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What we learned about the role of antenatal magnesium sulfate for the prevention of cerebral palsy

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Abstract

Based on the convincing case control study of Nelson and Grether which suggested that the administration of magnesium sulfate to mothers prior to early preterm birth might protect their offspring from cerebral palsy, and a pilot study by John Hauth et al. at the University of Alabama at Birmingham, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, with co-funding from the National Institute of Neurologic Disorders and Stroke embarked on the Beneficial Effects of Antenatal Magnesium (BEAM) Trial in 1997.

Keywords

Magnesium sulfate; Cerebral palsy

Based on the convincing case control study of Nelson and Grether[1] which suggested that the administration of magnesium sulfate to mothers prior to early preterm birth might protect their offspring from cerebral palsy, and a pilot study by John Hauth et al at. the University of Alabama at Birmingham, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network, with co-funding from the National Institute of Neurologic Disorders and Stroke (NINDS), embarked on the Beneficial Effects of Antenatal Magnesium (BEAM) Trial in 1997.[2]

The BEAM Trial had to overcome two main obstacles before it could be initiated. First, there was considerable skepticism over the feasibility of the trial, as at the time magnesium sulfate was widely used as a tocolytic (thus precluding randomization of most patients in preterm labor) and for seizure prophylaxis in women with pre-eclampsia.[3] This obstacle was dealt with by providing a review of the evidence that did not show benefit for tocolysis,[4] excluding women with pre-eclampsia, and building a formal one-year feasibility assessment into the trial protocol. Another obstacle was the suggestion in one small pilot study that

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magnesium sulfate might increase the risk of pediatric mortality.[5] In response, the NINDS convened a review group to assess the evidence related to maternally-administered magnesium sulfate and perinatal harm. This group recommended that the BEAM trial go forward with close safety monitoring.

The BEAM Trial was a double-masked, placebo-controlled randomized clinical trial.[2] Pregnant women were eligible for the trial if they were at least 24 weeks' gestation but no more than 31 weeks and 6 days, carrying either a singleton or twin gestation, and (1) had ruptured membranes, (2) were undergoing an indicated delivery, or (3) were in advanced preterm labor. The trial protocol forbade tocolysis. Women were allocated to magnesium sulfate or a matching placebo. In the magnesium sulfate group, women were to receive a 6 g intravenous loading dose, followed by 2 g/h intravenously for up to 12 h. If, at 12 h, delivery was not deemed imminent, the magnesium sulfate was discontinued, to be resumed if delivery threatened prior to 33 weeks, 6 days. The primary study outcome was a composite of death (fetal or infant death by 1 year corrected age) or moderate or severe cerebral palsy at 2 years of corrected age (essentially, the inability to walk without aids at the age of 2). Centrally trained and certified examiners, masked to group allocation, made the diagnosis of cerebral palsy. The unit of analysis for the primary outcome was the pregnancy, that is, in twin gestations, the primary outcome could be met only once. The statistical analysis was performed according to the intention-to-treat principle.

A total of 2241 women were enrolled in the trial, the first in December 1997, and the last in May 2004. The baseline characteristics of the enrolled women were similar in the two groups. The average gestational age at enrollment was 28 weeks, and at delivery it was 30 weeks. No serious adverse maternal or neonatal effects were attributable to the study treatment. Follow-up was achieved for 96% of the enrolled children.

The trial was designed with a composite primary outcome—death or cerebral palsy. It was hypothesized that death rate would not be different between the two treatment groups, but that cerebral palsy would be decreased in the magnesium sulfate treated group. Because death would be a competing variable, it was determined that the primary outcome had to include death. The primary outcome of the trial was not different in the two treatment groups —the rate in the magnesium treated group was 11.3% and in the placebo group it was 11.7%, relative risk (RR) = 0.97, 95% CI: 0.77–1.23.

However, the primary outcome does not provide a fully informed picture of the results of the trial. The larger component of the primary outcome composite was fetal or infant death, not cerebral palsy. Death occurred at a rate of in 9.5% in the magnesium sulfate group, and 8.5% in the placebo group (P = N.S.). Most of the difference in the rates of death between groups was the result of an imbalance in the rate of undiagnosed major, life-threatening fetal anomalies (chromosomal or structural) in the two groups. With their exclusion, the rates of death were virtually identical between groups, 8.3% and 8.1% respectively. In contrast, the rate of moderate or severe cerebral palsy, the other component of the primary outcome, was significantly lower in magnesium group, 1.9% compared to 3.5%, RR = 0.55, 95% CI: 0.32–0.95. In planning the trial, we assumed that death would occur less frequently than moderate or severe cerebral palsy, not more frequently, as turned out to be the case. This higher than

expected death rate, and lower than expected rate of CP, in retrospect, doomed the trial to be negative from the standpoint of the primary outcome, as the majority of the primary outcome was not influenced by magnesium sulfate and this greatly reduced the statistical power to detect a difference in the composite outcome. Only a much larger trial (or a meta-analysis as discussed below) would have the statistical power to be able show a difference in the primary outcome.

From the standpoint of cerebral palsy reduction (the main impetus for the trial), BEAM was clearly a positive trial—not only was the rate of moderate or severe cerebral palsy lower in the magnesium sulfate group, all forms of cerebral palsy were significantly lower (Table 1). In children born to women randomized before 28 weeks of gestation, the rate of moderate or severe cerebral palsy was 2.7% in the magnesium group, and 6.0% in the placebo group, RR = 0.45, 95% CI: 0.23–0.87, which translates to a number needed-to-treat of about 30 to prevent a case of disabling cerebral palsy. Although a larger trial than the BEAM trial has not been done, three other trials of magnesium sulfate for the prevention of cerebral palsy have been performed and data from those trials have been combined with the BEAM data into a meta-analysis of 4446 children which shows that not only does magnesium sulfate lower the risk of cerebral palsy (RR = 0.71, 95% CI: 0.55–0.91), but also the combined outcome of fetal or infant death or cerebral palsy (RR = 0.85, 95% CI: 0.74–0.98).[6] An analysis by Conde-Agudelo and Romero concluded that the cost to prevent a case of cerebral palsy with magnesium sulfate would be $10,291.[7] Since the lifetime medical cost for a person with CP was estimated to be $921,000 in 2003,[8] use of magnesium sulfate to prevent cerebral palsy is therefore highly cost-beneficial.

Since publication of the BEAM Trial and the Cochrane meta-analysis, the clinical use of magnesium sulfate for the prevention of cerebral palsy has become increasingly widespread. Australia, New Zealand, Canada, the United Kingdom, and the Netherlands have developed national guidelines for the use of magnesium sulfate to prevent cerebral palsy. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine, in their joint Obstetric Care Consensus on Periviable Birth, recommend the maternal administration of magnesium sulfate when delivery is threatened and imminent at or beyond 24 weeks of gestation (and that it be considered as early as 23 weeks).[9] ACOG sets the upper gestational age limit for the use of magnesium sulfate for neuroprotection as 31 weeks and 6 days, and has published a Patient Safety Checklist for the use of neuroprotective magnesium sulfate.[10]

Subsequent to the publication of the magnesium sulfate randomized trials, evaluations of the use of magnesium sulfate for fetal neuroprotection in actual clinical practice have been conducted. In one, Gibbins et al.[11] evaluated the use of magnesium sulfate at a large women's hospital in the four-year period after publication of the BEAM trial. They found that the use of magnesium sulfate in women delivering before 32 weeks increased from 20% in the first study year to 94% in the fourth year. The therapy was well targeted: over the study period, 84% of women receiving magnesium sulfate delivered before 32 weeks, and the median number of treatment courses was one. No serious maternal or perinatal adverse events were attributed to magnesium sulfate. On the basis of their analysis, the authors concluded that it was feasible "to implement a magnesium sulfate cerebral palsy prevention

protocol into clinical practice." Another feasibility study showed that implementing a protocol for prevention of cerebral palsy by magnesium sulfate is feasible in a tertiary obstetric center.[12] A research survey conducted by the Nurse Coordinators of the MFMU Network provides insight into the uptake and utilization of magnesium sulfate for neuroprotection across the MFMU Network. Bousleiman and her Network Coordinator colleagues[13] conducted a self-administered survey from January through May 2011 involving 329 obstetricians at 21 hospitals associated with the MFMU Network, 91% of whom reported that they used magnesium sulfate for neuroprotection. As part of this same study, actual use of magnesium sulfate among eligible women delivered by the same obstetricians was assessed for the time period January 2010 and February 2011 and was found to be 71%, and, as would be expected, higher among those who reported using magnesium sulfate than those who reported not using it. Thus, by 2011, utilization of magnesium sulfate was high among responding obstetricians at MFMU Network hospitals, but not perfect.

Secondary analyses of the BEAM trial have provided insight into the neonatal safety of maternally-administered magnesium sulfate. Johnson et al.,[14] in a secondary analysis involving 1507 infants from the BEAM trial, evaluated the association of cord blood magnesium concentration and neonatal resuscitation which was categorized in the following hierarchy: none, oxygen only, bag-mask ventilation with oxygen, intubation, and chest compressions. They found no association between cord blood magnesium concentration and the need for delivery room resuscitation, either overall or for specific levels of resuscitation. In multivariate analysis, only general anesthesia (positively) and gestational age (negatively) correlated with the need for resuscitation (Table 2). Thus their analysis provided reassurance that the fetal concentrations of magnesium sulfate achieved with use of magnesium sulfate for neuroprotection are not associated with neonatal depression.

In another secondary analysis of the BEAM trial, Hirtz et al.[15] found that for infants in the trial born before 32 weeks of gestation, magnesium sulfate was associated with a reduction in the rate of neonatal cranial ultrasound echolucencies or echodensities. Even though both of these ultrasound abnormalities are strong predictors of subsequently-diagnosed cerebral palsy, the reduction in echolucencies explained only 21% of the effect of magnesium on cerebral palsy, and the reduction in echodensities explained only 20% (Table 3). Multiple other secondary analyses from the BEAM trial have been conducted and their results published by the MFMU (Table 4).

Recruitment to the BEAM trial was slow (61/2 years of maternal enrollment followed by more than 2 years of follow-up of the children enrolled as fetuses) and relatively expensive, but, ultimately, the BEAM trial was a great success for the MFMU Network and the NINDS, and, more importantly, for the offspring of women who deliver very preterm. Had the Network not been able to enroll such a large number of women and achieve such a high rate of follow-up, the available evidence from smaller clinical trials may not have been strong enough to support using magnesium sulfate for fetal neuroprotection as mainstream practice, where its use has been estimated to have the potential to prevent 1000 cases of disabling cerebral palsy every year in the United States alone.[16] In short, the BEAM trial stands among the best arguments for the purpose and mission of the MFMU Network.

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Table 1 –

Cerebral palsy in the BEAM Trial according to group allocation.

	Cerebral Palsy (%)	
	Magnesium sulfate group	**Placebo group**
Mild	2.2	3.7
Moderate	1.5	2.0
Severe	0.5	1.6
Total *	4.2	7.3

* $P = 0.004$.

Table 2 –

Multivariate analysis of risk for delivery room resuscitation in the BEAM study.

Variable	Odds ratio	95% CI
Cord magnesium concentration[a]	0.92	0.83–1.03
General anesthesia	2.51	1.72–3.68
Maternal narcotics	0.97	0.80–1.19
Gestational age[b]	0.63	0.60–0.66

Modified from Johnson LH et al.[14].

[a]For each 1.0 mEq/L increase.

[b]For each 1-week increase.

Table 3 –

Association of cranial ultrasound findings in children born <32 weeks' gestation and CP, and mediation of the association of magnesium sulfate and CP.

Ultrasound abnormality	Cerebral palsy		Cerebral palsy explained by the abnormal ultrasound (%)
	Odds ratio	95% CI	
Echodensity	9.6	4.9–19.1	20
Echolucency	12.6	7.4–21.5	21
PVL	34.9	16.6–73.4	3
Ventriculomegaly	6.8	4.0–11.5	1
IVH Grade III or IV	12.4	6.4–24.0	11

IVH, intraventricular hemorrhage; PVL, periventricular leucomalacia. (Modified from Hirtz DG et al.[15])

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Table 4 –

Additional MFMU publications based on BEAM Trial data.

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