

## EDITORIALS



## Antenatal Magnesium Sulfate for Neuroprotection before Preterm Birth?

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Preterm infants are at increased risk for serious, lifelong neurologic abnormalities such as cerebral palsy.<sup>1,2</sup> As the survival of preterm infants has improved with advances in perinatal care,<sup>2</sup> the occurrence of cerebral palsy has increased further, since infants who would previously have died now survive with their cerebral pathology. Currently, more than 30% of children with cerebral palsy are born preterm.<sup>1</sup>

Compounding these concerns are the trends, particularly in the United States, to increases in preterm birth.<sup>3</sup> An emphasis on improving the survival of very preterm infants without associated strategies to prevent preterm birth or the neurologic disorders associated with it results in substantial costs to society and anguish for parents.

Limited data have suggested that magnesium sulfate may have neuroprotective effects on babies born preterm.<sup>4</sup> Magnesium sulfate has been widely used for tocolysis in the United States,<sup>5</sup> although studies show that it is ineffective for this indication<sup>6</sup> but is effective for the treatment and prevention of eclampsia.<sup>7</sup> In several observational studies, preterm infants whose mothers received magnesium sulfate were reported to have marked reductions in cerebral palsy, as compared with infants of untreated mothers.<sup>8</sup> Although biologically plausible mechanisms by which magnesium sulfate might be neuroprotective, such as the blocking of glutamate receptors,<sup>9</sup> have been proposed, not all observational studies have shown an association between the use of magnesium sulfate and a reduced risk of cerebral palsy.<sup>10</sup> Moreover, because they were not randomized, controlled trials, such observational studies cannot show whether any association reflects cause and effect

or is a result of unmeasured or unknown confounding factors.

The Cochrane review<sup>4</sup> on the use of magnesium sulfate for neuroprotection of the fetus in women at risk for preterm birth included four randomized, placebo-controlled trials<sup>11-14</sup> involving 3701 babies and concluded that the role of magnesium sulfate "is not yet established." The meta-analysis overall did not show any significant effect of magnesium sulfate on either death (relative risk, 0.97; 95% confidence interval [CI], 0.74 to 1.28) or cerebral palsy (relative risk, 0.77; 95% CI, 0.56 to 1.06), but there was a significant reduction in the rate of substantial gross motor dysfunction (relative risk, 0.56; 95% CI, 0.33 to 0.97). There was significant statistical heterogeneity for mortality among the trials, with one<sup>12</sup> but not the other three<sup>11,13,14</sup> showing an increased risk of perinatal death. The different main reasons for preterm birth (preeclampsia in one<sup>13</sup> and preterm labor in the others<sup>11,12,14</sup>), gestational ages at the time of treatment (range, <30 to <37 weeks), and treatment regimens among the trials (all of which could influence risks for both death and cerebral palsy) make it difficult to interpret pooled treatment effects.

In this issue of the *Journal*, Rouse et al.<sup>15</sup> report the results of a multicenter, placebo-controlled, randomized trial in which 2241 women at imminent risk for preterm birth between 24 and 31 weeks of gestation were randomly assigned to receive either intravenous magnesium sulfate (a 6-g bolus infused for 20 to 30 minutes, followed by a maintenance infusion of 2 g per hour) or placebo.

Participants were at high risk for spontaneous preterm birth because of preterm prelabor rupture

of the membranes (87%) or advanced preterm labor (10%), or they anticipated imminent, indicated preterm birth (3%). Women with hypertension or preeclampsia, for whom the use of magnesium sulfate is recommended,<sup>7</sup> were ineligible. Of particular note is that almost one fifth of the enrolled women had already received magnesium sulfate medication before enrollment, reflecting the continued high rate of use for tocolysis in the United States,<sup>5</sup> despite the lack of efficacy.<sup>6</sup> Strengths of this trial are the similarity of the treatment groups at randomization, the use of a placebo and blinding, the high rates of adherence to the assigned medication, and the high follow-up rate for the primary outcome (95.6%).

The study showed no significant reduction in the risk of the composite primary outcome of death or moderate or severe cerebral palsy in the magnesium sulfate group as compared with the placebo group. In prespecified analyses of the individual components of the primary outcome, there was no significant difference between the groups in the overall risk of death in the period up to 1 year (9.5% vs. 8.5%), but there was a significant reduction in moderate or severe cerebral palsy among children whose mothers received magnesium sulfate (1.9% vs. 3.5%; relative risk, 0.55; 95% CI, 0.32 to 0.95;  $P=0.03$ ). The estimated number needed to treat to avoid one child having moderate or severe cerebral palsy was 64.

Although the result for the primary outcome was null, benefits of magnesium sulfate were noted in two secondary infant outcomes. As compared with the placebo group, the magnesium sulfate group had significantly reduced rates of cerebral palsy overall (4.2% vs. 7.3%), and the distribution of severity of cerebral palsy differed ( $P$  for trend=0.004). Adverse maternal effects (e.g., flushing, sweating, and discomfort at the site of intravenous injection) were more likely in the magnesium sulfate group, as was stopping the study medication, although there were no life-threatening events. Neonatal morbidity was not significantly reduced by exposure to magnesium sulfate.

The findings of Rouse and colleagues are consistent with the pooled results<sup>4</sup> of the four previous relevant randomized trials.<sup>11-14</sup> These results provide additional reassurance that magnesium sulfate, when used for neuroprotection, does not significantly increase neonatal or infant mortality and, therefore, that the reduction in the rates of

cerebral palsy with the use of magnesium sulfate does not seem to be attributable to higher mortality rates among infants with brain damage.

Is it now time to recommend this treatment? Although promising, we would advise caution because of the differences between the populations that were eligible for entry into the individual studies and the different protocols used. Better understanding is needed of factors that might influence the likelihood that offspring will benefit from maternal magnesium sulfate treatment, such as the reason for imminent preterm birth, the dose of magnesium sulfate, and the timing of administration relative to birth and gestational age.

A meta-analysis involving individual patient data from the various trials might help to answer these questions, better guide clinical-practice recommendations, and frame future research. Information from long-term follow-up of children whose mothers received antenatal magnesium sulfate also is needed to clarify the neuroprotective role of this therapy before preterm birth.

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## Treatment of Myeloma — Are We Making Progress?

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In this issue of the *Journal*, San Miguel et al.<sup>1</sup> describe the benefit of combining bortezomib with melphalan plus prednisone, as compared with melphalan plus prednisone alone, as initial therapy for patients with myeloma who are not candidates for hematopoietic stem-cell transplantation. The critical comparative statistics leave no doubt that combination therapy with bortezomib is superior to melphalan plus prednisone alone. But how does this clear-cut evidence inform treatment decisions? To effectively apply these findings to clinical practice in the appropriate setting, we need prospective comparisons with other available options, valid uniform standards for those comparisons, and greater consideration of toxic effects and factors influencing the quality of life, along with outcomes.

The use of bortezomib in this regimen was approved by the Food and Drug Administration (FDA) on June 20 on the basis of the study by San Miguel et al. (ClinicalTrials.gov number, NCT00111319). The approval affirmed and acknowledged the role of bortezomib as initial therapy for patients not eligible for autologous stem-cell transplantation. Additional data that have not yet been evaluated by the FDA also support the use of bortezomib in patients undergoing transplantation, both as pretransplantation induction therapy and as part of a high-dose chemotherapy conditioning regimen.<sup>2</sup> Additional nuances include the particular benefit of combination therapy with bortezomib in patients with high-risk molecular genetic features or renal impairment.<sup>3</sup> Thus, bortezomib, which has an established role in the treatment of relapsed or refractory myeloma, also has potential for a broad and expanding role as initial therapy.

How do we interpret the results of this study? And how should the results influence clinical practice? First, the results need to be examined in the larger context of other emerging treatments and the results of other important trials involving patients with myeloma. In recent trials, two other agents (thalidomide and lenalidomide) have been shown to have clinically significant activity when used as single agents. It is therefore important to examine how the results of this trial of bortezomib compare with other options, including either thalidomide or lenalidomide plus either dexamethasone or melphalan-prednisone.<sup>4-9</sup> Cross-trial comparisons are always difficult (and never recommended with enthusiasm) but are essential in this situation, and much of the data from the study by San Miguel et al. are helpful in this regard. More than 70% of patients receiving bortezomib had a partial or complete response, as compared with 35% in the control group; the rates of complete response were 30% and 4% in the two groups, respectively ( $P < 0.001$ ). The median duration of the response was 19.9 months in the bortezomib group, as compared with 13.1 months in the control group. These data are very similar to those in studies of lenalidomide plus dexamethasone and of melphalan-prednisone plus either thalidomide or lenalidomide.<sup>5-9</sup> The estimated overall survival in the bortezomib group was 83% at 30 months, as compared with 82% at 2 years in patients 65 years of age or older who received lenalidomide plus low-dose dexamethasone, 80% at 2 years in those receiving melphalan-prednisone plus thalidomide, and 90% at 2 years in those receiving melphalan-prednisone plus lenalidomide.<sup>6-9</sup> Thus, all four combination therapies appear promising, but no data are avail-