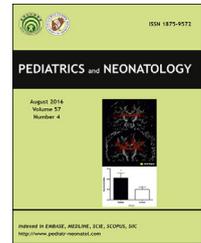


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Original Article

Maternal magnesium sulfate administration increases early-onset hyperkalemia risk in premature infants: A propensity score-matched, case-control study

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Key Words

magnesium sulfate;
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premature infant

Abstract *Background:* Magnesium sulfate (MgSO₄) is a common substance administered to pregnant women with preeclampsia or eclampsia to prevent and treat seizures or gestational hypertension. This study aimed to evaluate whether administering maternal magnesium sulfate increased the risk of early-onset hyperkalemia in preterm infants.

Methods: This single-center, propensity score-matched, case-control study examined preterm infants born within 24–36 weeks of gestation using electronic medical records between January 2015 and June 2019, in the Saitama City Hospital, Japan. We categorized infants according to their maternal MgSO₄ administration status. After adjusting for perinatal information and maternal treatment, we compared the incidence of the variables, including neonatal hyperkalemia, within 24 h after birth between the matched cohorts. All infants in Model 1 were analyzed separately, while in Model 2 infants with birth weight of less than 1000 g were excluded.

Results: We enrolled 421 infants (maternal MgSO₄ group, 124; control group, 297). Ninety-five infants in Model 1 and 86 in Model 2 were matched in each group using propensity scores, respectively. In the matched cohorts of both models, infants in the maternal MgSO₄ group had a higher hyperkalemia incidence than did those in the control group (42.1% vs. 7.4% in Model 1, 44.2% vs. 5.8% in Model 2, respectively; $p < 0.0001$). However, there was no relationship between the duration of intrauterine exposure to MgSO₄ and early-onset neonatal hyperkalemia incidence.

Conclusion: Our study demonstrated that maternal MgSO₄ administration, even for a short period of time, may increase the risk of early-onset hyperkalemia in preterm infants.

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Accordingly, physicians should be cautious when administering serum potassium to infants born to mothers administered MgSO₄, especially within 24 h after birth.

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Abbreviations

Cr	creatinine
EMRs	electronic medical records
FENa	fractional sodium excretion
GFR	glomerular filtration rate
K ⁺	potassium
MgSO ₄	magnesium sulfate
NOHK	non-oliguric hyperkalemia

1. Introduction

Magnesium sulfate (MgSO₄) is frequently administered to pregnant women with preeclampsia or eclampsia to prevent and treat seizures or gestational hypertension.¹ Furthermore, the Ministry of Health, Labour and Welfare of Japan approved MgSO₄ as a tocolytic agent covered by public health insurance. Hence, MgSO₄ is also administered to pregnant women at risk of premature labor due to uterine contractions in Japan.

MgSO₄ also affects fetal neuroprotection, especially in preterm infants.^{2,3} However, previous studies have indicated that intrauterine MgSO₄ may increase the risk of early complications, such as hypotonia, respiratory failure, feeding intolerance, intraventricular hemorrhage, cardiac failure, and patent ductus arteriosus, in newborns.^{4–6} Although many reports have examined the morbidity of infants born to mothers administered MgSO₄, to the best of our knowledge, there are only three reports regarding this matter written in English,^{7–9} including one case report on the serum potassium (K⁺) levels of premature newborns exposed to intrauterine MgSO₄. Nevertheless, the effects of MgSO₄ on newborns remain unclear. Therefore, we conducted a retrospective case–control study to determine whether antenatal MgSO₄ administration increased the risk of early-onset neonatal hyperkalemia in preterm infants. Moreover, we used propensity score-matching to eliminate the effects of confounders and hypothesized the mechanisms of MgSO₄ underlying the increase in the aforementioned risk by measuring serum and urine electrolyte samples.

2. Materials and methods

2.1. Study design and participants

We screened the Saitama City Hospital's electronic medical records (EMRs) for infants born at 24–36 weeks of gestation between January 2015 and June 2019. We observed 997 premature infants who were hospitalized in the neonatal intensive care unit or stepdown neonatal units during the study period (Fig. 1). The exclusion criteria were as follows:

1) the presence of samples in which hemolysis was suspected or those with a lack of at least two-point blood sampling; as in most cases with only single serum potassium data-assessing blood samples, the samples were taken immediately after birth, and the subsequent course could not be followed (n = 502); 2) infants born in and transferred from another hospital after birth due to various missing perinatal data (n = 46); 3) congenital malformations, including chromosomal abnormalities, congenital anomalies of the kidneys and urinary tract, and complex congenital heart diseases (n = 9); 4) infants requiring thoracotomy or laparotomy (n = 3); 5) persistent severe acidemia and/or hypothermia (n = 3); 6) hyperinsulinic hypoglycemia (n = 1); 7) mortality within 28 days of birth (n = 2); and 8) infants deemed to be inappropriate due to other issues (n = 10). The infants were categorized into either the MgSO₄ (n = 124) or control (n = 297) group, according to whether maternal MgSO₄ was administered.

2.2. Clinical evaluation of neonates and mothers

Mothers in the MgSO₄ group were administered a routine loading infusion of 4 g of MgSO₄ over 30 min, followed by a maintenance dose rate of 1–2 g/h (equivalent to 0.2–0.4 g/h of Mg).^{10,11} MgSO₄ administration was at a maximum dose of 2 g/h and continued until at least 4 h before delivery.¹² Neonatal hyperkalemia was defined as a serum K⁺ level of >6.0 mmol/L, with onset defined as the first time of recording such a measurement.^{9,13,14} We considered the peak serum K⁺ level within 24 h of birth as the highest serum K⁺ level because hyperkalemia in infants born to mothers with MgSO₄ was unexceptionally recognized within 24 h of birth in our preliminary study. From EMRs, we collected the perinatal information of the mothers and infants; the infants' vital signs, clinical symptoms, and urine volume; and laboratory data, including maternal serum electrolytes and urinary electrolytes. Additionally, we measured maternal serum Mg levels directly before, and on the delivery day. Infant urine output was measured by weighing wet diapers. Data are expressed in g/kg/h.

2.3. Statistical methods

Continuous variables are presented as mean ± standard deviation or median (interquartile range, IQR), and categorized data are presented as n (%). We compared the means between both groups using Student's *t*-test for normal distributions and the Mann–Whitney U-test for non-normal distributions. The Shapiro–Wilk test was performed to analyze the normality distribution of each variable. Fisher's exact test was performed to compare categorical data.

To overcome the bias regarding the different distribution of covariates among patients in both groups, we

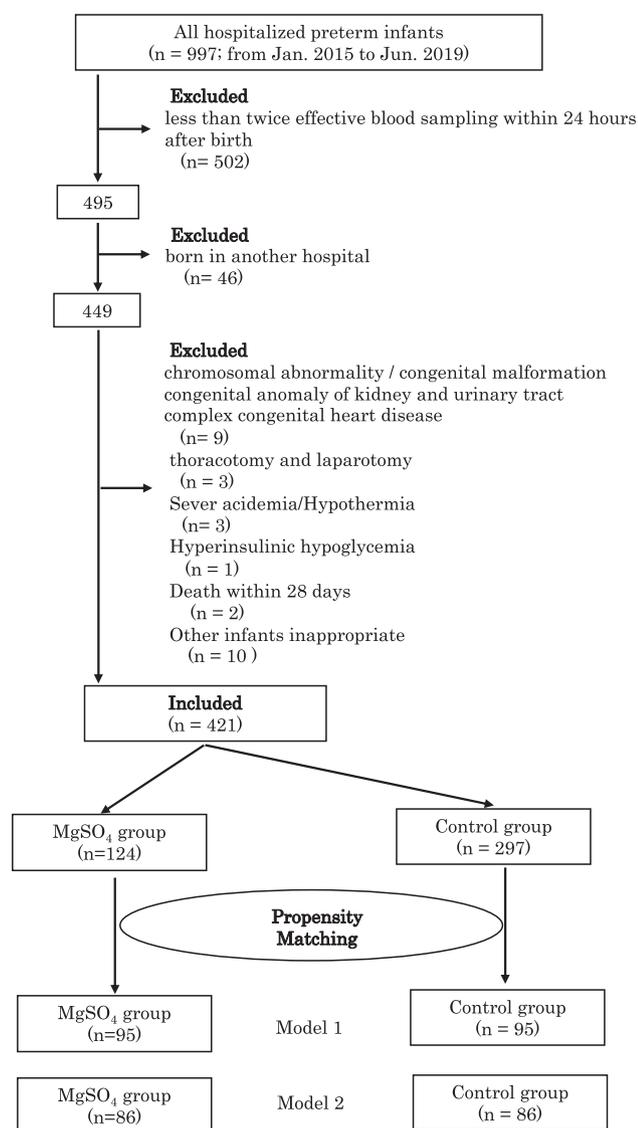


Figure 1 Flowchart representing infant selection and the exclusion processes in the study.

performed a propensity-score-matched analysis with 1:1 matching using a multiple logistic regression model to predict patient probability (Model 1). Propensity score matching was also performed on Model 2, excluding infants with a birth weight of less than 1000 g, since non-oliguric hyperkalemia is common in such infants.

We matched each case to a control having the most similar calculated propensity score with a caliper width of 0.2. Propensity scores were calculated using the following five matching variables according to their p-values on a univariate analysis: hypertensive disorders of pregnancy, maternal ritodrine administration, antenatal steroid use, gestational age, and infant birth weight.

Statistical analysis was performed using JMP version 15 (SAS Institute Inc., Cary, NC, USA). A p-value of <0.05 was considered statistically significant.

3. Results

Our patient selection flowchart is presented in Fig. 1. A total of 421 infants (MgSO₄ group, 124; and control group, 297) were evaluated. In this study, MgSO₄ was used to treat threatened premature labor or pregnancy-induced hypertension. The median duration of MgSO₄ treatment was 6.0 (IQR, 1.3–15) days. Table 1 presents the baseline maternal characteristics of each group. We performed a 1:1 propensity score-matching analysis to eliminate baseline variations using the abovementioned five variables because the different backgrounds of the MgSO₄ and control groups as observed on the univariate analysis may have affected outcomes. Finally, 95 neonates in Model 1 and 86 in Model 2 were selected to match each group (Table 2a and 2b). As expected, serum Mg levels were significantly higher in the MgSO₄ group than in the control group ($p < 0.0001$). In the matching cohort, hyperkalemia was significantly more prevalent in the MgSO₄ group than in the hyperkalemia group (42.1% vs. 7.4% in Model 1, 44.2% vs. 5.8% in Model 2, respectively; $p < 0.0001$). There were no significant differences in gestational age, birth weight, blood pressure, fractional sodium excretion (FENa), urine K⁺/creatinine (Cr), 5 min Apgar score, gender, respiratory distress, and urine output between groups.

Considering the effects of cumulative Mg doses caused by long-term maternal use, hyperkalemia incidence was compared between infants born to mothers administered MgSO₄ for >48 h and those born to mothers administered MgSO₄ for <48 h. The incidence was similar between groups (Table 3).

4. Discussion

In this study, we demonstrated an association between maternal MgSO₄ and early-onset neonatal hyperkalemia in preterm infants. The doses and injection methods of MgSO₄, and the serum Mg levels of infants in this study were similar to those reported in previous studies.^{15,16} We collected all sample data within 24 h of birth because hyperkalemia in infants born to mothers receiving MgSO₄ has been unexceptionally recognized within this time in our preliminary study.¹⁷ A propensity score-matching analysis revealed that maternal MgSO₄ increased hyperkalemia risk (Table 2). To our knowledge, only three studies in the literature in English, including one case report,^{7–9} have studied this topic. Moreover, several published papers and abstracts of case series on this topic in the literature in Japanese have indicated a correlation between antenatal MgSO₄ and neonatal hyperkalemia since Hosoda et al. reported the first case of antenatal MgSO₄-induced neonatal hyperkalemia in 2008.¹⁸

Furthermore, the case–control study by Aoki et al. comparing premature infants born before 32 weeks of gestation with non-oliguric hyperkalemia (NOHK) and those without NOHK confirmed that intrauterine MgSO₄ exposure, but not maternal ritodrine, was an independent risk factor for NOHK.⁹ Recently, Yada et al. have reported in a retrospective cohort study using a nationwide obstetrical database that maternal MgSO₄ together with ritodrine has a

Table 1 Baseline characteristics of the unmatched cohort.

	Unmatched cohort				
	MgSO ₄ group (n = 124)	%	Control group (n = 297)	%	p Value
Maternal age (years, median [IQR])	33 [28–37]		33 [30–36]		0.52
Multiparous	56	45.5	149	50.5	0.35
Multiple pregnancies	38	30.7	105	35.7	0.35
Gestational diabetes	2	1.6	15	5.1	0.10
Hypertensive disorders of pregnancy	31	25.0	22	7.4	<0.0001
Antenatal ritodrine use	94	75.8	194	65.3	0.035
Antenatal steroid use	95	76.6	108	36.4	<0.0001
Caesarean delivery	100	80.7	225	75.8	0.28
Gestational age (weeks, median [IQR])	33 [30–34]		35 [34–36]		<0.0001
Birth weight (gram, median [IQR])	1736 [1292–2135]		2164 [1856–2403]		<0.0001
Duration of magnesium sulfate use (days, median [IQR])	6 [1.25–15]				

Results are presented as numbers unless indicated otherwise. IQR, interquartile range.

synergic effect associated with neonatal hyperkalemia after birth in mid-to late-preterm infants born at 32–36 weeks of gestation, concluding that hyperkalemia incidence in women receiving MgSO₄ only was not different from those receiving ritodrine only.⁷

Our study initially targeted all infants born at 24–36 weeks of gestation (Model 1). Additionally, we performed an analysis that focused on infants with birth weights of 1000 g or more as Model 2. This was done because a wide range of variations, from extremely premature infants to near-term infants existed in the complete selected infant population, and generally, NOHK is not uncommon in extremely low birth weight infants. However, both models demonstrated that maternal MgSO₄ increased the risk of neonatal hyperkalemia after birth.

Our report also provides valuable data to hypothesize about the mechanisms of maternal MgSO₄ underlying newborn hyperkalemia incidence. To the best of our knowledge, this is the first report to analyze serum and urine samples. Currently, the mechanisms of maternal MgSO₄ underlying hyperkalemia incidence occurrence have not yet been fully elucidated. However, three hypotheses that for this mechanism have been proposed.^{8,9,19} First, renal K⁺ excretion decreases when the glomerular filtration rate (GFR) decreases. Second, distal tubular K⁺ excretion is compromised, and renal K⁺ clearance is low in newborns, even when corrected for low GFR. The third hypothesis is immature activity of Na⁺/K⁺-ATPase in cell membranes, which causes K⁺ to shift from the intracellular to the extracellular space. Furthermore, maternal serum Mg easily passes through the placenta, followed by fetal hypermagnesemia, possibly inhibiting the influx of K⁺ into cells by inhibiting Na⁺/K⁺-ATPase. Moreover, in a rabbit study, the mean activity of Na⁺/K⁺-ATPase of the proximal convoluted tubules during the first week of life has been reported to be one-third of the mean adult value.²⁰ Bara et al. have shown that Mg is a modulator of the Na⁺ and K⁺ ion transportation systems in numerous tissues, thereby revealing that extracellular Mg inhibits Na⁺/K⁺-ATPase at high concentration.²¹

However, we did not observe any significant differences in urine output and urine K/Cr between the MgSO₄ and control groups in this study. This result may exclude the possibility of the first and second aforementioned mechanisms.

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine support the short-term use of MgSO₄ (usually ≤48 h).^{7,22} The median duration of maternal MgSO₄ treatment was 6 days, since the leading societies for obstetrics in Japan have allowed long-term tocolysis unlike other countries. Aoki et al. suggested a dose-dependent relationship between maternal MgSO₄ administration and newborn hyperkalemia.²³ In this study, we analyzed data by dividing the patients into two groups, MgSO₄ treatment for <48 h and MgSO₄ treatment for >48 h groups (Table 3). Contradicting the study of Aoki et al., we did not observe any relationship between the duration of intrauterine exposure to MgSO₄ and the early neonatal hyperkalemia incidence, even though the treatment time in our study was similar to theirs. Although the reasons behind this difference are currently unclear, it should be noted that neonatal hyperkalemia was caused even by short-term MgSO₄ treatment. This may be clinically important since the short-term use of maternal MgSO₄ is widely administered for fetal neuroprotection, prevention or treatment of seizures, preeclampsia or eclampsia.²⁴

This study has several limitations. First, it was a single-center, retrospective, case–control study design, meaning that there is a possibility of selection bias; nevertheless, we adjusted for several confounders using the propensity score-matching. Furthermore, due to the retrospective nature of this study, the time to obtain clinical samples varied from patient to patient, and at least two blood samples were required. Second, we were unable to collect the urine laboratory data of all infants, which resulted in missing urine outputs, FENa, and urine K/Cr values, which had not been analyzed in previous reports.

Maternal administration of MgSO₄ is a risk factor for early neonatal hyperkalemia. This study showed that this phenomenon occurred following both the short- and long-term

Table 2 Neonatal clinical features of the matched cohort. (a) Model 1 (b) Model 2.

(a)							
	MgSO ₄ group (n = 95)	%	missing data	Control group (n = 95)	%	missing data	p value
Umbilical artery pH (mean ± SD)	7.33 ± 0.06		4	7.29 ± 0.12		11	0.02
Gestational age (weeks, mean ± SD)	33 ± 3.1		0	32 ± 3.2		0	0.71
Birth weight (grams, mean ± SD)	1836 ± 521		0	1824 ± 625		0	0.88
Lowest systolic blood pressure within 24 h (mmHg, mean ± SD)	54 ± 8.4		4	51 ± 7.8		0	0.09
Serum calcium (mg/dL, mean ± SD)	9.0 ± 0.74		1	9.3 ± 0.73		0	0.0012
Serum inorganic phosphorous (mg/dL, mean ± SD)	6.2 ± 0.98		8	5.4 ± 1.13		6	<0.0001
Serum alkaline phosphatase (U/L, mean ± SD)	805 ± 322		2	651 ± 212		3	0.0002
Serum magnesium (mg/dL, mean ± SD)	4.1 ± 1.2		11	2.2 ± 0.9		17	<0.0001
Serum sodium (mmol/dL, mean ± SD)	135.0 ± 4.7		4	136.9 ± 3.4		1	0.002
FENa (% mean ± SD)	1.83 ± 1.7		54	1.10 ± 0.6		85	0.18
urine K/Cr (mmol/L/g · Cr, mean ± SD)	1.34 ± 0.94		55	1.60 ± 0.39		85	0.40
Caffeine administration within 24 h of birth	20	21.1	0	9	9.6	0	0.04
5 min Apgar <7	17	17.8	0	10	10.5	0	0.21
Male gender	53	55.8	0	61	64.2	0	0.30
Respiratory distress	62	65.3	0	72	75.8	0	0.15
Urine output <1.0 (g/kg/hr)	17	18.1	1	17	18.1	1	1.00
Hyperkalemia (serum potassium >6.0 mmol/ dL)	40	42.1	0	7	7.4	0	<0.0001
(b)							
	MgSO ₄ group (n = 86)	%	missing data	Control group (n = 86)	%	missing data	p value
Umbilical artery pH (mean ± SD)	7.33 ± 0.07		1	7.30 ± 0.01		0	0.05
Gestational age (weeks, mean ± SD)	32.4 ± 3.0		0	32.9 ± 2.9		0	0.34
Birth weight (grams, mean ± SD)	1804 ± 547		0	1855 ± 562		0	0.55
Lowest systolic blood pressure within 24 h (mmHg, mean ± SD)	53 ± 8.5		0	52 ± 7.0		0	0.43
Serum calcium (mg/dL, mean ± SD)	9.0 ± 0.75		0	9.4 ± 0.71		3	0.005
Serum inorganic phosphorous (mg/dL, mean ± SD)	6.1 ± 1.02		6	5.3 ± 1.01		4	0.0001
Serum alkaline phosphatase (U/L, mean ± SD)	811 ± 306		1	652 ± 210		3	0.0001
Serum magnesium (mg/dL, mean ± SD)	4.1 ± 1.2		9	2.2 ± 0.8		19	<0.0001
Serum sodium (mmol/dL, mean ± SD)	134.6 ± 4.7		4	136.8 ± 3.2		2	0.0006

(continued on next page)

Table 2 (continued)

(b)	MgSO ₄ group (n = 86)	%	missing data	Control group (n = 86)	%	missing data	p value
FENa (%; mean ± SD)	1.8 ± 1.6		50	1.1 ± 0.6		75	0.20
urine K/Cr (mmol/L/g · Cr, mean ± SD)	1.3 ± 0.9		55	1.5 ± 0.4		85	0.47
Caffeine administration within 24 h s of birth	15	17.4	0	10	11.8	0	0.29
5 min Apgar <7	17	19.8	0	12	14	0	0.30
Male gender	48	55.8	0	56	65.1	0	0.21
Respiratory distress	57	67.1	0	65	75.6	0	0.22
Urine output <1.0 (g/kg/hr)	18	21.2	1	11	13.1	2	0.16
Hyperkalemia (serum potassium >6.0 mmol/ dL)	38	44.2	0	5	5.8	0	<0.0001

Results are presented as numbers unless indicated otherwise.

Table 3 Relationship between the duration of intrauterine exposure to MgSO₄ and early-onset neonatal hyperkalemia incidence.

	Infant serum K ⁺ > 6.0	Infant serum K ⁺ < 6.0	
Maternal MgSO ₄ treatment duration <48 h	14 (43.8)	18 (56.3)	32
Maternal MgSO ₄ treatment duration >48 h	36 (39.1)	56 (60.9)	92
	50	74	124

$p = 0.68$.

administration of maternal MgSO₄. Therefore, medical professionals should pay attention to the serum K⁺ of infants born to mothers receiving MgSO₄, especially within 24 h of birth.

Statement of ethics

This study protocol was approved by the ethics committee of the Saitama City Hospital, approval number A2811.

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Author contributions

S.O-S. and K.I. designed the study. S.O-S. performed statistical analyses, and K.I. and T.T. checked the statistical results. K.I. supervised the study. All authors reviewed the manuscript and played an important role in the critical revision of the manuscript.

Data availability statement

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

Declaration of competing interest

The authors have no conflicts of interest to declare.

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