Antenatal Magnesium Sulfate, Necrotizing Enterocolitis, and Death among Neonates < 28 Weeks Gestation

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Abstract

Objective This study aims to examine the relationship between antenatal magnesium sulfate ($MgSO_4$) and neonatal death and/or severe necrotizing enterocolitis (NEC) among infants < 28 weeks.

Methods Secondary analysis of a multicenter randomized trial of antenatal $MgSO_4$ versus placebo administered to women to prevent death and cerebral palsy. Neonates < 28 weeks were included. The primary outcome was neonatal death before NICU discharge, and/or severe NEC (Bell criteria stage II/III). Neonates with and without death/severe NEC were compared.

Results A total of 697 neonates met the criteria. Out of which 150 (21.5%) died and/or were diagnosed with severe NEC. Antenatal $MgSO_4$ exposure was not associated with death/severe NEC in infants < 28 weeks. In a subgroup analysis of neonates < 26 weeks, treatment group assignment to antenatal $MgSO_4$ was associated with an increased odds of death/severe NEC (adjusted odds ratio: 1.90, 95% confidence interval: 1.12–3.22, $p = 0.017$).

Conclusions Among neonates < 26 weeks, antenatal $MgSO_4$ was associated with death and severe NEC. Further prospective study in larger populations is needed.

Keywords
- magnesium sulfate
- preterm delivery
- necrotizing enterocolitis

Multiple studies have investigated the use of antenatal magnesium sulfate ($MgSO_4$) to prevent cerebral palsy (CP) in the offspring.[1–4] The majority of these studies have shown that antenatal $MgSO_4$ reduces the risk of gross motor dysfunction and CP among surviving early preterm infants. A meta-analysis and Cochrane review support these findings; thus, it is now standard of care in the United States to administer $MgSO_4$ before an expected early preterm delivery (< 32 weeks).[5,6] However, a few investigators have recently questioned the standardized antenatal $MgSO_4$ clinical administration protocol,[7] and others are continuing to explore possible neonatal risks associated with $MgSO_4$ use.

A recent publication reported a possible association between antenatal $MgSO_4$ use and spontaneous intestinal perforation (SIP) among extremely low-birth-weight infants. Rattray et al performed a retrospective review of 155 extremely low-birth-weight infants (< 1,000 g) to examine the risk of SIP and/or death in relationship to antenatal $MgSO_4$

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use.[8] They found a higher rate of SIP and/or death among infants who had received $MgSO_4$ (30.4 vs. 20.5% in those without $MgSO_4$ exposure, $p = 0.28$); the effect was most pronounced among those delivered < 25 weeks gestation (odds ratio [OR]: 9.7, $p < 0.01$).

SIP is common among very premature neonates, affecting approximately 5% of extremely low-birth-weight neonates, and is associated with a 10 to 36% mortality rate.[9,10] Necrotizing enterocolitis (NEC) is a separate, generally more severe gastrointestinal disorder, affecting approximately 10% of extremely low-birth-weight neonates. The mortality rate of severe NEC is 30 to 50% and significant long-term morbidity is common amongst survivors.[11] Differentiation between NEC and SIP is usually based on physical examination, clinical manifestations (NEC typically more systemic), and radiographic findings (pneumatosis intestinalis is present only in NEC). These conditions can be diagnosed clinically, though intraoperative evaluation is the only way to truly distinguish between the two entities. The etiology of NEC is multifactorial, and includes bacterial proliferation and overgrowth as well as ischemic necrosis of the intestinal mucosa.[12] The etiology of SIP is poorly understood but is also likely multifactorial.[13] Although different processes, disruption of normal intestinal flora, motility, and/or mucosal integrity may contribute to the development of both.

We sought to examine factors associated with neonatal death and NEC, and to investigate the relationship between $MgSO_4$ exposure, neonatal death, and NEC among infants delivered < 28 weeks gestation.

Materials and Methods

This is a secondary analysis of a multicenter randomized controlled trial conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network of antenatal $MgSO_4$ versus placebo administered to women at imminent risk for preterm delivery less than 32 weeks gestation. The aim of the primary study was to investigate the role of antenatal $MgSO_4$ in the prevention of death and CP in their offspring. The methods and results from the primary study have been previously published.[4] Briefly, the main trial found that fetal exposure to $MgSO_4$ did not reduce the combined risk of moderate or severe CP or death, but the rate of moderate-to-severe CP was reduced among survivors (1.9 vs. 3.5%; relative risk, 0.55; 95% confidence interval [CI], 0.32–0.95). All participants provided written informed consent at the time of enrollment in the original study. This secondary analysis was performed on a de-identified data set, and was reviewed by our local institutional review board (IRB) and determined to be nonhuman subjects research and therefore exempt from IRB approval.

Singleton and twin infants admitted, randomized, and delivered between 23.0 and 27.9 weeks gestation were included in this secondary analysis. Enrollment occurred from December 1997 through May 2004. Infants with chromosomal abnormalities, major congenital malformations, and/or with incomplete outcomes were excluded. Gestational age was determined by the best obstetric estimate per previously published criteria.[14] Infants were classified as small for gestational age if their birth weight was less than the 10th percentile based on gender- and gestational-age-specific contemporary birth norms.[15] Trained research nurses obtained data on neonatal outcomes during hospitalization and at discharge. Specifically, each neonate was assessed for the presence of or history of intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, retinopathy of prematurity, and NEC. Additionally, charts were reviewed to determine if the neonate had one or more documented (culture proven) episode(s) of sepsis during their hospitalization.[4]

The primary outcome of this secondary analysis was the incidence of death before initial neonatal hospital discharge and/or diagnosis of moderate or severe (stage II or III) NEC. NEC was diagnosed based on the clinical staging system of Bell, et al.[16] We also examined factors associated with neonatal death and stage II/III NEC individually. Information on SIP was not available because it was not specifically collected in the primary study.

Demographics, pregnancy characteristics, and neonatal outcomes were compared between children with and without death and/or stage II/III NEC. These univariable analyses were conducted using Student *t*-test, chi-square, and analysis of variance, as appropriate. Data were then analyzed by multivariable regression using backward regression, to test for an interaction between $MgSO_4$ exposure and death and/or stage II/III NEC. Exposure to $MgSO_4$ and factors with a p value <0.20 remained in the final models. Initial covariates included in each regression model were delivery gestational age, treatment group assignment (randomization to $MgSO_4$ or placebo), fetal sex, small for gestational age, chorioamnionitis, cesarean section, neonatal hypotension during initial resuscitation, postnatal exposure to indomethacin, neonatal sepsis, and intraventricular hemorrhage. A preplanned subgroup analysis was also performed for neonates delivered < 26 weeks gestation. Data were analyzed using Stata version 13.1 (StataCorp LP, College Station, TX).

Results

Of 2,444 neonates randomized in the original study, 697 neonates delivered < 28 weeks gestation met inclusion criteria for this secondary analysis (►**Fig. 1**). From this group, 114 babies (16.3%) were diagnosed with NEC, including 47 with stage I, 25 with stage II, and 42 with stage III NEC. Death was increasingly likely with higher stages of NEC (8.5% with stage I, 28.0% with stage II, and 50.0% with stage III, $p < 0.001$). A total of 111 neonates died before initial hospital discharge, at a median 13 days of life (interquartile range [IQR]: 2–37).

Overall, 150 (21.5%) babies died and/or were diagnosed with stage II/III NEC during their initial NICU hospitalization and met criteria for the primary outcome. The 67 neonates with stage II/III NEC were initially diagnosed with NEC at a median 20 (IQR: 13–40) days of life. Neonates who died or developed stage II/III NEC were more likely to be small for gestational age, and were enrolled and subsequently delivered earlier than those

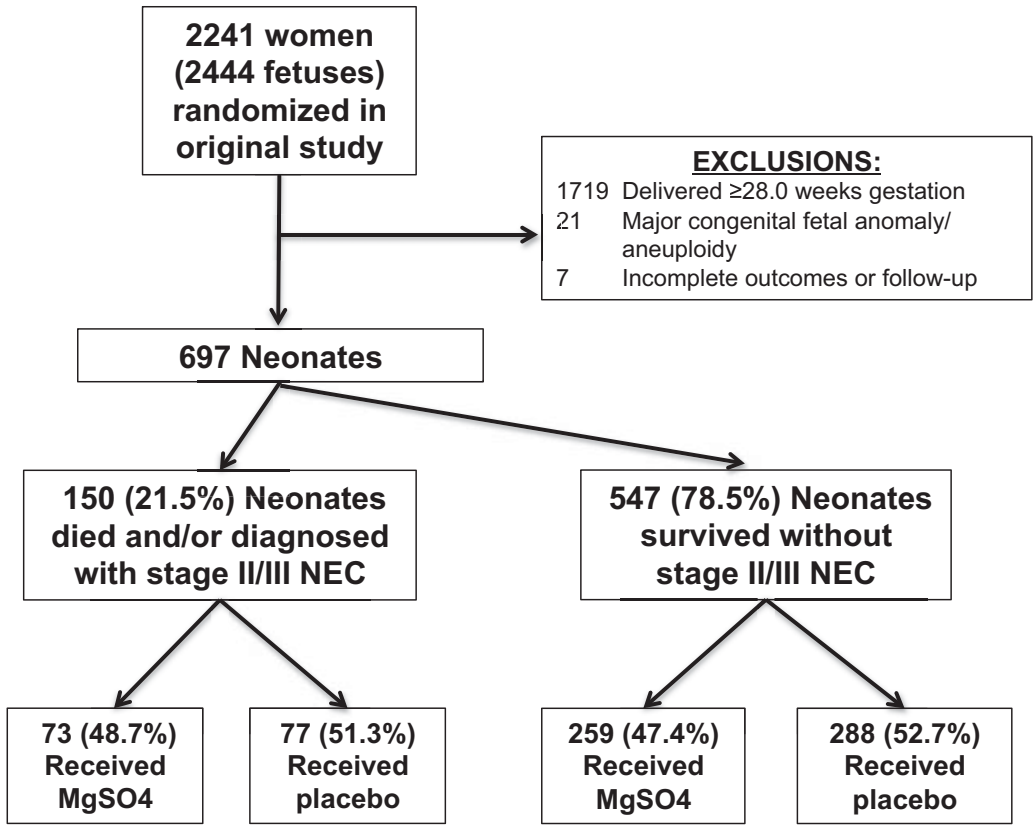

Fig. 1 Inclusion criteria.

neonatal survivors who did not have severe NEC. Demographic and baseline characteristics were otherwise similar between those with and without the adverse outcome and are compared in ►**Table 1**. Delivery characteristics and initial neonatal outcomes are shown in ►**Table 2**.

After adjusting for confounders, delivery gestational age, neonatal sepsis, postnatal exposure to indomethacin, male sex, and cesarean section remained associated with our primary outcome of neonatal death or stage II/III NEC (►**Table 3**). In the overall cohort of neonates delivered < 28 weeks, those randomized to antenatal $MgSO_4$ were not at increased odds of death or stage II/III NEC. Randomization to $MgSO_4$ was also not associated with elevated odds of the individual outcomes of death and stage II/III NEC among those delivered < 28 weeks gestation in multivariable models (data not shown).

Overall, 293 neonates (42.0%) were delivered less than 26.0 weeks gestation. As expected, these very premature neonates were more likely to die or develop stage II/III NEC compared with babies delivered 26.0 to 27.9 weeks (87/293, 29.7% vs. 63/404, 15.6%, $p < 0.001$). Of babies delivered < 26 weeks gestation, 148 (50.5%) were randomized to receive $MgSO_4$ in the original study. Of these, 53/148 (35.8%) died or developed stage II/III NEC, compared with 34/145 (23.5%) babies who received placebo ($p = 0.021$), unadjusted OR, 1.82 (95% CI: 1.10–3.03, $p = 0.021$). In multivariable models, treatment group assignment to antenatal $MgSO_4$ remained associated with an increased odds of death or stage III NEC (adjusted odds ratio [aOR]: 1.90, 95% CI: 1.12–3.22, $p = 0.017$), even when controlling for confounders including delivery gestational age and small for gestational age (►**Table 4**). This finding appeared to be driven primarily by an increased risk of death. In additional multivariable models, randomization to $MgSO_4$ was associated with death with an aOR of 1.83 (95% CI: 1.03–3.27, $p = 0.040$). This is in contrast to the model with stage II/III NEC alone as the dependent variable, where randomization to $MgSO_4$ was not associated with this adverse outcome (aOR: 1.38, 95% CI: 0.64–3.00, $p = 0.414$).

Discussion

We report no association between randomization to antenatal $MgSO_4$ for fetal neuroprotection and the combined outcome of death and/or stage II/III NEC among very preterm neonates delivered < 28 weeks gestation. In the subgroup of neonates delivered < 26 weeks gestation, there was an association between randomization to $MgSO_4$ and these adverse outcomes.

The reason for this association is unclear. $MgSO_4$ readily crosses the placenta, with a high correlation between fetal and maternal $MgSO_4$ levels.[17] The time between antenatal $MgSO_4$ exposure and NEC diagnosis at a median of 20 days of life (IQR: 13–40) suggests there is not a direct causal relationship; $MgSO_4$ is likely one contributing "environmental" factor to the development of NEC. Various biological effects of $MgSO_4$ may affect the integrity of the gastrointestinal tract and may contribute to the development of SIP and/or NEC. Higher $MgSO_4$ levels are associated with intestinal dysmotility and fecal impaction among adults; it is reasonable to

Table 1 Maternal demographic and baseline characteristics at randomization

Characteristic	NICU death or stage II/III NEC $N = 150$	Survived NICU, no stage II/III NEC $N = 547$	*p* Value
Maternal age (y)	26.7 ± 6.0	26.5 ± 6.1	0.756
Maternal prepregnancy body mass index (kg/m^2)	26.7 ± 6.8	27.5 ± 7.3	0.263
Married	74 (49.3)	259 (47.5)	0.694
Race/ethnicity			0.290
African-American	72 (48.0)	262 (47.9)	
Caucasian	54 (36.0)	184 (33.6)	
Hispanic	24 (16.0)	88 (16.1)	
Other	0 (0)	13 (2.3)	
Maternal education: highest level completed	12.0 (± 2.3)	12.0 (± 2.3)	0.700
No prenatal care	9 (6.0)	36 (6.6)	0.797
Smoking during pregnancy	35 (23.3)	148 (27.1)	0.359
Alcohol use during pregnancy	14 (9.3)	48 (8.8)	0.832
Illicit drug use during pregnancy	18 (12.0)	45 (8.2)	0.153
Gestational age at randomization (wks)	25.2 ± 1.0	25.6 ± 1.1	< 0.001
Randomized to magnesium sulfate	73 (48.7)	259 (47.4)	0.775
Preterm premature rupture of membranes	127 (84.7)	480 (87.8)	0.318

Abbreviations: NICU, neonatal intensive care unit; NEC, necrotizing enterocolitis

hypothesize that this might also occur in neonates.[18] Decreased intestinal motility could also result in bacterial overgrowth, leading to NEC. The immature epithelium in premature newborns is more sensitive to bacteria and bacterial translocation, which may contribute to changing the intestinal microbiome, causing intestinal damage and NEC.[19] In rat models, $MgSO_4$ has also been shown to reduce mesenteric blood flow in vivo.[20,21] A reduction in mesenteric blood flow in neonates may cause vulnerability to ischemic bowel injury. As both SIP and NEC are multifactorial, the combination of an immature gastrointestinal tract, $MgSO_4$, and other genetic or environmental risk factors may be sufficient to trigger for the development of these severe complications. We hypothesize that these adverse effects are found only among the most premature neonates due to the extreme fragility and immaturity of the gastrointestinal tract < 26 weeks gestation. However, the exact mechanism (s) are unknown, and we are unable to investigate these etiologies using the current study design.

Our results have some similarities to those reported by Rattray and colleagues. They found a 30% incidence of SIP and/or death during the time period when an antenatal $MgSO_4$ for neuroprotection protocol was implemented, in contrast to SIP and/or death rates of 13% off protocol.[8] Rattray included all neonates with birthweight < 1,000 g; in contrast, our study included those delivered < 28 weeks gestation. In both studies, however, the findings were most significant for neonates delivered < 26 weeks gestation. We performed this subgroup analysis due to known increases in risk for NEC in infants born < 26 weeks gestational age.[22]

Our findings are in contrast to other studies that have shown no association between NEC and antenatal $MgSO_4$. Ghidini et al performed a retrospective cohort study comparing the rate of $MgSO_4$ exposure before birth among 23 infants diagnosed with NEC to 46 controls, and found a similar proportion of babies were exposed to $MgSO_4$ in each group (30 vs. 39%, $p = 0.4$).[23] In another retrospective cohort study of 401 infants delivered 23 to 34 weeks gestation, approximately half were exposed to $MgSO_4$, and there was no apparent relationship between $MgSO_4$ exposure and NEC.[24] Although neither study demonstrated an association between $MgSO_4$ and NEC, these studies were retrospective and nonrandomized, included infants delivered across a large gestational age range (with a lower overall incidence of NEC), and were ultimately underpowered.

Although prenatal indomethacin exposure classically has been associated with an increased risk of NEC, we were unable to confirm those findings in the present study. Historically, the association between postnatal indomethacin exposure and NEC has been less consistent, and some reports have endorsed a protective association while others have noted a potentially negative association.[26,27] In our study, we found a reduced likelihood of stage II/III NEC among those neonates delivered < 28 weeks who were exposed to postnatal indomethacin (aOR: 0.63, 95% CI: 0.42–0.94).

This study has several strengths. This was a large, prospectively collected cohort. All mothers randomized to receive $MgSO_4$ did so per study protocol (with set loading and maintenance dosing, and uniform conditions for drug initiation and discontinuation). All neonates were evaluated in a standardized fashion by trained research nurses and

Table 2 Delivery characteristics and initial neonatal outcomes. Unless otherwise specified, data are listed as *n* (%)

Characteristic	NICU death and/or stage II/III NEC $N = 150$	Survived NICU, no stage II/III NEC $N = 547$	*p* Value
Gestational age at delivery (wks)	25.8 ± 1.1	26.3 ± 1.0	< 0.001
Antenatal exposure to indomethacin	11 (7.3)	47 (8.6)	0.621
Received antenatal corticosteroids	145 (96.7)	528 (96.5)	0.934
Chorioamnionitis	19 (12.7)	97 (17.7)	0.140
Magnesium sulfate infusing at delivery[a]	41/73 (56.2)	152/259 (58.7)	0.700
Mean total amount (g) of magnesium sulfate received (± SD)[a]	33.0 ± 19.8	33.9 ± 18.2	0.595
Mean cord blood magnesium sulfate level, mEq/L (± SD)[b]	2.64 ± 1.1	2.67 ± 0.8	0.890
Cesarean section	77 (51.3)	256 (46.8)	0.325
Male fetus	87 (58.0)	269 (49.2)	0.056
Birthweight (g)	757 ± 164	872 ± 181	< 0.001
Small for gestational age	20 (13.3)	24 (4.4)	< 0.001
Median 1-min Apgar score (IQR)	4 (2–6)	5 (3–7)	< 0.001
Median 5-min Apgar score (IQR)	7 (5–8)	7 (6–8)	< 0.001
Neonatal hypotension in the delivery room	9 (6.0)	21 (3.8)	0.248
Neonatal hypotension requiring treatment at any time	117 (78.0)	183 (33.5)	< 0.001
Patent ductus arteriosus requiring therapy	50 (33.3)	179 (32.7)	0.888
Postnatal exposure to indomethacin	57 (38.0)	234 (42.8)	0.293
Culture-proven sepsis	81 (54.0)	183 (33.5)	< 0.001
Neonatal seizures (suspected or confirmed)	14 (9.3)	22 (4.0)	0.009
Any intraventricular hemorrhage	41 (33.3)	159 (29.5)	0.403
Severe intraventricular hemorrhage (grade III or IV)	15 (12.2)	31 (5.8)	0.011

Abbreviations: IQR, interquartile range; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; SD, standard deviation.
[a]Of 332 neonates randomized to receive $MgSO_4$.
[b]Of 170 neonates randomized to receive $MgSO_4$ with cord blood $MgSO_4$ levels available.

physicians. We had comprehensive pregnancy information, and were able to incorporate these data into our analyses and multivariable models.

This study should be interpreted with several limitations in mind. We were limited by data collected at the time of the initial study, and therefore were unable to examine SIP as an outcome. As with all unplanned secondary analyses, there is a possibility that reported findings may represent spurious results. Although NEC and SIP are different processes, intraoperative evaluation is the only way to truly distinguish between the two entities, and it is possible that there was some degree of diagnostic overlap in this dataset. Additionally, we had limited information regarding specifics of the

Table 3 Multivariable regression results for association with neonatal death and/or stage II/III NEC for all 697 neonates delivered < 28 wks

	OR (95% CI)	*p* Value
Delivery gestational age (per 1 wk increment)	0.67 (0.56–0.81)	< 0.001
Neonatal sepsis	2.14 (1.45–3.16)	< 0.001
Small for gestational age	2.88 (1.49–5.57)	0.002
Postnatal exposure to indomethacin	0.63 (0.42–0.94)	0.023
Male fetus	1.34 (0.91–1.96)	0.134
Randomized to receive magnesium sulfate	1.01 (0.69–1.47)	0.965

Abbreviations: CI, confidence interval; NEC, necrotizing enterocolitis; OR, odds ratio.

Table 4 Multivariable regression results. Shown are factors associated with neonatal death and/or stage II/III NEC among 293 neonates delivered < 26 wks

	OR (95% CI)	*p* Value
Delivery gestational age (per 1 wk increment)	0.52 (0.31–0.88)	0.015
Randomized to receive magnesium sulfate	1.90 (1.12–3.22)	0.017
Small for gestational age	2.47 (1.04–5.85)	0.041
Male fetus	1.47 (0.87–2.471)	0.153

Abbreviations: CI, confidence interval; NEC, necrotizing enterocolitis; OR, odds ratio.

care received in the NICU after delivery. Although we were able to account for some postnatal risk factors previously associated with NEC (e.g., indomethacin exposure, hypotension), we were unable to control for others (e.g., neonatal steroid exposure, antibiotic exposure, breast milk exposure, and probiotic use). Lack of important neonatal covariables may significantly influence the results. Due to the enrollment criteria for the primary study, the vast majority of children were delivered following PPROM. It is unclear whether these results are applicable to a more general preterm population. However, prior studies examining outcomes stratified by preterm birth indication suggest similar outcomes regardless of delivery indication.[28,29]

Perhaps our most significant limitation is that these data are not contemporary. The original trial enrolled women and infants between December 1997 and May 2004. Since that time, there have been decreases in rates of NEC, as well as improvements in management of NEC. However, the incidence of NEC in our study is similar to most contemporary data. Our study population was remarkable for an overall NEC incidence of 16.4%, and a stage II/III NEC incidence of 9.6%. Recent reports from other centers describe the incidence of NEC to be 3 to 15%,[30,31] and unpublished data from the University of Utah (provided by author B. A. Y.) from 2011 to 2014 show an overall NEC rate of 10% among infants born < 28 weeks. It should be noted that a raw comparison of NEC incidence does not account for the competing outcome of death.

The study by Rattray et al, taken in combination with our findings, raise concern regarding the use of $MgSO_4$ at the earliest gestational ages, at least in the standardized dosage utilized in our parent study. However, the study design and level of evidence provided here is insufficient to, and should not, change current clinical practice. Infants born < 26 weeks are those at highest risk for CP, and thus have the highest potential neuroprotective benefit from antenatal $MgSO_4$ use. The authors strongly feel that in lieu of more rigorous evidence, obstetrical care providers should continue to administer antenatal $MgSO_4$ to all eligible patients per local protocols. These findings urgently need to be verified in more contemporary cohorts (ideally, prospectively collected). In future investigations, careful attention should be paid to maternal–fetal and neonatal pharmacokinetics, and associated outcomes to determine if there is a dose–response effect. In the meantime, obstetrical care providers should ensure that neonatologists are aware of antenatal $MgSO_4$ use, and should have a high index of suspicion for severe gastrointestinal complications when caring for neonates delivered < 26 weeks gestation, particularly if exposed to antenatal $MgSO_4$.

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