OBSTETRICS

Antenatal magnesium sulfate exposure and acute cardiorespiratory events in preterm infants

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OBJECTIVE: Antenatal magnesium (anteMg) is used for various obstetric indications including fetal neuroprotection. Infants exposed to anteMg may be at risk for respiratory depression and delivery room (DR) resuscitation. The study objective was to compare the risk of acute cardiorespiratory events among preterm infants who were and were not exposed to anteMg.

STUDY DESIGN: This was a retrospective analysis of prospective data collected in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network's Generic Database from April 1, 2011, through March 31, 2012. The primary outcome was DR intubation or respiratory support at birth or on day 1 of life. Secondary outcomes were invasive mechanical ventilation, hypotension treatment, neonatal morbidities, and mortality. Logistic regression analysis evaluated the risk of primary outcome after adjustment for covariates.

RESULTS: We evaluated 1544 infants <29 weeks' gestational age (1091 in anteMg group and 453 in nonexposed group). Mothers in the anteMg group were more likely to have higher education, pregnancy-induced hypertension, and antenatal corticosteroids, while their infants were younger in gestation and weighed less ($P < .05$). The primary outcome (odds ratio [OR], 1.2; 95% confidence interval [CI], 0.88—1.65) was similar between groups. Hypotension treatment (OR, 0.70; 95% CI, 0.51—0.97) and invasive mechanical ventilation (OR, 0.54; 95% CI, 0.41—0.72) were significantly less in the anteMg group.

CONCLUSION: Among preterm infants age <29 weeks' gestation, anteMg exposure was not associated with an increase in cardiorespiratory events in the early newborn period. The safety of anteMg as measured by the need for DR intubation or respiratory support on day 1 of life was comparable between groups.

Key words: antenatal magnesium, nasal continuous positive airway pressure, neonatal resuscitation, preterm infants

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Magnesium sulfate ($MgSO_4$)[1] is commonly used in obstetrics. Indications include seizure prevention in women with preeclampsia and tocolysis for women in preterm labor to prolong the pregnancy, enabling administration of antenatal corticosteroids (ANS). In addition, a recent Cochrane review of the 5 clinical trials of $MgSO_4$ given to women at risk of preterm delivery for neuroprotection of the fetus demonstrated a significant reduction in risk of cerebral palsy among preterm infants who had been exposed to $MgSO_4$.[2] Magnesium is involved 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.[3,4] While most adverse effects of maternal antenatal magnesium (anteMg) administration are minor, including treatment cessation, life-threatening adverse effects such as maternal death, cardiac arrest, or respiratory arrest have been reported in iatrogenic overdose of $MgSO_4$.[4-6] Neonatal consequences of anteMg administration and the safety profile of its use in preterm infants are unclear. Magnesium crosses the placenta readily with cord magnesium concentrations reaching approximately 70-100% of maternal concentrations after several hours of infusion. Due to delayed fetal urinary excretion, fetal serum and amniotic fluid concentrations can exceed maternal concentrations during prolonged therapy (>72 hours). Maternal serum magnesium concentration has been shown to be highly correlated with fetal serum concentration. Thus, symptoms of central nervous system depression (hypotonia and drowsiness) or cardiorespiratory (CR) effects such as fetal heart rate variability and decreased fetal breathing movements may be seen even when these mothers have therapeutic serum magnesium levels of ~4-8 mg/dL.[7] In the Magnesium and Neurological Endpoints Trial, anteMg used for either neuroprotection or tocolysis at 24-33 weeks' gestation was associated with higher composite adverse pediatric outcomes (risk of death, any intraventricular hemorrhage, periventricular leukomalacia, and cerebral palsy) among infants exposed to anteMg compared to those not exposed (odds ratio, 2.0; 95% confidence interval, 0.99−4.1; $P = .07$).[8,9] Retrospective cohort studies of anteMg for preterm labor, preeclampsia, and prevention of eclampsia have demonstrated adverse events in the newborn that included hypotonia, delivery room (DR) intubation, admission to special care nursery, and a dose-dependent risk for patent ductus arteriosus (PDA) compared to infants not exposed to anteMg.[10,11] The Cochrane review by Crowther et al[12] on the safety and effectiveness of $MgSO_4$ in preterm labor noted 2 fetal deaths in 1 study and no differences in total pediatric mortality, while the review by Doyle et al[2] on the use of $MgSO_4$ for neuroprotection in preterm births showed no difference in pediatric mortality.

In 2010, the American College of Obstetricians and Gynecologists (ACOG) 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] Thus, 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 those preterm infants age <29 weeks of gestation exposed to anteMg are at risk of adverse CR effects compared to infants not exposed to anteMg.

Materials and Methods

Study design and patient population

In this 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 (NRN). All infants born between 23 0/7 and 28 6/7 weeks' gestation and enrolled in the Generic Database (GDB) registry from April 1, 2011, through March 31, 2012, were included in the study. Trained research personnel prospectively collected sociodemographic and clinical data from birth until death, discharge, or 120 days of age as part of the GDB registry. Each center's institutional review board approved the study and data collection procedures. The decision to use anteMg was made by the clinician and recorded in the database; the indication for use was not collected. In addition, we do not have information on the protocols for magnesium use in our data registry. Exposure to anteMg was defined by maternal therapy with $MgSO_4$ during the admission that resulted in the delivery of the infant. Gestational age was determined by best obstetric estimate. CR events include DR intubation, use of any respiratory support, and treatment of hypotension in the first 24 hours of life. The primary outcome was defined as the need for DR intubation or the use of any respiratory support at birth or in the first 24 hours of life. Only infants who were intubated (even if transiently) to allow positive pressure ventilation for breathing were included and coded as "yes" for DR intubation. If intubation was done for suctioning or to give surfactant and immediately removed, it is not included. Modes of respiratory support included high-frequency ventilation, oscillator, and jet; conventional ventilation, intermittent mandatory ventilation, synchronized intermittent mandatory ventilation, and/or assist control; and nasal synchronized intermittent mandatory ventilation or continuous positive airway pressure (CPAP) via nasal prongs. Use of high-frequency ventilation and conventional ventilation was defined as invasive mechanical ventilation (MV). Secondary outcomes were the following: continued need for any modes of respiratory support on the third day of life; hypotension in the first 24 hours of life defined by treatment with volume expansion, vasopressors, and/or corticosteroid; and presence of a PDA requiring either medical or surgical treatment. The decision to treat hypotension and treatments used were at the discretion of the clinical team. Other neonatal data included age at first and full enteral feeds; duration of ventilation and oxygen support; morbidities including bronchopulmonary dysplasia, retinopathy of prematurity, sepsis, and necrotizing