

Antenatal Magnesium Sulfate Reduced Intestinal Morbidities Requiring Surgery in Preterm Infants With Extremely Low Gestational Age: A Retrospective Cohort Study

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Abstract

Background Antenatal magnesium sulfate is widely used as a tocolytic, for maternal seizures, and for seizure prophylaxis in preeclampsia. Recent studies have suggested that antenatal magnesium sulfate use is associated with favorable neurodevelopmental outcomes in preterm infants. However, there are concerns regarding the neonatal effects of antenatal magnesium sulfate, especially regarding gastrointestinal morbidities. This study aims to explore the effects of antenatal magnesium sulfate on intestinal morbidities requiring surgery in preterm infants.

Methods This was a retrospective cohort study of 181 preterm infants who were born at less than 28 weeks of gestational age. Subjects were categorized as infants exposed to antenatal magnesium sulfate and those not exposed to antenatal magnesium sulfate.

Results Antenatal magnesium sulfate was associated with a lower incidence of surgical conditions of the intestine (OR 0.393, 95% CI 0.170–0.905). Multivariate analysis showed that the duration of antenatal magnesium sulfate use was associated with surgical conditions of the intestine (adjusted OR 0.766, 95% CI 0.589–0.997). In the < 26 weeks of gestational age subgroup, use of antenatal magnesium sulfate was significantly associated with decreased intestinal morbidities requiring surgery (adjusted OR 0.234, 95% CI 0.060–0.922).

Conclusion Antenatal magnesium sulfate use appears to have a protective effect on intestinal morbidities requiring surgery in preterm infants in a duration-dependent manner. Association of antenatal magnesium sulfate use and decreased intestinal morbidities requiring surgery was more distinct in preterm infants < 26 weeks of gestational age.

Background

Antenatal magnesium sulfate (MgSO_4) has been widely used as a tocolytic and for the treatment of eclampsia.[1] Since randomized control trials showed that antenatal MgSO_4 is associated with a reduced risk of CP in surviving infants without major adverse outcomes[2–5], the short-term use of MgSO_4 for fetal neuroprotection before preterm delivery has been recommended.[6, 7] Recent systematic reviews concluded that the administration of intravenous MgSO_4 to mothers who are at risk of early preterm delivery reduced the risk of neurodevelopmental disability in their surviving children.[8, 9]

However, the US Food and Drug Administration has advised against the use of MgSO_4 injections for more than 5–7 days when intending to stop preterm labor in pregnant women because MgSO_4 has the potential to cause skeletal abnormalities in developing babies.[6] There have also been several concerns regarding the adverse effects of antenatal MgSO_4 on the neonatal outcomes of preterm infants.[10–12] In a small randomized controlled study, higher levels of umbilical cord ionized magnesium at delivery were associated with adverse outcomes.[11] A secondary analysis of neonates < 26 weeks of age in a multicenter randomized trial for neuroprotection showed that antenatal MgSO_4 was associated with an increased risk of death or severe necrotizing enterocolitis (NEC).[10] However, the association between antenatal MgSO_4 and morbidities of the gastrointestinal (GI) tract in preterm infants is still controversial in extremely preterm infants.[13]

Therefore, our study aims to explore the effects of antenatal MgSO_4 on the neonatal outcomes of preterm infants, including intestinal morbidities requiring surgical interventions.

Methods

This was a retrospective cohort study of preterm infants who were born at less than 28 weeks of gestation and who were admitted to the Seoul National University Children's Hospital neonatal intensive care unit between January 2011 and December 2015. Infants with major congenital anomalies and maternal preeclampsia were excluded from the study population. One patient who experienced iatrogenic gastric perforation was excluded. They were categorized as infants with antenatal MgSO₄ and without antenatal MgSO₄. Indications of antenatal MgSO₄ included preterm labor and neuroprotection. The protocol for the antenatal MgSO₄ treatment of preterm labor was a loading dose of 4 g infused over 30 minutes followed by a maintenance dose of 2 g per hour, which could be titrated according to the effect. For neuroprotection of the fetus, a loading dose of 6 g infused over 30 minutes followed by a maintenance dose of 2 g per hour was used.

Medical records of perinatal factors, including the cumulative dose of antenatal MgSO₄ and the duration of antenatal MgSO₄ during the last 7 days of pregnancy, as well as the maternal level of serum magnesium before delivery, were reviewed and analyzed. Data on the neonatal factors and outcomes, including the neonatal blood magnesium level and intestinal injuries, such as NEC, spontaneous intestinal perforation (SIP), and meconium obstruction (MO) requiring surgery, were collected. Data on respiratory distress syndrome, patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), sepsis, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), hypotension during the first week, ibuprofen use during the first week, postnatal steroid use, duration of invasive ventilation and time to full feeding were also collected.

Intestinal morbidity requiring surgery was considered when surgical intervention was conducted for NEC, SIP or MO. NEC was diagnosed according to Bell's staging criteria and SIP when isolated bowel perforation was present without evidence of NEC or MO [14]. MO was suspected when premature infants had problems with meconium passage accompanied by abdominal distension and feeding intolerance. It was diagnosed if persistent or progressive gaseous bowel distension was noted on plain radiography, along with the presence of hypoechoic meconium-filled bowel loops and distended proximal bowel loops observed by sonography.[15, 16] Glycerin enema was used as the first-line therapy for a few days, and ultrasonography-guided water-soluble contrast enema was performed if the condition was not resolved. If contrast enema failed to relieve the obstruction, surgical intervention was carried out.

Statistical analysis was performed with STATA version 11.0. Wilcoxon rank-sum tests for continuous data and chi square tests for categorical data were used. A *P* value < 0.05 was considered statistically significant in all analyses. Univariate logistic regression analysis was conducted for intestinal injury requiring surgery, and factors with *p* < 0.10 in the univariate analysis were included in multivariate analysis to evaluate the association between maternal MgSO₄ use and intestinal injury requiring surgery. Next, duration of MgSO₄, cumulative dose of MgSO₄, maternal Mg level and neonatal Mg level were used in the multivariate logistic regression analysis. Subgroup analysis of those born before 26 weeks of gestation was also conducted.

Results

During the study period, 202 infants born at less than 28 weeks of gestational age (GA) were admitted to the Seoul National University Hospital neonatal intensive care unit. Four infants with major congenital anomalies and sixteen with preeclampsia were excluded from the study population. Among 181 infants, 109 (60.2%) were exposed to antenatal MgSO₄, including 100 infants for preterm labor and 9 infants for neuroprotection (Fig. 1). The GA (25.6 vs. 26.3 weeks) and birthweights (720 vs. 850 grams) were comparable between the no antenatal MgSO₄ group and the antenatal MgSO₄ group (Table 1). A higher cesarean section rate was found in the no antenatal MgSO₄ group (54.2

vs. 34.9%, $P=0.015$). The maternal magnesium level was higher in the antenatal $MgSO_4$ group (1.8 vs. 3.2 mg/dl, $P<0.001$).

Table 1
Demographics of the study population according to the antenatal administration of magnesium sulfate

	No antenatal $MgSO_4$ (n = 72)	Antenatal $MgSO_4$ (n = 109)	P value
GA (week)	25.6 (24-26.9)	26.3 (24.4–27.4)	0.172
GA < 26 weeks	40 (55.6)	46 (42.2)	0.095
Birthweight (gram)	720 (595–950)	850 (610–1000)	0.140
SGA	6 (8.3)	11 (10.1)	0.798
C/S	39 (54.2)	38 (34.9)	0.014
Male	30 (41.7)	60 (55.1)	0.095
PPROM	40 (55.6)	56 (51.4)	0.649
hCAM	35 (48.6)	61 (56)	0.363
AS 1 min	2.5 (1–5)	3 (1–5)	0.423
AS 5 min	5 (3–7)	6 (4–7)	0.083
Antenatal steroid	58 (80.6)	92 (84.4)	0.548
Multiple birth	47 (65.3)	68 (62.4)	0.753
Cumulative Mg dose (g)	-	38.3 (8.7-123.6)	-
Maternal Mg level (mg/dl)	1.8 (1.7–2.5)	3.2 (2.2–3.9)	< 0.001
MgSO ₄ , magnesium sulfate; GA, gestational age; SGA, small for gestational age; C/S, cesarean section; PPRM, preterm premature rupture of membrane; hCAM, histologic chorioamnionitis; AS, Apgar score			
Values are expressed as N (%) or median (interquartile range)			

The neonatal magnesium level was higher in the antenatal $MgSO_4$ group (1.8 vs. 2.9 mg/dl, $P<0.001$). There were no significant differences in neonatal morbidities in terms of respiratory distress syndrome, hypotension during the first week of life, moderate to severe BPD, sepsis, severe IVH and ROP requiring operation (Table 2). NEC and surgical NEC were comparable between the two groups. The incidence of SIP was higher in the no antenatal $MgSO_4$ group (5.6% vs. 0%, $P=0.024$). Any intestinal morbidities requiring surgery (22.2% vs. 10.1%, $P=0.033$) were lower in the antenatal $MgSO_4$ group. The duration of invasive ventilation and the time to full enteral feeding were not different between the two groups.

Table 2
Clinical courses and neonatal outcomes of the study population

Table 2.			
	No antenatal MgSO₄ (n = 72)	Antenatal MgSO₄ (n = 109)	P value
Neonatal Mg level (mg/dl)	1.8 (1.6–2.1)	2.9 (2.3–3.6)	< 0.001
RDS	66 (91.8)	93 (85.3)	0.248
Hypotension during the first week	43 (59.7)	55 (50.5)	0.228
Ibuprofen during the first week	24 (33.3)	38 (34.9)	0.874
Treated PDA	42 (58.3)	66 (60.6)	0.877
NEC	12 (16.7)	13 (11.9)	0.386
Surgical NEC	8 (11.1)	6 (5.6)	0.256
SIP	4 (5.6)	0 (0)	0.024
Meconium obstruction requiring surgery	4 (5.6)	5 (4.6)	0.743
Intestinal morbidities requiring surgery	16 (22.2)	11 (10.1)	0.033
Moderate to severe BPD	34 (47.2)	45 (41.7)	0.540
Postnatal steroid for BPD	7 (9.7)	10 (9.2)	1.000
Sepsis	23 (31.9)	25 (22.9)	0.228
IVH ≥ grade 3	4 (5.6)	13 (11.9)	0.196
ROP operation	18 (25)	33 (30.3)	0.501
Mortality	24 (33.3)	29 (26.6)	0.404
Invasive ventilation duration	16 (4–50.5)	13 (3–35)	0.192
Time to full feeding	21 (15–31)	18 (14–27)	0.221

MgSO₄, magnesium sulfate; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity

Values are expressed as N (%) or Median (interquartile range)

The univariate regression analysis showed that low GA, treated PDA and antenatal MgSO₄ were associated with surgical conditions of the intestine (Table 3). Small for gestational age (SGA) had an odds ratio of 2.689, without statistical significance (95% CI 0.864–8.374, p = 0.088). Multivariate logistic regression showed that low GA, SGA and treated PDA were significantly associated with surgical conditions of the intestine, while the association of maternal MgSO₄ became insignificant (adjusted OR 0.543, 95% CI 0.167–1.030). When logistic analysis was conducted in the subgroup of those with GA < 26 weeks, maternal MgSO₄ was associated with surgical conditions of the intestine (adjusted OR 0.234, 95% CI 0.060–0.922). The multivariate logistic regression analysis in the total population showed

that duration of antenatal MgSO₄ use was associated with surgical conditions of the intestine, while cumulative dose of MgSO₄, maternal Mg level and neonatal Mg level had no associations with surgical conditions of the intestine (Table 4).

Table 3
Univariate and multivariate regression analyses for intestinal morbidities requiring surgery

	OR	95% CI	P value	adjOR[†]	95% CI	P value
All neonates						
GA (weeks)	0.759	[0.588 , 0.979]	0.034	0.670	[0.491 , 0.914]	0.011
SGA	2.689	[0.864 , 8.374]	0.088	5.372	[1.331 , 21.682]	0.018
Treated PDA	6.667	[1.926 , 23.070]	0.003	12.504	[3.015 , 51.857]	0.001
Maternal MgSO ₄ Use	0.393	[0.170 , 0.905]	0.028	0.415	[0.167 , 1.030]	0.058
Neonates with GA < 26 weeks						
GA (weeks)	0.680	[0.380 , 1.217]	0.194	0.298	[0.126 , 0.707]	0.006
SGA	0.787	[0.156 , 3.977]	0.772	4.824	[0.382 , 60.861]	0.224
Treated PDA	17.455	[2.192 , 138.985]	0.007	63.357	[5.001 , 802.688]	0.001
Maternal MgSO ₄ Use	0.285	[0.090 , 0.897]	0.032	0.234	[0.060 , 0.922]	0.038
[†] Adjusted for GA, SGA, treated PDA and maternal MgSO ₄ Use. GA, gestational age; SGA, small for gestational age; PDA, patent ductus arteriosus						

Table 4

Univariate and multivariate logistic regression analyses for magnesium-related factors for intestinal morbidities requiring surgery

	OR	95% CI	<i>P</i> value	adjOR [†]	95% CI	<i>P</i> value
Duration of MgSO ₄ (day)	0.764	[0.594 , 0.983]	0.036	0.766	[0.589 , 0.997]	0.047
Cumulative dose of MgSO ₄ (/10 g)	0.942	[0.874 , 1.015]	0.114	0.944	[0.874 , 1.021]	0.148
Maternal Mg level (mg/dl)	0.983	[0.717 , 1.346]	0.913	0.988	[0.738 , 1.323]	0.935
Neonatal Mg level (mg/dl)	0.926	[0.637 , 1.346]	0.687	0.988	[0.671 , 1.455]	0.952

[†]Adjusted for GA, SGA and treated PDA. *GA*, gestational age; *SGA*, small for gestational age; *PDA*, patent ductus arteriosus

Discussion

The current study showed that antenatal MgSO₄ was associated with low incidence of intestinal morbidities requiring surgery in preterm infants with GA less than 26 weeks. In the total study population, duration of exposure to antenatal MgSO₄ was associated with decreased risk of intestinal injury needing surgery. There were no differences in mortality and other morbidities such as RDS, IVH and BPD between infants with and without antenatal MgSO₄.

Antenatal MgSO₄ has been used widely according to maternal and fetal conditions. Since benefits in terms of the neurodevelopmental outcomes were found in prospective randomized trials [2, 3], antenatal MgSO₄ is now recommended for fetal neuroprotection in anticipation of preterm delivery in very preterm infants [17]. As the use of antenatal MgSO₄ has been highlighted, concerns have been raised regarding the neonatal adverse effects of antenatal MgSO₄ because magnesium can block calcium entry into cells, leading to muscle weakness and intestinal atony in the offspring.[10]

A clinical study showed a significant negative relationship between the mean blood flow velocity and the time from birth to the blood flow velocity measurement in antenatal MgSO₄-exposed infants.[18] In the secondary analysis of a prospective study, antenatal exposure to MgSO₄ was associated with death or severe NEC in infants with a GA less than 26 weeks.[2, 10] Furthermore, a study of historical comparisons by Rattray et al reported that antenatal MgSO₄ was associated with SIP and death.[12]

However, another secondary analysis of a prospective trial reported that newborns with higher magnesium levels did not show any adverse non-neurological effects.[19] Moreover, a meta-analysis of 5 randomized controlled studies concluded that there were no statistically significant differences in neonatal secondary outcomes, such as IVH, periventricular leukomalacia, NEC, RDS, ROP or chronic lung disease.[20]

In the aforementioned secondary analysis study, although the combined outcome of death and severe NEC was associated with maternal antenatal MgSO₄ administration in infants who were GA less than 26 weeks, NEC alone was not associated with antenatal MgSO₄. [10] Caution should be taken in the interpretation of the combined

outcome of NEC and death because the two conditions were not competitive as death and BPD. Although Rattray et al reported the association between antenatal MgSO₄ and SIP, but SGA was not included in the analysis.[12] As the development of intestinal morbidities may be influenced by various causes, factors such as GA, SGA and medication history should be considered and coanalyzed to investigate factors associated with these conditions. For instance, SIP was associated with intrauterine growth restriction and PDA with delayed meconium passage in VLBW infants. [21, 22]

Although this was a retrospective study, the cumulative dose of antenatal MgSO₄, duration of antenatal MgSO₄ and level of magnesium were calculated and analyzed thoroughly. Factors associated with intestinal morbidities such as GA, SGA, and treated PDA were also reviewed. The results of the present study are consistent with the report from a nationwide database from North America, reporting that antenatal MgSO₄ exposure in extremely preterm neonates was associated with reduced risk of a combined outcome of death, NEC and SIP.[23] In a retrospective study from a tertiary-level NICU, cumulative dose of MgSO₄ was associated with a combined outcome of death, NEC and SIP.[24] Although a protective role of antenatal MgSO₄ has been raised, the physiologically beneficial effect of magnesium on the intestine of preterm infants is not yet fully understood. One study of grass carp showed that magnesium deficiency suppressed the growth and damaged the intestinal structural integrity of the fish.[25] A preclinical study of mice demonstrated that prophylactic oral administration of magnesium ameliorates induced colitis through the inhibition of colonic mast cell activation.[26]

This was a single-center retrospective design, and the indications for antenatal MgSO₄ included not only neuroprotection but also preterm labor. However, the dosages of the antenatal MgSO₄ treatments for preterm labor and for neuroprotection were similar in our institution, and the data regarding duration, cumulative dosage and level of serum magnesium were reviewed. Mothers with preeclampsia, an important indication for antenatal MgSO₄, were excluded because the maternal environment in this condition can affect vascular development of the intestine.[27, 28]

Conclusions

This retrospective cohort study suggested the benefit of antenatal MgSO₄ in the reduction of intestinal injury requiring surgical intervention in extremely preterm infants in a duration-dependent manner, especially in those with a GA less than 26 weeks at birth. Further study with a large population might be required to clarify the beneficial effect of antenatal MgSO₄.

Abbreviations

MgSO₄

antenatal magnesium sulfate; NEC:necrotizing enterocolitis; GI:gastrointestinal; SIP:spontaneous intestinal perforation; MO:meconium obstruction; PDA:patent ductus arteriosus; BPD:bronchopulmonary dysplasia; IVH:intraventricular hemorrhage; ROP:retinopathy of prematurity; GA:gestational age; SGA:small for gestational age

Declarations

Ethics approval and consent to participate

This study protocol was reviewed and approved by the Institutional Review Board of the Seoul National University Hospital (No. 1904-069-1026). Written informed consent was obtained from the parents of the participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing interests

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Author contributions

Seh Hyun Kim designed the study, performed data analysis and drafted the manuscript. Yoo-Jin Kim, Seung Hyun Shin, and Hannah Cho helped to collect and interpret the data. Seung Han Shin designed the study, performed data analysis, interpreted the data and gave final approval of the version to be published. Ee-Kyung Kim and Han-Suk Kim monitored the study and gave final approval of the version to be published. Subeen Hong helped to collect and interpret the data. Seung Mi Lee helped to design the study and gave final approval of the version to be published.

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Figures

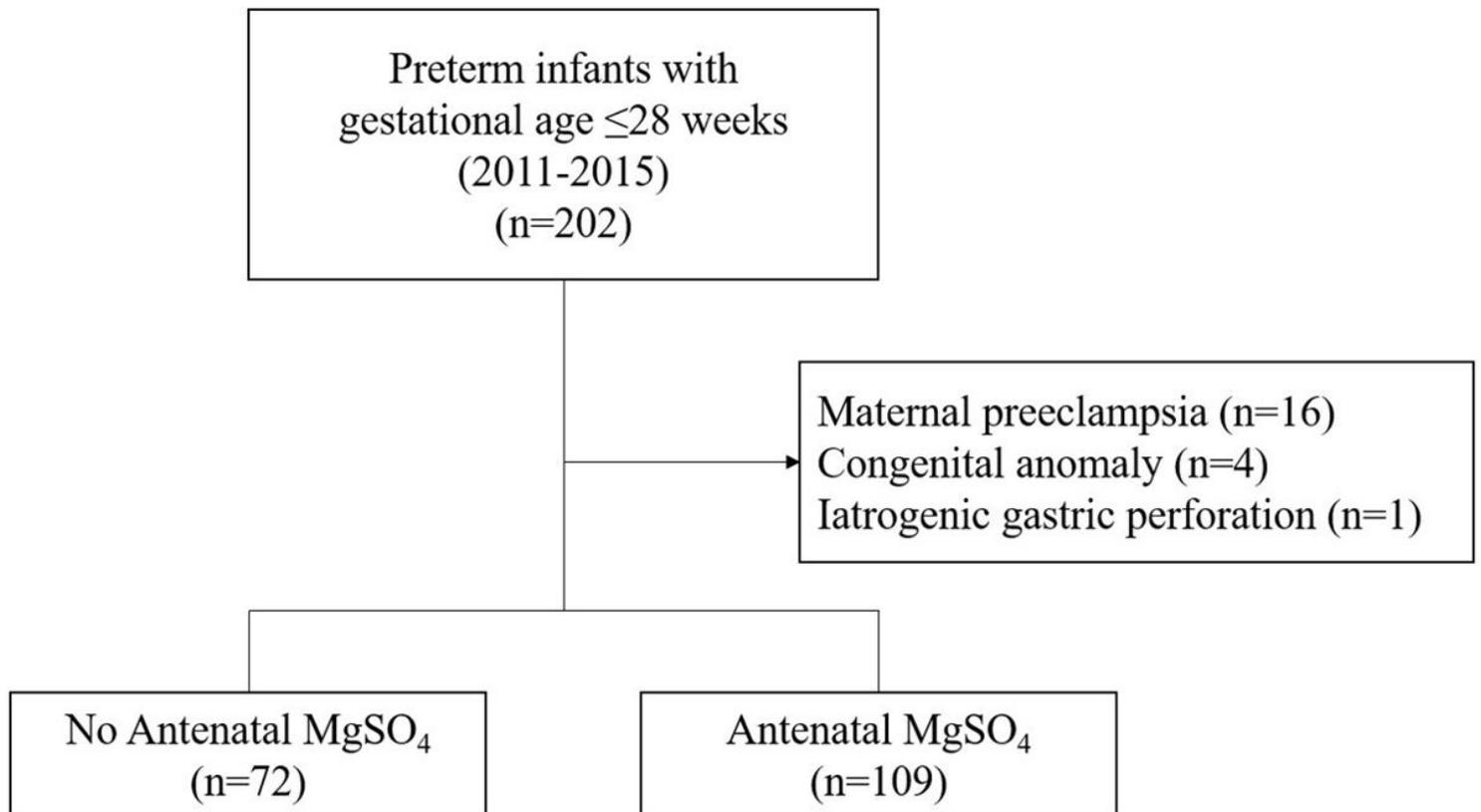


Figure 1

Flow diagram of the study population