JPPT | Clinical Investigation

Effects of Maternal Magnesium Sulfate Treatment on Neonatal Feeding Tolerance

Meghan K. Belden, PharmD; Sarah Gnadt, PharmD; and Ann Ebert, PharmD

OBJECTIVE To determine whether antenatal exposure to magnesium sulfate has an effect on neonatal enteral feeding tolerance.

METHODS In this single-center, retrospective, observational study, charts of pregnant women who received intravenous magnesium sulfate infusions prior to delivery between July 1, 2012, and July 31, 2013, were reviewed. Neonates born at 24 weeks' gestational age or greater admitted to the neonatal intensive care unit (NICU) whose mothers received magnesium sulfate infusions prior to delivery were included. Neonates with independent factors that could lead to feeding intolerance were excluded. The primary outcome was incidence of neonatal enteral feeding intolerance measured by deviations from the NICU feeding protocol. Secondary outcomes included days on parenteral nutrition, incidence of necrotizing enterocolitis, time to first stool, and urine output in the first 72 hours of life.

RESULTS Cumulative maternal magnesium sulfate dose was significantly higher in the enteral feeding intolerance group than those infants who tolerated enteral feeds (70.4 ± 52.3 vs 47.4 ± 40.1 g; p = 0.04). Infants exposed to more than 80 g of maternal magnesium sulfate therapy were more likely to develop enteral feeding intolerance (44% vs 22%; p = 0.04). Multivariate logistic regression indicated that prematurity and cumulative maternal magnesium sulfate dose were the strongest predictors of neonatal enteral feeding intolerance.

CONCLUSIONS Infants of mothers who received more than 80 g of intravenous magnesium sulfate prior to delivery were more likely to develop feeding intolerance. Prematurity also was a significant predictor of intolerance.

ABBREVIATIONS BMI, body mass index; NICU, neonatal intensive care unit

KEYWORDS enteral nutrition; magnesium; magnesium sulfate; neonate; tocolytic agents

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Introduction

Magnesium sulfate is widely used in obstetrics with indications recognized by the American College of Obstetricians and Gynecologists for the prevention and treatment of seizures in women with preeclampsia or eclampsia, fetal neuroprotection before anticipated delivery at less than 32 weeks' gestation, and prolongation of pregnancy to allow for administration of antenatal corticosteroids in pregnant women between 24 and 34 weeks' gestation who are at risk of preterm delivery within 7 days.[1] Although magnesium sulfate has been shown to have beneficial effects for these indications, it is essential to consider the effects this treatment could have on the neonate. It was anecdotally observed in the research institution's neonatal intensive care unit (NICU) that infants born to mothers who were treated with magnesium sulfate prior to delivery had more difficulty tolerating enteral feeds. Enteral feeds have many beneficial effects for the neonate, including promotion of gastrointestinal adaptation, maintenance of gut integrity, and reduction of infection risk.[2] Additionally, the alternative to enteral feedings is parenteral nutrition, which carries additional risks, such as hypertriglyceridemia, cholestasis, metabolic bone disease, and sepsis.[2]

There are 2 proposed mechanisms of neonatal enteral feeding intolerance secondary to maternal magnesium sulfate exposure, including reduced gastrointestinal motility and limited magnesium sulfate clearance. It is thought that the gastrointestinal dysmotility is caused by magnesium's replacement of calcium in smooth muscle cells, which disrupts actin and myosin interactions and reduces contractility.[3] The effects of magnesium may be prolonged or exaggerated because of the infants' limited magnesium sulfate clearance, which is secondary to their immature renal function as magnesium sulfate is renally eliminated.

The aim of the study was to determine whether antenatal exposure to magnesium sulfate has an effect on neonatal enteral feeding tolerance.

Methods

This was a retrospective, observational study of infants born to mothers who were admitted to the research institution's labor and delivery unit between July 1, 2012, and July 31, 2013. The study center is a 448-bed, not-for-profit, community hospital in Madison, Wisconsin, with a very large labor and delivery unit. Approximately 3700 deliveries are performed at the research institution each year, which is the most of any hospital in Wisconsin. It also houses a 38-bed, level 3 NICU with more than 450 admissions annually. The study protocol was approved by the Institutional Review Board at the research institution in October 2013.

Women treated with magnesium sulfate at the time of delivery were identified through a query of PeriData.Net database, which was developed by the Wisconsin Association for Perinatal Care and is used by most labor and delivery units in Wisconsin to collect quality improvement information. At the research institution, the typical magnesium sulfate treatment course for neuroprotection and preeclampsia is a 4-g bolus intravenously, followed by a 2 g/hr intravenous infusion until delivery or cessation of labor. Neonates born at 24 weeks' gestational age or greater who were admitted to the NICU and whose mothers received magnesium sulfate infusions prior to delivery were eligible for inclusion in the study. Neonates with independent factors that could lead to feeding intolerance—including congenital abnormalities, such as neonatal gastroschisis and neonatal abstinence syndrome—were excluded. Cumulative maternal magnesium sulfate dose prior to delivery was used to quantify the extent of the infant's exposure.

The primary outcome was incidence of neonatal enteral feeding intolerance, which was a composite outcome defined as deviation from the research institution's standard NICU feeding protocols (Tables 1 through 3) related to time to initiation of enteral feeds, time to non-trophic enteral feeds, and time to full enteral feeds. All time points were measured by day of life, with day of birth defined as Day 0. Non-trophic enteral feeds were defined as greater than 20 mL/kg/day, and full enteral feeds was defined as 150 mL/kg/day or the goal defined for the infant by the medical team. All infants were fed intermittently with maternal breast milk, donor breast milk, or a variety of formulas based on the infants' nutritional needs. Secondary outcomes included days on parenteral nutrition, incidence of necrotizing enterocolitis, time to first stool, and urine output in the first 72 hours of life.

The association between neonatal feeding intolerance and discrete variables was analyzed using the χ^2 test, and 2-tailed *t*-test was used for continuous variables. The Kruskal-Wallis test was implemented to assess ordinal variables, and a multivariate logistic regression was performed to compare various maternal and neonatal characteristics as predictors of neonatal enteral feeding intolerance. Two-sided p values less than 0.05 were considered significant.

Table 1. Neonatal Intensive Care Unit Enteral Feeding Protocol for Infants < 1250 g at Birth

Day of Life	Total Daily Feeding Volume
2–3	10 mL/kg/day
4–6	20 mL/kg/day
7–11	Advance by 20 mL/kg/day
12	Fortify 120 mL/kg/day to 22 kCal/oz
13	Fortify 120 mL/kg/day to 24 kCal/oz
14	140 mL/kg/day
15–16	150–160 mL/kg/day

Table 2. Neonatal Intensive Care Unit Enteral Feeding Protocol for Infants 1250 to 1500 g at Birth

Day of Life	Total Daily Feeding Volume
2–3	20 mL/kg/day
4–9	Advance by 20 mL/kg/day
10	Fortify 120 mL/kg/day to 22 kCal/oz
11	Fortify 120 mL/kg/day to 24 kCal/oz
12	140 mL/kg/day
13–14	150–160 mL/kg/day

Table 3. Neonatal Intensive Care Unit Enteral Feeding Protocol for Infants >1500 g at Birth

Day of Life	Total Daily Feeding Volume
2–3	20 mL/kg/day
3–8	Advance by 20–40 mL/kg/day
4–9	Fortify 100–120 mL/kg/day to 22 kCal/oz
5–10	Fortify 100–120 mL/kg/day to 24 kCal/oz
6–11	Advance by 20–40 mL/kg/day to 140 mL/kg/day
8–13	150–160 mL/kg/day

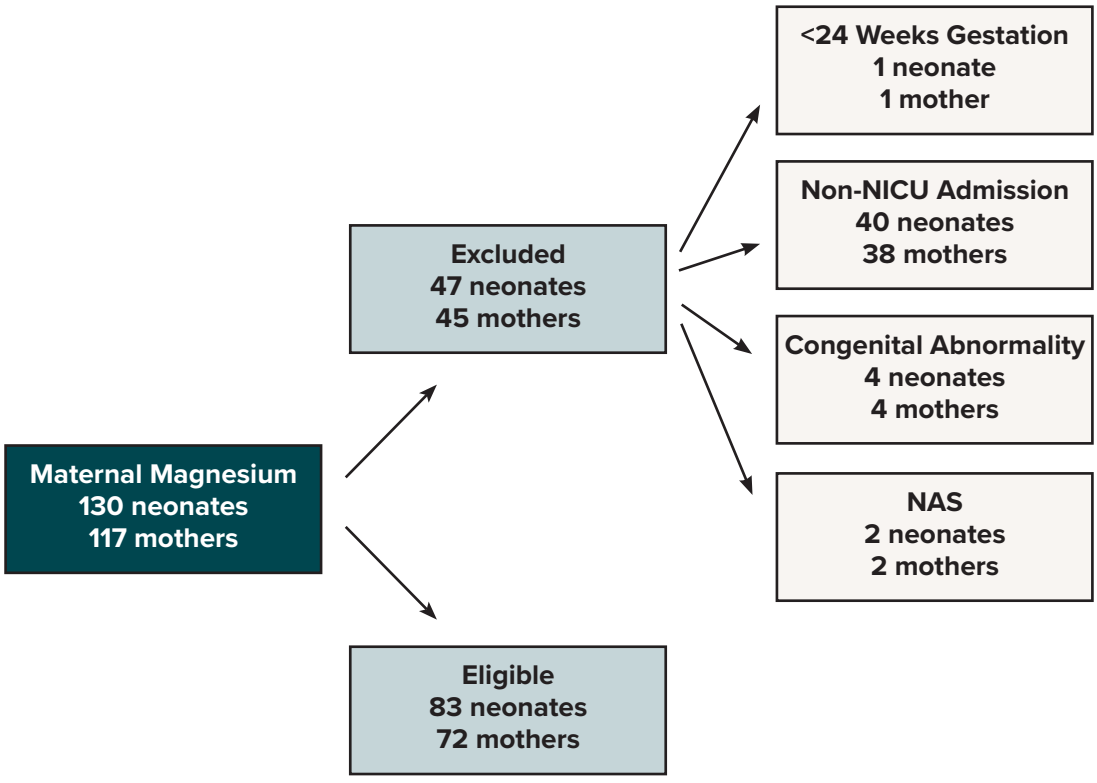
Results

Between July 1, 2012, and July 31, 2013, a total of 117 women were treated with magnesium sulfate prior to delivery at the research institution. Based on inclusion and exclusion criteria, 83 neonates born to 72 mothers were eligible for this analysis (Figure). Congenital abnormalities leading to exclusion included neonatal gastroschisis, tracheoesophageal fistula, and craniofacial abnormalities with ileal stricture.

Maternal and Neonatal Baseline Characteristics

Maternal baseline characteristics for this study population are shown in Table 4. Of these characteristics,

Figure. Flow diagram summarizing patient eligibility, including inclusion and exclusion criteria.



only betamethasone administration was associated with a higher incidence of neonatal enteral feeding intolerance (97% vs 73%; $p < 0.005$). Further analysis using logistic regression analysis showed that none of these characteristics were significant predictors of feeding intolerance.

Table 5 denotes the neonatal baseline characteristics for this study population. Table 6 describes the study population, comparing gestational age and maternal magnesium dose across birth weights grouped by feeding protocol assignment. Gestational age, birth weight, and 1-minute and 5-minute Apgar scores were all significantly lower in those infants with enteral feeding intolerance (Table 7). Further analysis using logistic regression showed that gestational age was the most powerful neonatal characteristic predicting enteral feeding intolerance.

Table 4. Maternal Baseline Characteristics for the Study Population (n = 83)

Characteristics	Result
Age, yr	29 ± 6
BMI	33.3 ± 8.5
Vaginal delivery, %	40
Antihypertensive therapy, %	41
Betamethasone, %	83
Indication for magnesium, %	
Preeclampsia	43
Neuroprotection	59
Preterm labor	49

BMI, body mass index

Primary Outcome

Feeding intolerance was noted in 34 infants (41%) included in this study. Of the 34 patients with the assignment of feeding intolerance, deviation from the

Table 5. Neonatal Baseline Characteristics for the Study Population (n = 83)

Demographics	
Gestational age, wk	30.9 ± 3.2
Birth weight, g	1554 ± 615
1-min Apgar	5.7 ± 2.5
5-min Apgar	7.6 ± 1.8
Male, %	48
Singleton, %	75
Resuscitation required, %	82
Hypotonia at birth, %	25

Table 6. Neonatal Baseline Characteristics Comparing Birth Weight, Gestational Age, and Maternal Magnesium Dose

Baseline	Birth Weight		
	< 1250 g (n = 23)	1250–1500 g (n = 13)	> 1500 g (n = 48)
Gestational age, wk	27 ± 2.5	31 ± 1.7	33 ± 1.8
Maternal magnesium dose, g	86.5 ± 59.4	32.3 ± 25.2	49.1 ± 36.7

feeding protocol occurred at initiation of feeds in 13 infants (38%), advancement to non-trophic feeds in 17 infants (50%), and progression to full feeds in 4 infants (12%). Cumulative maternal magnesium sulfate dose was significantly larger in the enteral feeding intolerance group than in those infants who tolerated enteral feeds (70.4 ± 52.3 vs 47.4 ± 40.1 g; p = 0.04). When assessing for the lowest cumulative maternal magnesium sulfate dose that resulted in a significantly higher rate of neonatal enteral feeding intolerance, it was found that infants exposed to more than 80 g of maternal magnesium sulfate therapy were more likely to develop enteral feeding intolerance (44% vs 22%; p = 0.04). Although not statistically significant, descriptive statistics show that cumulative magnesium exposure was greater in infants with feeding intolerance when grouped by weight-based feeding protocol (Table 8). Additionally, indomethacin administration was associated with a higher incidence of neonatal enteral feeding intolerance (29% vs 2%; p < 0.001). Because of the significant differences in baseline characteristics between infants that exhibited enteral feeding intolerance and those that did not, a multivariate logistic regression was performed. This analysis accounted for the differences between groups and was used to determine which neonatal and maternal characteristics were most predictive of neonatal enteral feeding intolerance. The strongest predictors were prematurity and cumulative maternal magnesium sulfate dose.

Secondary Outcomes

Secondary outcomes for this study are shown in Table 9. Secondary outcomes were used to assess the proposed mechanisms of feeding intolerance. Days on parenteral nutrition was significantly longer in the feeding intolerance group (21.5 vs 3.7 days; p < 0.001), which is intuitive because the alternative to enteral feedings is parenteral nutrition. Additionally, days on parenteral nutrition was significantly longer for infants less than 30 weeks' gestation (25.7 vs 5.1 days; p < 0.001) and infants exposed to at least 80 g of maternal magnesium treatment (21.1 vs 6.4 days; p < 0.01). Time to first stool was also significantly longer in the feeding intolerance group (3.4 vs 1.8 days; p < 0.05), signifying that reduced gastrointestinal motility could be a factor contributing to the neonatal enteral feeding intolerance associated with maternal magnesium sulfate therapy. There was no significant difference in urine output between groups (3.1 vs 2.9 mL/kg/hr; p = 0.25), demonstrating that reduced magnesium sulfate clearance was likely not a factor in the development of enteral feeding intolerance in the infants. Additionally, there was a significantly higher incidence of necrotizing enterocolitis in the feeding intolerance group (14.7% vs 2.0%; p = 0.03). Infants at risk for and receiving a diagnosis of necrotizing enterocolitis typically have all enteral feedings held, which led to deviation from the feeding protocols.

Discussion

Current literature in this area is significantly lacking. Evidence that is available suggests similar findings. A retrospective, single-center cohort study included 6654 infants whose mothers were treated with intravenous magnesium sulfate for prevention or treatment of preeclampsia and found that there was an increasing likelihood of neonatal hypotonia as well as lower Apgar scores at 1 and 5 minutes as maternal serum magnesium levels increased.[4] From this study, it was inferred that global hypotonia could translate to smooth muscle hypotonia and reduced gastrointestinal motility, leading to enteral feeding intolerance. In a retrospective, blinded cohort study of 139 infants born to women treated with magnesium sulfate prior to delivery, it was found that larger cumulative maternal magnesium sulfate dose was associated with lower 1- and 5-minute Apgar scores as well as a longer time to initiation of

Table 7. Selected Neonatal Baseline Characteristics in Relation to Neonatal Enteral Feeding Intolerance

Baseline	Intolerance (n = 34)	Tolerance (n = 49)	p Value
Gestational age, wk	28.7 ± 3.0	32.4 ± 2.2	< 0.001
Birth weight, g	1171 ± 428	1819 ± 587	< 0.001
1-min Apgar	4.9 ± 2.5	6.2 ± 2.3	0.01
5-min Apgar	6.9 ± 2.3	8.1 ± 1.1	0.04

Table 8. Cumulative Maternal Magnesium Dose in Relation to Neonatal Enteral Feeding Intolerance and Weight-Based Feeding Protocol Assignment

Birth Weight	Maternal Magnesium Dose, g		p Value
	Intolerance (n = 34)	Tolerance (n = 49)	
< 1250 g, n = 23	93.1 ± 53.9	67.7 ± 75.0	0.47
1250–1500 g, n = 13	35.1 ± 31.3	27.8 ± 11.9	0.57
> 1500 g, n = 48	58.8 ± 45.7	46.7 ± 34.6	0.48

enteral feeds and a higher rate of delayed initiation of enteral feeds.[5] Finally, a retrospective cohort study included 264 infants born to women with preeclampsia and found fluid and nutritional support was required more often in infants exposed to magnesium prior to delivery, likely due to poor feeding as a result of gastrointestinal dysmotility.[6] Of note, all of these were secondary outcomes.

Differences did exist in maternal and neonatal baseline characteristics when comparing infants with enteral feeding intolerance to those that tolerated enteral feeds. Maternal betamethasone administration was associated with a higher incidence of neonatal enteral feeding intolerance. Betamethasone is only indicated at less than 34 weeks' gestation, and women would typically receive at least a 48-hour course of magnesium sulfate during the administration of betamethasone. Therefore, it is possible that infants born to mothers treated with betamethasone had not only lower gestational ages but also received a larger exposure to magnesium sulfate, both of which may have contributed to feeding intolerance. Additionally, infants who received indomethacin for the treatment of patent ductus arteriosus were more likely to develop enteral feeding intolerance than those who did not receive therapy. It is current practice to hold enteral feedings or delay advancement of enteral feeds during administration of indomethacin in the research institution's NICU, which would account for this finding.

There are several limitations to this study. First, there are inherent limitations in the retrospective, observational design. Because of the difficulty of finding matched controls for a cohort study, cumulative doses of maternal magnesium sulfate were compared. The small sample size limited the power of the statistical analysis. Additionally, bias may have been introduced with the exclusion of infants who were not admitted to the NICU. This was necessary for the purposes of adequate data collection because monitoring is not as robust in the nursery, but a more acutely ill patient population may have been selected. Additionally, there was a lack of serum concentration monitoring related to maternal and neonatal magnesium sulfate exposure as well as neonatal renal function. At the research institution, the standard of practice is to obtain maternal serum magnesium levels only if the woman is exhibiting signs of magnesium toxicity, such as loss of patellar reflexes, somnolence, or flushing.[7] Additionally, lab draws were limited in the neonatal population at the research institution because of pain and risk of iatrogenic anemia. This led to the use of cumulative maternal magnesium sulfate dose as a marker of maternal and neonatal magnesium sulfate exposure and urine output as a marker of neonatal renal function. Finally, the reason for deviation from the feeding protocol was not assessed. Therefore, it is not known whether the deviation was truly due to feeding intolerance or if there could have been other factors, such as physician preference or acuity of illness.

In the future, consideration should be given to developing a more conservative feeding protocol for infants exposed to greater than 80 g of maternal magnesium sulfate therapy prior to delivery and performing additional analysis with a cohort study design and control group.

Infants of mothers who received more than 80 g of intravenous magnesium sulfate prior to delivery were significantly more likely to develop feeding intolerance. Prematurity was also a significant predictor of neonatal enteral feeding intolerance. Reduced gastrointestinal motility could be a factor in feeding intolerance secondary to magnesium sulfate exposure based on analysis of time to first stool. However, decreased magnesium sulfate clearance does not appear to contribute to neonatal feeding intolerance secondary to magnesium sulfate exposure.

Table 9. Analysis of Secondary Outcomes Comparing Infants With Enteral Feeding Intolerance to Those Who Tolerated Feeds

Secondary Outcome	Intolerance (n = 34)	Tolerance (n = 49)	p Value
PN days	21.5 ± 23.7	3.7 ± 4.0	< 0.001
First stool, day of life	3.4 ± 3.0	1.8 ± 1.0	< 0.05
UOP, mL/kg/hr	3.1 ± 0.9	2.9 ± 0.5	0.25

PN, parenteral nutrition; UOP, urine output

ARTICLE INFORMATION

Affiliations Children's Hospital of Wisconsin, Milwaukee, Wisconsin (MKB); and UnityPoint–Meriter, Madison, Wisconsin (SG, AE)

Correspondence Meghan K. Belden, PharmD; mkbrodhead@gmail.com

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