CORRELATION BETWEEN MATERNAL CUMULATIVE DOSE OF INTRAPARTUM MAGNESIUM SULFATE AND CORD BLOOD MAGNESIUM LEVEL

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Abstract. Magnesium sulfate ($MgSO_4$) is given for several obstetric indications, even though its adverse effect on newly born infants is of major concern. The aim of this study was to investigate the relationship between maternal cumulative dose of magnesium sulfate (M-Mg) and cord blood magnesium (C-Mg) concentration. Sixty-three infants from 57 mothers who received intrapartum $MgSO_4$ were enrolled. The median gestational age was 37 weeks and the median 1- and 5-minute Apgar scores were both greater than 7. Median [interquartile range] M-Mg level and median duration of $MgSO_4$ infusion was 18.4 [9.9, 40.9] grams and 6.7 [2.9, 14.4] hours, respectively. The mean ± standard deviation C-Mg was 4.5±1.3 mg/dl. The relationship between M-Mg and C-Mg was non-linear, with a correlation coefficient (*r*) of 0.55. Eight infants (12.7%) developed apneic episodes. There were no significant differences in mean C-Mg and mean M-Mg levels between infants with and without apnea [5.2±1.9 *vs* 4.4±1.2 mg/dl; *p*=0.32; and, 17.8±22.6 *vs* 58.3±69.6 mg/dl; *p*=0.06, respectively]. In conclusion, no statistically significant association was found between M-Mg and C-Mg levels. Given the relatively small number of samples with high M-Mg level, the results of this study may not apply to infants whose mothers are exposed to prolonged maternal $MgSO_4$ administration.

Keywords: apnea, cord blood, intrapartum, magnesium level, magnesium sulfate, pregnancy

INTRODUCTION

Magnesium sulfate ($MgSO_4$) is given for several obstetric indications. Though commonly used for seizure prophylaxis in pregnancy-induced hypertension during the intrapartum period, $MgSO_4$ is also prescribed as a tocolytic agent and for prenatal neuroprotective purposes in very preterm infants (Elliott, 1983; Dommisse, 1990; Sibai, 2005; Doyle *et al*, 2009; Crowther *et al*, 2014; Oddie *et al*, 2015). Since indications for $MgSO_4$ in pregnant women occur mostly during the intrapartum period while the fetomaternal connection is still intact, potential adverse effects of $MgSO_4$ on infants are a major concern. Study in women with preeclampsia showed a relationship between maternal serum magnesium level and hypotonia or lowered Apgar scores in their offspring (Abbassi-Ghanavati *et al*, 2012; Basu *et al*, 2012; Girsen *et al*, 2015). Other studies in very preterm infants whose mothers received $MgSO_4$ administration for neuroprotection found no significant associations between $MgSO_4$ ex-

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posure and rates of respiratory depression or the need for intensive birth resuscitation (Johnson *et al*, 2012; De Jesus *et al*, 2015; Drassinower *et al*, 2015; Weisz *et al*, 2015).

Magnesium-related adverse events in newly born infants are blood concentration-dependent at birth (Abbassi-Ghanavati *et al*, 2012). Experimental study of perfused rat placenta demonstrated that magnesium is transported via a protein-binding mechanism, and it was found that umbilical blood level reached at least 70% of maternal blood level (Husain and Mughal, 1992; Nandakumaran *et al*, 2002). A cross-sectional study in preeclampsia women who received $MgSO_4$ found a strong positive correlation between maternal blood level and cord blood level (Boriboonhirunsarn *et al*, 2012). However in clinical practice, magnesium level in maternal serum or cord blood is not routinely monitored as a predictor of neonatal adverse effects unless a mother exhibits signs and symptoms of hypermagnesemia. Cumulative dose and duration of $MgSO_4$ administration prior to delivery have not been confirmed as being related to infant outcomes.

Accordingly, the primary objective of this study was to investigate the relationship between maternal cumulative dose of intrapartum $MgSO_4$ and cord blood magnesium (C-Mg) concentration. The secondary objective was to evaluate association between M-Mg and the development of neonatal apnea.

MATERIALS AND METHODS

This prospective cross sectional study was conducted in pregnant women who received intrapartum $MgSO_4$ administration at the Department of Obstetrics and Gynecology, Siriraj Hospital during the May 2015 to October 2015 study period. Siriraj Hospital is Thailand's largest tertiary referral center. Written informed consent was obtained from all participating patients prior to their inclusion in this study. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

During the study period until now, $MgSO_4$ was and remains the primary drug used for seizure prophylaxis in pregnancy-associated hypertension during the intrapartum period. $MgSO_4$ is also prescribed as a second choice tocolytic agent if a patient does not respond to betamimetics. $MgSO_4$ is not routinely used for its neuroprotection effects in very preterm infants. Our $MgSO_4$ administration protocol was initiated with a loading dose of 4 grams given intravenously, followed by 2 grams/hour as a continuous infusion. Pregnant women who received intravenous $MgSO_4$ during the intrapartum period were included. Women that were known to have any fetal condition that affects infant neurological ability were excluded, including congenital anomalies and major chromosome abnormalities. Women who were under general anesthesia were also excluded because neonatal respiratory depression could occur (Mattingly *et al*, 2003).

Following the third stage of delivery, 2 ml of umbilical venous blood was drawn by the obstetrician and sent within 2 hours to our hospital's central laboratory for magnesium level (C-Mg) analysis using the colorimetric end-point and modification of the calcium O-cresolphthaleincomplexone (OCPC) reaction technique. Cord blood samples from individual infants of multifetal pregnancy were collected and separately analyzed. A post-delivery medical chart review was conducted for each patient by one of the co-investigators (BY) to collect and record related demographic and clinical data, and the amount of $MgSO_4$ given to the patient hourly prior to delivery. Gestational age was recorded in complete weeks using either ultrasonographic assessment during the first trimester or by physical assessment. According to hospital policy, infants who are born to a

mother receiving $MgSO_4$ are admitted to one of our neonatal wards for careful observation and management. Both the data collector and the primary physicians were blinded to cord blood magnesium levels. However, infant caregivers knew patient history of maternal $MgSO_4$ administration, including duration of administration and cumulative dose. Ventilator support and oxygen therapy were ordered, as needed. Target peripheral oxygen saturation was 91% to 95% in preterm infants who received oxygen supplementation, and at least 95% in term infants. Diagnosis of apnea was made based on clinical observation of respiratory pause with concurrent desaturation or bradycardia. In this study, we focused only on apneic episodes that developed during the first 72 hours of life. Information regarding the presence of hypotonia was requested from the physician who performed the physical assessment upon admission.

Sample size calculation and statistical analysis

Data analysis was performed using SPSS Statistics version 20 (IBM, Armonk, NY). The sample size was calculated based on an expected correlation coefficient (*r*) of 0.8, a type I error of 0.05 (2-sided), and a type II error of 0.20. With a 20% increase in sample size to compensate for participant drop out, a total of 62 samples were required to test for a difference between the null hypotheses at an *r* of 0.6 and the alternative *r* of 0.8. M-Mg is defined as the total cumulative dose of $MgSO_4$ that the mother received during the intrapartum period, and C-Mg is defined as cord blood magnesium concentration. The relationship between M-Mg and C-Mg was visualized on a scatter plot, and Pearson correlation coefficient was calculated if the relationship appeared to be linear. Differences in M-Mg and C-Mg in infants who developed apnea versus those that did not develop apnea were compared using Mann-Whitney *U* test and Student's *t*-test, respectively. Statistical analysis using SPSS software version 20.0 (IBM, Armonk, NY). Data are reported as number and percentage, mean ± standard deviation, or median and interquartile range. A *p*-value <0.05 was considered to be statistically significant.

RESULTS

Seventy pregnant women who received intrapartum $MgSO_4$ administration during the study period gave their consent to participate in this study. A flow chart describing study enrollment and the umbilical cord blood collection process (63 cord blood samples from 57 mothers) is shown in Fig 1. Demographic and clinical characteristics of pregnant women (*n*=57) and infants (*n*=63) are given in Table 1. Forty-eight (84.2%) mothers received $MgSO_4$ for seizure prophylaxis from pregnancy-induced hypertension, while the other 9 (15.8%) women were given $MgSO_4$ due to preterm labor. The median [IQR; interquartile range] duration of $MgSO_4$ infusion was 6.7 [2.9, 14.4] hours. The M-Mg level ranged from 5 to 129 grams, with a median [IQR] level of 18.4 [9.9, 40.9] grams.

The median [IQR] gestational age of infants was 37.0 [33, 38] weeks. Among 28 preterm infants, 15 (26.3%) were born at less than 34 weeks gestation and the other 13 (22.8%) were born at 34 to 36 weeks gestation. Eleven (20.6%) infants had very-low birth weight (birth weight less than 1,500 grams) and 24 (38.1%) infants had low-birth weight (less than 2,500 grams). Both the 1- and 5-minute median Apgar scores were greater than 7. Three (4.8%) infants required intubation in the delivery suite. Hypotonia was noted in 15 (23.8%) infants. Eight (12.7%) infants developed at least one apneic episode during their first 72 hours of life and 3 (4.8%) infants had hypotension.

The mean ± standard deviation (SD) C-Mg level was 4.5±1.3 mg/dl. A non-linear relationship was observed between M-Mg and C-Mg, as demonstrated in Fig 2. A positive linear relationship presents from M-Mg of 5 grams

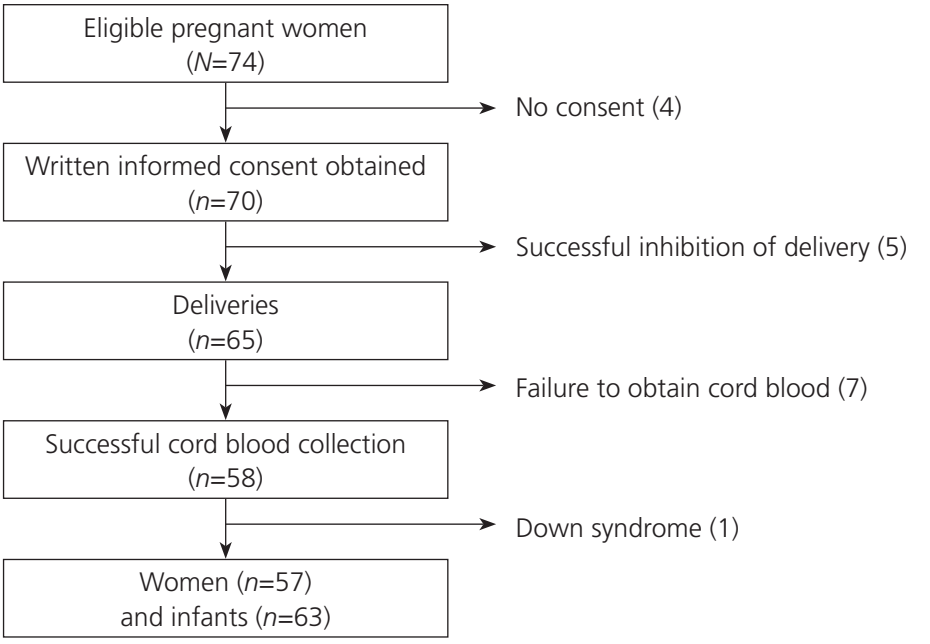

Fig 1– Flow chart describing study enrollment and the umbilical cord blood collection process.

Table 1
Demographic, anthropometric, and clinical characteristics of pregnant women (*n*=57) and infants (*n*=63).

Pregnant women	
Age (yrs), mean±SD	29.0±6.8
Maternal risk factors, *n* (%)	
Preeclampsia	42 (73.7%)
Diabetes	11 (19.3%)
Infants	
Birth weight (g), mean±SD	2,311.0±778.4
Male gender, *n* (%)	36 (57.1%)
Intubation during birth resuscitation, *n* (%)	3 (4.8%)
Gestational age (wks), median [IQR]	37.0 [33, 38]
1-minute Apgar score, median [IQR]	8 [7, 9]
5-minute Apgar score, median [IQR]	9 [9, 10]

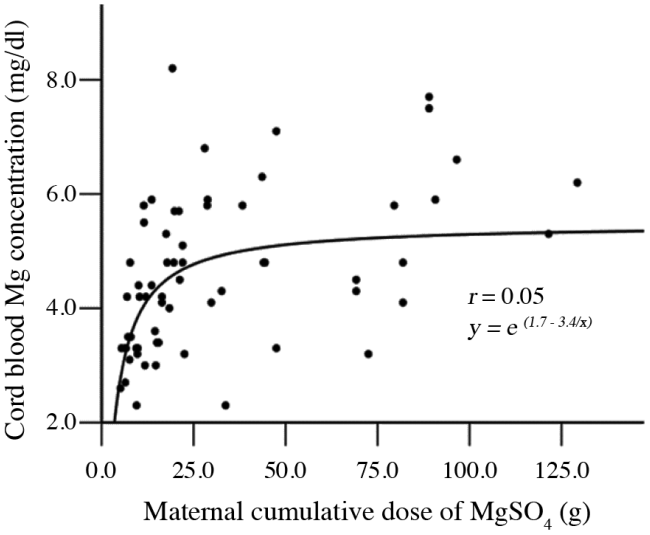

Fig 2– Scatter plot of maternal accumulative doses of magnesium sulfate administration relative to magnesium level in umbilical cord blood.

to an approximate value of 50 grams, but not at higher cumulative doses. Using non-linear regression analysis, the following equation was used to predict C-Mg level: $y = e^{(1.7 - 3.4/x)}$ (x = M-Mg, y = predicted C-Mg). The coefficient of determination (r^2) for this equation is 0.31 with an r of 0.55.

In order to explore the effect of duration of $MgSO_4$ administration on the relationship between M-Mg and C-Mg, scatter plots of the two variables at 4, 8, 12, and 24 hours prior to delivery were generated. The correlation coefficients were found to increase over time (0.2, 0.43, 0.53, and 0.64 at 4, 8, 12, and 24 hours, respectively). Eight (12.7%) infants developed at least one apneic episode during their first 72 hours of life. Infants who developed postnatal apnea had significantly lower gestational age and birth weight than infants that did not develop apnea (mean gestational age: 31.3±2.4 *vs* 36.5±2.7 weeks; $p<0.01$; and, birth weight: 1,307.5±444.9 *vs* 2,457.0±706.5 grams; $p<0.01$). No significant difference was observed for median M-Mg level between infants who had apnea versus those who did not have apnea (17.8±22.6 *vs* 58.3±69.6 mg/dl; $p=0.06$). Similarly, no significant difference was observed for mean C-Mg level between infants who had apnea versus those who did not have apnea (5.2±1.9 *vs* 4.4±1.2 mg/dl; $p=0.32$). Gestational age was found to be the only factor that significantly predicts apnea (odds ratio=0.41, 95% CI: 0.22-0.78). The adjusted odds ratio for apneic occurrence to birth weight and gestational age variables was 1.01 (95% CI: 0.98-1.04).

DISCUSSION

This study was conducted to explore and evaluate clinical concerns relating to the use of $MgSO_4$ in pregnancy according to a well planned blood sampling management. Specifically, we set forth to investigate the relationship between maternal cumulative dose of intrapartum magnesium sulfate (M-Mg) and cord blood magnesium (C-Mg) concentration with a prespecified sample sizes. $MgSO_4$ level in cord blood was chosen as a surrogate to reflect level of magnesium exposure in the infant. Cord blood samples collected immediately after delivery

were sent to our hospital's central laboratory for analysis.

In this study, we found no cumulative effect of maternal $MgSO_4$ on cord blood magnesium level, based on the observed non-linear relationship (r = 0.55). The ability to predict C-Mg from the non-linear regression model equation was also rather poor (r^2 = 0.31). Maternal cumulative dose is not a proper surrogate for indicating level of fetal exposure or for predicting an infant's risk of developing adverse outcomes. The results of the present study are consistent with those of previous studies that found poor to moderate correlation between maternal cumulative dose and either cord blood or infant's magnesium level (r range: 0.35-0.65) (Boriboonhirunsarn *et al*, 2012; Borja-Del-Rosario *et al*, 2014; Sherwin *et al*, 2014). The non-linear relationship could be due to the protein-binding mechanism of transport that becomes a protective factor when an abnormally high level of maternal serum magnesium is encountered (Brookfield *et al*, 2016). Moreover, the ability of maternal and fetal excretion via the urinary system acts as another balancing control (Gortzak-Uzan *et al*, 2005). It was reported that women with pregnancy-induced hypertension have decreased magnesium transfer to their fetus (Yang *et al*, 2014; Brookfield *et al*, 2016). This could be another explanation for the low to moderate correlation between M-Mg and C-Mg in many studies (Boriboonhirunsarn *et al*, 2012; Borja-Del-Rosario *et al*, 2014; Sherwin *et al*, 2014). However, the correlation seems to improve with longer duration of $MgSO_4$ administration. We found the r at 24 hours of $MgSO_4$ accumulation to be better than the correlation coefficients at 8 and 12 hours of accumulation. This finding indicates that the transfer of magnesium from the maternal side to the fetus increases as duration of exposure increases. A pharmacokinetic study of magnesium level in pregnant women found that blood level tended to be more stable after approximately 20 hours of $MgSO_4$ administration (Brookfield *et al*, 2016). Unfortunately and due to the limited number of infants that were exposed to maternal $MgSO_4$ administration for longer than 24 hours in this study, we were not able to evaluate association at a longer duration of $MgSO_4$ accumulation.

Regarding the use of M-Mg to predict the risk of adverse outcomes in infants, there was a trend toward higher M-Mg level in infants who developed apnea within 72 hours of life than in infants who did not develop apnea (p=0.06). C-Mg level did not show any significant association with development of apnea. Given the fact that all infants that developed apnea were the most premature of all infants in the study, the odds ratio for developing apnea after adjusting for gestational age and birth weight remained non-significant. We, therefore, conclude that the apneic episodes observed in this study were not caused by M-Mg. Accordingly, physicians can use $MgSO_4$ in indicated pregnant women safely and without concern for adverse effect to infants. However, our samples were collected from mothers who received cumulative $MgSO_4$ administration that ranged from 5 to 129 grams. Moreover, only 8 infants were delivered by mothers who received $MgSO_4$ for longer than 24 hours. Our results may not be generalizable to cases with long duration exposure to $MgSO_4$ and/or cases that received a very high cumulative dose of $MgSO_4$. That acknowledged, $MgSO_4$ is commonly used in pregnancy-induced hypertension and this indication for use normally does not require prolonged $MgSO_4$ administration.

In summary, the relationship between cumulative dose of $MgSO_4$ administered during the intrapartum period and cord blood magnesium level is non-linear. No significant correlation was observed between cumulative dose of maternal $MgSO_4$ and development of neonatal apnea. Due to limited number of high cumulative dose samples, application of our results to infants exposed to prolonged maternal $MgSO_4$ administration should be performed cautiously.

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CONFLICTS OF INTEREST

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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