Effect of Cord Blood Magnesium Level at Birth on Non-neurologic Neonatal Outcomes

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Abstract

Objective We examined the effects of magnesium sulfate on non-neurologic neonatal outcomes with respect to cord blood magnesium level.

Study Design We conducted a secondary analysis of the Maternal-Fetal Medicine Units Beneficial Effects of Antenatal Magnesium (MFMU BEAM) trial comparing the upper and lower quintiles of cord blood magnesium level. Outcomes included cerebral palsy (CP), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and assessments of mental and motor disability. Logistic regression was used to estimate adjusted odds ratios (aORs) of each outcome, controlling for gestational age (GA), birth weight, and treatment group (TG).

Results A total of 1,254 women of the 2,444 included in the BEAM trial had cord blood magnesium levels recorded. GA and birth weight were lower and TG was more common in the upper quintile cohort ($p < 0.001$). Neonates in the upper quintile were more likely to have severe NEC (OR, 2.41, 95% confidence interval [CI]: 1.11–5.24), ROP (OR, 1.65, 95% CI: 1.05–2.59), and BPD (OR, 1.70, 95% CI: 1.04–2.73). Adjustment for covariates demonstrated no difference in the NEC, ROP, and BPD rates, although there was a decrease in rates of mental disability index < 70 which was not seen in the unadjusted analysis (aOR, 0.49, 95% CI: 0.25–0.99).

Conclusion Higher cord blood magnesium levels do not appear to have adverse non-neurologic effects on the neonate and may demonstrate improvement in neurologic outcomes.

Keywords
- magnesium sulfate
- necrotizing enterocolitis
- bronchopulmonary dysplasia
- neuroprotection
- pregnancy
- preterm birth

Antenatal magnesium sulfate administration to mothers at risk of preterm delivery reduces the risk of moderate to severe cerebral palsy (CP).[1–3] Although this therapy is routinely used in attempts to prevent CP in the offspring, the dose and optimal timing of administration are unclear.[4,5] Animal models support a reduction in inflammation as the mechanism of action; however, human studies are lacking.[6,7] Antenatal magnesium sulfate is also used for maternal seizure prophylaxis in the setting of maternal preeclampsia in addition to neonatal neuroprotection.[8]

Questions regarding non-neurologic neonatal effects are arising with increasing use of antenatal magnesium sulfate for neonatal neuroprotection. Several studies indicate that there may be adverse gastrointestinal effects of antenatal magnesium

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exposure including spontaneous intestinal perforation or necrotizing enterocolitis.[9,10] Furthermore, long-term follow-up from international magnesium studies call into question the school-age benefits of antenatal administration.[11]

Antenatal magnesium sulfate is intended to improve neonatal neurologic outcomes, but not at the expense of other non-neurologic outcomes. Therefore, we sought to understand both neurologic and non-neurologic outcomes based on cord blood magnesium levels at birth. We hypothesized that at very high magnesium sulfate levels, there would be evidence of an increased rate of neonatal non-neurologic adverse outcomes based on prior evidence regarding neonatal intestinal perforation and necrotizing enterocolitis (NEC).[9,10]

Study Design

This study is a secondary cohort analysis of the Maternal-Fetal Medicine Units Beneficial Effects of Antenatal Magnesium (MFMU BEAM) trial.[1] This randomized controlled trial was performed at 20 centers between 1997 and 2004. Our study, based on publicly available data, was reviewed and deemed exempt by the Duke University Health System Institutional Review Board (eIRB# Pro00065517). This article was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement: guidelines for reporting observational studies.[12]

Rouse et al previously described data collection procedures for the parent study.[1] Data collection occurred at enrollment, delivery, and at scheduled infant follow-up visits at 6, 12, and 24 months of age corrected for prematurity. The initial trial included women considered at high risk of preterm birth between 24 and 31 weeks. This risk was based on presentation with rupture of membranes between 22 and 31 weeks, spontaneous labor with cervical dilation of 4 to 8 cm, or providers anticipated an indicated preterm delivery within 2 to 24 hours. As part of the original trial, cord blood samples were collected at delivery on a subset of the population and analyzed for magnesium level.[1]

The primary analysis of this secondary cohort study was to determine the effect of antenatal magnesium exposure on non-neurologic neonatal outcomes among women at risk of preterm birth. Comparison groups for the primary analysis were assigned based on the upper quintile of magnesium cord blood levels ($\geq$ 2.9 mg/mL) and the lower quintile ($\leq$ 1.5 mg/mL). Upper and lower quintiles were chosen as the cutoff levels represent clinically significant magnesium levels in the neonate.[13] The primary outcomes were the rate of any NEC, severe NEC (Bell's Stage II or III), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), respiratory distress syndrome (RDS), neonatal hypotension in the delivery room, or definite neonatal sepsis. Secondary outcomes were neurologic outcomes including, any CP at age 2 years, moderate to severe CP, severe intraventricular hemorrhage (IVH), mental disability index (MDI), or physical disability index (PDI) score less than 70 on the Bayley Scales of Infant Development II administered at the 2-year examination, or death.

In the parent study, participants were randomly assigned in a double-blind fashion to receive either intravenous magnesium sulfate or placebo. Magnesium sulfate was administered starting with a loading dose of 6 g infused over 20 to 30 minutes followed by a maintenance infusion of 2 g per hour. If delivery did not occur after 12 hours, then the infusion was stopped and restarted when delivery was deemed imminent. The loading dose was repeated prior to restarting the infusion if more than 6 hours passed after stopping the infusion. As previously described, umbilical cord blood was collected immediately after delivery and serum was separated and frozen. Total serum magnesium was measured using the Olympus chemistry analyzer in a central laboratory (Quest Diagnostics, Van Nuys, CA).[14]

Baseline characteristics between those with upper and lower quintile of cord blood magnesium levels were described. Continuous variables were compared using a Student's *t*-test and categorical variables were compared using a chi-square or Wilcoxon-rank sum test. Neonatal outcomes were then reported as unadjusted odds ratios (OR) with 95% confidence intervals (CIs) using logistic regression. Next, multivariable logistic regression modeling for the outcomes was constructed to account for differences between treatment groups. These models were constructed even for nonsignificant outcomes as an exploratory analysis. We controlled for variables that differed between treatment groups by a p-value of < 0.1 or those clinical variables that a priori were felt to be of clinical importance: birth weight, gestational age at birth, and treatment group. The output of the multivariable logistic regression model was then reported as adjusted ORs with 95% CIs. All statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). A p-value of < 0.05 was considered statistically significant for all analyses.

Results

Of the 2,444 pregnancies in the parent study, we excluded 1,190 pregnancies due to multiple gestation, chromosomal abnormalities, stillbirth, congenital anomalies, or missing cord blood magnesium level. There were 259 pregnancies with cord blood magnesium level $\geq$ 2.9 mg/mL and 389 pregnancies with cord blood magnesium $\leq$ 1.5 mg/mL, which represent the upper and lower quintiles. Quintiles did not have equivalent numbers of pregnancies because there were many pregnancies with magnesium level of 1.5 mg/mL (►**Fig. 1**).

Demographic characteristics between infants in the upper and lower quintiles of cord blood magnesium levels demonstrated that the two groups were similar in age, race, body mass index, years of education, antenatal corticosteroid administration rate, and neonatal sex. However, there were differences in gestational age at delivery, birth weight, and treatment group (►**Table 1**).

The primary analysis of the effect of cord blood magnesium level on non-neurologic neonatal outcomes demonstrated a significant increase in the rate of severe NEC (6.6% vs. 2.8%,

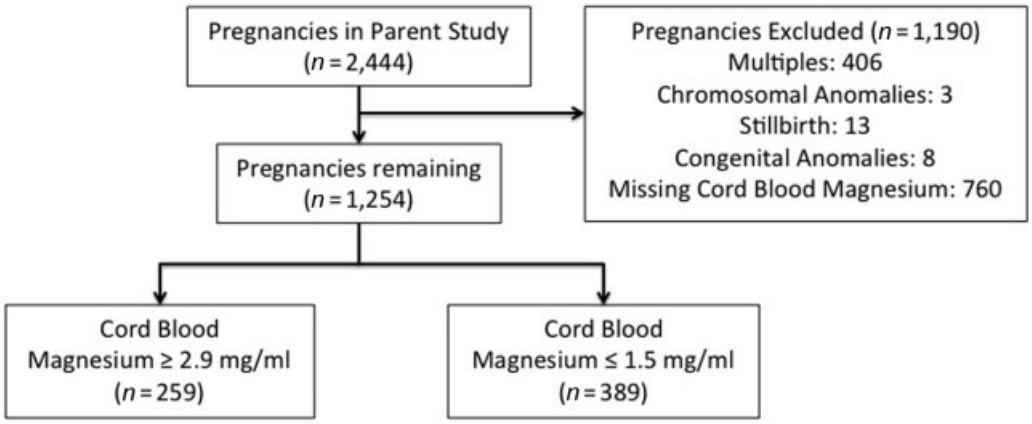

Fig. 1 Flow diagram of study participants.

$p = 0.02$), BPD (15.1% vs. 9.5%, $p = 0.03$), and ROP (17.4% vs. 11.3%, $p = 0.03$) with elevated cord blood magnesium. No significant differences were noted in the rates of NEC, RDS, hypotension in the delivery room, or definite neonatal sepsis. In adjusted analysis, there were no significant differences in the rates of NEC, severe NEC, BPD, RDS, or definite sepsis. However, a decreased rate of hypotension in the delivery room (OR, 0.16, 95% CI: 0.03–0.68) with higher cord blood magnesium level was noted (►**Table 2**).

Secondary analysis of the effect of cord blood magnesium level on neonatal neurologic outcomes demonstrated no significant differences in rates of any CP, moderate/severe CP, any IVH, severe IVH, MDI < 70, PDI < 70, or death at < 15 months. In adjusted analysis, there was a small decrease in the rates of MDI < 70 with the higher cord blood magnesium levels, adjusted OR of 0.49 (95% CI: 0.25–0.99) (►**Table 3**).

Comment

No significant non-neurologic effects were noted in the setting of elevated cord blood magnesium levels after adjustment for covariates in this study. Furthermore, in exploratory analysis there was possible benefit to the elevated levels of cord blood magnesium with a decrease in the rate of MDI < 70 on the Bayley II examination.

Previous studies indicate that there may be evidence of adverse neonatal gastrointestinal outcomes in the setting of antenatal magnesium exposure. The potential mechanism of intestinal injury is unclear, though the physiologic actions of

Table 1 Baseline characteristics of high and low cord blood magnesium levels

Characteristics	Magnesium level $\geq$ 2.9 mg/ml ($n = 259$)	Magnesium level $\leq$ 1.5 mg/ml ($n = 389$)	*p*-Value
Maternal age (y ± SD)	25.2 ± 6.4	25.4 ± 6.0	0.70
Maternal race, *n* (%)			0.13
African American	116 (44.8)	154 (39.6)	
Caucasian	99 (38.2)	147 (37.8)	
Hispanic	37 (14.3)	82 (21.1)	
Asian	3 (1.2)	1 (0.3)	
Native American/Other	4 (1.5)	5 (1.3)	
Maternal BMI (BMI ± SD)	24.8 ± 6.0	25.6 ± 6.3	0.16
Maternal y of education (y ± SD)	11.6 ± 2.2	11.9 ± 2.6	0.27
Antenatal corticosteroids, *n* (%)	252 (97.3)	378 (97.2)	0.92
Gestational age at delivery (wk ± SD)	29w5d ± 2w2d	31w0d ± 3w0d	< 0.0001
Birth weight (g ± SD)	1421.6 ± 421.9	1682.6 ± 585.2	< 0.0001
Neonatal male sex, *n* (%)	107 (41.3)	179 (46.0)	0.24
Magnesium sulfate administration, *n* (%)	249 (96.1)	98 (25.2)	< 0.0001

Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2 Non-neurologic neonatal outcomes

Outcomes	Mg $\geq$ 2.9, n (%)	Mg $\leq$ 1.5, n (%)	*p*-Value	OR	Adjusted OR
NEC, *n* (%)	25 (9.7)	23 (5.9)	0.08	1.70 (0.94–3.08)	0.99 (0.42–2.52)
Severe NEC (Gr 2 or 3), *n* (%)	17 (6.6)	11 (2.8)	0.02	2.41 (1.11–5.24)	1.56 (0.51–5.58)
ROP, *n* (%)	45 (17.4)	44 (11.3)	0.03	1.65 (1.05–2.59)	1.53 (0.64–3.88)
BPD, *n* (%)	39 (15.1)	37 (9.5)	0.03	1.70 (1.04–2.73)	0.73 (0.31–1.75)
RDS, *n* (%)	119 (45.6)	158 (40.6)	0.18	1.24 (0.91–1.71)	0.73 (0.31–1.75)
Hypotension in delivery room, *n* (%)	3 (1.2)	9 (2.3)	0.29	0.50 (0.11–1.68)	0.16 (0.03–0.68)
Culture-proven sepsis, *n* (%)	34 (13.1)	42 (10.8)	0.37	1.25 (0.77–2.02)	0.79 (0.36–1.74)

Abbreviations: BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; OR, odds ratios; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.
Note: Adjusted analysis for birth weight, gestational age at birth, and treatment group.

magnesium reveal biologic plausibility. In smooth muscle, including myometrium and vascular smooth muscle, magnesium competitively inhibits calcium entry causing decreased oscillations in calcium concentrations and contractility. This may be active in fetal and neonatal intestinal peristalsis leading to bowel dilation and subsequent perforation or NEC.

An observational study by Rattray et al demonstrated an increase in spontaneous intestinal perforation or death in infants exposed to antenatal magnesium with delivery below 25 weeks. A higher magnesium infusion rate at delivery was associated with an increased rate of adverse outcomes in this study.[9] Closer examination of this prior study reveals that the comparison cohorts were from different nonconcurrent time intervals, thereby increasing the risk of bias. Kamyar et al also demonstrated an increased rate of severe NEC in the population with gestational age at birth $<$ 28 weeks.[10] While we did find increased rates of severe NEC in the unadjusted analysis, adjustment for gestational age, birth weight, and treatment group removed any evidence of an increased rate of severe NEC in the higher cord blood magnesium group.

BPD and ROP were also more frequently seen in the high cord blood magnesium group. Adjustment for covariates removed this effect. This indicates that these outcomes were more associated with gestational age and birth weight as opposed to magnesium level. On the other hand, there was a decreased rate of hypotension in the delivery room for neonates with the high cord blood magnesium levels seen in the adjusted analysis. The cause of this benefit is not obvious, but may be reflected by improved intrapartum placental function manifesting as improved equilibration of maternal and fetal magnesium levels.

Cord blood magnesium level at delivery serves as a potential marker of treatment effect. Palatnik et al determined that cord blood level at delivery was not significantly different between those infants with CP or death as compared with those without in the BEAM trial.[4] This approach marginalized the treatment effect by focusing on magnesium level as an outcome variable as opposed to a predictive variable. In comparison, we found a potential benefit with improved Bayley II mental indices in the group with the highest cord blood magnesium levels at delivery. The results found in our study are related with those of Turitz et al who demonstrated a reduction in CP with close proximity of magnesium exposure to time of birth.[15] This variable is likely correlated with cord blood magnesium level.

With regards to magnesium sulfate safety and neonatal toxicity, Johnson et al demonstrated that there was no relationship between cord blood magnesium level and need for delivery room resuscitation.[14] Here, we find that there is no evidence of long-term adverse neurologic or non-neurologic neonatal effects of increased cord blood magnesium levels at birth. This study adds to the evidence for antenatal magnesium sulfate safety.

Table 3 Neonatal neurologic outcomes

Outcomes	Mg $\geq$ 2.9, n (%)	Mg $\leq$ 1.5, n (%)	*p*-Value	OR	Adjusted OR
Any CP at 2 y age, *n* (%)	7 (3.1)	8 (2.3)	0.55	0.74 (0.26–2.13)	0.24 (0.04–1.42)
Moderate/Severe CP, *n* (%)	4 (1.6)	2 (0.54)	0.18	0.33 (0.05–1.69)	0.09 (0.01–1.27)
Severe IVH, *n* (%)	4 (1.6)	7 (1.9)	0.26	0.42 (0.06–1.74)	0.14 (0.02–1.04)
MDI $<$ 70, *n* (%)	28 (13.3)	57 (17.6)	0.18	1.40 (0.86–2.30)	0.49 (0.25–0.99)
PDI $<$ 70, *n* (%)	25 (11.7)	43 (13.2)	0.61	1.15 (0.68–1.96)	0.94 (0.43–2.13)

Abbreviations: CP, cerebral palsy; IVH, intraventricular hemorrhage; MDI, mental disability index; OR, odds ratios; PDI, physical disability index.
Note: Adjusted analysis for birth weight, gestational age at birth, and treatment group.

Our study has several strengths. As a secondary analysis of a large prospective randomized cohort trial, information bias is minimized as data were collected in a prospective, unbiased manner. As a retrospective cohort study, there are several limitations. The primary limitation of this study is the significantly lower gestational age at birth and birth weight in the elevated magnesium cord blood group. This is evidenced by the fact that adverse non-neurologic outcomes were no longer seen when adjustment for these factors was included. Additionally, there is a large difference in the patients randomized to treatment with magnesium sulfate between the upper and lower cord blood magnesium cohorts, indicating that magnesium sulfate administration is closely related to cord blood magnesium levels and may confound the analysis. The secondary nature of this study limits the analysis to variables previously collected and precludes the collection of missing information. Additionally, the majority of participants delivered between 30 and 32 weeks' gestation; therefore, we are unable to assess for non-neurologic effects across gestational ages, particularly at the periviable gestational ages.

In summary, we did not find any significant non-neurologic neonatal effects of antenatal magnesium sulfate therapy based on cord blood magnesium levels at birth. Despite the reassuring results in the present study, the lack of significant benefit to significantly elevated magnesium levels advocates for further studies to tailor magnesium dosing and administration to avoid adverse effects while maintaining improved neurologic outcomes.

Note

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Conflict of Interest

None.

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