it introduced the exciting possibility that magnesium sulfate (an inexpensive drug already used extensively by U.S. obstetricians) might provide the foundation for a practical and affordable fetal neuropreventive treatment strategy. Since then, three published trials (other than MagNET, referenced above) have tested the hypothesis of fetal neuroprotection from antenatal pharmacologic magnesium sulfate. These include 1) the Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO4), published in 2003,2 2) the PREMAG study from France, published in 2007,4 and updated in 2008 (Marret S, Marpeau L, Bénichou J. Benefit of magnesium sulfate given before very preterm birth to protect infant brain [letter]. Pediatrics 2008;121:225–6), and most recently 3) the trial from the MFMU Network, published in 2008.1

ACTOMGSO4

In this study, more than 1,200 preterm laboring women at less than 30 weeks of gestation were randomly assigned to receive either magnesium sulfate (4 g over 30 minutes, followed by 2 g/h up to 24
hours maximum), or saline placebo, before delivery. For purposes of later discussion, it is relevant that 1) the median exposure to magnesium sulfate prophylaxis in ACTOMgSO4 was less than 10.5 g, and that 2) just over 10% of the 522 subjects assigned to magnesium sulfate actually received as much as the maximum 28 g allowable in the study protocol. At these comparatively low-dose exposures, motor dysfunction at 2 years of age among children of mothers assigned to magnesium sulfate was significantly reduced compared with children of mothers assigned to placebo (17% compared with 22.7%, RR 0.75, 95% CI 0.59–0.96). The outcome of cerebral palsy, likewise, was reduced in those exposed to magnesium sulfate (6.8% compared with 8.2%), although this difference was not statistically significant (difference $\Delta=1.4\%$ [8.2–6.8% $\pm$ 1.4%]; $P=0.38$). Additionally, the data favored a reduction in pediatric mortality (13.8% compared with 17.1%) among those treated with magnesium sulfate, but again, the difference did not reach statistical significance ($\Delta=3.3\%$; $P=0.19$). For the primary outcome of interest, a composite variable of death or cerebral palsy (deemed especially important given that neonates having early deaths cannot be evaluated for a diagnosis of cerebral palsy at 2 years of age), a large-magnitude and nearly significant reduction was noted in the magnesium sulfate treated (19.8%) compared with unexposed (24.0%) children ($\Delta=4.2\%$; $P=0.09$) (Table 1).

PREMAG

This was a second randomized trial (excluding tocolytic magnesium sulfate) that was designed to determine whether extremely low-dose intravenous antenatal magnesium sulfate would be neuroprotective. Five hundred seventy-three gravidas, at less than 33 weeks of gestational age, having deliveries planned or anticipated within 24 hours of admission, were randomly assigned to either treatment (a single 4-g magnesium sulfate bolus infusion) or saline placebo. Children of mothers having predelivery magnesium sulfate had a reduction in gross motor dysfunction (17.6%), compared with children of mothers assigned to placebo (21.8%), a difference that was nearly significant ($\Delta=4.2\%$; adjusted OR 0.65, 95% CI 0.41–1.02; $P=0.06$). Similarly, a trend toward reduction in cerebral palsy was observed among magnesium sulfate exposed children compared with controls (7.0% compared with 10.2%, $\Delta=3.2\%$; $P=0.13$). The outcome of pediatric mortality was also reduced among the treatment cohort (9.7%) compared with controls (11.3%), although, again, the difference did not reach statistical significance ($\Delta=1.6\%$; $P=0.31$). Likewise, the composite variable of death or cerebral palsy was reduced in the treatment group compared with controls (16.1% compared with 20.2%; $\Delta=4.1\%$) a difference of substantial magnitude that nearly reached statistical significance ($P=0.07$).

MATERNAL–FETAL MEDICINE UNITS NETWORK

In the most recently published study, a multicenter trial from the Eunice Kennedy Shriver National Institute of Child Health and Human Development MFMU Network, women at imminent risk for delivery between 24 weeks and 31 weeks of gestation were randomly assigned to receive magnesium sulfate treatment or saline placebo. The magnesium sulfate dosing protocol, more complicated than in previous studies, deserves scrutiny: Women assigned to treatment received a 6-g magnesium bolus over 20 minutes to 30 minutes, followed by continuous infusion at 2 g/h. Controls received matching volumes of saline. If delivery had not occurred within 12 hours and periodic contractions abated, infusions were discontinued, but restarted when delivery was again considered imminent. For recurrent cases in which more than 6 hours had elapsed since discontinuation of infusion, an additional loading dose (6 g magnesium sulfate in the treatment group) was also given. Women already tocolyzed with magnesium sulfate before randomization (n=402) were not excluded from the trial. Importantly, because of the potential for multiple and prolonged exposures, the median total dose of magnesium sulfate in the treatment arm, 31.5 g, was much higher than in either ACTOMgSO4 (less than 10.5 g), or PREMAG (4 g).

In the MFMU Network study, 2,241 women underwent randomization. Importantly, for the trial’s primary outcome of interest, a composite variable of death or cerebral palsy, differences between magnesium sulfate and placebo were both small and statis-

### Table 1. Comparing the Three Recent Neupreventive Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Magnesium Sulfate (g)</th>
<th>CP (%)</th>
<th>Death (%)</th>
<th>Death or CP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTOMgSO4</td>
<td>Less than 10.5*</td>
<td>+1.4</td>
<td>+3.3</td>
<td>+4.2</td>
</tr>
<tr>
<td>PREMAG</td>
<td>4 only</td>
<td>+3.2</td>
<td>+1.6</td>
<td>+4.1</td>
</tr>
<tr>
<td>MFMU</td>
<td>31.5*</td>
<td>+1.6†</td>
<td>(-1.0)</td>
<td>+0.4</td>
</tr>
</tbody>
</table>

CP, cerebral palsy; ACTOMgSO4, Australasian Collaborative Trial of Magnesium Sulphate; MFMU, Maternal–Fetal Medicine Units. Positive numbers reflect a beneficial difference; negative numbers reflect a nonbeneficial difference.

* Median exposure.
† Statistically significant.
tically insignificant (11.3% compared with 11.7%, respectively; Δ+0.4%; P=.80). For the outcome of moderate or severe cerebral palsy, a reduction among children of magnesium sulfate–treated women, compared with those receiving placebo, was statistically significant (1.9% compared with 3.5%, respectively; Δ+1.6%; P=.03). Regarding pediatric mortality, on the other hand, there was a relevant excess of six deaths among children of mothers treated with magnesium sulfate, although this difference did not reach statistical significance (9.5% compared with 8.5%; Δ−1.0%; P=.41).

**COMPARISONS AMONG THE CEREBRAL PALSY PROPHYLAXIS TRIALS**

Comparing the three prophylactic magnesium sulfate trials (Table 1), it seems there may be clinically important pediatric benefits from antenatal magnesium in lower dosages. For the outcome of cerebral palsy, there was a clear inclination toward improved outcomes in all treatment groups, that, interestingly, was nearly equivalent (Δ+1.4%), or better (Δ+3.2%), in the low-dose trials than was observed in the higher-dose MFMU Network study (Δ+1.6%). Not only that, but results from the low-dose trials, ACTOMgSO₄ (less than 10.5 g), and PREMAG (4 g), favored a reduction in pediatric mortality among the magnesium treatment groups compared with placebo controls (Δ+3.3% and Δ+1.6%, respectively) as well. This, however, contrasts with the high-dose (31.5 g) MFMU Network study in which there was increased mortality among children in the treatment group (Δ−1.0%). Accordingly, for the most clinically important outcome, the composite variable of death or cerebral palsy, the marginal protective benefit observed in the high-dose MFMU Network trial disappeared almost completely (Δ+0.4%) due to increased pediatric deaths among the treated cohort. Conversely, for this composite variable, both lower-dose trials (ACTOMgSO₄ and PREMAG) favored improved outcomes of substantial magnitude among the treated cohort (Δ+4.2% and Δ+4.1%, respectively).

The very recently published meta-analysis of magnesium neuroprophylaxis from Cochrane, using data from the neuropreventive trials discussed above, as well as MagnNET,² found that antenatal magnesium sulfate treatment of women at risk for preterm birth reduced risk of death or cerebral palsy (RR 0.85, 95% CI 0.74–0.98),₅ supporting the concept of neuroprophylactic magnesium sulfate. However, it is critical that this meta-analysis not be viewed as an endorsement of any of the individual research protocols contributing data for review. For example, close inspection indicates that clinical use of the MFMU Network high-dose protocol¹ might succeed in modestly reducing the prevalence of cerebral palsy; however, it would do so with unacceptable toxicity (mortality in susceptible fetuses), partially negating the overall benefit that might have been accrued by neuroprotection. Contrarily, the protocols employed in ACTOMgSO₄ and PREMAG seem to have approximated dosages of magnesium sulfate that provided neuroprotection without incurring toxicity. Unfortunately, unlike the MFMU Network trial (which was adequately powered but inadvertently employed dosages of magnesium sulfate that were too high), the low-dose trials (due to small sample size) seem to have been underpowered, individually, to achieve statistical significance of their beneficial effect (although significance was later detected in meta-analysis).

**CONCLUSION**

Although much remains to be learned, there are currently sufficient data with which to make evidence-based recommendations regarding the role of magnesium sulfate in contemporary obstetric practice. For preeclampsia seizure prophylaxis, a vigilantly monitored infusion of magnesium sulfate improves maternal safety without evident pediatric harm. Contrarily, at the high dosages employed for tocolysis, not only is there absent evidence of tocolytic benefit, but the preponderance of data indicates toxicity to susceptible fetuses as well. Finally, for the prevention of cerebral palsy, clinical outcomes subsequent to antenatal “prophylactic” magnesium sulfate remain insufficiently characterized. Although there likely is a clinically important protective effect in very low doses (apparently around 10 g or less), there is also a signal indicating a trade-off toward fetal toxicity and death with increasing doses. It is axiomatic that drugs perform optimally at levels within a “therapeutic window,” below which they are ineffective and above which they are increasingly toxic. Likewise, drug therapies should be used only with firm evidence that benefits exceed risks. For preeclampsia, magnesium sulfate has met this requirement and remains the drug of choice at current well-established doses. For tocolysis, magnesium sulfate clearly has not met this requirement and should now be viewed as contraindicated. Finally, in comparatively modest dosages, recent data are compelling that neuroprotection can be safely achieved without the toxicity expected at higher doses. Ideally, either 1) further meta-analysis of available individual patient data, thus accounting for the precise magnesium sulfate dosages among subjects or 2) the conduct of a sufficiently powered...
randomized trial using targeted low dosages will confirm this observation and clarify optimal safe dosing for neuroprophylaxis.

REFERENCES


