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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.

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 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

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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.

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.

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

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.