Increased Risk of Meconium-Related Ileus in Extremely Premature Infants Exposed to Antenatal Magnesium Sulfate

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Keywords

Meconium · Meconium-related ileus · Antenatal magnesium sulfate · Neuroprotection · Extremely premature infants

Abstract

Introduction: We experienced an increased incidence of meconium-related ileus (MRI) in extremely premature infants (EPIs) while adopting the antenatal magnesium sulfate (MgSO₄) protocol for fetal neuroprotection in our neonatal intensive care unit. This study aimed to test whether antenatal MgSO₄ use was associated with increased risk of MRI in EPIs. **Methods:** The incidences of complicated MRI requiring aggressive enema or surgical intervention and other intestinal complications were compared among period 1 (January 2012–December 2013, *n* = 79), before adoption of the antenatal MgSO₄ protocol for fetal neuroprotection; period 2 (January 2014–March 2016, *n* = 72), when the protocol was adopted; and period 3 (April 2016–September 2018, *n* = 75), when the protocol was temporarily withdrawn due to concern regarding intestinal complications in EPIs. **Results:** Despite similar baseline clinical characteristics among infants across the study periods, the MRI and MRI with surgical treat-

ment incidences were higher in period 2 than those in periods 1 and 3 (13% vs. 8% and 6%, *p* = 0.391, and 11% vs. 0% and 1%, *p* = 0.001, respectively). In multivariable analysis, exposure to antenatal MgSO₄ independently increased the risk of MRI (adjusted odds ratio, 3.8; 95% confidence interval, 1.4, 10.6). **Conclusion:** Antenatal MgSO₄ may increase the risk of MRI, frequently requiring surgical intervention, in EPIs with a gestational age of 25 weeks or less.

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Introduction

Although MgSO₄ is no longer recommended for tocolysis according to a recent systematic review, it has been widely used as a tocolytic agent for the treatment of eclampsia and preeclampsia [1–3]. Since the fetal neuroprotective effect of antenatal MgSO₄ was suggested in 1995 [4], 4 large randomized clinical trials (RCTs) and subsequent meta-analysis showed that antenatal MgSO₄ could reduce cerebral palsy and gross motor dysfunction in survivors [5–12]. In 2010, the American College of Obstetricians and Gynecologists (ACOG) recommended the use of antenatal MgSO₄ in women at risk of preterm birth

before 32 weeks of gestation, although the meta-analyses did not include a sufficient number of infants with a gestational age (GA) of 25 weeks or less [9, 10, 13].

Accordingly, the protocol for the antenatal use of MgSO₄ for fetal neuroprotection was adopted in our routine practice in January 2014. However, we thereafter observed an increased incidence of neonatal meconium problems including delayed meconium passage, feeding intolerance, abdominal distention, severe ileus on plain abdominal radiographs, and need for an aggressive enema procedure with gastrografen or surgical intervention, suggesting the diagnosis of meconium-related ileus (MRI). MRI developed exclusively in extremely preterm infants (EPIs) born at a GA of 25 weeks or less. Because of this observation and a literature review showing an association between MgSO₄ and neonatal intestinal complications including necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) [14, 15], we withdrew the protocol for routine MgSO₄ use for fetal neuroprotection in March 2016. Therefore, the purpose of the present study was to thoroughly investigate whether antenatal MgSO₄ use for fetal neuroprotection was associated with increased risk of MRI in EPIs by comparing the incidence of MRI among the periods before, during, and after the adoption of the routine MgSO₄ protocol.

Methods

The medical records of 231 EPIs born from 22 weeks, 0 days, to 25 weeks, 6 days, of gestation and admitted to the Samsung Medical Center neonatal intensive care unit (NICU) between July 2012 and December 2018 were reviewed. Infants who died within the first 48 h ($n = 2$), had congenital intestinal anomalies ($n = 1$, esophageal atresia), or were born at another hospital ($n = 2$) were excluded; a total of 226 infants were finally included and analyzed in this study. In period 1 (January 2012–December 2013, $n = 79$), antenatal MgSO₄ was used to treat eclampsia/preeclampsia or for tocolytic purposes. In period 2 (January 2014–March 2016, $n = 72$), antenatal MgSO₄ was routinely used for fetal neuroprotection, apart from the conventional purposes of preterm delivery. However, the routine use protocol of antenatal MgSO₄ for fetal neuroprotection was withdrawn because of concerns about intestinal complications including MRI in EPIs (period 3, April 2016–September 2018, $n = 75$). Antenatal MgSO₄ treatment for fetal neuroprotection was administered with an intravenous loading dose of 4 g over 15–20 min, followed by a maintenance infusion of 1 g per hour for 24 h for women having imminent preterm. For the treatment of severe preeclampsia and eclampsia, MgSO₄ was administered at the same loading dose, followed by a maintenance infusion of 1 g per hour and discontinued at 24 h after delivery. As we did not use antenatal MgSO₄ as a tocolytic, the data regarding MgSO₄ use for tocolysis were based on medical charts from another hospital before the women were transferred.

Fig. 1. Enema protocol for delayed meconium passage in extremely premature infants.

MRI is defined as an intestinal obstruction due to meconium without cystic fibrosis [16–18]. In the present study, MRI was suspected in infants showing severe abdominal distention, feeding intolerance, marked ileus on abdominal radiography, and no meconium passage for the first 5 days after birth in the absence of other intestinal diseases including NEC, SIP, intestinal atresia, or anorectal malformation. Together with the clinical symptoms described above, we defined MRI as requiring a gastrografen enema with or without the assistance of abdominal ultrasonography on day 6 of life or after [19, 20]. In the absence of any symptoms/signs, delayed meconium passage was not diagnosed by MRI and was not treated. In contrast to MRI, NEC was staged in accordance with the modified Bell's criteria. NEC ($\geq 2b$) was diagnosed when there was definite radiographic evidence of pneumatosis intestinalis and ascites, along with the characteristic systemic and abdominal signs. In the surgical NEC cases, the diagnosis was confirmed on the basis of intraoperative findings of necrotic bowel and histologic findings, including ischemic necrosis.

Figure 1 illustrates the MRI management protocol in our unit. In the case of meconium obstruction with intestinal perforation, emergency surgical intervention of manual meconium evacuation and stoma formation was performed. Even without intestinal perforation, surgery was performed in the case of severe and progressive ileus accompanied by metabolic acidosis ($\text{pH} < 7.1$) and/or respiratory compromise (increase in ventilator settings) directly due to severe abdominal distention. Minimal enteral feeding (20 mL/kg/day) was usually started within the first few hours after birth and maintained for the first week of life. The infants were fed with formula for the first 2–3 days of life and their mother's breast

Table 1. Baseline and MgSO₄-related clinical characteristics of the study population

	Period 1 (n = 79)	Period 2 (n = 72)	Period 3 (n = 75)	p value
<i>Baseline characteristics</i>				
Gestational age, weeks (min, max)	24.0±0.9 (22 ⁺¹ , 25 ⁺⁶)	24.2±0.1 (22 ⁺⁵ , 25 ⁺⁶)	23.9±0.9 (22 ⁺¹ , 25 ⁺⁶)	0.201
Birth weight, g (min, max)	667±145 (320, 940)	683±134 (300, 950)	667±129 (380, 940)	0.719
Male, n (%)	45 (57)	39 (54)	39 (52)	0.825
Small for gestational age, n (%)	13 (16)	11 (15)	13 (17)	0.945
Apgar score at 1 min	4.3±1.6	4.4±1.4	4.3±1.7	0.957
Apgar score at 5 min	6.8±1.9	6.9±1.3	7.0±1.6	0.546
Cesarean delivery, n (%)	57 (72)	55 (76)	39 (52)	0.003
Antenatal steroid use, n (%)	76 (94)	66 (92)	73 (97)	0.325
Preterm premature rupture of membranes, n (%)	30 (38)	22 (31)	37 (49)	0.063
Histologic chorioamnionitis, n (%)	50 (63)	40 (56)	57 (87)	0.031
Preeclampsia, n (%)	5 (6)	6 (8)	4 (5)	0.759
Gestational diabetes, n (%)	2 (3)	1 (1)	1 (1)	0.816
<i>Antenatal MgSO₄ use, n (%)</i>				
For any purpose	19 (24)	56 (78)	16 (21)	<0.001
For neuroprotection	1 (3)	40 (56)	0 (0)	
For severe preeclampsia	5 (6)	6 (8)	4 (5)	
For tocolysis	13 (16)	10 (14)	12 (16)	
<i>Serum MgSO₄ level of EPIs</i>				
Initial level (<1 h), mg/dL	2.6±1.3	2.8±0.9	2.3±0.6	0.021
Peak level within the first week, mg/dL	2.8±1.0	3.0±0.7	2.7±0.5	<0.001
Initial ionized calcium level, mmol/L	1.26±0.17	1.28±0.14	1.25±0.15	0.408
Total intake on day 1, mL/kg/day	70±7	73±6	71±10	0.888
Total intake on day 7, mL/kg/day	110±12	109±18	113±13	0.932
<i>Type of milk during the first month or until alive, n (%)</i>				
Exclusive breastfeeding	34 (43)	37 (51)	40 (53)	0.231
Partial breastfeeding	31 (39)	23 (32)	31 (41)	
Formula milk	8 (10)	6 (8)	2 (3)	
Nil per os	6 (8)	6 (8)	2 (3)	

MgSO₄, magnesium sulfate; EPI, extremely premature infant.

milk thereafter. We subsequently increased the feeding amount at the end of the first week in increments of 10–20 mL/kg/day to reach full feeding (120–150 mL/kg/day) if tolerated. The feeding protocol was applied consistently throughout the study period.

We collected data on baseline clinical characteristics including GA, birth weight, sex, Apgar scores at 1 and 5 min, cesarean section, histologic chorioamnionitis, and other perinatal data. Data on gestational diabetes and small for gestational age were also collected because they are known to be associated with delayed meconium passage [21, 22]. Histologic chorioamnionitis was defined according to the criteria of Redline et al. [23]. Data on antenatal MgSO₄ use and the initial and peak serum magnesium levels in the neonatal patients were also collected. We also collected data on the serum ionized calcium level, small for gestational age status, and gestational age because these could affect the serum magnesium level in neonates. The major neonatal outcome data, including mortality, intraventricular hemorrhage (grades III and IV), retinopathy of prematurity (≥stage 3), moderate to severe bronchopulmonary dysplasia, and blood culture-proven sepsis during hos-

pitalization, were collected. The neurodevelopmental outcomes at the corrected age of 18–24 months included the incidence of cerebral palsy, defined as a Palisano gross motor function score of ≥2, bilateral hearing loss, bilateral visual loss, cognitive impairment, psychomotor impairment, and z-score of weight, height, and head circumference. Cognitive impairment was defined as a mental developmental index of <70 on the Bayley Scales of Infant Development (BSID) II or a cognitive score of <70 or a language score of <70 on the BSID-III. Psychomotor impairment was defined as a psychomotor developmental index of <70 on the BSID-II or a motor score of <70 on the BSID-III. The intestinal complications included MRI, MRI requiring surgery, NEC, and SIP. NEC was staged according to modified Bell's criteria; SIP was defined based on surgical and/or histologic findings of the absence of ischemic bowel change with or without focal hemorrhagic necrosis [24]. We also collected surgical outcome data for MRI, including operative findings, procedures, postnatal age at operation, and take-down operations.

Table 2. Neonatal outcomes including intestinal complications in extremely premature infants

	Period 1 (n = 79)	Period 2 (n = 72)	Period 3 (n = 75)	p value
<i>Intestinal complication, n (%)</i>				
Meconium-related ileus requiring gastrografin enema	5 (6)	9 (13)	6 (8)	0.391
Meconium-related ileus requiring surgery	0 (0)	8 (11)	1 (1)	0.001
Spontaneous intestinal perforation	1 (1)	2 (3)	4 (5)	0.340
Necrotizing enterocolitis, stage $\geq 2b$	16 (20)	22 (31)	19 (25)	0.346
Necrotizing enterocolitis perforation	9 (11)	8 (11)	9 (12)	0.768
Intestinal surgery for spontaneous intestinal perforation or necrotizing enterocolitis perforation	10 (13)	10 (14)	13 (17)	0.823
<i>Other neonatal outcomes, n (%)</i>				
In-hospital mortality	16 (20)	19 (26)	29 (39)	0.037
Intraventricular hemorrhage grade III–IV	14 (18)	14 (20)	7 (10)	0.183
Retinopathy of prematurity stage ≥ 3	25 (32)	20 (28)	11 (29)	0.890
Bronchopulmonary dysplasia, moderate to severe	32 (41)	33 (46)	44 (59)	0.070
Acute kidney injury	6 (8)	5 (7)	2 (3)	0.368
Blood culture-proven sepsis	35 (44)	22 (31)	27 (36)	0.211
<i>Neurodevelopmental outcomes at the corrected age of 18–24 months</i>				
Mortality after hospital discharge, n (%)	0 (0)	0 (0)	0 (0)	
Cerebral palsy, n (%)	6/60 (10)	4/52 (8)	6/44 (14)	0.631
Hearing loss, n (%)	1/60 (2)	2/52 (4)	2/44 (5)	0.677
Blindness, n (%)	3/60 (5)	0/52 (0)	0/44 (0)	0.087
Cognitive impairment, n (%)	14/40 (35)	23/48 (48)	14/40 (35)	0.352
Psychomotor impairment, n (%)	14/40 (35)	12/48 (25)	9/40 (23)	0.475
Weight (z-score)	-1.16 ± 1.32	-1.07 ± 0.99	-0.80 ± 0.99	0.323
Height (z-score)	-1.18 ± 1.32	-1.11 ± 1.21	-1.04 ± 1.23	0.853
Head circumference (z-score)	-0.95 ± 1.22	-0.79 ± 0.96	-1.23 ± 1.46	0.237

Baseline characteristics and outcomes were compared among periods 1, 2, and 3 using χ^2 or Fisher's exact tests for categorical variables, analysis of variance or Student's *t* test for parametric continuous variables, and Kruskal-Wallis test or Wilcoxon rank-sum tests for nonparametric continuous variables. Binary logistic regression was used to calculate the adjusted odds ratios (ORs) of the exposure versus nonexposure to antenatal MgSO₄ for intestinal complications. The variables adjusted for in the multivariable analyses included the gestational age, antenatal steroid use, and histologic chorioamnionitis. *p* values of <0.05 were considered statistically significant. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and STATA 14.0 (StataCorp, College Station, TX, USA). The Institutional Review Board of the Samsung Medical Center approved the study and waived the requirement for informed consent for the retrospective chart review (IRB No. SMC 2016-09-113).

Results

Ninety-one (40%) infants received antenatal MgSO₄ during the study periods (Table 1). The rate of antenatal MgSO₄ use was the highest in period 2 (78%) compared

to the rates in periods 1 (24%) and 3 (21%). Regarding baseline characteristics, infants in period 3 showed a significantly lower rate of cesarean section and a higher rate of histologic chorioamnionitis. Otherwise, there were no differences among the periods. The serum MgSO₄ level tested within the first hour of life was the highest in period 2 (2.8 ± 0.9 mg/dL) compared to the levels in periods 1 (2.6 ± 1.3) and 3 (2.3 ± 0.6 mg/dL). Similarly, the peak serum MgSO₄ level within the first week was the highest in period 2 compared to those in periods 1 and 3. These initial and peak serum MgSO₄ levels were within the reference range, according to a recently published meta-analysis showing the changes in the serum magnesium level in preterm infants [25]. In addition, there was no difference in the breastfeeding rate between the periods.

Although the incidence of MRI was the highest in period 2 compared to those in periods 1 and 3, the difference did not reach statistical significance (Table 2). However, the number of infants who underwent surgery due to MRI was significantly higher in period 2 (8/72, 11%), whereas none and 1 infant underwent surgery due to MRI

Table 3. Surgical outcomes of MRI

Case (GA, weeks; birth weight, g)	Period	Antenatal MgSO ₄ (purpose)	Operative finding and procedure	Ostomy formation	Date of operation, postnatal day	Take-down operation (postnatal day)	Mortality during hospitalization	Cause of death
#1 (22 ⁺² ; 300)	2	–	Ileal meconium obstruction and perforation	Ileostomy	10	Expired before take-down operation	+	Sepsis
#2 (24 ⁺¹ ; 430)	2	+ (PE)	Jejunal meconium obstruction and perforation	Jejunostomy	13	Expired before take-down operation	+	Chronic lung disease, pulmonary hypertension
#3 (25 ⁺² ; 750)	2	+ (NP)	Ileal meconium obstruction and perforation	Ileostomy	26	+ (156)		
#4 (25 ⁺⁰ ; 750)	2	+ (TO)	Ileal meconium obstruction, colonic meconium obstruction and perforation	Ileostomy, colostomy	12	+ (103)		
#5 (23 ⁺⁴ ; 660)	2	+ (NP)	Ileal meconium obstruction and perforation	Ileostomy	11	+ (108)		
#6 (22 ⁺⁵ ; 500)	2	+ (NP)	Ileal meconium obstruction and perforation	Ileostomy	12	Expired before take-down operation	+	Peritonitis after MRI surgery
#7 (22 ⁺⁵ ; 450)	2	–	Jejunal meconium obstruction	Jejunostomy	30	Expired before take-down operation	+	
#8 (24 ⁺¹ ; 690)	2	+ (NP)	Ileal meconium obstruction	Ileostomy	38	+ (120)		Acute kidney injury
#9 (22 ⁺³ ; 610)	3	+ (TO)	Jejunal meconium obstruction	Jejunostomy	30	+ (154)	+	Chronic lung disease, suspected sepsis

GA, gestational age; PE, preeclampsia treatment; NP, neuroprotection; MRI, meconium-related ileus; TO, tocolytic purpose.

during periods 1 and 3, respectively. There were no cases of cystic fibrosis during the study period. There were no differences in the incidence of NEC, SIP, and intestinal surgery among the study periods. Among other neonatal outcome variables, in-hospital mortality was significantly higher in period 3 than those in periods 1 and 2; otherwise, there were no differences. Further analysis adjusting the rate of cesarean section and chorioamnionitis showed no difference in the in-hospital mortality among the 3 periods ($p = 0.337$). There were also no differences in the neurodevelopmental outcomes at the corrected age of 18–24 months. The surgical outcomes of the infants who underwent surgical procedures due to MRI are shown in Table 3. Among the 9 infants who underwent surgery for

MRI, 7 had received antenatal MgSO₄, and 5 infants died during NICU hospitalization. One infant died on day 42 due to peritonitis following MRI surgery.

In the multivariable analysis, the adjusted ORs of MgSO₄ exposed versus unexposed for MRI and MRI requiring surgery, respectively, were 3.8 (95% confidence interval [CI]: 1.4, 10.6) and 14.1 (95% CI: 2.1, 92.2), a statistically significant difference (Table 4). The adjusted OR of MgSO₄ exposure for fetal neuroprotection versus unexposed for MRI was 3.6 (95% CI: 1.1, 13.2). In contrast, no differences in adjusted ORs were observed for NEC, SIP, or intestinal surgery for any reason between MgSO₄-exposed and -unexposed infants. The risk of MRI requiring surgical treatment was increased independently in in-

Table 4. The risks of intestinal complications in extremely premature infants with and without exposure to antenatal MgSO₄

	MgSO ₄ exposed, n (%) (N = 91)	MgSO ₄ exposed for fetal neuroprotection, n (%) (N = 41)	MgSO ₄ unexposed, n (%) (N = 135)	p value*	p value [†]	Adjusted OR ^a (95% CI)
Meconium-related ileus	13 (14)	5 (12)	7 (5)	0.018	0.119	3.8 (1.4, 10.6)
Meconium-related ileus requiring surgery	7 (8)	4 (10)	2 (2)	0.019	0.011	14.1 (2.1, 92.2)
Spontaneous intestinal perforation	3 (3)	1 (2)	4 (3)	0.887	0.860	1.1 (0.2, 5.4)
Necrotizing enterocolitis stage ≥2b	21 (23)	11 (27)	36 (27)	0.542	0.984	0.9 (0.5, 1.7)
Necrotizing enterocolitis perforation	6 (7)	3 (7)	20 (14)	0.057	0.212	0.5 (0.2, 1.2)
Intestinal surgery for any reason	13 (14)	7 (17)	26 (19)	0.332	0.753	0.9 (0.4, 1.9)

MgSO₄, magnesium sulfate; OR, odds ratio; CI, confidence interval. *MgSO₄ exposed versus MgSO₄ unexposed. [†] MgSO₄ exposed for fetal neuroprotection versus MgSO₄ unexposed. ^a Odds ratios of MgSO₄ exposed versus MgSO₄ unexposed, adjusted for gestational age, antenatal steroid use, and histologic chorioamnionitis.

fants with a lower GA (adjusted OR: 0.3, 95% CI: 0.1, 0.67 per week increase of GA) and with exposure to antenatal MgSO₄ (adjusted OR: 14.1, 95% CI: 2.1, 92.2).

Discussion

The results of the present study demonstrated the association between antenatal MgSO₄ use and neonatal MRI in EPIs. Infants who were exposed to antenatal MgSO₄ for any reason or for the sake of fetal neuroprotection showed increased odds of complicated MRI with aggressive gastrografin enema or surgical treatment compared to nonexposed infants.

Since the observation by Nelson and Grether [4] that antenatal MgSO₄ might have fetal neuroprotective effects, subsequent large-scale multicenter RCTs revealed that antenatal MgSO₄ use reduced the incidence of cerebral palsy and gross motor dysfunction in preterm infants [5–12]. However, these randomized clinical trials did not include a sufficient number of EPIs born with a GA of 22–25 weeks; therefore, the benefit and the risk of antenatal use of MgSO₄ for neuroprotection were not rigorously investigated in these tiny infants. The lowest GA among the infants enrolled in the Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO₄) trial was 25 weeks 5 days; moreover, only 18% of infants enrolled in the MAGnesium sulphate for Prevention of Eclampsia (Magpie) trial had a GA of <34 weeks, and the median GAs of the infants enrolled in the PREterm brain protection by MAGnesium sulphate (PREMAG) and Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) trials were 30 and 28 weeks, respectively [5–8]. Furthermore, Rattray et al. [14] suggested an association

between antenatal MgSO₄ use and SIP exclusively in EPIs with GA <25 weeks. Kamyar et al. [15] also showed a link between antenatal MgSO₄ use and NEC in infants with GA <26 weeks. In contrast, in our previous study of premature infants with GAs of 24–31 weeks, exposure to antenatal MgSO₄ did not increase the risk of NEC or SIP [26]. This result is in line with those of several recent reports that observed no difference in the odds of NEC or SIP between MgSO₄-exposed and -unexposed infants [27, 28]. In the present study, we also investigated the relationship between antenatal MgSO₄ use and intestinal complications including NEC and SIP in younger infants with GAs of 22–25 weeks and observed no significant association. However, we did observe a significant increase in MRI incidence in infants exposed to antenatal MgSO₄ compared to that in nonexposed infants.

The association between antenatal MgSO₄ use and neonatal meconium problems has long been explored. In the 1970s, Cooney et al. [29] and Sokal et al. [30], respectively, showed that maternal and neonatal hypermagnesemia could result in the development of meconium plug syndrome. As MgSO₄ administered to the mother rapidly passes through the placenta, the serum level in the fetus rose immediately. Because MgSO₄ is a competitive antagonist of calcium ions, a high MgSO₄ level can reduce intestinal contractility, leading to intestinal atony and fecal impaction [20, 31–33]. Simultaneously, MgSO₄ administration can compromise mesenteric blood flow and increase cerebral blood flow [34, 35]. Furthermore, the mineral composition of meconium in preterm infants was found to differ from that in term infants. The meconium in preterm infants had higher concentrations of calcium, copper, iron, and phosphorus than those in term infants [36], leading to underdeveloped intestinal struc-

tures and functions prone to delayed meconium evacuation after birth in preterm infants. In preterm infants, the first day of meconium passage was delayed compared to that in term infants inversely proportional to the GA [37]. Despite the biologic plausibility and clinical observation that extremely premature babies are prone to MRI [18, 29, 30, 38], few studies have extensively investigated the risk of MRI in antenatal MgSO_4 -exposed EPIs.

It is well known that surgical intervention and general anesthesia increase the incidence of neurodevelopmental impairment in preterm infants. Previous studies using national registry data showed that surgery during NICU hospitalization in preterm infants was an independent risk factor for various neurodevelopmental impairments at the age of 2 years or later [39, 40]. Therefore, the question of whether surgery in this early and vulnerable period of life might offset the beneficial fetal neuroprotective effect should be answered. Although there was no difference observed in the neurodevelopmental outcomes between the periods in our study, randomized trials with predefined primary endpoints and appropriately calculated sample sizes are needed to confirm the effect of fetal neuroprotection in EPIs. Infants with GA <25 weeks should be specifically investigated in future RCTs with sufficient power to confirm the causality between antenatal MgSO_4 use and postnatal surgical MRI and to reassess the fetal neuroprotective effects of antenatal MgSO_4 .

It is challenging to differentiate MRI from NEC in EPIs, and stringent diagnosis is a prerequisite for further analysis. In this study, NEC was diagnosed in cases showing definite radiographic evidence of pneumatosis and ascites. The characteristic abdominal and systemic findings of NEC, including abdominal wall bruising, hypotension, bradycardia, coagulopathy, thrombocytopenia, and neutropenia, helped us distinguish NEC from MRI. In addition, all surgical NEC cases showed operative findings of necrotic bowel and postoperative pathologic findings of ischemic necrosis. In contrast, all surgical MRI cases showed jejunal or ileal obstruction by meconium, which was manually extracted, and normal intestinal histology without ischemic necrosis or hemorrhagic infarction.

The limitations of this study include the retrospective nature of the study design and the single-center study design with a relatively small number of patients. MgSO_4 usage could not be controlled completely during the study period because of a substantial number of mothers transferred from other hospitals and because antenatal MgSO_4 treatment has multiple obstetric indications besides fetal neuroprotection (Table 1). We defined MRI arbitrarily in the present study due to the absence of a commonly ac-

cepted definition. Enema procedures with gastrografin are known to be effective in meconium evacuation in preterm infants with delayed meconium passage, thus avoiding the use of surgical resection with enterostomy [41, 42]. However, because these procedures are not a universal practice and the procedure protocol varies worldwide, generalizing our results on the incidence of MRI needs to be done with caution. In addition, the neonatal in-hospital mortality in period 3 was higher than those in periods 1 and 2. While there was no difference in the baseline characteristics, including the gestational age, birth weight, and Apgar score, the cesarean section rate was the lowest in period 3. It is well known that the mode of delivery does not affect the mortality or morbidity rate in preterm infants. However, recent prospective cohort studies and systematic reviews have shown the protective effect of cesarean section on neonatal mortality in EPIs at the threshold of viability [43–45]. Because our study population had an extremely low gestational age (≤ 25 weeks), we speculated that the highest mortality rate in period 3 might be partly attributed to the lowest cesarean section rate, along with the highest histologic chorioamnionitis rate therein. Further analysis adjusting for the cesarean section and chorioamnionitis rates showed no difference in the in-hospital mortality rate between the 3 periods. A recent systematic review showed no association between antenatal MgSO_4 treatment and neonatal mortality [46]. Thus, these antepartum and intrapartum factors might have contributed to the difference in the mortality rates between the study periods regardless of antenatal MgSO_4 usage. These limitations notwithstanding, the strength of the present study is that the impact of the adoption of antenatal MgSO_4 for fetal neuroprotection was clearly demonstrated through changes in MRI-related surgery in friable EPIs before and after the adoption period.

Conclusions

Our data showed that antenatal MgSO_4 use might increase the risk of MRI in EPIs, eventually requiring surgical intervention in a substantial number of cases. No previous studies have rigorously addressed the association of antenatal MgSO_4 use and MRI in these extremely tiny babies. Because antenatal MgSO_4 is widely used for fetal neuroprotection according to the recommendation by the ACOG and other committees [47], future studies to test the safety and benefit of antenatal MgSO_4 regarding the risk of undergoing surgery for MRI are urgently needed in EPIs with GAs of 25 weeks or less.

Statement of Ethics

The Institutional Review Board (IRB) of the Samsung Medical Center approved the study and waived the requirement for informed consent for the retrospective chart review (IRB No. SMC 2016-09-113).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Se In Sung, MD, PhD, contributed to research project conception, organization, and execution; statistical analysis execution; and manuscript preparation – writing of the first draft and review

and critique. So Yoon Ahn, MD, PhD, contributed to research project execution, statistical analysis design and review and critique, and manuscript preparation – review and critique. Suk-Joo Choi, MD, PhD, contributed to research project conception and organization and statistical analysis review and critique. Soo-young Oh, MD, PhD, contributed to research project conception and statistical analysis review and critique. Cheong-Rae Roh, MD, PhD, contributed to research project conception and statistical analysis review and critique. Misun Yang, MD, contributed to research project organization and execution and statistical analysis design and execution. Yun Sil Chang, MD, PhD, contributed to research project conception and organization and manuscript preparation – writing of the first draft and review and critique. Won Soon Park, MD, PhD, contributed to research project conception and manuscript preparation – review and critique.

Data Availability Statement

Data are available from the institutional ethics committee (contact via the corresponding author) for researchers who meet the criteria for access to confidential data.

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