Does magnesium exposure affect neonatal resuscitation?

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OBJECTIVE: Research on immediate neonatal resuscitation suggests that maternal magnesium exposure may be associated with increased risk of low Apgar scores, hypotonia, and neonatal intensive care unit admission. However, not all studies support these associations. Our objective was to determine whether exposure to magnesium at the time of delivery affects initial neonatal resuscitation.

STUDY DESIGN: This is a secondary analysis of the Randomized Controlled Trial of Magnesium Sulfate for the Prevention of Cerebral Palsy that evaluated whether the study drug (magnesium or placebo) that was administered at the time of delivery was associated with increased risk for a composite adverse neonatal resuscitation outcome (5-minute Apgar score <7, oxygen administration in the delivery room, intubation, chest compressions, hypotension, and hypotonicity). A subgroup analysis was performed among patients who delivered at ≥30 weeks of gestation. Log-linear regression was used to control for possible confounders.

RESULTS: Data for 1047 patients were analyzed, of whom 461 neonates (44%) were exposed to magnesium. There was no increased risk for the primary composite outcome associated with magnesium exposure. Individual adverse neonatal outcomes and other secondary short-term neonatal outcomes that were evaluated also did not demonstrate an association with magnesium exposure.

CONCLUSION: Exposure to magnesium sulfate did not affect neonatal resuscitation or other short-term outcomes. These findings may be useful in planning neonatal care and patient counseling.

Key words: immediate neonatal resuscitation, magnesium sulfate, neonatal outcome, neuroprotection

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Magnesium sulfate (MgSO4) is a commonly used drug in obstetrics; indications include tocolysis for women in preterm labor and seizure prophylaxis in the setting of preeclampsia.[1] More recently, a major randomized trial demonstrated that MgSO4 is neuroprotective for preterm infants when administered before delivery and reduces risk for cerebral palsy.[2] Magnesium decreases smooth muscle contractility and interferes with acetylcholine release in the neuromuscular junction, which leads to stabilization of the cell membrane and prevention of central nervous system excitability.[3] At toxic levels, MgSO4 may cause muscular weakness, respiratory depression, and cardiac arrest.[4]

Research evidence on the effects of magnesium on immediate neonatal resuscitation suggests that magnesium exposure may be associated with increased risk of low Apgar scores, hypotonia, and neonatal intensive care unit admission.[5-7] However, not all studies support these associations.[8,9] A previous analysis from a major, multicenter, randomized controlled trial to assess the benefit of magnesium in the prevention of cerebral palsy for preterm infants found that, on an intent-to-treat basis, magnesium was not associated with increased adverse outcomes during neonatal resuscitation after delivery.[2] However, this analysis included patients who delivered with minimal magnesium exposure or who delivered after magnesium had been discontinued or who delivered at term, which is an approach that may bias the analysis towards no detection of an association. Currently, The American Academy of Pediatrics lists MgSO4 among the medications that may cause respiratory depression in the newborn infant.[10]

Given the limits of previous analyses, our objective was to determine whether exposure to MgSO4 at the time of delivery affects initial neonatal resuscitation in preterm infants who receive the drug for neuroprotection.

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TABLE 1
Demographic characteristics

Variable	Magnesium sulfate	Placebo	*P* value
All patients, n (%)	461 (44.0)	586 (56.0)	
Mean age, y ± SD	26.2 ± 5.8	25.8 ± 5.5	.22
Mean education, y ± SD	11.7 ± 2.4	11.6 ± 2.5	.67
Married, n (%)	231 (50.1)	249 (42.7)	.02
Nulliparous, n (%)	174 (27.7)	218 (37.2)	.85
Previous preterm birth, n (%)	133 (28.9)	156 (26.6)	.42
No prenatal care, n (%)	27 (5.9)	47 (8.0)	.18
Alcohol, n (%)	46 (10.0)	46 (7.9)	.22
Smoking, n (%)	136 (29.5)	157 (26.8)	.33
Illicit drugs, n (%)	54 (11.7)	61 (10.4)	.50
Race, n (%)			.71
African American	203 (44.0)	274 (46.8)	
White	171 (37.1)	201 (34.3)	
Hispanic	74 (16.1)	99 (16.9)	
Asian	7 (1.5)	5 (0.8)	
Other	5 (1.3)	8 (1.2)	
Body mass index, n (%)			.41
<18.5 kg/m^2	74 (16.1)	87 (14.9)	
18.5-24.9 kg/m^2	201 (43.6)	232 (39.6)	
25-29.9 kg/m^2	90 (19.5)	131 (22.3)	
≥ 30 kg/m^2	96 (20.8)	136 (23.2)	

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Materials and Methods

This is a secondary analysis of the Randomized Controlled Trial of Magnesium Sulfate for the Prevention of Cerebral Palsy that was conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Development's Maternal-Fetal Medicine Units Network.[2] The parent multicenter trial enrolled women in 20 centers across the United States from 1997-2004 to determine whether antenatal MgSO4 administration decreased the rate of cerebral palsy or death. Women at very high risk for preterm delivery between 24 and 31 weeks of gestation were assigned randomly to MgSO4 or placebo. For this current analysis, the exposure of interest was the study drug exposure; we included singleton pregnancies if they were receiving magnesium or placebo at the time of delivery. Women were excluded if they were exposed for <3 hours, if they delivered after 32 weeks of gestation, or if they had stillbirths or neonates with major congenital anomalies. Patients with missing outcome data were also excluded. This analysis was approved by the institutional review board at Columbia University Medical Center.

The parent trial protocol included women at imminent risk for preterm delivery (2241 women) between 24 and 31 weeks of gestation. The MgSO4 arm received a 6-g loading dose over 20 minutes, followed by a 2-g per hour infusion until delivery or for at least 12 hours if delivery did not occur. Retreatment with the study drug was initiated if delivery was once again anticipated. If ≥ 6 hours had passed since the discontinuation of the study medication, a second 6-g loading dose was given at the time of retreatment. Duration of study drug exposure and total grams of MgSO4 administered were recorded.

For this analysis, 2 exposure groups were defined: (1) those who received MgSO4 at the time of delivery and (2) those who received placebo. Women who were exposed to the study drug (MgSO4 or placebo) for <3 hours were excluded. The primary outcome was a composite adverse neonatal resuscitation outcome that included any of the following events: a 5-minute Apgar score <7, oxygen administration in the delivery room, intubation, chest compressions, hypotension treated with vasopressors, and/or generalized hypotonicity. Secondary outcomes included all the components of the primary outcome and respiratory distress syndrome, mechanical ventilation, seizures, intraventricular hemorrhage, and death. Given the association between gestational age and immediate neonatal outcomes, a subgroup analysis was performed among patients who delivered at ≥ 30 weeks of gestation. Patient demographic variables and other characteristics were compared with the use of the chi-square test for categoric variables and the Student *t* test for continuous variables, as appropriate. Significance was set at a probability value of $< .05$. We fit a log linear regression model to control for possible confounders; the model included covariates that were known or suspected to be associated with the primary outcome and covariates that were found to significantly differ in the univariate analysis. We chose a log linear over a logistic regression model because the former allows estimating true relative risks.[11,12] The sample size was determined by the number of patients who were enrolled in the parent trial and included 461 experimental subjects and 586 control subjects. A power analysis based on the fixed sample size revealed a minimum detectable effect size of <0.88 or >1.11 risk ratio for the intervention based on a power of 80% and a type I error of 5%, assuming an incidence in our primary outcome of 70%, which was based on previously published data.[2]