

Hvidovre d. 28.09.09

Kære kollega

Vi er en gruppe af obstetrikere og neonatologer (Morten Hedegaard og Gorm Greisen fra Rigshospitalet, Jannie Dalby Salvig og Tine Brink Henriksen fra Skejby Sygehus samt Niels Jørgen Secher, Ole Pryds og Lene Huusom fra Hvidovre Hospital) som overvejer at lave et projekt om **Magnesium Sulfat (MgSO₄) som forebyggelse for cerebral parese blandt prætermfødt børn.**

Vi har haft møde med henblik på at diskutere om man ud fra eksisterende litteratur kan anbefale allerede nu at indføre behandling med MgSO₄ eller om man skal udføre en ny randomiseret undersøgelse. Vi har indtryk af at behandlingen endnu ikke er indført i Danmark, og vi har været i kontakt med engelske, svenske og norske obstetrikere, som heller ikke mener at MgSO₄ anvendes i deres lande. Vi overvejer derfor at lave en multicenter undersøgelse på alle større danske, svenske og norske føde- og neonatal afdelinger for at forsøge at belyse emnet bedre.

Der er siden 2002 lavet fem prospektive randomiserede studier, som undersøger effekten af MgSO₄ på cerebral parese. Der er stor forskel på studiernes størrelse og inklusionskriterier, og resultaterne er ikke entydige. Dog er der en tendens i alle undersøgelserne, på nær en, som peger i retning af, at der er beskyttende effekt af MgSO₄ på cerebral parese. Der er endvidere udført en meta-analyse af de fem studier (Cochrane review), som finder en reduktion i cerebral parese forekomsten blandt børn af kvinder som var behandlet med MgSO₄ (RR 0.68; 95 % CI, 0.54-0.87). På trods af dette er der fortsat stor tvivl om, hvorvidt det er tilrådeligt at indføre behandlingen med MgSO₄ til præterme fødende. Tvivlen i forhold til at indføre behandlingen går blandt andet på studierne forskellighed.

De nærmere rammer for studiet er ikke endeligt fastlagt, men der bliver muligvis tale om at inkludere kvinder med truende for tidlig fødsel under 30 til 32 uger i gestationsalder. Kvinderne vil blive randomiseret til MgSO₄ eller placebo. Vi forestiller os at MgSO₄ kan gives sammen med Tractocile, og muligvis kan tractocile tilføres afdelingen vederlagsfrit via forskningmidler.

Vi vil derfor høre om I kan have interesse i at indgå i et sådant projekt, og hvis der er interesse for det i Danmark vil vi, som anført, udvide undersøgelsen til også at foregå i Sverige og Norge. Såfremt projektet har jeres interesse vil vi bede jer om at videresende denne skrivelse til rette vedkommende på neonatal afdelingen, som I samarbejder med.

Håber at høre fra jer på nedenstående e-mail adresser. Hvis der viser sig interesse for projektet vil vi indkalde til et møde.

Med venlig hilsen

Niels Jørgen Secher, Overlæge, Professor, Gyn/Obs Afdeling, Hvidovre Hospital
(njsecher@dadlnet.dk)

Lene Huusom, Afdelingslæge, Gyn/Obs Afdeling, Hvidovre Hospital
(lene.huusom@mail.dk)

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(Artikel giver et overblik over alle fem randomiserede undersøgelser, se nedenfor).

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Magnesium for neuroprophylaxis: fact or fiction?

[Alison G. Cahill, MD, MSCl_a](#), [Aaron B. Caughey, MD, PhD_b](#)

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**MgSO₄ for CP prevention:
too good to be true?** George A.
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The use of magnesium for prevention of cerebral palsy in preterm infants has been a pressing clinical question for some time. This issue was recently brought to the forefront again after the completion of a large trial conducted by the Maternal-Fetal Medicine Units Network and published by Rouse et al in August, 2008 in the *New England Journal of Medicine*. After review of the complex body of literature on this topic, and the recent addition of this important piece of evidence, we discussed the “pros” and “cons” of the evidence-based use of magnesium for prevention of cerebral palsy at the annual meeting for the Society of Maternal-Fetal Medicine as a luncheon roundtable.

The evidence currently available does not make the clinical decision of whether or not to use magnesium for the prevention of cerebral palsy as clear as we would hope. It appears that despite well-designed and executed studies on this critically important topic in obstetrics, the answer to the question of whether evidence-based medicine supports the use of magnesium for neuroprophylaxis in preterm infants remains unclear.

Key words: [cerebral palsy](#), [magnesium](#), [neuroprophylaxis](#), [preterm](#)

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Cerebral palsy (CP) is rare, occurring in 1.6 of 1000 live births. It is the name given to a heterogeneous group of chronic, nonprogressive disabilities of the central nervous system. Our knowledge of CP has evolved since British surgeon William Little declared in the 1860s that all cases were due to intrapartum events.¹ About half of all cases of CP occur in term infants, in which the incidence is 1 in 1500. Preterm infants have a much higher incidence of CP, and the risk is indirectly proportional to the gestational age at delivery. The rate of CP in very low-birthweight (VLBW) infants is 4-8%.²

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In the late 1980s, observational data emerged in the form of secondary analyses of studies involving VLBW infants, describing an association between magnesium sulfate (MgSO₄) exposure and infants' neurologic outcomes. Van de Bor et al³ noted a decreased rate of intraventricular hemorrhage (IVH) in VLBW infants born to women with preeclampsia compared with those born to women without preeclampsia. Leviton et al noted similar findings.⁴

At the time, the hypothesis was that intracranial hemorrhage might lead to CP and that the association between the lower rate of IVH and preeclampsia might be explained by exposure to MgSO₄. Shortly thereafter, in a study of women without preeclampsia, Kuban et al noted a lower rate of intracranial hemorrhage in VLBW infants born to women exposed to MgSO₄ for tocolysis compared with infants born to women with no such exposure.⁵

The first study from the United States to address this topic was published in 1995 by Nelson and Grether.⁶ They performed a case-control study of VLBW infants surviving until age 3 years, comparing those with CP with those without CP and found a lower rate of MgSO₄ exposure in infants with CP compared with those without CP (7.1% vs 36%; odds ratio, 0.14; 95% confidence interval [CI], 0.05-0.51). Other small observational studies followed with similar findings. Arguably these small, observational studies had limitations, but the early data suggested a protective effect for MgSO₄ against development of CP in VLBW infants.


Of course, it is important to ask how this treatment might work. As we noted previously, the initial association was seen as a decrease in IVH of VLBW infants born to mothers with preeclampsia; infants of preeclamptic mothers had fewer cerebral hemorrhages. However, although the evidence of MgSO₄ exposure and decreased rates of cerebral hemorrhage proved inconsistent, the observation of decreased rates of CP in children of women exposed to MgSO₄ persisted.

Many hypotheses and preliminary animal models have described how MgSO₄ might protect the infant brain from cerebral palsy.² For example, some researchers have proposed an excitotoxicity model, in which magnesium inhibits calcium influx by blocking N-methyl-D-aspartic acid receptors. When neurons are damaged, they are unable to maintain glutamate homeostasis, leading to a cascade involving the influx of calcium and ultimately, neuronal cell death. This pathway is blocked by magnesium. Others have proposed a vasoactive mechanism; magnesium causes vasodilation and may specifically cause cerebral vasodilation, increasing cerebral blood flow for a positive effect.

Another proposed mechanism for the magnesium effect, which stems primarily from animal models of posttraumatic brain injury, involves the reduction of oxygen free radicals. Yet another hypothesis centers on a reduction in inflammatory cytokines: magnesium-deficient rats have increases in inflammatory cytokines and neurologic injury.^{2, 7} The truth is that excitement generated by the emergence of observational data that linked MgSO₄ exposure with an apparent decrease in the rate of CP, a devastating birth outcome, has overshadowed the search for a mechanism. Although pursuit of the etiologic pathway persists, we still do not truly understand how MgSO₄ might actually protect neurons from injury.

With that background, we will review the 5 prospective, randomized controlled trials (RCTs) that have examined the use of MgSO₄ for neuroprophylaxis and the prevention of CP. These studies were published from 2002 to 2008 and vary in size, population studied, location of study, and dosing of MgSO₄. We will review them chronologically.


MagNET

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The first study to be completed and published, the Magnesium and Neurologic Endpoints Trial (MagNET), was performed by Mittendorf et al.⁸ It was conducted at 16 centers in Chicago, IL, from 1995 to 1997. The study population included women who were either experiencing preterm labor or preterm premature rupture of membranes (PPROM); each was carrying a singleton or twins at less than 34 weeks' gestation. There were 2 protocols: 1 examined MgSO₄ use for tocolysis, and the other examined its use purely for CP prevention. The primary outcomes were neonatal and infant mortality, periventricular leukomalacia, IVH, and CP.

Of the 149 women enrolled in the MagNET, 92 were randomized to the tocolysis protocol, and 57 were randomized to the neuroprophylaxis arm. The 4 outcomes were examined as a combined primary outcome deemed "adverse events." In the tocolysis segment, 29% (16/55) of the newborns whose mothers had received MgSO₄ experienced an adverse event as compared with 18% (9/51) of women who had received placebo ($P = .18$). In the neuroprophylaxis arm, 37% (11/30) of the newborns whose mother had received MgSO₄ experienced an adverse event as compared with 21% (6/29) of those who had received placebo ($P = .25$). When these 2 arms were combined, 32% of infants whose mother received MgSO₄ experienced adverse events compared with 19% of those whose mother received placebo ($P = .07$). Although not statistically significant, these findings certainly raised concerns that MgSO₄ might be harmful, rather than beneficial, to neonates.

ACTOMgSO₄


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Data from the Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO₄) Collaborative Group were published in 2003.⁹ The population, recruited from 16 centers in Australia or New Zealand, consisted specifically of women who were likely to deliver within 24 hours (eg, they had advanced cervical dilation, severe preeclampsia, or intrauterine growth retardation [IUGR] with worrisome Doppler findings). Participants were randomized to infusions of MgSO₄ or normal saline; MgSO₄ was administered as a 4 g loading infusion over 20 minutes, followed by a maintenance infusion of 1 g/h for 24 hours, maximum. The primary outcomes were total neonatal and infant mortality, occurrence of CP, and a combined outcome of death or CP.

The vast majority of the 1062 women in this study received the 4 g loading dose of MgSO₄ or placebo. However, only a small minority (70/535 in the MgSO₄ group and 77/527 in the placebo group) actually received the entire 24 hour infusion. Thus, this was a very select population with approximately 14% of the women delivering within 24 hours. The neonates were followed up and assessed at age 2 years. In contrast to the prior study, 19.8% of the neonates born to women who received MgSO₄ died or had CP, compared with 24% ($P = .09$) of neonates born to women who received placebo.

When the researchers looked at a secondary outcome, gross motor dysfunction, they found a decrease among neonates born to women who received MgSO₄ compared with those whose mothers received placebo (3.4% vs 6.6%; $P = .02$). Similarly, the combined outcome of gross motor dysfunction or death was reduced in the children born to women treated with MgSO₄ (17% vs 22.7%; $P = .02$).

MAGPIE


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A secondary analysis of the MAGnesium Sulphate for the Prevention of Eclampsia (MAGPIE) trial is the next relevant study.¹⁰ The original MAGPIE study demonstrated that the risk of seizures (eclampsia) among preeclamptic women was 58% lower among those randomized to MgSO₄.¹¹ Conducted at 175 hospitals in 33 countries from 1998 to 2001, it included women with preeclampsia, only 24% of whom were at less than 33 weeks' gestation. The protocol involved randomization to a 4 g bolus of MgSO₄ followed by continuous infusion of 1 g/h or infusion of placebo (normal saline).

In the follow-up study, 2895 of 4483 eligible children were assessed at 18 months of age. There were

essentially no differences in the outcomes, with a death rate of 13.8% among the children of women who received MgSO₄ vs 12.5% of those born to women who received placebo (relative risk [RR], 1.11; 95% CI, 0.93-1.32). A small difference was noted in the rates of neurosensory disability: 1.3% among toddlers of women treated with MgSO₄ and 1.9% among those of women who received placebo, but this was not statistically significant (RR, 0.72; 95% CI, 0.40-1.32).


PREMAG

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In 2008, Marret et al¹² published a letter to the editor of the journal *Pediatrics*, describing follow-up data from an RCT of MgSO₄ vs placebo. Their original study was conducted at 13 centers in France from 1997 to 2003.¹³ Like Crowther et al⁹ did in the ACTOMgSO₄, the PREMAG Trial Collaborative Group randomized women who were believed likely to deliver within 24 hours. Subjects received a 4 g bolus of MgSO₄ followed by continuous infusion of 1 g/h or normal saline. A total of 564 women were randomized, and data were analyzed with 508 women completing the loading dose of drug or placebo.

At 2 year follow-up, the researchers identified interesting trends among the 688 babies delivered to participants. Perinatal mortality rates were quite similar between the 2 groups: 9.4% among infants born to women randomized to MgSO₄ vs 10.4% among infants born to women receiving placebo. The CP rate was lower in children of women who received MgSO₄ (16.1% vs 20.2%; *P* = .07). Finally, the combined outcome of gross motor dysfunction or death was lower in the children of women who received MgSO₄ (25.6% vs 30.8%; *P* = .02).


BEAM

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Finally, in 2008 Rouse et al¹⁴ published results from the Beneficial Effects of Antenatal Magnesium Sulfate Trial (BEAM) in the *New England Journal of Medicine*. This large, multicenter trial was conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network at 20 centers from 1997 to 2004. It included women at less than 32 weeks' gestation, and 87% of the participants had PPRM. Women were randomized to a 6 g bolus of MgSO₄ followed by a continuous infusion of 2 g/h or to a placebo. If the women did not deliver after 12 hours, the infusion was stopped. However, if subjects again began progressing toward delivery, the infusion was restarted, or if more than 6 hours had passed since treatment had been discontinued, a repeat bolus of MgSO₄ was first administered.

In this large study, 2241 women were randomized, and their neonates were followed up and assessed at 2 years of age. The primary outcome was a composite of moderate or severe CP or death among babies born to participants. Among infants born to mothers who received MgSO₄, the rate was 11.3% vs 11.7% among babies born to women in the placebo group (RR, 0.97; 95% CI, 0.77-1.23). When the researchers looked at mortality and CP separately, the mortality rate was similar in the 2 groups: 9.5% in the MgSO₄ group and 8.5% in the placebo group (RR, 1.12; 95% CI, 0.85-1.47). However, when examining the risk of CP alone, researchers found that moderate or severe CP was significantly less likely to occur among children born to women treated with MgSO₄. The rate was 1.9% in the MgSO₄ group and 3.5% in the placebo group (RR, 0.55; 95% CI, 0.32-0.95).

How do we proceed?

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Pro

Once the BEAM results are added to the existing data, particularly those pertaining to the question of MgSO₄'s potential benefit in neuroprophylaxis, it appears that we should consider using MgSO₄ to prevent neurologic complications of pregnancy in the neonate.

Con

Whereas numerous strengths can be cited in the BEAM study, the results could also be interpreted as negative.¹⁴ It can be instinctive to conclude that the reason investigators choose a composite as the primary outcome of a study investigating a rare outcome is for logistical and power reasons, but that is not the case in this study. The primary outcome was chosen for a much more important reason, specific to the science: competing risks. Just as Crowther et al⁹ did in their study, Rouse et al¹⁴ chose the composite outcome of CP or death because death is a competing risk for the outcome of interest: CP. Infants who die before their first birthday cannot be evaluated for CP, but the risk factors that led to these preterm infants' deaths are the same as those for CP. There was no difference in the rate of composite outcome between the MgSO₄ and placebo groups.

It is difficult, remembering why a composite outcome was chosen, to evaluate 1 component of the outcome without the other. Although there was a statistically significant decrease in the rate of CP in the MgSO₄ group, there was a higher death rate in the MgSO₄ group as well, but it did not reach statistical significance. It is worth asking how many of the 99 infants who died in the MgSO₄ group would have needed to survive and be diagnosed with CP for the results to no longer be statistically significant. The answer is 2. Just 2 more cases of CP in the MgSO₄ group would cause the confidence interval to cross unity and cause the results to lose statistical significance. When we look at it this way, it is difficult to think about changing practice based on such statistically unstable results from just 1 study.

Pro

The importance of looking at the composite outcome of death plus CP because of their competing nature can be appreciated. However, the latter criticism of statistical instability plays well if you had only the single study. Consider that there are 5 studies, 4 of them using MgSO₄ purely for neuroprophylaxis. With these multiple studies, 1 way to examine the evidence as a whole is with a metaanalysis. Indeed, a recent metaanalysis was just published for the Cochrane Database by Doyle et al.¹⁵ In this analysis of the 5 studies, we noted no difference in neonatal or childhood mortality (RR, 1.04; 95% CI, 0.92-1.17), but a reduction in CP (RR, 0.68; 95% CI, 0.54-0.87) in the offspring of women treated with MgSO₄ was evident. There was also a reduction in substantial gross motor dysfunction (RR 0.60; 95% CI, 0.43-0.83). The authors concluded that “the evidence now supports antenatal magnesium as a neuroprotective agent against CP.”

Con

So now we should change practice based on a metaanalysis? Two points argue against that; 1 is specific to this body of evidence, and the other is a broader point regarding clinical decision making. To start, the 2009 Cochrane metaanalysis combined the 4 best pieces of evidence in which MgSO₄ was given with the primary intent of neuroprophylaxis.¹⁵ Although you may present the statistical tests for heterogeneity with insignificant *P* values, indicating that the studies are alike enough to be combined, there is a very important difference between statistical heterogeneity and clinical heterogeneity. In this case, it is like combining clinical apples and oranges. These studies differed in a multitude of ways, including the populations studied, treatment dosing and schedule, outcome, and measure.

Let's look at the 2 studies that carry the greatest weight in the Cochrane metaanalysis, those headed by Crowther et al⁹ (ACTOMgSO₄) and Rouse and colleagues^{14, 15} (BEAM), as an example. These 2 studies alone had significant differences: enrollment risk for preterm birth, MgSO₄ dosing, and lower gestational age limit of inclusion. Only 8% of patients in the ACTOMgSO₄ had PPRM, whereas 86% of the population in the BEAM study was enrolled because of PPRM.

We do not know a great deal about the cause of CP or the effect of MgSO₄, but we do know that the a priori risk for CP and death is not the same for infants of women with PPRM compared with those without, so it becomes difficult to understand how it is clinically sound to combine these studies.

On a broader point, there is the question of whether clinical decisions are best based on data from large RCTs or metaanalyses. This was elegantly discussed by Scifres et al¹⁶ in a recent clinical opinion in the *American Journal of Obstetrics and Gynecology*. The authors used the clinical question of whether aspirin is helpful in preeclampsia prevention as their example, but a point they make is important for this topic as well. They noted that there have been several large, well-done trials to test the hypothesis that aspirin prevents preeclampsia, and they have been negative. But a metaanalysis that combined these trials found evidence for effect.

Certainly it is tempting to want to statistically combine studies in search of an answer. And metaanalysis is a powerful and important tool, but its intent was to allow one to combine small trials of limited power that have similar trends in results to detect an answer that may have been missed (type 2 error). It seems less appropriate to combine large trials that were powered to detect a difference but did not find one.

This is an important consideration on the topic of MgSO₄ for the prevention of CP. The BEAM study by Rouse et al¹⁴ was not underpowered. Rather, it was an extremely well-designed and well-executed study, powered for a biologically important and carefully chosen outcome, which, unfortunately, did not yield the result we had hoped for.

Pro

As I am sure you know, Scifres et al¹⁶ concluded that “when available, large, randomized clinical trials should be used to guide clinical practice.” Unfortunately, we have several large RCTs, but they do not fully answer the question in this case. In the case of aspirin, it does appear that the information provided by the metaanalysis is helpful in guiding use of aspirin for prevention of preeclampsia. Similarly, the Cochrane metaanalysis helps us consider the breadth of the literature as opposed to just the individual studies. In this setting, in which no other studies are likely to be forthcoming in the near future, this is the evidence we have to consider.

To address the first point, in terms of clinical heterogeneity, if one considers just the 4 neuroprotective trials, the findings support the use of MgSO₄ for CP prevention even more. In examining the ACTOMgSO₄, PREMAG study, and BEAM study along with the neuroprotective arm of the MagNET, we found a reduction in the combined outcome of death or CP (RR, 0.85; 95% CI, 0.74-0.98).^{8, 9, 13, 14} Furthermore, I think the fact that these findings persisted in a broad range of populations is just more evidence that the treatment is generalizable to a wide range of etiologies for preterm birth, including PPROM, unstoppable preterm labor, severe preeclampsia, disconcerting fetal testing results, or IUGR.

Con

Well, I am glad you mentioned the reduction seen in the 4 neuroprotective studies because it brings us full circle. Looking closely at the combined outcome table from the Cochrane 2009 metaanalysis, we should ask the same question we asked before.¹⁵ How many additional cases of CP and death would it take to make the combined results of those 4 trials lose statistical significance? The answer is that it would take roughly 1 additional case of CP or death from the BEAM study; because of the significant weight it carries in the metaanalysis, that would yield an insignificant result.¹⁴ Should we really base our decisions on results that are this statistically unstable?

Pro

You have made this point about statistical instability twice now. Unfortunately, we do not get a do-over with clinical trials. The results that were produced by these studies are what they are, and again, in the metaanalysis of the 4 neuroprotective studies, we find that there is a reduction in the combined outcome of death or CP (RR, 0.85; 95% CI, 0.74-0.98). Although this is a small effect, it is statistically significant.

To get a sense of the clinical meaning of such findings, it can be helpful to use a number-needed-to-treat (NNT) analysis. In these populations, the overall rate of CP was about 5%. If we use the RR of 0.68, then we find that approximately 63 women would need to be treated with prophylactic MgSO₄ to prevent 1 case of CP. In the higher-risk group of women who were likely to deliver prior to 28 weeks' gestation, the risk of CP is higher at 6.2%, and the effect size is larger with an RR of 0.45; the NNT would be 29. However, in a lower-risk group of women beyond 28 weeks' gestation, in which the risk of CP is 1.3% and the RR is 0.71, the NNT would be 265.

One might consider the potential benefits of MgSO₄ within the framework of decision analysis. Treating with MgSO₄, a medication we have used freely in obstetrics, may induce more maternal side effects. However, balancing a few side effects against the potential for preventing CP tips the scale in favor of MgSO₄.

Con

When you put it that way, the balance seems favorable. But MgSO₄ is not water, even though we have given it for so long and for so many indications in obstetrics that it is easy to feel that way. I think we could all agree to live with some nausea and vomiting, and more importantly, our patients could if we were preventing an outcome as devastating as CP. But the studies designed to test the hypothesis that MgSO₄ prevents CP are not of sufficient size to evaluate the major maternal morbidities associated with MgSO₄ exposure. For that, we need to turn to the preeclampsia literature, in which studies such as the MAGPIE trial administered MgSO₄ to a much larger cohort of women to examine its antiseizure effect in those with preeclampsia.¹¹ Among the 5055 women who received MgSO₄ in the MAGPIE trial, there were 67 medication errors and 2 women had significant events (cardiac arrest and arrhythmia). We could conservatively estimate that 1 in 5000 women could die from MgSO₄ exposure. Even if that balance seems acceptable, how would the use of MgSO₄ actually be accomplished in practice?

Pro

I can appreciate your warning about using the medication appropriately to avoid a medication error. I will take this opportunity, because you used the medication errors from the MAGPIE trial as an example, to point out that the MAGPIE study was conducted in multiple countries and, in particular, in developing countries with very different medical safety guidelines.¹¹ So although there are maternal complications seen with MgSO₄ use, I am concerned about your calculation of maternal mortality seen in 1 in 5000 uses.

With regard to how we might use the MgSO₄, I think we should turn back to the studies. I think we have a variety of options. First, we could treat all women at risk for preterm birth or those who present with preterm contractions. Second, we could treat just women at acute risk of preterm birth, similar to the methods used in the 3 largest trials. Third, we could treat women at the highest risk of preterm birth, who also have the highest risk of CP occurring in their neonates; those whose pregnancies are earlier than 28 weeks' gestation.

Interestingly, in a subgroup analysis by gestational age from the BEAM paper, CP rates among neonates born before 28 weeks' gestation were 2.7% among those whose mothers were treated with MgSO₄ and 6.0% among those whose mothers received placebo.¹⁴ In women beyond 28 weeks of gestation, the rates in neonates were identical: 1.3% in each group. Perhaps the protective effect of MgSO₄ is beneficial only in neonates of earlier gestational age.

In terms of the exact protocol, this is also challenging. No clear difference in dose-response effect between administering the 4 g bolus dose followed by the 1 g/h infusion and the 6 g bolus dose followed by the 2 g/h infusion has been identified. Thus, one could consider using the lower-dosage protocol, which is then less likely to lead to maternal side effects. I would suggest administering the protocol used by Rouse et al¹⁴ in the BEAM study, in which any woman whose MgSO₄ had been discontinued more than 6 hours earlier, got another bolus dose when the risk of preterm birth increases again.

Con

That seems as confusing as deciding whether there is evidence to give this treatment. The protocol one follows depends on how convinced one is by the data in a particular trial? Does that mean that if the results of the Cochrane metaanalysis led you to change your practice, it is a protocol toss-up?


Pro

In conclusion, given the breadth of evidence, it is time for us to start using MgSO₄ for neuroprophylaxis. This is commonly prescribed on labor and delivery units for tocolysis in women in preterm labor and for seizure prophylaxis in women with preeclampsia, a group likely to compose a large proportion of the women having a preterm birth anyway. The average benefit appears to be such that you would need to treat 63 women to prevent 1 case of CP, but in women less than 28 weeks' gestation, you might need to treat as few as 29 women to prevent 1 case of CP. I think the specific protocol needs to be decided at the institutional level. Still, physicians might routinely recommend MgSO₄ to women prior to 28 weeks' gestation and simply offer it to women at 28 weeks' gestation and beyond because of the findings among the different strata.

Con

CP is a devastating outcome, and we, as obstetricians, must continue on our path for greater understanding of its causal pathway and ways to prevent it. Unfortunately, as we stand here today, it shares a causal pathway with stillbirth and death and cannot be studied in isolation of these latter outcomes, as was acknowledged by the talented scientists who chose composite outcomes in the studies we have highlighted. And, much to our disappointment, the most recent BEAM trial by Rouse et al¹⁴ was negative in its findings for an effect of MgSO₄ on the prevention of CP and stillbirth.¹⁴ Whereas a patient-level metaanalysis may help us identify a specific patient population for which this therapy would be of benefit, our current body of evidence does not support a clear change of practice to the use of MgSO₄ for neuroprophylaxis in patients at risk for preterm birth.

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^a Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Washington University–St Louis, St Louis, MO

^b Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California–San Francisco, San Francisco, CA

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