

Research Article

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Magnesium Sulfate for Fetal Neuroprotection: Correlation between Maternal and Infant Serum Magnesium Concentrations

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Abstract

Background: Pregnant women at risk for preterm labor are commonly treated with magnesium sulfate (MgSO₄) for fetal neuroprotection. Randomized controlled studies have shown that this treatment is associated with decreased risk of cerebral palsy. Nevertheless, the optimal MgSO₄ dose for neuro protection has not been determined. Moreover, some studies suggest a potential toxic effect associated with high MgSO₄ treatment dose and that elevated serum infant Mg concentrations (iMgC) may also be associated with an increased risk for various morbidities and mortality.

Objective: To determine the correlation between maternal and infant serum Mg concentration among preterm infants exposed to MgSO₄ for neuroprotection. Finding a correlation may contribute to decision-making regarding continuation or discontinuation of maternal treatment prior to delivery.

Study Design: A total of 60 infants born at <32 weeks gestational age and exposed to MgSO₄ for neuroprotection were enrolled. The correlation between maternal serum Mg concentration (mMgC) drawn at <48 hours prior to birth and infant iMgC drawn immediately after birth was assessed. Additional factors such as total Mg treatment dose, interval between treatment initiation, treatment discontinuation and birth, as well as other maternal and infant characteristics were assessed as possible contributors.

Results: Complete data were available for 60 mother-infant dyads. Mean infant gestational age was 28.8 ± 2.23 weeks. Median and inter quartile range (IQR) of total MgSO₄ dose, mMgC and iMgC were 45g (25-88), 4.6 (4.1-5.3) and 3.8 (3.1-4.2) mg/dL respectively. Maternal Mg concentration and iMgC correlated significantly (r=0.433 p=0.001). In multiple regression analysis duration between first loading and birth (b=-0.031 p=0.004) and female gender (b=0.412 p=0.029) also correlated with iMgC.

Conclusion: Serum magnesium concentration in preterm infants treated for neuroprotection correlates with mMgC. This correlation may serve as a non-invasive tool for estimation of fetal Mg concentration in exposed fetuses during maternal treatment.

Keywords: Femur Fracture, Femoral Fracture, Child Abuse, NAI, Inflicted Injury, Australia

Abbreviations: iMgC: Infant Mg Concentrations; mMgC: Maternal Serum Mg Concentration; IQR: Interquartile Range; CP: Cerebral Palsy; ACOG: American College of Obstetrics and Gynecology; IVH: Intraventricular Hemorrhage; NICU: Neonatal Intensive Care Units

Background and Literature Review

In a retrospective case control study that was published by Nelson et al. [1] in 1995, a decreased risk for cerebral palsy (CP) was demonstrated among preterm infants exposed to tocolytic MgSO₄ compared to those not exposed. Subsequently, several large prospective studies and a systematic review of the literature reinforced these findings, advocating MgSO₄ administration to reduce the occurrence of CP and death among preterm infants [2-5]. In 2010, the American College of Obstetrics and Gynecology (ACOG) published its recommendations which supported the use of MgSO₄ for fetal neuroprotection. It also advocated the necessity of defining treatment protocols and

appropriate Mg dosage, as those used for neuroprotection have been adopted empirically from protocols used for seizure prophylaxis in preeclampsia [6]. Interestingly, studies that used a low total dose of MgSO₄ (<10 g) did not show any significant adverse effects to exposed infants, while when higher doses were used, mainly for tocolysis, a trend towards increased perinatal mortality was demonstrated. Therefore the use of MgSO₄ for tocolysis is currently no longer recommended [3,4,7-12]. Other recent studies that investigated early outcomes among preterm infants treated for neuroprotection demonstrated an association with an increased risk for intraventricular hemorrhage (IVH), impaired intestinal blood flow in the first few hours after birth, spontaneous intestinal perforation, increased admission to

neonatal intensive care units (NICU) and need for intubation [13-16]. Taken together, these findings suggest a possible therapeutic window for Mg, beyond which the neuroprotective effect diminishes and adverse toxic effects occur. Currently, MgSO₄ treatment for neuroprotection is commonly given when imminent preterm labor is suspected. Nevertheless, studies investigating the optimal total dose, optimal iMgC and appropriate timing for achieving neuroprotection are lacking. Magnesium has been shown to be transferred to the fetus through the placenta, so that high maternal concentrations may theoretically result in fetal hypermagnesemia [17]. A first step toward understanding the above and also toward controlling iMgC for safety reasons would be to confirm a correlation between maternal and infant serum Mg concentration as well as to identify additional factors that may affect this correlation. Such a correlation could serve as an indirect tool to monitor exposed fetuses. The current study aimed to answer these questions.

Study Design

This study is a retrospective chart review of infants admitted to a single tertiary care NICU between January 2012 and February 2015. Included in the study were all preterm infants born <32 weeks' gestation during the study period without congenital anomalies or known genetic disorders whose mothers were treated with MgSO₄ for the indication of neuroprotection during pregnancy. Only those whose mothers had MgSO₄ infusion and documented serum Mg concentration within <48 hours prior to delivery and also documented iMgC within two hours after birth were included. Pregnant women at imminent risk of preterm delivery receive an intravenous loading dose of 5 g MgSO₄ over 30 minutes, followed by continuous infusion of 2 g per hour for 12 hours. If delivery does not occur within 12 hours, treatment is discontinued. Infusion may be resumed if imminent labor is again perceived. If more than six hours elapsed since discontinuation of the initial infusion, an additional loading dose is given. Maternal Mg concentration is drawn 6-7 hours after initiation of treatment and repeated again after 24 hours if treatment has been continued. According to hospital laboratories, normal serum Mg concentration ranges from 1.9 to 2.7 mg/dL. Infant Mg concentration is routinely screened immediately after initial stabilization as part of admission blood workup (among those who were exposed to magnesium). This practice was initiated in our NICU due to the known adverse effects associated with elevated Mg concentrations in adults.

Data Collection and Neonatal Outcomes

Data were collected from medical maternal and infant charts using a specific data collection form and included the following: date of first maternal loading dose and first mMgC (6 hours after loading dose), number of total loading doses, total Mg dose until delivery, last available mMgC. Also documented were indication of which MgSO₄ treatment was given, multiple pregnancy, maternal age, gestation number and mode of delivery. Infants'

characteristics included gender, gestational age, birth weight, Apgar scores and iMgC after birth. This study was approved by the hospital Institutional Review Board. The Hospital Ethics Committee waived the need for informed consent, as this was an observational audit of normal practice.

Statistical Analysis

Data were summarized using central tendency (mean, median), spread tendency (standard deviation, inter quartile range, minimum and maximum) and proportions as appropriate in order to characterize the study cohort. Pearson correlation was constructed to determine the direction and magnitude of the association between maternal and infant Mg concentrations. A multiple linear stepwise regressions including different potential covariates such as maternal and infant characteristics to predict infant Mg concentrations was conducted. All statistical analyses were performed using SPSS version 21. A P-value of <0.05 was considered statistically significant.

Results

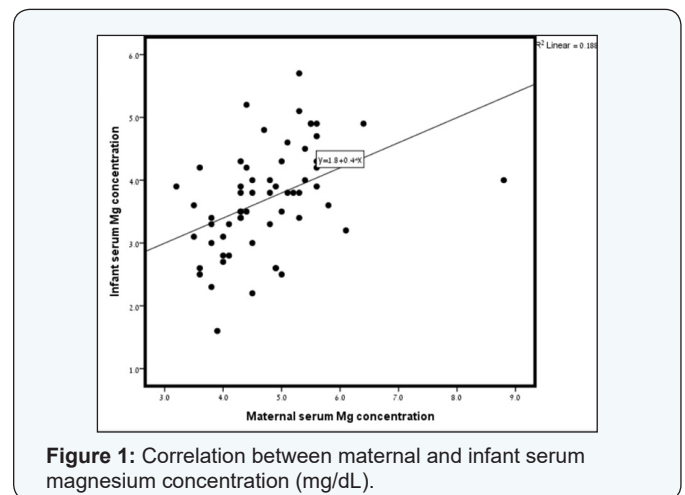


Figure 1: Correlation between maternal and infant serum magnesium concentration (mg/dL).

A total of 346 infants were born during the study period at <32 weeks gestational age. Magnesium sulfate was administered to 232 (67.0%) mothers. A total of 60 mother-infant dyads met the study criteria i.e., MgSO₄ was administered for neuroprotection within 48 hours prior to delivery, mMgC were documented during this period and iMgC was documented after birth. Table 1 shows baseline characteristics of the participants. Table 2 shows MgSO₄ treatment characteristics as well as iMgC and mMgC. The median (IQR) maternal and iMgC were 4.6 (4.1-5.3) and 3.8 (3.1-4.2) mg/dL, respectively. We found positive and significant correlation between mMgC and iMgC ($r = 0.0443$ $p = 0.001$) (Figure 1). However, the explained variability was $R^2 = 0.188$ (18.8%), indicating that other variables may also be needed to explain the iMgC. Multivariate analyses were performed using stepwise linear regression to estimate whether selected clinical and demographic characteristics may further predict the observed variability in iMgC. (The following variables were included in the

multivariate model: last documented mMgC, interval between last documented maternal mMgC and birth, mMgC six hours from first loading, total maternal MgSO₄ dose, duration between withholding treatment and delivery, interval between first Mg loading dose and delivery, number of maternal loading doses, maternal age, multiple gestation, mode of delivery, gestational age, infant gender, Apgar scores at 1 min. Table 3 displays the results of the final analysis (final step). The residual unexplained variability increased ($R^2 = 0.34$). Preterm infants whose mothers had a higher mMgC, a shorter time interval between first Mg loading dose and delivery and female gender had a higher Mg concentration.

Table 1: Maternal and infant characteristics.

| | N=60 |
|-------------------------------|-----------------------|
| Maternal Age (y) | 30.2 ± 5.9 |
| Primigravida | 29 (48.3) |
| <i>In vitro</i> fertilization | 17 (28.3) |
| Prenatal steroids | 54 (90.0) |
| Cesarean delivery | 30 (50.0) |
| Multiple | 30.2 ± 5.9 |
| Birth weight (g) | 28 (46.7) |
| Gestational age | 1113 ± 375 |
| Male/female | 28.8± 2.2 |
| Apgar 1 min <6 | 27 (45.0) / 33 (55.0) |
| Apgar 5 min <6 | 11 (18.3) |
| Maternal Age (y) | 0 |

Data are presented as mean ± SD or N (%)

Table 2: Magnesium Sulfate treatment characteristics.

| Variable | Median (IQR) |
|---|------------------|
| Total mMg dose (gr) | 45.0 (25.0-88.7) |
| mMg concentration 6 h from first loading dose (mg/dL) | 4.4 (3.9- 4.9) |
| mMg concentration < 48 h prior to delivery (mg/dL) | 4.6 (4.1-5.3) |
| Infant Mg level after birth (mg/dL) | 3.8 (3.1-4.2) |
| Number of loading doses | 1.0 (1.0-2.0) |
| Interval between first loading dose and birth (day) | 2 (1.0-11.0) |
| Interval between last mMg concentration and birth (h) | 5 (9-14.25) |

Table 3: Predictors of infant serum Mg concentration using multiple linear regression.

| Variables | Standardized Coefficients- Beta | p-Value |
|---|---------------------------------|---------|
| Maternal Mg concentration prior to delivery | 0.435 | <0.001 |
| Interval between first loading dose and birth | -0.031 | 0.004 |
| Infant gender | 0.412 | 0.029 |
| | | |

Adjusted for Maternal Mg concentration 6h from first loading, total maternal dose, duration between withholding treatment and delivery, number of loading doses, maternal age, twin, *In vitro* fertilization, gestational age, type of delivery, Apgar at 1 minute, Apgar at 5 minutes and birth weight.

Discussion

The present study is the first to provide evidence for a correlation between maternal and infant serum Mg concentrations among preterm infants (< 32 weeks GA) exposed to MgSO₄ for neuroprotection. It is also the first to account for detailed factors associated with maternal treatment, such as total exposure dose and time interval between initiation and withholding treatment and birth. The statistical analysis points to substantial variability ($R^2 \sim 0.19$), which could be explained by the contribution of additional factors. Gender and time interval between first loading dose and birth were identified as significant contributors, thus increasing the R^2 value to 0.34. The importance of the above findings is twofold: First, they provide evidence that maternal blood sampling during MgSO₄ infusion may be useful in predicting iMgC when given for neuroprotection. Second, these findings may be used for future studies targeted to define the optimal iMgC for achieving fetal neuroprotection on the one hand and preventing toxic effect on the other. A correlation between maternal and cord/infant serum Mg concentration with a similar high unexplained variability ($R^2 = 0.19$) has already been demonstrated in two studies [18,19]. In these studies, however, MgSO₄ was administered for a different indication (i.e., preeclampsia), and the study population was born at an older gestational age. Sherwin et al. [19] found that the high unexplained variability improved after accounting for other confounders, so that cesarean section and multiple gestations were identified as associated with lower iMgC while pregnancies complicated by preeclampsia resulted in a higher iMgC concentration. No association between iMgC and maternal BMI or weight change during pregnancy was demonstrated. Sherwin did not account for factors associated with maternal treatment regimen as potential confounders. Boriboonhirunsarn et al. [18] studied the correlation between maternal and cord blood Mg concentration. Like the study by Sherwin, in this study MgSO₄ was used to treat preeclampsia and most infants were not preterm (mean age of 38.1 weeks). Cord blood was sent immediately after delivery for Mg analysis. A positive direct

correlation was found between total maternal and cord blood Mg concentration, total treatment dosage and duration of infusion. We also identified the duration between treatment initiation and birth as correlating with iMgC but not total exposure dose. An explanation of the absence of such a correlation may rely on the difference between the treatment protocols for preeclampsia vs. neuroprotection. While the preeclamptic women in the Boriboonhirunsarn study were treated continuously for a mean duration of five hours, those treated for neuroprotection were treated intermittently for a mean of three days. It is possible that treatment-free intervals which occur frequently when MgSO₄ is given for neuroprotection caused fluctuations in blood Mg concentration.

Fetal Mg balance has not been thoroughly studied due to the apparent ethical and technical issues in doing so (i.e., direct measurement of fetal Mg level would require fetal blood sampling). This balance is thought to be regulated by a number of mechanisms, including placental transport and reabsorption in the fetal kidney [20]. Fetal serum Mg concentration has been shown to increase within one hour of maternal treatment with MgSO₄ for tocolysis, with urinary excretion via the fetal kidney leading to an amniotic fluid buildup three hours after exposure that never exceeding the concentration measured in maternal serum [17,21]. Gestational age was not found to correlate with iMgC as fractional excretion of Mg was the same in premature infants as in term infants (<2%) [22]. The present study supports the above finding, as iMgC was also not found to be associated with birth weight or gestational age. The association between iMgC and gender has not been described previously. Additional studies are required to clarify this finding. The “best MgSO₄ dosage” or “optimal iMgC” for achieving neuroprotection has not been defined, nor has the exact mechanism through which magnesium decreases risk of developing cerebral palsy. A putative therapeutic window for Mg has been suggested, below which there is no measurable effect and above which there is no added value though fetal toxicity may take place [10,11,23]. In animal studies a high dose of MgSO₄ has been suggested to cause neuronal death in various brain areas [24]. In preterm infants not exposed to MgSO₄, increased baseline serum Mg concentrations were associated with unfavorable developmental outcome [12]. In the present study, the median Mg exposure dose was high compared to the one used in published randomized trials (45vs. 4-31gr) that investigated MgSO₄ treatment for neuroprotection [3,4,7]. In this study, we calculated total Mg exposure dose as the amount of Mg given to the women from the first loading dose until the time of birth. Although our institutions’ MgSO₄ protocol for neuroprotection is based on protocols published in the literature, a higher total exposure dose was achieved. In clinical practice high total exposure doses are unavoidable as the total number of allowed repeated doses has not been defined and repeated treatment courses are indicated as long as there is a threat of premature delivery. This practice exposes fetuses to repeated courses of MgSO₄, resulting in total exposure doses significantly higher than those studied. These data are alarming in light of the

gap in knowledge regarding the optimal treatment dose and the evidence for toxicity associated with high exposure dose. The current study did not find a correlation between the number of loading doses or total exposure dose and iMgC. The above highlights the importance of long-term follow-up studies of infants exposed to repeated Mg treatment and in relation to total Mg dose. Our study has several limitations. The major limitation is its relatively small sample size and the retrospective method of data collection. In addition, there was variability between the mothers in terms of total Mg treatment dosage and timing of mMg sampling in relation to the time of delivery. As timing of preterm delivery usually cannot be predicted, this obstacle probably cannot be overcome. Nevertheless, several biases were eliminated. The study cohort included only preterm neonates born prior to 32 weeks. It also included only those treated with MgSO₄ for the indication of neuroprotection. We also excluded mothers that were not exposed to treatment within 48 hours prior to delivery, thus reducing some of the biases inherent in the study method.

Summary and Conclusion

In summary, our data show that there is a correlation between mMgC and iMgC among preterm infants exposed to MgSO₄ for neuroprotection. Additional variables, among them those associated with maternal treatment regimen, were also shown to potentially affect iMgC. We have also shown that in practice fetuses are exposed to much higher doses than those studied in randomized trials. Taken together these data point out the ACOG’s call for the need of further study of optimal magnesium protocol and dosage when given for neuroprotection.

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