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Antenatal Magnesium Sulfate Exposure and Acute Cardiorespiratory Events in Preterm Infants

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Presentation: The findings of this study have been presented at the annual Pediatric Academic Society meeting, May 4-7, 2013, Washington, DC.

Condensation: Antenatal magnesium exposure in preterm infants was not associated with adverse cardiorespiratory events postnatally and appears to be safe for preterm infants.

Abstract

Objective—Antenatal magnesium (anteMg) is used for tocolysis, pregnancy-induced hypertension (PIH) and neuroprotection for preterm birth. Infants exposed to anteMg are at risk for respiratory depression and resuscitation in the delivery room (DR). The study objective was to compare the risk of acute cardio-respiratory (CR) events among preterm infants exposed to anteMg and those unexposed (noMg).

Study Design—This was a retrospective analysis of prospective data collected in the NICHD Neonatal Research Network's Generic Database from 4/1/11 to 3/31/12. The primary outcome was DR intubation or mechanical ventilation (MV) at birth or on day 1 of life. Secondary outcomes were endotracheal MV (eMV), hypotension and other neonatal morbidities and mortality. Logistic regression analysis evaluated the risk of primary outcomes after adjustment for gestational age (GA), center, antenatal steroids (ANS) and PIH/eclampsia.

Results—We evaluated 1,544 infants <29 weeks GA (1,091 in anteMg group and 453 in noMg group). Mothers in the anteMg group were more likely to have higher education, PIH/eclampsia and ANS; while their infants were younger in gestation and weighed less ($P<0.05$). The primary outcome, mortality and neonatal morbidities were similar between groups; while eMV and hypotension were significantly less among the anteMg group compared to the noMg group. AnteMg exposure was significantly associated with decreased risk of hypotension on day 1 of life and eMV on day 3 of life in the regression analysis.

Conclusion—Preterm infants <29 weeks GA who were exposed to anteMg did not suffer worse CR outcomes compared to those without exposure.

Keywords

antenatal magnesium; nasal CPAP; neonatal resuscitation; preterm infants

Introduction

Magnesium sulfate ($MgSO_4$)[1] is commonly used in Obstetrics for a variety of indications. These include seizure prevention in women with preeclampsia and tocolysis to prolong the pregnancy enabling administration of antenatal corticosteroids (ANS). More recently, $MgSO_4$ given to women at risk of preterm delivery has also been shown to reduce the risk of cerebral palsy among preterm infants.[2, 3] Magnesium has been implicated in many cellular processes; is a cofactor for numerous reactions; and acts as a calcium-channel blocker to reduce myometrial contractions and control vasomotor tone.[4, 5] In the mother, common side effects of magnesium include lethargy, dizziness, flushing, nausea, vomiting and blurred vision.[5] More serious side effects such as respiratory depression and arrest are rare and are usually associated with high serum magnesium levels.[6] Neonatal consequences of antenatal magnesium (anteMg) administration and the safety profile of its use in preterm infants are unclear. Some reports suggest that anteMg may adversely affect the neonate, while others showed no differences in neonatal mortality or morbidity. In the Magnesium and Neurological Endpoints Trial (MagNET), anteMg used for either neuroprotection or tocolysis at 24 to 33 weeks gestation was associated with a higher risk of adverse outcomes in the infant [death, any intraventricular hemorrhage (IVH), periventricular leukomalacia

(PVL) and cerebral palsy (CP)] compared to infants not exposed to anteMg (OR 2.0, 95% CI 0.99-4.1; $P = .07$).[7, 8] A retrospective cohort study of anteMg for prevention of eclampsia noted that longer exposure to anteMg resulted to higher maternal serum magnesium levels and adverse events in the newborn including more episodes of hypotonia, delivery room (DR) intubation and admission to special care nursery.[9] Another cohort study of extremely low birth weight infants exposed to anteMg for maternal preeclampsia or preterm labor found a dose-dependent risk for patent ductus arteriosus (PDA) compared to those infants not exposed to anteMg.[10] However, the Cochrane review by Crowther et al. and another review by Mercer et al. on the use of $MgSO_4$ as a tocolytic agent found similar rates of neonatal mortality or morbidity among exposed and unexposed infants.[5, 11] Similarly, secondary outcomes from the two large RCTs of anteMg versus placebo for fetal neuroprotection failed to demonstrate significant differences in the neonatal mortality and morbidity, including DR resuscitation and hypotension requiring treatment with vasopressors.[2, 3] Lastly, further analysis from the Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) Trial found no association between cord blood magnesium level and the need for DR resuscitation.[12]

In 2010, the American College of Obstetricians and Gynecologists issued a Committee Opinion on the use of $MgSO_4$ for fetal neuroprotection stating that “the available evidence suggests that $MgSO_4$ given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants.”[13] This report led to widespread use of $MgSO_4$ among women in preterm labor for fetal neuroprotection. We undertook this Phase IV study of the real world safety and effectiveness of $MgSO_4$ for fetal neuroprotection outside a clinical trial setting. We hypothesized that preterm infants <29 weeks of gestation exposed to anteMg are at risk of adverse cardiorespiratory (CR) effects compared to infants not exposed to anteMg.

Material and Methods

Study Design and Patient Population

In this large retrospective cohort study, CR events were compared between preterm neonates with and without exposure to anteMg born at 18 centers of *The Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network's (NRN). Infants born between 23 0/7 weeks and 28 6/7 weeks gestation and enrolled in the GDB from April 1, 2011 to March 31, 2012 were included in the study. Trained research personnel prospectively collected socio-demographic and clinical data from birth until death, discharge, or at 120 days of age as part of the NRN Generic Database (GDB) registry. Each center's Institutional Review Board approved the study and data collection procedures. The use of anteMg was recorded in the database; the indication for use was not. Exposure to antenatal magnesium was defined by maternal therapy with $MgSO_4$ during the admission that resulted in the delivery of the infant. Gestational age (GA) was determined by best obstetric estimate. CR events include intubation, use of any MV and treatment of hypotension in the first 24 hr. of life. The primary outcome was defined as the need for DR intubation or the need for any mechanical ventilation (MV) at birth or in the first 24 hours of life. Modes of MV included high frequency ventilation (HFV), oscillator and jet; conventional ventilation (CV), intermittent mandatory ventilation, synchronized

intermittent mandatory ventilation (SIMV) and/or assist control; nasal SIMV or continuous positive airway pressure (CPAP) via nasal prongs. Use of HFV and CV was defined as endotracheal MV (eMV). Secondary outcomes were the following: continued need for any modes of MV on the 3rd day of life; hypotension in the first 24 hours of life defined as the need for volume expansion, vasopressors and/or corticosteroid; and presence of a PDA requiring either medical or surgical treatment. Other neonatal data included age at first and full enteral feeds, duration of ventilation and oxygen support, morbidities including bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), sepsis, and necrotizing enterocolitis (NEC), length of hospitalization, and mortality.

Sample Size Calculation and Statistical Analysis

Our study cohort included all infants who met the GA criteria and who were part of the GDB registry. Infants were grouped into exposed (anteMg) and unexposed (noMg) groups. Based on the NRN's SUPPORT trial with inborn infants of the same GA category,[14] 34% of infants randomized to nasal CPAP needed intubation in the DR. Thus, we assumed a 30% rate of DR intubation in the noMg group and a 45% rate of DR intubation in the anteMg group. A total sample size of 326 (163 in each group) was needed to demonstrate statistical significance with α=0.05, power=0.80 in a 2 tailed test. Since $MgSO_4$ is being increasingly used for fetal neuroprotection, it is possible that more infants may be exposed to anteMg than not. In that case, assuming a 2:1 ratio of anteMg exposed versus non-exposed infants, we calculated a sample size of 122 and 244 in the two groups respectively. Based on the above sample size calculations, patients in the GDB registry were sufficient to detect even smaller differences in CR outcomes than estimated.

Data were analyzed using SAS statistical software version 9.3. Baseline maternal and neonatal clinical characteristics were compared using Chi-square test and Fisher's exact test for categorical variables and *t*-test for continuous variables. Medians were tested using Wilcoxon test. A *P* value of <0.05 was considered significant. Multivariate logistic regression models were used to determine the association between anteMg exposure and the primary outcome and other CR events such as hypotension and the risk of PDA. Covariates adjusted in the models included center, GA, ANS and pregnancy-induced hypertension (PIH)/eclampsia. Results were presented as odds ratio (OR) and 95% confidence interval (CI).

Results

There were 1,756 infants born at the 18 participating centers of the NRN's GDB registry who met the eligibility criteria. We excluded 212 infants due to either missing information or masked responses (these infants were part of other clinical trials) regarding anteMg use or missing primary outcome. Thus, 1,544 infants were evaluated including 1,091 (70.7%) infants in the anteMg group and 453 (29.3%) infants in the noMg group. Mothers of infants in the anteMg group were more likely to have ≥ high school education, preeclampsia/eclampsia and to have received ANS; while their infants were younger in gestation and weighed less (Table 1). Five percent of infants in the noMg group had a diagnosis of congenital or chromosomal defect versus 3% of infants in the anteMg group (*P* = 0.043).

One patient in each group had limited care including withdrawal of life support at birth due to a prenatal diagnosis of congenital or chromosomal anomalies.

DR intubation and any MV use during the first day of life were similar between groups. The anteMg group was less likely to need hypotension treatment on day 1 of life or to require eMV on either day 1 or day 3 of life compared to noMg group (Table 2). Infants in the anteMg group had more days free of MV in the first 28 days of life; however, morbidities and mortality, as well as ages at first and full enteral feedings were similar between groups (Table 3). AnteMg exposure was significantly associated with lower risk for hypotension treatment on day 1 of life and eMV on day 3 of life in the regression model even after adjusting for covariates (Table 4).

Comment

In this large cohort of preterm infants < 29 weeks of gestation in the GDB registry during the period April 1, 2011 to March 31, 2012, more than two-thirds were exposed to anteMg. Women who received anteMg were more likely to receive ANS and to have PIH/Eclampsia. We found no correlation between exposure to anteMg and increased risk of acute CR events in the immediate postnatal period. Infants in the anteMg group were found to have lower risk for eMV on day 3 of life and treatment for hypotension on day 1of life despite having lower birth weight (BW) and younger in GA than infants in the noMg group. Furthermore, infants exposed to anteMg were not at higher risk for DR resuscitation, neonatal morbidities, mortality, delayed feedings or longer hospitalization.

$MgSO_4$ has been used for obstetric indications for many decades. Despite the familiarity and comfort of use of this drug by obstetricians, there are concerns about the potential postnatal adverse effects of anteMg exposure. In the 6th edition of the Neonatal Resuscitation Textbook, $MgSO_4$ is listed as one of the drugs administered to the mother that can cause respiratory depression in newborns.[15] The U.S. Food and Drug Administration (FDA) recently warned against the use of $MgSO_4$ for more than 5-7 days as a tocolytic among women in preterm labor due to findings of low calcium levels in the developing fetus or baby that may lead to osteopenia and fractures. Since both the metaanalysis of randomized controlled trials of $MgSO_4$ for fetal neuroprotection[16] and the ACOG opinion statement endorse the use of $MgSO_4$ in women at risk of preterm birth to reduce the risk of cerebral palsy in surviving infants[13], we anticipate widespread use of antenatal $MgSO_4$ will occur. Thus, it is important to clarify if anteMg use is associated with significant acute CR events such as risk of DR intubation, invasive MV, and treatment for hypotension, as most of the exposed infants will be born preterm and at risk of these morbidities.

We found that infants in the anteMg group were less likely to need treatment for hypotension on day 1 of life and to receive eMV on day 3 of life. In contrast to our findings of reduced risk of acute CR events, most studies on neonates exposed to anteMg have shown either harmful effects[7-10] or no difference in terms of neonatal morbidity or mortality.[2, 3] In the BEAM trial, anteMg exposure among preterm infants was found to have no correlation with intubation and resuscitation in the DR and hypotension requiring vasopressors.[2] In the secondary analysis study of the BEAM trial, Johnson et al. did not find any correlation

between the cord blood magnesium level and the need for DR intubation or resuscitation among preterm infants exposed to anteMg for neuroprotection.[12] We speculate that studies on use of DR CPAP have changed the practice of routine intubation on all extremely preterm infants and may have influenced the results of this study towards the use of non-invasive ventilation.[14, 17, 18]

Although previous studies found no correlation between anteMg exposure and risk for hypotension in infants,[2, 12] we found that infants exposed to anteMg were less likely to have experienced severe hypotension requiring corticosteroid treatment. We recorded the level of treatment for hypotension and noted that infants exposed to anteMg were more likely to have received fluid boluses; however, treatment with corticosteroid was significantly higher in the noMg group while the use of inotropes was similar between the two groups. Magnesium has many physiological functions that are essential for key cellular processes and it is known to improve cardiovascular functions by regulation of vascular tone through vasodilation.[4] A secondary study from the Australian Collaborative Trial of Magnesium Sulfate investigating the systemic blood flow in preterm infants showed higher use of volume expansion and low superior vena cava (SVC) flow on cardiac echocardiography at 10-12 hr. of age among infants exposed to anteMg (N=48) compared to those not exposed (N=39); however, inotrope use did not differ between the two groups.[19] Low systemic blood flow in preterm infants during the first day of life has been known to be associated with decreasing gestational age, increasing mean airway pressure and reduction in myocardial contractility.[20, 21] Exposure to anteMg has been reported to help stabilize blood pressure changes in the first 48 hours of life[22] while volume expansion has been shown to improve the SVC flow among preterm infants;[23] these reports support our findings of lower risk for hypotension treatment among infants in the anteMg group despite having lower GA compared to the noMg group. In addition, more infants in the noMg group required eMV on both day 1 and 3 of life, thus, they may have higher mean airway pressure as a result of invasive MV. We speculate that the combination of eMV and lack of exposure to anteMg may have placed infants in the noMg group at higher risk for severe hypotension requiring corticosteroid treatment in the immediate postnatal period.

There were several limitations to our study. First, indications for use, dosages and receipt of anteMg in a previous admission were not collected in the GDB registry. The dosages for anteMg vary with each indication and the use of high dosages leading to high postnatal serum magnesium levels can certainly affect the CR status of the infant at birth. Despite this limitation, the study period chosen is reflective of current perinatal and neonatal practices, as most women presenting in preterm labor are now receiving $MgSO_4$ for fetal neuroprotection. In addition, the dosage range used for neuroprotection has not been shown to result in high postnatal serum magnesium levels that would be associated with acute CR events at birth. Other limitations include the retrospective nature of the study; reliance on information in the database; and missing information in the database. Lastly, we do not have information regarding the serum magnesium levels of the mothers. The strengths of this study are the large number and diverse group of high risk preterm infants included in the real world setting outside a randomized clinical trial setting. In addition, the study period chosen is relatively recent and so reflects recent practice with regards to anteMg use.

In conclusion, anteMg exposure among infants <29 weeks gestation was not associated with worse CR events when compared to unexposed infants. AnteMg was associated with reduced risk of hypotension in the first day of life and eMV on day 3 of life. AnteMg, as used in this population, appears to be safe for preterm infants.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. One behalf of the NRN, Dr. Abhik Das (DCC Principal Investigator) and Mr. Douglas Kendrick (DCC Statistician) had full access to all of the data in the study, and with the NRN Center Principal Investigators, take responsibility for the integrity of the data and accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1

Comparison of Baseline Clinical Characteristics

Clinical Characteristics	AnteMg N = 1,091	NoMg N = 453	*P*-value
Maternal	% /Median (Q1,Q3)	% /Median (Q1, Q3)	
Age in years	28 (23, 32)	27 (22, 32)	0.320
African-American	42	43	0.641
Married marital status	46	43	0.199
Education			
< high school degree	15	22	0.001*
High school degree or >	59	50	
Unknown	26	29	
Prenatal care	96	95	0.189
Preeclampsia/eclampsia	33	17	<.0001*
Histologic chorioamnionitis[1]	51	48	0.455
Antenatal Corticosteroids (ANS)	96	76	<.0001*
Complete course of ANS	75	55	<.0001*
C-section	66	68	0.261
Infant			
Gestational age, weeks	26 (25, 27)	27 (25, 28)	0.012*
Birth weight, grams	840 (685, 1,020)	910 (710, 1,100)	<.0001*
Small for gestational age[2]	10	7	0.169
Male gender	54	50	0.254
Apgar scores at 1 minute	4 (2, 6)	4 (2, 6)	0.217
Apgar scores at 5 minute	7 (6, 8)	7 (5, 8)	0.091
Delivery room resuscitation[3]	86	87	0.665
Anomalies	3	5	0.043*

Percentages were tested with a continuity-adjusted χ^2 test

*P value < 0.05 is considered significant.

[1] In ~19% of cases, either no pathology was performed or the data was missing.

[2] SGA was defined weight < 10th percentile based on Alexander's growth curve.

[3] Delivery room resuscitation is defined as receipt of any of the following: positive pressure ventilation via bag and mask, any CPAP devices, intubation, chest compression and epinephrine.

Table 2

Comparison of Primary and Secondary Outcomes

Outcomes	AnteMg N = 1,091	NoMg N = 453	*P*-value
Primary Outcomes	%	%	
Delivery Room Intubation	68	72	0.157
Day 1 - Mechanical ventilation (MV)[1]	95	95	0.670
Day 1 - Endotracheal MV (eMV)[2]	63	70	0.023*
Secondary Outcomes			
Day 3 – MV	89	92	0.190
Day 3 – eMV	51	62	0.0002*
Day 1- Hypotension	24	29	0.043*
Treatment:			
Fluid Bolus	72	61	
Vasopressor/inotrope	68	72	
Corticosteroid	10	18	
PDA (medical or surgical)	31	31	0.954

Percentages were tested with a continuity-adjusted χ^2 test.

*P value < 0.05 is considered significant.

[1]MV includes CV, HFV, nasal SIMV, CPAP.

[2]eMV includes CV and HFV only.

Table 3

Comparison of Neonatal Mortality and Morbidity

Other neonatal outcomes *Percentages*	**AnteMg N = 1,091**	**NoMg N 453**	***P*-value**
Respiratory distress syndrome[1]	98	98	0.747
Pulmonary hemorrhage	6	4	0.289
Traditional BPD[2]	45	45	1.0
Late-onset sepsis/meningitis[3]	24	19	0.085
NEC[4] Stage II or greater	9	8	0.351
ROP (any stage)	54	57	0.359
Intraventricular or parenchymal hemorrhage[5]	13	15	0.294
Cystic PVL[6]	3	5	0.150
Mortality	13	16	0.223
Medians (Q1, Q3)			
Age at first enteral feeding	4 (2, 5)	4 (2, 6)	0.554
Age at full enteral feeds (120ml/kg/day)	19 (14, 28)	21 (14, 29)	0.242
Cumulative days on MV[7,8]	31 (10, 52)	32 (11,54)	0.871
Cumulative days of oxygen support[8]	47 (14, 84)	47 (16, 85)	0.635
Days free of MV[7,8] in 1st 28 days of life	20 (3, 27)	18 (1, 26)	0.036*
Days free of oxygen support in 1st 28 days of life	3 (0, 15)	2 (0, 14)	0.122
Length of hospital stay[9]	87 (62, 112)	81 (59, 111)	0.621

Percentages were tested with a continuity-adjusted χ^2 test

* *P* value < 0.05 is considered significant.

[1] Based on clinical features and requirement of oxygen/ positive pressure support > 6 hrs. in the first 24 hours of life.

[2] Oxygen use at 36 weeks postmenstrual age.

[3] Based on culture proven blood and cerebrospinal fluid infection taken after 72 hr. of age.

[4] Defined by Bell's staging.

[5] Presence of intraventricular or intraparenchymal hemorrhage on head ultrasound.

[6] Based on cranial ultrasound findings at 28 days or 36 weeks PMA.

[7] MV includes CV, HFV, nasal SIMV, CPAP. (Option to change MV to Assisted ventilation or AV)

[8] Cumulative days on MV or oxygen support were analyzed solely on survivors; deaths were excluded.

[9] Length of hospital stay was analyzed with a Kaplan-Meier log rank test.

Table 4

Multivariate Logistic regression Model Estimating the Effects of AnteMg Exposure and Risk of Acute CR Events

CR Events	Odds Ratio	95% CI	*P*-value
DR Intubation	1.20	(0.88, 1.65)	0.246
Day 1 – MV[1,3]	1.22	(0.65, 2.30)	0.540
Day 1 – eMV[2]	0.78	(0.58, 1.06)	0.109
Day 3 – MV[1]	0.65	(0.40, 1.04)	0.070
Day 3 – eMV[2]	0.54	(0.41, 0.72)	<.0001*
Hypotension	0.70	(0.51, 0.97)	0.031*
PDA (medical and surgical)	1.06	(0.80, 1.40)	0.696

Coviarates: Center, GA, ANS, PIH/Eclampsia

** P* value < 0.05 is considered significant.

[1] MV includes CV, HFV, nasal SIMV, CPAP.

[2] eMV includes CV and HFV only.

[3] Four centers which had zero cells were combined with other centers so that modeling could produce valid results.