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Magnesium Sulfate Neuroprotection: Time to Start?

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Learning Objectives: *After participating in this activity, the obstetrician/gynecologist should be better able to:*

1. *Define the role of preterm birth as a risk factor for cerebral palsy.*
2. *Predict the percent reduction in cerebral palsy, the number needed to treat to prevent a case of cerebral palsy, and the cost of preventing a case of cerebral palsy due to magnesium sulfate.*
3. *Formulate a clinical protocol for the administration of magnesium sulfate for neuroprotection.*

Can We Prevent Cerebral Palsy?

Among the disorders that might befall a newborn, surely one of the most feared is cerebral palsy (CP). The effects on movement and muscle control that attend this chronic neurologic disorder are well known and can be devastating. These individuals may require a lifetime of special care, and their quality of life can be significantly compromised. On a less personal basis, CP also poses a major public health concern. With an incidence of 3–4 per 1000, there are approximately 800,000 individuals with CP in the United States and an additional 8000 new cases per year. Because lifetime costs exceed $1 million, the cumulative lifetime cost of all individuals with CP born in the United States in the single year 2003 has been estimated at $11.5 billion.[1] Despite the fact that only a small percentage of cases results from malpractice, the daunting costs associated with caring for these individuals leads many parents to seek money through the tort system, adding legal costs and probably medical costs associated with defensive medicine.

Obstetrically based strategies to prevent CP have been disappointing. Electronic fetal monitoring, for example, has failed to reduce the incidence of CP, largely because so few CP cases have a preventable intrapartum etiology. Other possible causes of CP in the term newborn remain elusive, are likely heterogeneous, and may or may not be amenable to easy prevention.

Although only approximately 3.7% of babies are born prior to 34 weeks gestation, 25% of CP cases arise from these preterm newborns, making prematurity a major risk factor.[1] Unfortunately, efforts to prevent preterm birth have failed thus far, and the overall preterm birth rate is increasing. Coincident with this rise in prematurity, newborn survival, especially at the extremes of prematurity where CP is most common, has increased. Accordingly, the prematurity-associated attributable risk of CP continues to rise. Until and unless we are able to turn the tide on preterm birth, prevention of CP in the premature newborn may be our best hope for making significant inroads in the incidence of CP. This article reviews recent information on the potential neuroprotective effects of magnesium sulfate in the preterm fetus. After reading it, the obstetrician/gynecologist will be able to define the role and cost effectiveness of magnesium sulfate in the prevention of cerebral palsy in the preterm infant and be able to formulate a clinical protocol for the use of magnesium sulfate for neuroprotection.

CP and Magnesium Sulfate: How Did This Get Started?

As survival of increasingly premature babies became more common in the last century, increasing periventricular-

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The author has disclosed that the use of magnesium sulfate for neuroprotection as discussed in this article has not been approved by the U.S. Food and Drug Administration.

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intraventricular hemorrhage (PIVH) and periventricular leukomalacia (PVL) was seen, and investigators began to study risk factors for these neuroradiographic antecedents of CP. An epidemiologic study by van de Bor et al. in 1987 prospectively analyzed the occurrence of PIVH in preterm infants born prior to 32 weeks gestation.[2] One of the few factors that was statistically linked to a reduced risk of PIVH on logistic regression analysis was maternal preeclampsia. This interesting finding was confirmed in subsequent studies.[3,4]

Magnesium sulfate is commonly used to prevent eclamptic seizures in women with preeclampsia, so the question became whether preeclampsia or magnesium sulfate might be protective. The first case-control study to address this question explicitly was by Nelson and Grether in 1995.[5] They studied 42 very low birthweight (<1500 g) infants with CP and compared the likelihood of magnesium sulfate administration with that of 75 unaffected controls. The odds ratio for receipt of magnesium sulfate among the affected newborns was 0.14, and this very strong effect persisted after control for multiple other obstetric factors, including whether magnesium sulfate was administered for preterm labor or for preeclampsia. In other words, it appeared that magnesium sulfate was responsible for the neuroprotective effect.

At least eight other retrospective case-control or cohort studies followed to address the same question: does maternal administration of magnesium sulfate for either preeclampsia or preterm labor prevent CP? The results of these studies were decidedly mixed, with two additional positive studies showing similar strong odds ratios, and six negative studies. The retrospective studies are summarized in Table 1.[5–13] It is interesting to speculate as to whether further studies would have been conducted if the results of the initial study by Nelson and Grether had been negative instead of positive.

With these data in hand, two reasonable questions arose: 1) Is it biologically plausible that magnesium sulfate might prevent CP? and 2) Can the putative neuroprotective effect of magnesium sulfate be demonstrated in prospective randomized controlled trials (RCTs)?

Biologic Plausibility

Soon after the Nelson and Grether study, Goldenberg and Rouse reviewed the potential causes of CP in preterm infants, enumerating three distinct pathways:[14] 1) PIVH may result from fluctuations in blood flow in the fragile, immature periventricular vasculature, related at least in part to defective autoregulation; 2) perinatal hypoxia might injure periventricular neurons, manifesting as PVL; and 3) cytokines (and possibly other inflammatory mediators related to infection or other inflammatory causes of preterm delivery) may directly injure periventricular neurons, again manifesting as PVL.

Although far from being completely understood, magnesium sulfate has at least the potential to alter all three of these harmful pathways. Magnesium regulates numerous biologic functions involved in membrane excitability and vascular tone. By stabilizing vascular tone, fluctuations in blood flow leading to PIVH might be reduced. Hypoxic cell death might be reduced by blocking N-methyl-D-aspartate receptors and cytokine-mediated cell death prevented by directly down-regulating cytokine

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Table 1. Summary of Retrospective Studies

First Author, Year	Study Design	No. of Patients (Case/Control or Total)	Inclusion Criteria	Outcome Measure	Odds Ratio
Nelson, 1995	Case control	43/75	<1500 g	Mod/ severe CP	0.14
O'Shea, 1998	Case control	80/240	500–1500 g	CP	NS
Wilson-Costello, 1998	Case control	72/72	<1500 g	CP or other	NS
Grether, 2000	Case control	170/288	<2000 g/33 weeks, no HTN	CP	NS
Matsuda, 2000	Case control	22/170	26–30 weeks	CP	0.13
Boyle, 2000	Case control	97/110	<750 g, no HTN	CP	NS
Costantine, 2007	Case control	19/38	<1000 g	CP	NS
Schendel, 1996	Cohort	1097	<1500 g	Death/ CP/MR	NS death 0.11 CP
Paneth, 1997	Cohort	1105	<2000 g	IVH/PVL/ CP	NS

CP, cerebral palsy; IVH, intraventricular hemorrhage; HTN, hypertension; MR, mental retardation; NS, not significant; PVL, periventricular leukomalacia.

Table 2. Summary of Randomized Controlled Trials

Trial	Location/ No. of Centers/ No. of Countries	No. of Infants	Entry Diagnosis	Relative Risk of CP (95% CI)
MagNET	United States/1/1	165	64% tocolytic 36% neuroprotection	NS
ACTOMgSO4	Australia/16/2	1255	63% PTL 9% PROM 15% Pre-e	0.85 (0.56–1.31)
Magpie	International/ 125/19	805	100% Pre-e	0.66 (0.11–3.94)
PREMAG	France/13/1	688	85% PTL 61% PROM	0.70 (0.41–1.19)
BEAM	United States/ 20/1	2444	10% PTL 87% PROM	0.59 (0.40–0.85)

CP, cerebral palsy; NS, not significant; Pre-e, preeclampsia; PTL, preterm labor; PROM, preterm rupture of membranes.

release. More recent studies have also focused on magnesium's ability to inhibit the adverse actions of oxygen radicals and excitatory amino acids on preoligodendrocytes.[15,16] Although much remains to be learned regarding the etiology of CP and magnesium's biologic actions in pharmacologic doses, the threshold of biologic plausibility seems to be met. Based on the preliminary epidemiologic and retrospective studies and biologic plausibility, undertaking time-consuming and expensive RCTs seemed worthwhile.

Neuroprotection Randomized Controlled Trials

In conjunction with Goldenberg and Rouse's review, the National Institute of Child Health and Human Development began a multicenter prospective RCT to determine whether magnesium sulfate can prevent CP. This trial took 10 years and cost $25 million to complete. During this time, four other RCTs were also completed to analyze this important question.

The first study, MagNET, was described originally as a letter in the *Lancet* with additional data analysis and patient accumulation eventually published in multiple journals over the next several years.[17–19] This small (n = 169) single-center study had a complex, four-arm design and was not adequately powered to demonstrate a reduction in the occurrence of CP. Accordingly, it demonstrated no effect of magnesium sulfate administration on the occurrence of CP or fetal death. Unplanned post hoc analyses led to some concerns regarding an increased risk of death with higher doses and/or levels of magnesium sulfate and led to termination of the study. (These concerns are addressed in the section on dosage.)

After this initial small study, four large, multicenter RCTs investigated the effect of magnesium sulfate on the occurrence of CP and neonatal death. The five total studies are summarized in Table 2.[17–23] Three of the studies (Australasian Collaborative Trial of Magnesium Sulphate [ACTOMgSO4], PREMAG in France, and Beneficial Effects of Antenatal Magnesium Sulfate [BEAM]) were specifically designed to test the effect of magnesium sulfate administration on women at increased risk for preterm delivery due to preterm labor, preterm rupture of membranes, or other obstetric complications.[20–22] The fourth study, the Magpie trial, was a secondary analysis of the original study investigating the effectiveness of magnesium sulfate for prevention of eclampsia.[23] Each study had slightly different inclusion and exclusion criteria as well as protocols for magnesium sulfate administration. The study endpoints also varied in severity of CP and inclusion of other, less-standardized criteria such as "substantial gross motor delay" in ACTOMgSO4. Importantly, the endpoint in all of the RCTs was CP or death; it is important to ensure we are not preventing CP at the cost of an increased mortality rate. As shown in Table 2, all studies demonstrated a reduction in the occurrence of CP with magnesium sulfate administration, although this only reached statistical significance in the BEAM study. No study demonstrated a significant risk of neonatal death.

Meta-Analyses

These five RCTs formed the basis of two recent meta-analyses. The designs of the meta-analyses were similar and are summarized in Table 3.[24,25] The five studies yielded more than 5200 infants randomized to magnesium sulfate or placebo. There was a significant reduction in the risk of CP (relative risk [RR] 0.69–0.70) and moderate to severe CP (RR 0.60–0.64). There was no effect on total pediatric mortality (RR 1.01). Importantly, the meta-analyses are

Table 3. Meta-Analyses

First Author, Year	No. of Women	No. of Infants	Relative Risk of CP	Relative Risk of Moderate/ Severe CP	Relative Risk of Death or Moderate/ Severe CP	Relative Risk of Total Pediatric Mortality	NNT <30 Weeks	NNT <32–34 Weeks
Conde-Agudelo, 2009	4796	5357	0.69 (0.55–0.88)	0.64 (0.44–0.92)	NR	1.01 (0.89–1.14)	NR	52
Costantine, 2009	NR	5235	0.7 (0.55–0.89)	0.60 (0.43–0.84)	0.85 (0.73–0.99)	1.01 (0.89–1.14)	46	56

CP, cerebral palsy; NNT, number needed to treat; NR, not reported.

robust and homogeneous. In simple terms, this means that the results of the meta-analyses are not influenced by a few cases or slight alterations in statistical analysis, and that all of the studies had similar results. These characteristics strongly increase the likelihood that the results of the meta-analyses are not due to chance. Together, these five studies and two meta-analyses make a compelling case for magnesium sulfate administration to prevent CP in pregnancies at risk for preterm delivery.

Before adopting the routine administration of magnesium sulfate to women at risk for preterm birth however, several important additional questions need to be addressed. Would such a protocol be cost effective? Would it be safe for the mother? Is there a fetal or newborn risk? What dosing strategy should be used, and which patients should be included? These questions will be addressed in the following sections.

Cost Effectiveness

To address the cost-effectiveness issues, it is first important to ask a basic question: how many women will have to receive magnesium sulfate to prevent a single case of CP? This will be a function of how commonly CP occurs and to what extent magnesium sulfate prevents it. This statistic is referred to as the *number needed to treat* (NNT). The meta-analyses answer this question. If the efforts were focused only on women before 30 weeks gestation, approximately 46 women would need to be treated to prevent a case of CP. If we treat all the way to 34 weeks gestation, 56 women will need to be treated to prevent a case of CP. Certainly, these numbers compare favorably to other obstetric interventions such as administration of magnesium sulfate to prevent eclampsia in women with severe preeclampsia (NNT approximately 70) or performance of elective repeat cesarean section to prevent uterine rupture (NNT approximately 150).

The next step is to analyze the cost of administering the magnesium sulfate. As magnesium sulfate is very inexpensive, this cost is low, and had been estimated at approximately $180 per patient. Using the NNT of 56, $10,200 would be spent to prevent a case of CP. This calculation assumes that all women given magnesium sulfate will deliver. In practice, some women probably will receive magnesium sulfate because they are at risk to deliver early but do not. Although this increases the cost of prevention, it seems that this strategy will be a bargain to prevent a disease with a lifetime cost of more than $1 million, not to mention the tragic quality-of-life issues.

Maternal Safety

The issue of maternal safety is important: we do not want to jeopardize maternal health in our efforts to prevent CP. The meta-analysis by Conde-Agudelo and Romero summarizes the secondary study outcomes related to maternal safety.[24] There were no effects on maternal death, cardiac or respiratory arrest, pulmonary edema, respiratory depression, severe postpartum hemorrhage, or cesarean section. There was an increased risk of maternal hypotension and tachycardia. Not surprisingly, there was an increased incidence of side effects commonly associated with magnesium sulfate administration such as flushing, nausea or vomiting, and sweating.

Obstetric providers are well aware of the dangers of magnesium sulfate overdose. Magnesium sulfate is frequently used in labor and delivery units, and physicians and nurses are familiar with its usage and alert to signs and symptoms of toxicity. However, magnesium sulfate has a relatively narrow therapeutic window. Levels of 4–7 mg/dL are commonly seen in patients receiving magnesium sulfate for preeclampsia or preterm labor. Deep tendon reflexes will disappear at approximately 10 mg/dL, and respiratory arrest can occur at approximately 15 mg/dL, or just over twice the upper end of the therapeutic range. As hospitals institute routine administration of magnesium sulfate to prevent CP, attention to patient safety protocols is in order, including drills for the care of a pregnant woman in cardiac arrest, review of the use of calcium gluconate to treat magnesium sulfate overdose, and so on.

A common scenario in cases of maternal death from inadvertent overdose of magnesium sulfate is the unintentional rapid administration of an entire bag of intravenous fluids containing a lethal dose (20 g or more) of magnesium sulfate. A simple strategy employed at many hospitals is the avoidance of putting a lethal dose of magnesium sulfate in a bag of intravenous fluid. For example, if 10 g magnesium sulfate is mixed in 500 mL of fluid, even the inadvertent rapid administration of the entire bag of fluid will not result in maternal death. This is a simple safety protocol that warrants widespread adoption.

Fetal and Newborn Safety

The authors of the first small, single center RCT, MagNET, found what they considered to be a relatively high rate of total pediatric (fetal + neonatal + postneonatal)

mortality.[17] They undertook several unplanned, post hoc analyses of their data. Criticisms of their analyses are well documented and extensive. The original study design was complex, with four arms enrolling women with either preeclampsia or preterm labor, and the preterm labor group further divided into a tocolytic or neuroprotection arm. It has been suggested that the mortality rate in the patients exposed to magnesium sulfate was typical, and that the rate was unusually low in the placebo group. Additionally, concern was raised that there was unequal ascertainment of death between the treatment and placebo groups, with more effort expended to document deaths in the treatment group, especially late deaths. There were a total of nine deaths among the patients who received magnesium sulfate.

At least some of the deaths should have been excluded from further analysis as they had other obvious causes (e.g., twin–twin transfusion syndrome [two deaths], multiple congenital anomalies [one death]); if this had been done, significance would have vanished. Five deaths occurred remote from magnesium sulfate administration, often after hospital discharge and/or months after delivery, calling into question biologic plausibility. Without the late deaths, the findings were not significant. Twins were unevenly allocated between the two groups and should also have been excluded. The authors briefly attempted to enlist supporting data from the Cox et al. RCT of magnesium sulfate as a tocolytic, claiming an increased risk of death in that study as well.[26] This claim was soundly refuted by a senior author of that study.

The MagNET authors were able to find some statistically significant associations during post hoc analysis, which showed an increased risk of death with total magnesium sulfate administration exceeding 48 g (an arbitrary threshold and only after excluding women who received magnesium sulfate for preeclampsia); and a higher median total ionized umbilical cord magnesium level among a subset of deaths (one of whom was stillborn) compared with levels in a subset of survivors. From these findings, they concluded that lower doses of magnesium sulfate, as might be given for preeclampsia, were safe (and possibly neuroprotective), but that higher doses, as might be given for tocolysis, caused pediatric mortality, the "death dose–response hypothesis."

There are an almost unlimited number of post hoc analyses that can be performed with any study. As such, investigators will always be able to find some post hoc comparisons that meet the criteria of statistical significance. Although this can be a valuable exercise to generate hypotheses for future study, it is not appropriate to reach conclusions from such analyses. Further, the hypothesis that magnesium sulfate causes deaths, especially late deaths, is unsupported by animal data or biologic plausibility, unlike the CP prevention hypothesis. How might magnesium sulfate cause pediatric death months after hospital discharge? The authors' original conclusion that "*if* (emphasis added) this relationship is confirmed by experimentation with animals or through the conduct of a large RCT at other institutions, it is possible that tocolytic magnesium will be found to be associated with the [excess] deaths" was correct. Unfortunately, the post hoc analysis based on a total of nine deaths was accepted by some at face value and formed the basis of a Cochrane review and controversial editorial.[27,28]

Table 4. Dosing Regimens

Trial	Regimen	Stop If	Restart If
BEAM	6 g/20–30 min then 2 g/hr	Birth, or 12 hr and birth no longer imminent	Birth is again imminent; if > 6 hr, re-bolus
ACTOMgSO4	4 g/20 min then 1 g/hr	Birth or 24 hr	NA
PREMAG	4 g/30 min	NA	NA
Magpie	4 g/15 min then 1 g/hr	Birth or 24 hr	NA
MagNET	4 g then 2–3 g/hr	NR	NR

NA, not applicable; NR, not reported.

Did larger studies support the death dose–response hypothesis that magnesium sulfate, especially at higher doses, causes pediatric mortality? The largest retrospective study to address this issue analyzed outcomes from nearly 13,000 exposed newborns.[29] This study found a highly statistically significant *reduction* in newborn mortality (odds ratio [OR] 0.67, $p = 0.0005$) in association with magnesium sulfate exposure, and this effect persisted whether magnesium sulfate was given for preeclampsia or for preterm labor.

The other four large, multicenter RCTs also addressed the issue of mortality.[20–23] As shown in Table 3, no study found an effect on mortality, and both meta-analyses demonstrated an RR for newborn death of 1.01. Neither did the meta-analyses find an association with other indicators of neonatal morbidity such as low Apgar score, neonatal seizure, respiratory distress syndrome, bronchopulmonary dysplasia, need for ventilation, or necrotizing enterocolitis. Finally, to lay the death dose–response hypothesis to rest, Rouse and co-investigators analyzed outcomes for fetuses exposed to the highest doses of magnesium sulfate in the BEAM trial.[22] The highest total dose quartile (dose range, 44–201 g) had an OR for death of 1.01. The highest cord blood magnesium quartile had an OR for death of 0.89. Although it would certainly be prudent to continue to collect data on fetal and infant mortality from future studies, the data overwhelmingly refute the death dose–response hypothesis and suggest that the initial findings suggesting a link between magnesium sulfate administration and pediatric mortality occurred due to chance.

Which Magnesium Sulfate Protocol to Use?

Table 4 list the five RCTs with the various dosing regimens used. There are differences in loading dose (4 or 6 g), maintenance dose (none, 1 or 2 g/hr), length of time maintenance dose is continued, use of re-bolus or not, and re-initiation of the maintenance infusion.

Magnesium sulfate readily crosses the placenta, with detectable levels in the fetus by approximately 1 hour and

near equilibrium with the maternal compartment by about 4 hours. Maternal levels decrease after infusion is discontinued; half-life is approximately 6 hours. Although the mechanism of action whereby magnesium sulfate prevents CP is incompletely understood, it is presumed that it relies on an increased tissue level of magnesium in the fetus/newborn around the time of birth. Accordingly, in practice, it would seem prudent to use a protocol that optimizes the chances of a pharmacologic fetal level at birth. Although understandable from a study design standpoint, it might not make sense in clinical practice simply to administer a 4-g loading dose alone if the patient does not deliver for several days. There have been no attempts to analyze the five RCTs further and determine whether anything can be learned about the optimal dosing strategy. Given the difficulty and expense of RCTs, it seems unlikely that a dose-finding study will be conducted in the future. Therefore, what regimen should clinicians use?

It may be noteworthy that the study that showed the largest reduction in CP is the BEAM trial, which used the highest dosing regimen (6-g bolus, 2 g/hr maintenance, and provision for a re-bolus if birth again became imminent).[22] It is unknown whether the improved results in this study occurred by chance or are due to the more aggressive dosing regimen. Some might advocate this regimen be adopted to ensure we are giving enough magnesium.

On the other hand, the improved results of the BEAM study might have occurred because care was taken to ensure that magnesium sulfate was present at delivery by use of a continuous infusion and a re-bolus protocol. Further, the 6-g bolus and higher infusion rate may interfere with patient and/or provider acceptability and may provide a lesser margin of maternal safety. Concerns regarding increased side effects, uterine atony, inadvertent tocolysis, and complications related to co-administration of calcium channel-blockers might be raised. Those who think that higher doses of magnesium sulfate might lead to an increase in pediatric mortality would favor a lower dose, although these concerns appear unfounded. Finally, it should be recalled that there are considerable data from studies in which magnesium sulfate was given for preeclampsia showing a reduction in CP; these studies generally used a lower magnesium sulfate dose. Although these lower doses are effective in preventing eclampsia; there is no *a priori* reason to suspect they will be less effective at preventing CP.

Pending further information (secondary analysis of the prevention studies, animal data establishing an effective level, etc.), my institution uses a hybrid protocol of a 4-g bolus, 1 g/hr maintenance, and re-bolus if magnesium sulfate has been withheld for more than 6 hours. Given that it takes approximately 4 hours for magnesium sulfate levels to reach a steady state in the fetus, we attempt to begin the infusion at least 4 hours prior to birth if possible but would give it as late as 1 hour prior to birth. We discontinue magnesium sulfate after 12 hours if preterm birth no longer appears imminent. It seems reasonable for clinicians to adopt any of the protocols from the four large RCTs.[20–23]

For clinicians using nifedipine or other calcium channel-blockers routinely for tocolysis or for blood pressure control in association with preeclampsia, the issue of co-administration will inevitably arise. Although there are data to suggest this practice is safe, many clinicians remain wary of significant hypotension or other cardiovascular complications on the basis of personal or anecdotal experience. On our service, we minimize co-administration of these medications, although the occasional brief overlap may occur.

Patient Inclusion

As listed in Table 2, the various studies had gestational age cutoffs of 30–34 weeks gestation. Although the risk of CP increases at earlier gestational ages, the meta-analyses both support administration up to 34 weeks gestation. The NNT (56) with treatment all the way up to 34 weeks gestation is not substantially higher than the NNT (46) if treatment is only offered to 30 weeks gestation. We have chosen to include pregnancies up to 34 weeks gestation for neuroprotection. Other clinicians might reasonably choose cut-offs of 30 or 32 weeks gestation.

Clinicians will need to select the specific patients to treat with magnesium sulfate for neuroprotection. Women with planned indicated preterm births will be easily identified. Women admitted with preterm rupture of membranes probably do not warrant empiric treatment unless regular contractions are noted. Women admitted with preterm labor probably do not warrant routine treatment unless they are failing tocolysis tests and have progressive cervical dilation. However, treatment must be individualized.

Finally, as detailed in the meta-analyses, it cannot be determined whether magnesium sulfate is more or less effective in twins vs. singletons. Given that there is no reason to suspect magnesium sulfate would be less effective in multiple gestations, and given that multiple gestations make up a significant portion of preterm deliveries, we choose to use it in all births up to 34 weeks gestation regardless of plurality.

Clinical Scenarios

The following five common clinical scenarios typify patients who would be candidates for magnesium sulfate neuroprotection.

Preterm Labor, Receiving Tocolytic Magnesium Sulfate

A patient is admitted at 26 weeks gestation with preterm labor. Her contractions have subsided with magnesium sulfate, currently being administered at 3 g/hr, and indomethacin. Amniocentesis is performed and indicates chorioamnionitis. The magnesium sulfate is reduced to 1 g/hr to continue until delivery, indomethacin is discontinued, and antibiotics and Pitocin are given.

Preterm Labor, on Nifedipine

A patient hospitalized with preterm labor is stable on nifedipine. She begins having increased contractions and is found to be 6 cm dilated. Magnesium sulfate 4-g bolus is

given, waiting until 3–4 hours after the last dose of nifedipine if possible. After completing the magnesium sulfate bolus, the infusion is continued until delivery at 1 g/hr.

Preterm Rupture of Membranes

A patient with preterm rupture of membranes at 29 weeks gestation is admitted for expectant management. She is initially contracting and receives magnesium sulfate 4-g bolus then 1 g/hr. The contractions subside, and the magnesium sulfate is discontinued after 12 hours. She begins to actively contract again 12 hours later and is found to be 7 cm dilated. As more than 6 hours have elapsed, she receives a second 4-g bolus and then an infusion of 1 g/hr until delivery.

Indicated Preterm Birth

A patient is admitted with severe growth restriction, oligohydramnios, and reversed end-diastolic velocity on umbilical cord velocimetry at 31 weeks gestation. She is given betamethasone with planned cesarean birth in 48 hours. Four hours preoperatively, she is given a 4-g bolus of magnesium sulfate and then a 1-g/hr infusion until delivery.

Preeclampsia

A patient is admitted with severe preeclampsia at 35 weeks gestation. She is given a 4-g bolus of magnesium sulfate and then an infusion of 2 g/hr, and induction of labor is started. As she is already receiving magnesium sulfate for seizure prophylaxis, no alteration in her care is required.

Conclusions

It is gratifying to reflect on the course of this research, which progressed from an unbiased observation ("preeclampsia is associated with a decreased risk of CP") to conclusive meta-analyses demonstrating the effectiveness of magnesium sulfate for neuroprotection. Although hardly a panacea, solid research evidence seems to indicate that magnesium sulfate given to women delivering prior to 34 weeks gestation will help reduce the incidence of CP, and this conclusion has been endorsed by a recent Cochrane review.[30] On the basis of these findings, it's time to start!

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1. The prematurity-related attributable risk for cerebral palsy is
- **A.** 10%
- **B.** 25%
- **C.** 35%
- **D.** 50%

2. Most cases of cerebral palsy result from intrapartum hypoxemia.
- **A.** True
- **B.** False

3. Magnesium sulfate should be
- **A.** given to women at high risk of delivering prior to 30–34 weeks
- **B.** administered as a loading dose of 4–6 g followed by an infusion of 1–2 g/hr
- **C.** discontinued after 12–24 hours if birth is no longer imminent
- **D.** all of the above

4. Periventricular-intraventricular hemorrhage in the newborn is commonly associated with development of cerebral palsy.
- **A.** True
- **B.** False

5. The biologic mechanism whereby magnesium sulfate prevents cerebral palsy is well understood, and a dose-response curve has been established.
- **A.** True
- **B.** False

6. A total maternal magnesium dose of 48 g or more is clearly related to an increased rate of total pediatric mortality.
- **A.** True
- **B.** False

7. The relative risk of neonatal mortality related to maternal administration of magnesium sulfate in the meta-analyses is approximately
- **A.** 0.5
- **B.** 0.75
- **C.** 1.0
- **D.** 1.25

8. The administration of magnesium sulfate to women that deliver a preterm baby appears to reduce the likelihood of cerebral palsy by approximately
- **A.** 10%–20%
- **B.** 20%–30%
- **C.** 30%–40%
- **D.** 40%–50%

9. The number of women that need to be treated to prevent a case of cerebral palsy is approximately
- **A.** 10
- **B.** 50
- **C.** 100
- **D.** 1000

10. The cost of magnesium sulfate administration to prevent a case of cerebral palsy is approximately
- **A.** $100
- **B.** $1000
- **C.** $10,000
- **D.** $100,000