Lack of Evidence for Time or Dose Relationship between Antenatal Magnesium Sulfate and Intestinal Injury in Extremely Preterm Neonates

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Keywords

Magnesium sulfate · Necrotizing enterocolitis · Spontaneous intestinal perforation

Abstract

Background: Recent studies reported conflicting results on the relationship between antenatal magnesium sulfate (MgSO₄) exposure and neonatal intestinal injury. Most studies have not assessed MgSO₄ exposure quantitatively and none reported the exposure timing. **Objectives:** The aim of this work was to assess whether there is a temporal or dose-dependent relationship between antenatal MgSO₄ exposure and intestinal injury in extremely preterm neonates. **Methods:** A retrospective study was made of inborn neonates with gestational age ≤28 weeks and/or birth weights ≤1,000 g. Primary outcomes included necrotizing enterocolitis (NEC), spontaneous intestinal perforation (SIP), and/or death prior to discharge or in the first 2 weeks of life. Outcome comparisons were made based on the timing of

MgSO₄ exposure, within 7 days (Mg7D) or within 3 days (Mg3D) of birth. Total cumulative doses for the Mg3D group were also computed. **Results:** A total of 302 neonates were included, 210 in the Mg7D group, out of whom 179 (85.2%) constituted the Mg3D group. There were no differences noted when comparing MgSO₄ exposure timing and the likelihood of NEC, SIP, and/or death. This remained the same for subgroup analysis of neonates <26 weeks' gestation. Each 10-g increase in MgSO₄ cumulative dose correlated with a decrease in SIP/NEC/death by 18.9% prior to discharge and by 21.9% in the first 2 weeks of life. Small for gestational age (SGA) was a potential effect modifier by a likelihood ratio test with $p = 0.07$. **Conclusions:** Antenatal MgSO₄ exposure in extremely preterm neonates was not associated with an increased risk of intestinal injury or death, and might have reduced these complications in a dose-dependent manner in our study. This protective effect was more noticeable in SGA neonates.

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Introduction

Magnesium sulfate (MgSO_4) has been used in obstetric practice for tocolysis, management of preeclampsia, and for fetal neuroprotection in women with threatened preterm delivery [1]. The latter practice has been widely adopted after the American College of Obstetricians and Gynecologists (ACOG) released a Committee Opinion in 2010 encouraging MgSO_4 administration before anticipated early preterm birth to reduce the risk of cerebral palsy [2]. The recommendation was based on the results of three clinical trials that included 4,184 participants [3–5] and a Cochrane systematic review by Doyle et al. [6] in 2009. The systematic review concluded that the number of women needed to be treated to benefit 1 neonate by avoiding cerebral palsy is 63, without an increase in neonatal mortality or morbidities [6]. The ACOG, however, stated that comparison between the three major randomized clinical trials [3–5] was made difficult by differences in inclusion criteria, populations studied, MgSO_4 regimens, and outcomes studied between the trials [2].

Subsequently, a number of groups have investigated the relationship between antenatal MgSO_4 exposure and intestinal injury in premature neonates. In 2014, Rattray et al. [7] reported their experience with implementation of a protocol using MgSO_4 for neuroprotection. They found a higher incidence of death or spontaneous intestinal perforation (SIP) during protocol implementation as compared to prior to implementation and after discontinuation (30.4 vs. 20.5%, $p = 0.28$), with a stronger correlation for higher MgSO_4 dose and smaller neonates [7]. In a secondary analysis of the NICHD Maternal Fetal Medicine Units Network study [5], the authors reported there was a significantly elevated risk for death or severe necrotizing enterocolitis (NEC) in neonates with gestational age (GA) <26 weeks who were randomized to receive antenatal MgSO_4 , odds ratio (OR) = 1.9 (95% CI 1.12–3.22, $p = 0.017$) [8]. In these two studies MgSO_4 for neuroprotection regimens were in accordance with the NICHD Maternal Fetal Medicine Units Network study [5]. However, two larger reports by the Pediatrix Medical Group and the Canadian Neonatal Network showed no increase in neonatal adverse outcomes in relationship to any antenatal MgSO_4 exposure [9, 10].

While MgSO_4 infusion protocols vary among institutions in dose, duration, and criteria for reloading, most studies have assessed MgSO_4 exposure in a dichotomous fashion only: exposed or not [7–10]. Moreover, no previous study has reported on the timing of antenatal

MgSO_4 exposure in relation to birth or the onset of intestinal injury. Hence, it is difficult to arrive at a definitive conclusion regarding the association between antenatal MgSO_4 exposure and neonatal intestinal injury. We aimed to explore these variables to determine if there is a temporal or dose-dependent relationship between antenatal MgSO_4 exposure and neonatal intestinal injury in extremely preterm neonates.

Methods

Study Population

This was a retrospective study of neonates who were admitted to Pomona Valley Hospital Medical Center neonatal intensive care unit (NICU), Pomona, CA, USA, from January 2010 through December 2016. This is a tertiary level NICU with an annual average of 8,000 deliveries and 800 NICU admissions. Subjects included inborn neonates with birth weight $\leq 1,000$ g and/or GA ≤ 28 weeks with no congenital gastrointestinal anomalies. The study was approved by the hospital institutional review board.

MgSO₄ Protocol

In October 2012, MgSO_4 for the neuroprotection protocol was implemented in our center. Women with threatened preterm delivery at 24–32 weeks' gestation receive an MgSO_4 loading dose of 4 g over 30 min, followed by an infusion of 2 g/h for 12 h or until delivery. If delivery does not occur by 12 h, the infusion is stopped and resumed if delivery is thought to be imminent. Also, a repeat loading dose is administered if >6 h has passed after discontinuation of the infusion.

MgSO₄ Exposure

The following exposure groups were chosen to describe the different times of antenatal MgSO_4 exposure in relation to birth: neonates who received MgSO_4 within 7 days (Mg7D) or within 3 days (Mg3D) prior to birth. Among patients who delivered within 3 days, the number of MgSO_4 loading doses and cumulative doses were also compared to delineate any potential dose-dependent effect.

Outcomes of Interest

Primary outcomes included SIP (diagnosed intraoperatively or radiologically), NEC (Bell's staging criteria II or greater) [11], and death, either individually or combined. We analyzed these outcomes prior to hospital discharge or within 2 weeks of life. We also examined the likelihood of NEC, SIP, or death before and after MgSO_4 for neuroprotection protocol implementation.

Statistical Methods

For baseline characteristics, t test was used for continuous variables and χ^2 test for categorical variables. For the univariate analysis, χ^2 test was used to compare both individual and combined outcomes between exposure groups. The univariate association was examined for the entire cohort as well as the subcohort with GA <26 weeks. The MgSO_4 exposure effect was further examined with a multivariate logistic regression analysis after adjusting for significantly different baseline characteristics. Logistic regression

Fig. 1. Study population.

Table 1. Maternal, perinatal, and neonatal characteristics of the subjects

	Mg7D (n = 210)	No-Mg7D (n = 92)	p value
<i>Maternal characteristics</i>			
Age, years	28.1±6.4	27.5±6.5	0.43
Body mass index	31.3±6.6	29.9±7.8	0.14
Race			0.58
White	40 (19)	14 (15.2)	
Black	28 (13.3)	16 (17.4)	
Hispanic	112 (53.3)	52 (56.5)	
Other	30 (14.2)	10 (10.9)	
Illicit drug abuse	21 (10)	10 (10.9)	0.82
Maternal hypertension	62 (29.5)	13 (14.1)	0.004
<i>Perinatal characteristics</i>			
Prolonged rupture of membranes	54 (25.7)	24 (26.1)	0.95
Cesarean delivery	146 (69.5)	67 (72.8)	0.56
Antenatal steroids	200 (95.2)	59 (64.1)	<0.0001
Antenatal indomethacin	43 (20.5)	8 (8.7)	0.012
Multiple gestations	31 (14.8)	20 (21.7)	0.14
<i>Neonatal characteristics</i>			
Gestational age, weeks	26.2±1.9	26.1±2.1	0.6
Birth weight, g	804±212	812±231	0.8
Male sex	101 (48.1)	48 (52.2)	0.5
5-min Apgar score	7 (6–8)	7 (5–8)	0.078
SGA	36 (17.1)	14 (15.2)	0.68
Postnatal steroids	79 (37.6)	37 (40.2)	0.67
Postnatal NSAID treatment for PDA	73 (34.76)	40 (43.48)	0.15
First serum magnesium level within 72 h, mg/dL	2.7±0.9	2.1±0.4	<0.0001
Intraventricular hemorrhage grade III or higher	19 (9)	11 (12)	0.4
Late-onset sepsis	42 (20)	27 (29.3)	0.075

Data are presented as the mean ± SD, n (%), or median (IQR). SGA, small for gestational age; NSAID, non-steroidal anti-inflammatory drugs; PDA, patent ductus arteriosus.

Table 2. Comparison of outcomes among different exposure groups for all neonates and neonates with GA <26 weeks

	Mg7D	No-Mg7D	<i>p</i> value	Mg3D	No-Mg7D + No-Mg3D	<i>p</i> value	Mg3D	No-Mg3D	<i>p</i> value
<i>All neonates</i>	(<i>n</i> = 210)	(<i>n</i> = 92)		(<i>n</i> = 179)	(<i>n</i> = 123)		(<i>n</i> = 179)	(<i>n</i> = 31)	
SIP	20 (9.5)	8 (8.7)	0.82	18 (10.1)	10 (8.1)	0.57	18 (10.1)	2 (6.4)	0.53
Early SIP	19 (9.1)	7 (7.6)	0.68	17 (9.5)	9 (7.3)	0.54	17 (9.5)	2 (6.5)	0.75
NEC	15 (7.1)	7 (7.6)	0.89	13 (7.3)	9 (7.3)	0.98	13 (7.3)	2 (6.5)	0.87
Early NEC	4 (1.9)	1 (1.1)	0.61	3 (1.7)	2 (1.6)	0.97	3 (1.7)	1 (3.2)	0.56
Death	24 (11.4)	12 (13)	0.69	18 (10.1)	18 (14.6)	0.23	18 (10.1)	6 (19.4)	0.13
Early death	15 (7.1)	10 (10.9)	0.28	13 (7.3)	12 (9.8)	0.44	13 (7.3)	2 (6.5)	0.87
SIP/NEC/death	52 (24.8)	24 (26.1)	0.81	43 (24)	33 (26.8)	0.58	43 (24)	9 (29)	0.55
Early SIP/NEC/death	34 (16.2)	16 (17.4)	0.79	29 (16.2)	21 (17.1)	0.8412	29 (16.2)	5 (16.1)	0.99
<i>Neonates with GA <26 weeks</i>	(<i>n</i> = 90)	(<i>n</i> = 45)		(<i>n</i> = 75)	(<i>n</i> = 60)		(<i>n</i> = 75)	(<i>n</i> = 15)	
SIP	14 (15.6)	6 (13.3)	0.73	13 (17.3)	7 (11.7)	0.36	13 (17.3)	1 (6.7)	0.3
Early SIP	13 (14.4)	5 (11.1)	0.79	12 (16)	6 (10)	0.44	12 (16)	1 (6.7)	0.69
NEC	8 (8.9)	6 (13.3)	0.42	6 (8)	8 (13)	0.31	6 (8)	2 (13.3)	0.51
Early NEC	4 (4.4)	1 (2.2)	0.52	3 (4)	2 (3.3)	0.84	3 (4)	1 (6.7)	0.65
Death	18 (20)	10 (22.2)	0.76	13 (17.3)	15 (25)	0.27	13 (17.3)	5 (33.3)	0.16
Early death	12 (13.3)	9 (20)	0.31	10 (13.3)	11 (18.3)	0.43	10 (13.3)	2 (13.3)	1.0
SIP/NEC/death	34 (37.8)	20 (44.4)	0.46	27 (36)	27 (45)	0.29	27 (36)	7 (46.7)	0.44
Early SIP/NEC/death	26 (28.9)	13 (28.9)	1.0	22 (29.3)	17 (28.3)	0.9	22 (29.3)	4 (26.7)	0.83

Data are presented as *n* (%). SIP, spontaneous intestinal perforation; NEC, necrotizing enterocolitis.

modeling was used to examine the effect of MgSO₄ loads and cumulative doses on the outcomes among neonates who were exposed to antenatal MgSO₄ within 3 days prior to birth. Additionally, effect modification for all baseline characteristics was assessed with likelihood ratio tests.

Results

Baseline Characteristics

A total of 302 neonates met the inclusion criteria. From these, 210 (69.5%) were exposed to antenatal MgSO₄ within 7 days prior to birth, out of whom 179 (85.2%) were exposed within 3 days prior to birth (Fig. 1).

The subjects' maternal, perinatal, and neonatal characteristics (Table 1) were compared between the Mg7D group and the group of neonates not exposed to antenatal MgSO₄ within 7 days prior to birth (No-Mg7D). The Mg7D group had a significantly higher likelihood of maternal hypertension, exposure to antenatal steroids, and antenatal indomethacin. Also, a higher neonatal first serum magnesium level (when measured within 72 h of life) was detected in the Mg7D group. There were no other significant differences in perinatal

or neonatal characteristics between the Mg7D and No-Mg7D groups that might contribute to intestinal injury (Table 1).

MgSO₄ Time of Exposure and Outcomes

There were no differences noted between different MgSO₄ exposure timings and the likelihood of SIP, NEC, or death prior to hospital discharge or in the first 2 weeks of life (early). Combined outcomes also did not show significant differences. This was true for the entire cohort and in a subgroup analysis of neonates <26 weeks' gestation (Table 2).

Multivariate Analysis on Combined Outcomes

Maternal hypertension, antenatal steroids, and antenatal indomethacin were adjusted in the multivariate logistic regression (Table 3) on the combined outcome of SIP/NEC/death due to the differences observed in baseline characteristics comparisons (Table 1). After controlling for potential confounding variables there were no significant differences in the odds of SIP/NEC/death between the Mg7D and No-Mg7D groups prior to discharge, OR = 0.69 (95% CI 0.35–1.38, *p* = 0.29). This remained similar for early SIP/NEC/death as well with OR = 1.7 (95% CI 0.73–3.75, *p* = 0.22; Table 3).

Table 3. Results of multivariate logistic regression

Variable	Category	Parameter	SE	OR (95% CI)	<i>p</i> value
<i>Effect on SIP/NEC/death prior to discharge</i>					
Mg7D	Yes	−0.3664	0.3494	0.69 (0.35–1.38)	0.29
	No	(reference)			
Maternal hypertension		−0.8426	0.3879	0.43 (0.2–0.92)	0.03
Antenatal steroids		−1.2559	0.4061	0.28 (0.13–0.63)	0.002
Antenatal indomethacin		0.8936	0.3441	2.44 (1.24–4.8)	0.009
<i>Effect on SIP/NEC/death in the first 2 weeks of life</i>					
Mg7D	Yes	0.5067	0.4159	1.7 (0.73–3.75)	0.22
	No	(reference)			
Maternal hypertension		−0.7547	0.4532	0.47 (0.19–1.14)	0.096
Antenatal steroids		−1.4523	0.4500	0.23 (0.10–0.57)	0.0012
Antenatal indomethacin		0.5568	0.4010	1.75 (0.80–3.83)	0.16

Fig. 2. Comparison of early SIP/NEC/death ORs for Mg7D versus No-Mg7D among all, SGA, and non-SGA neonates.

Before and after MgSO₄ for Neuroprotection Protocol Implementation Analysis

The study included 112 neonates born before and 190 born after the protocol implementations. Subjects' maternal, perinatal, and neonatal characteristics showed no significant differences except the higher rate of exposure to antenatal MgSO₄ within 7 days of birth in the post-protocol group (pre. vs. post., 58.9 vs. 75.8%, $p = 0.003$). There was no difference in the rate of exposure to antenatal MgSO₄ within 3 days of birth (pre. vs. post., 53.5 vs. 62.6%, $p = 0.15$).

The likelihoods of intestinal injury and death were similar in the pre- versus post-protocol groups: SIP (10.7 vs. 8.4%, $p = 0.6$), NEC (8.9 vs. 6.3%, $p = 0.5$), or death (8.9 vs. 13.7%, $p = 0.3$). Among the 135 neonates with GA <26 weeks, 49 were born before and 86 after protocol implementation. The likelihood of adverse outcomes was not significantly different in the pre- versus post-protocol groups: SIP (22.4 vs. 10.4%, $p = 0.1$), NEC (12.2 vs. 9.3%, $p = 0.8$), or death (16.3 vs. 23.2%, $p = 0.4$).

MgSO₄ Dose-Dependent Effect

We examined the effect of MgSO₄ cumulative dose on the combined outcomes of SIP/NEC/death among the 179 neonates exposed to antenatal MgSO₄ within 3 days prior to birth (Mg3D). Based on logistic regression modeling, each 10-g increase in MgSO₄ cumulative dose correlated with an 18.9% decrease in SIP/NEC/death prior to discharge (95% CI 2.2–32.8%, $p = 0.028$) and a 21.9% decrease in early SIP/NEC/death (95% CI 1.4–38.1%, $p = 0.037$).

However, there was no significant association between the number of MgSO₄ loading doses and SIP/NEC/death prior to discharge, OR = 1.07 (95% CI 0.53–2.1, $p = 0.86$), or early SIP/NEC/death, OR = 1.08 (95% CI 0.48–2.4, $p = 0.86$).

Assessment on Effect Modification

Small for GA (SGA) status, defined as neonates with a birth weight below the 10th percentile for GA using Fenton and Kim [12] growth curves, was found to be

correlated with a reduction in SIP/NEC/ death in the Mg7D group by a likelihood ratio test with $p = 0.07$. The OR of early SIP/NEC/death for Mg7D versus No-Mg7D in SGA neonates was 0.23 (95% CI 0.04–1.19, $p = 0.079$). There was no difference demonstrated in the non-SGA neonates with OR = 1.19 (95% CI 0.58–2.47, $p = 0.63$; Fig. 2). The significance level of treatment effect in the SGA group was around the boundary ($p < 0.1$).

Discussion

Recent studies [7, 8] have raised concerns regarding the association between antenatal MgSO₄ exposure and intestinal injury or death in preterm neonates. In our cohort of 302 neonates with a birth weight $\leq 1,000$ g and/or GA ≤ 28 weeks, we found no relationship between antenatal MgSO₄ exposure and the individual or combined outcomes of SIP, NEC, or death. This remained true for the subset of neonates < 26 weeks GA. Our results complement data from the studies by the Pediatrix Medical Group [9] and the Canadian Neonatal Network [10]. Similarly, the original randomized controlled trials investigating antenatal MgSO₄ for neuroprotection [3–5] showed no increase in neonatal and pediatric adverse outcomes.

This is the first study to examine the temporal relationship between antenatal MgSO₄ exposure and adverse neonatal outcomes. MgSO₄ decreases intestinal peristalsis [13], can possibly alter mesenteric blood flow [14, 15], and is associated with feeding intolerance in neonates [16]. It also crosses the placenta freely with a linear relationship between maternal and neonatal levels [17–19]. However, neonatal intestinal injury and death can be caused by many contributing factors. Therefore, it was compelling for us to investigate if there is a temporal relationship between antenatal MgSO₄ exposure and the onset of intestinal injury or death. We found no association between different timing of antenatal MgSO₄ exposure (Mg7D and Mg3D) and the likelihood of an adverse outcome either prior to hospital discharge or in the first 2 weeks of life.

In contrast to the study by Rattray et al. [7], we observed no increase in the likelihood of SIP or death after the implementation of MgSO₄ for the neuroprotection protocol at our hospital. Moreover, we found that an increased MgSO₄ cumulative dose correlated with a reduction in SIP/NEC/death both early and prior to discharge. Our study included a larger population with a

longer post-protocol duration and a similar rate of exposure to antenatal MgSO₄ post-protocol.

It is noteworthy that the post-protocol group had a higher rate of exposure to antenatal MgSO₄ within 7 days of birth (pre. vs. post. 58.95 vs. 75.8%, $p = 0.003$) but not within 3 days of birth (pre. vs. post. 53.5 vs. 62.6%, $p = 0.15$), probably as the indication for 7 days of exposure was primarily for fetal neuroprotection.

Downey et al. [9] reported fewer SIP/NEC/deaths in neonates exposed to any antenatal MgSO₄ with OR = 0.84 (95% CI 0.77–0.9), which our results did not reproduce. However, we did find that each 10-g increase in MgSO₄ cumulative dose correlated with an 18.9% decrease in SIP/NEC/death prior to discharge (95% CI 2.2–32.8%, $p = 0.028$) and a 21.9% decrease in early SIP/NEC/death (95% CI 1.4–38.1%, $p = 0.037$). Their results were primarily driven by a reduction in death among neonates exposed to MgSO₄, OR = 0.76 (95% CI 0.70–0.83) [9]. This differs from the Cochrane review by Doyle et al. [6], which reported no difference in neonatal death during primary hospitalization, OR = 1.04 (95% CI 0.84–1.29). However, the Downey et al. [9] study had a significantly larger population (28,035 vs. 5,980) with an average lower birth weight, including only neonates $< 1,000$ g.

SGA represents a high-risk population for neonatal mortality and morbidities, including intestinal injury [20–22]. A possible protective effect of antenatal MgSO₄ in SGA neonates (Fig. 2) was an unexpected finding which was not previously reported in the literature. Marrs et al. [23] recently performed a secondary analysis of the NICHD Maternal Fetal Medicine Units Network randomized controlled trial of MgSO₄ for the prevention of cerebral palsy [5]. In their report, SGA neonates had similar rates of neonatal morbidities and mortality in comparison to non-SGA neonates. It is noteworthy that 54% of SGA neonates were randomized to receive antenatal MgSO₄ in this study [23]. We speculate that MgSO₄ exposure could have contributed to better neonatal outcomes in comparison to earlier studies [20–22].

This study's limitations include its retrospective nature and that it was performed at a single center. The chosen exposure timing of within 3 or 7 days of birth were exploratory, as previous studies did not report on the temporal relationship of MgSO₄ exposure and neonatal outcomes. Future studies might focus on narrower exposure timing, such as less than 24 h. Another limitation is the relatively small number of SGA neonates included in the analysis.

However, our report has unique strengths, including analyzing the cumulative dose and exposure timing of MgSO₄ in relation to birth, reporting on a contemporary cohort of neonates with no other practice changes that might have affected neonatal outcomes and complete outcome data without missing endpoints.

The present study supports the likelihood that antenatal MgSO₄ exposure in preterm neonates does not increase the risk of intestinal injury or death and may in fact reduce these complications at higher doses. This protective effect was more noticeable in SGA neonates. Future studies might clarify the treatment effects in this subgroup.

Statement of Ethics

The study was approved by the institutional review board of Pomona Valley Hospital Medical Center, Pomona, CA, USA. Informed consents were not required since it is a retrospective study.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.M. contributed to the conceptualization and design of the study, the collection, analysis, and interpretation of the data. He drafted the initial report and approved the final manuscript as submitted. C.B. contributed to the design of the study and the data collection. She reviewed all drafts of the report and approved the final manuscript as submitted. L.Z. contributed to the analysis and interpretation of the data. She contributed to all drafts of the report and approved the final manuscript as submitted. M.C. and H.R. contributed to the interpretation of the data. They contributed to all drafts of the report and approved the final manuscript as submitted. K.Y.B. contributed to the conceptualization and design of the study, and the collection and interpretation of the data. He contributed to all drafts of the report and approved the final manuscript as submitted.

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