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Association of Cord Blood Magnesium Concentration and Neonatal Resuscitation

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Abstract

Objective Assess the relationship between umbilical cord blood magnesium concentration and level of delivery room resuscitation received by neonates.

Study design Secondary analysis of a controlled fetal neuroprotection trial that enrolled women at imminent risk for delivery between 24 and 31 weeks' gestation and randomly allocated them to receive intravenous magnesium sulfate or placebo. The cohort included 1507 infants for whom total cord blood magnesium concentration and delivery room resuscitation information were available. Multivariable logistic regression was used to estimate the association between cord blood magnesium concentration and highest level of delivery room resuscitation, using the following hierarchy: none, oxygen only, bag-mask ventilation with oxygen, intubation or chest compressions.

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The authors declare no conflicts of interest.

Results—There was no relationship between cord blood magnesium and delivery room resuscitation (odds ratio [OR] 0.92 for each 1.0 mEq/L increase in magnesium; 95% confidence interval [CI]: 0.83-1.03). Maternal general anesthesia was associated with increased neonatal resuscitation (OR 2.51; 95% CI: 1.72-3.68). Each 1-week increase in gestational age at birth was associated with decreased neonatal resuscitation (OR 0.63; 95% CI: 0.60 – 0.66).

Conclusion—Cord blood magnesium concentration does not correlate with the level of delivery room resuscitation of infants exposed to magnesium sulfate for fetal neuroprotection.

Keywords

magnesium; cord blood; delivery room resuscitation

Magnesium is implicated in numerous physiologic and pharmacologic roles including the reduction of myometrial and other smooth muscle contractility, depression of CNS irritability, stabilization of cellular membranes and interference with acetylcholine release at the neuromuscular junction.(1-3) For decades, pregnant women have received magnesium sulfate (MgSO4) for either tocolysis or the prevention of eclampsia. Recently, multiple studies have demonstrated that antenatal treatment with MgSO4 reduces the risk of cerebral palsy among children born preterm.(4-6)

Adverse effects may occur in women who become hypermagnesemic during MgSO4 treatment. These include muscular weakness, diminished deep tendon reflexes and respiratory depression.(2) Similar adverse effects may occur in neonates exposed to MgSO4 antenatally. In clinical practice, infants whose mothers received MgSO4 for any indication are thought to be at risk for respiratory depression, and thus an increased need for delivery room resuscitation. For example, case reports suggest a relationship between fetal MgSO4 exposure and the need for resuscitation immediately after birth.(7, 8) To date, however, hypothesized adverse effects on neonates have not been proven. Despite the lack of definitive evidence linking fetal magnesium exposure and the need for resuscitation, the American Academy of Pediatrics and American Heart Association supported Neonatal Resuscitation Program (NRP) lists MgSO4 among maternally administered medications that might depress respirations in the newborn.(9)

Our objective in this secondary analysis of the largest trial of magnesium sulfate for fetal neuroprotection was to estimate the relationship between umbilical cord blood magnesium concentration and the need for resuscitation of infants immediately after delivery. In the primary analysis of the trial, there was no overall association between MgSO4 exposure and increased delivery room resuscitation.(4) However, this finding does not preclude a concentration-dependent effect. Therefore, in this investigation, we evaluated the association between cord blood magnesium concentration and delivery room resuscitation.

METHODS

This was a secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal Fetal Medicine Units (MFMU) Network trial of MgSO4 for the prevention of cerebral palsy.(4) From December 1997 through May 2004, women at imminent risk for preterm delivery between 24 and 31 weeks' gestation were randomized to receive intravenous MgSO4 or placebo. Magnesium sulfate (or matching placebo) was given to study participants intravenously as a 6 gram loading dose over 20 minutes followed by 2 grams infused each hour in minimal volume intravenous fluids. The infusion could be increased to a maximum of 4 grams per hour at the discretion of the physician and was continued for at least 12 hours if delivery did not occur. Retreatment with the study drug was given for recurrence of labor or anticipated delivery unless criteria for exclusion developed in the interim. The primary outcome was the composite of stillbirth or death by 1 year corrected age or moderate or severe cerebral palsy at 2 years corrected age. Details of the study are reported elsewhere.(4) Mother/neonate dyads included in the current analysis were enrolled in the original trial and had both cord blood magnesium concentration and delivery room resuscitation data recorded. Neonates who fulfilled these criteria were included in this analysis irrespective of the mother's allocation to magnesium or placebo. The institutional review board at each of the 20 participating centers approved participation in the trial. All participants gave written informed consent before enrollment.

Trained, certified research nurses collected data prospectively and included information on both maternal and neonatal characteristics, complications and outcomes. Data describing other medications given during labor, including anesthetic agents and analgesics, were abstracted from the mothers' charts. Gestational age at entry to the trial was determined according to a standard method predicated on the date of the last menstrual period and the results of the earliest available ultrasound.(10) Umbilical cord blood was collected immediately after delivery and serum was separated within 45 to 120 minutes following collection. Samples were frozen within 12 hours from the time the blood was collected and stored locally at -70° C until shipping to a central laboratory (Quest Diagnostics, Van Nuys, California). Total magnesium was measured using the Olympus chemistry analyzer, valid low= 0.4mEq/L (0.2mmol/L).

Neonatal delivery data recorded included the highest level of delivery room resuscitation received by the infant. The hierarchy of this variable (from lowest to highest) was none, followed by oxygen only, bag-mask ventilation with oxygen, intubation or chest compressions. All infants, including those labeled with a resuscitation variable of "none," received standard delivery room care.(9)

Statistical analyses

Statistical analyses were performed using SAS® statistical software (SAS institute, Cary, NC). The primary outcome was the highest level of delivery room resuscitation received by the infant. The primary exposure was cord blood magnesium concentration. Generalized estimating equations were used to account for the correlations between siblings of twin pregnancies. Proportional odds models within this framework allowed for regression analyses to measure the association between magnesium and the five-level ordinal resuscitation variable (none, oxygen only, bag-mask ventilation, intubation or chest compressions). These regression models were used for univariate analyses, as well as for multivariable analyses that controlled for gestational age, administration of maternal narcotics and general anesthesia. Odds ratios (OR; 95% Confidence Interval) were calculated for each of the predictor variables. Similar models were constructed with the dichotomous outcome of none vs. any resuscitation using ordinary logistic regression.

RESULTS

In the parent study, 2444 fetuses were randomized at 20 sites between December 1997 and May 2004. Of these, 924 were excluded from this secondary analysis because cord blood was unavailable either because clinical staff were unable to obtain it or there was an insufficient amount of blood available after other testing. There were 13 stillbirths. Our study cohort comprised 1507 infants with both cord blood magnesium concentration and delivery room resuscitation data. A total of 723 mothers (48.0%) were assigned to $MgSO_4$ and 784 mothers (52.0%) were assigned to placebo. Neonates in the present analysis were of more advanced gestational age, of higher birth weight and more often delivered vaginally than neonates for whom cord blood magnesium concentration was not available (Table I). The mean gestational age at delivery was 30.0 ± 2.9 weeks; only 28 (1.9%) infants were delivered after 37 weeks.

Of the 1507 infants, 252 (16.7%) received no additional resuscitation (Table II). For infants who received any form of resuscitation, oxygen only and intubation were the most common; 432 (28.7%) and 528 (35.0%) infants, respectively. Relatively few infants required chest compressions, n=46 (3.1%). Decreasing birth weight and gestational age at birth were associated with an increasing receipt of resuscitation. Infants who received chest compressions had a mean birth weight of 1050g, whereas those who received oxygen and those who did not receive any additional resuscitation had mean birth weights of 1660g and 1883g, respectively. The mean gestational age at birth decreased with increasing level of resuscitation ($p < 0.001$). Infants who received intubation or chest compressions tended to have lower 1- and 5-minute Apgar scores and greater exposure to general anesthesia.

Table III represents the univariate analysis of the highest level of resuscitation in relation to cord blood magnesium concentration. The mean magnesium concentration for the cohort was 2.05 ± 0.88 mEq/L which did not significantly differ across the highest level of resuscitation recorded ($p = 0.28$). Of the 1507 infants, 51 (3.4%) had magnesium concentrations greater than 4.0 mEq/L; only 6 (0.4%) had concentrations greater than 5.0 mEq/L. Additional (any) delivery room resuscitation was received by 45 (88.2%) of these 51 infants. The resuscitation received by the 6 infants with a magnesium concentration of >5.0 mEq/L included intubation (4), bag/mask (1) or oxygen (1).

We included cord blood magnesium concentration, gestational age at birth, administration of maternal narcotics, and general anesthesia in a multivariable logistic regression analysis to determine the association between the highest level of resuscitation (using the 5-level ordinal model) and cord blood magnesium concentration (Table IV). Cord blood magnesium concentration was not associated with an increased need for delivery room resuscitation (OR 0.92 for each 1.0 mEq/L increase in magnesium; 95% CI: 0.83-1.03). Maternal general anesthesia was associated with increased delivery room resuscitation (OR 2.51; 95% CI: 1.72-3.68) but maternal administration of narcotics was not (OR 0.97; 95% CI: 0.80-1.19).

For each 1-week increase in gestational age at birth there was decreased receipt of delivery room resuscitation (OR 0.63; 95% CI: 0.60 – 0.66).

An additional regression analysis was performed with resuscitation as a dichotomous variable, none vs. any, to again look for an association between the highest level of resuscitation and cord blood magnesium concentration. This model similarly included gestational age at birth, cord blood magnesium concentration, general anesthesia and maternal narcotics. This model yielded identical findings to the 5-level ordinal model, with no association between cord blood magnesium concentration and receipt of delivery room resuscitation (data not shown).

DISCUSSION

In the setting of MgSO4 administration for neuroprotection in anticipated preterm birth, we found no association between umbilical cord blood magnesium concentration and the receipt of an increased level of delivery room resuscitation in newborn infants, after adjusting for gestational age at birth and several intrapartum exposures. Exposure to general anesthesia was associated with a greater degree of neonatal resuscitation, an association that has previously been reported.(11-13) Not surprisingly, increasing gestational age at birth was associated with decreased receipt of delivery room resuscitation, consistent with previous reports.(13-15)

Previous studies appear to support our observation that cord blood concentrations of magnesium do not predict the need for neonatal resuscitation. For example, Lipsitz and English reported on 16 neonates with effects of hypermagnesemia, including mild respiratory depression, hypotonia and hyporeflexia following maternal exposure to MgSO4 for preeclampsia.(16) However, they found no correlation between Apgar scores or other clinical signs and cord blood magnesium concentration or need for resuscitation. In a case controlled study, Riaz et al reported a non-statistically significant increase in delivery room support, defined as bag-mask ventilation, in 26 MgSO4 exposed infants.(17) They reported these infants more likely to be hypotonic and to have lower Apgar scores. However, there was no association of these outcomes with cord blood magnesium concentration, maternal magnesium concentration, or total dose or duration of maternal MgSO4 exposure. In the parent trial for this secondary analysis, there was no statistically significant difference in rates of generalized hypotonia or the composite outcome of intubation and chest compressions among magnesium vs. placebo exposed infants.(4) Along with our results, these studies suggest that fetal MgSO4 exposure does not have adverse effects on delivery room resuscitation. Rather, the confounding circumstances that are associated with maternal MgSO4 treatment (e.g., early gestational age) may increase the likelihood of respiratory depression immediately after birth, thus leading to increased receipt of delivery room resuscitation.

Published literature related to intrapartum magnesium sulfate exposure has primarily addressed the neonate born to mothers with preeclampsia or eclampsia as the indication for magnesium exposure.(17-19) Few studies have focused exclusively on the preterm infant, and most have reported only Apgar scores or clinically subjective assessment scales as surrogate markers of the presumed impact of magnesium exposure on delivery room resuscitation. Despite reports of the effects of magnesium exposure on tone, Apgars or clinical assessment, none of these studies found a correlation between cord blood or serum magnesium concentration and the degree of neonatal depression.

There are several strengths and limitations to our study. We included a large number of infants. The magnesium concentration was measured at birth, and thus is the most accurate reflection of fetal magnesium levels. Clinicians who were resuscitating the infant were unaware of treatment assignment, and thus bias was limited. As for limitations, infants in our study had relatively low levels of magnesium in the cord blood (mean 2.05 ± 0.88 mEq/L), compared with other studies with a range 1.8-11.5mg/dL (1.5mEq/L-9.6mEq/L).(16-18, 20) Thus it is possible that very high concentrations of cord blood magnesium might be associated with a greater need for resuscitation. Of the 1507 infants, 51 (3.4%) had magnesium concentrations greater than 4.0 mEq/L and only 6 (0.4%) of these had concentrations greater than 5.0 mEq/L, with the majority of these infants receiving additional delivery room resuscitation. Thus, our analysis is not powered to look for an association at higher concentrations. It is worth emphasizing, however, that antenatal magnesium administration in the dose range utilized for neuroprotection rarely resulted in high cord blood magnesium concentrations, so even if a subsequent association were found, it would be applicable to only a small minority of infants exposed to magnesium sulfate for neuroprotection.

We did not investigate other reported side effects of $MgSO_4$ exposure, such as apnea/hypoventilation following admission or delayed feeding tolerance or ileus. In addition, our findings might not be applicable to term infants because our cohort was primarily composed of preterm infants, with only 28 (1.9%) infants greater than 37 weeks gestation at delivery. The threshold for delivery room intubation of extremely preterm infants (i.e. for surfactant administration) might vary across sites, however these data were not collected as part of this study.

In conclusion, we found no association between umbilical cord blood magnesium concentration and receipt of delivery room resuscitation of infants. This finding should motivate clinicians to further investigate an etiology for greater level of delivery room resuscitation, and to consider other potential contributing causes for the need for resuscitation. The findings of this analysis should allow providers to provide magnesium sulfate for neuroprotection without the concern that it will lead to additional invasive delivery room resuscitation measures.

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Appendix

In addition to the authors, other members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network are as follows:

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Table 1

Neonatal Characteristics and Intrapartum Care: Comparison of Those With and Without Available Cord Blood Magnesium Concentration

	Mg Concentration Not Available n=924	Mg Concentration Available n=1507	P-Value
Gestational age, wk*	29.3 ± 3.4	30.0 ± 2.9	<0.001
Birth weight, g	1324 ± 615	1472 ± 539	<0.001
Birth weight, ≤ 1500g	633 (68.7)	828 (54.9)	<0.001
Female	437 (47.3)	710 (47.1)	0.93
Mode of Delivery			
Vaginal (1456)	502 (54.4)	954 (63.3)	<0.001
Cesarean (973)	420 (45.6)	553 (36.7)	
Race			
African-American	400 (43.3)	645 (42.8)	0.74
Caucasian	330 (35.7)	580 (38.5)	
Hispanic	176 (19.0)	245 (16.3)	
Asian	4 (0.4)	16 (1.1)	
Native American	1 (0.1)	2 (0.1)	
Other	13 (1.4)	9 (1.3)	
1-minute Apgar	6 (4-8)	7 (5-8)	<0.001
1-minute Apgar <5	293 (31.9)	302 (20.1)	<0.001
5-minute Apgar	8 (7-9)	8 (7-9)	0.09
5-minute Apgar <7	225 (24.5)	229 (15.2)	<0.001
General Anesthesia	101 (12.5)	103 (7.3)	<0.001
Maternal Narcotics	297 (36.7)	521 (37.1)	0.90
Twin Gestation	91 (11.1)	112 (8.0)	<0.001

Data are presented as mean ± SD, n (%) or median (interquartile range)

*Gestational age at delivery

Table 2

Neonatal Characteristics and Intrapartum Care

	Highest Level of Resuscitation Recorded							
	None n=252	Oxygen only n=432	Bag/Mask and oxygen n=249	Intubation n=528	Chest Compressions n=46	P-Value 5-Level	Any n=1255	P-Value 2-Level
Gestational age, wk*	32.2 ± 2.8	31.1 ± 2.2	30.3 ± 2.3	28.2 ± 2.3	27.2 ± 2.7	<0.001	29.6 ± 2.7	<0.001
Birth weight, g	1883 ± 601	1660 ± 463	1492 ± 426	1150 ± 392	1050 ± 408	<0.001	1390 ± 485	<0.001
Birth weight, ≤ 1500g	67 (26.6)	154 (35.7)	131 (52.6)	436 (82.6)	40 (87.0)	<0.001	761 (60.6)	<0.001
Female	128 (50.8)	206 (47.7)	123 (49.4)	235 (44.5)	18 (39.1)	0.07	582 (46.4)	0.20
Mode of Delivery								
Vaginal (954)	201 (79.8)	314 (72.7)	140 (56.2)	276 (52.3)	23 (50.0)	<0.001	753 (60.0)	<0.001
Cesarean (553)	51 (20.2)	118 (27.3)	109 (43.8)	252 (47.7)	23 (50.0)		502 (40.0)	
Race								
African-American	114 (45.2)	185 (42.8)	104 (41.8)	221 (41.9)	21 (45.7)	0.84	531 (42.3)	0.66
Caucasian	96 (38.1)	166 (38.4)	92 (37.0)	204 (38.6)	22 (47.8)		484 (38.6)	
Hispanic	34 (13.5)	73 (16.9)	47 (18.9)	88 (16.7)	3 (6.5)		211 (16.8)	
Other	8 (3.2)	8 (1.9)	6 (2.4)	15 (2.8)	0 (0.0)		29 (2.4)	
1-minute Apgar	8 (7-9)	8 (7-8)	6 (5-7)	5 (4-7)	1 (1-3)	<0.001	7 (5-8)	<0.001
1-minute Apgar <5	6 (2.4)	8 (1.9)	57 (22.9)	190 (36.1)	41 (89.1)	<0.001	296 (23.6)	<0.001
5-minute Apgar	9 (8-9)	9 (8-9)	8 (7-9)	7 (6-8)	5 (2-6)	<0.001	8 (7-9)	<0.001
5-minute Apgar <7	5 (2.0)	10 (2.3)	26 (10.4)	150 (28.5)	38 (82.6)	<0.001	224 (17.9)	<0.001
General Anesthesia	2 (0.8)	23 (5.3)	18 (7.2)	63 (11.9)	9 (19.6)	<0.001	113 (9.0)	<0.001
Maternal Narcotics	87 (34.5)	170 (39.4)	97 (39.0)	187 (35.4)	12 (26.1)	0.45	466 (37.1)	0.44
Twin Gestation	28 (11.1)	54 (12.5)	36 (14.5)	91 (17.2)	5 (10.9)	0.05	186 (14.8)	0.20

Data are presented as mean ± SD, n (%), or median (interquartile range)

* Gestational age at delivery

Table 3

Level of Resuscitation by Cord Blood Magnesium Concentration

Magnesium concentration (mEq/L)	Highest Level of Resuscitation Recorded					
	None n=252	Oxygen only n=432	Bag/ Mask and oxygen n=249	Intubation n=528	Chest Compressions n=46	Any n=1255
< 1.0, n=52	12 (23.1)	13 (25.0)	10 (19.2)	15 (28.9)	2 (3.9)	40 (76.9)
1.0 - <2.0, n=900	167 (18.6)	257 (28.6)	134 (14.9)	317 (35.2)	25 (2.8)	733 (81.4)
2.0 - <3.0, n=279	38 (13.6)	66 (23.7)	57 (20.4)	108 (38.7)	10 (3.6)	241 (86.4)
3.0 - <4.0, n=225	29 (12.9)	75 (33.3)	42 (18.7)	70 (31.1)	9 (4.0)	196 (87.1)
4.0 - <5.0, n=45	6 (13.3)	20 (44.4)	5 (11.1)	14 (31.1)	0 (0)	39 (86.7)
≥5.0, n=6	0 (0)	1 (16.7)	1 (16.7)	4 (66.7)	0 (0)	6 (100.0)
Mean Magnesium concentration*	1.9 ±0.81	2.1 ±0.96	2.1 ±0.88	2.0 ±0.86	2.1 ±0.81	2.1 ±0.89

Data are presented as number (%) or mean ± standard deviation

*Mean magnesium concentration did not differ across the highest level of resuscitation recorded, p=0.28

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Table 4

Multivariable Analysis of Risk for Delivery Room Resuscitation*

Variable	Odds Ratio	95% Confidence Interval
Magnesium**	0.92	0.83-1.03
General Anesthesia	2.51	1.72-3.68
Maternal Narcotics	0.97	0.80-1.19
Gestational Age***	0.63	0.60-0.66

*Analysis of delivery room resuscitation as a 5-level ordinal variable and adjusted for magnesium, general anesthesia, maternal narcotics and gestational age

**For each 1.0mEq/L interval increase in cord magnesium concentration

***For each 1-week increase in gestational age