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Correlation of Total Dosage and Duration of Magnesium Sulfate Administration in Pregnant Women Associated with Magnesium Levels in Umbilical Cord Blood

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ABSTRACT

Objectives: To evaluate the correlation between the total dosage and duration of maternal magnesium sulfate ($MgSO_4$) administration and umbilical cord blood magnesium levels, and to determine clinically useful cutoff values associated with elevated neonatal magnesium concentrations.

Materials and Methods: The cross-sectional study included 47 pregnant women ≥ 24 weeks' gestation who received $MgSO_4$ following the regimen of loading dose 4 grams, followed by a maintenance dose of 2 gram/hour intravenously at Rajavithi Hospital. Maternal serum magnesium was collected within 1 hour before delivery, and umbilical cord blood samples were obtained immediately after placenta delivery. Total $MgSO_4$ dose, infusion duration, and biochemical parameters were recorded. Pearson's correlation, linear regression, and receiver operating characteristic (ROC) curve analysis were performed.

Results: Total dosage of $MgSO_4$ and infusion duration showed significant positive correlations with cord blood magnesium levels ($r = 0.65$, $p < 0.001$). Maternal serum magnesium demonstrated the strongest correlation ($r = 0.73$, $p < 0.001$) and remained an independent predictor in the multivariable model together with maternal serum creatinine. ROC analysis identified two clinically useful cutoff values for predicting cord magnesium ≥ 5 mg/dL: a total dose of 12.8 g (sensitivity 100%, specificity 71.4%) and an infusion duration of 280 minutes (sensitivity 100%, specificity 68.6%). A higher level of exposure, corresponding to 31.3 g of total dose or 855 minutes of infusion, yielded 100% specificity.

Conclusion: Both the total dosage of $MgSO_4$ and infusion duration were strong predictors of neonatal cord blood magnesium levels. The identified cutoff values provided practical guidance for assessing the risk of elevated neonatal magnesium exposure and support targeted newborn surveillance following maternal $MgSO_4$ therapy.

Keywords: magnesium sulfate, umbilical cord blood, pregnancy.

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ความสัมพันธ์ของปริมาณทั้งหมดและระยะเวลาในการให้แมกนีเซียมซัลเฟตในหญิงตั้งครรภ์ ที่สัมพันธ์กับระดับแมกนีเซียมในเลือดจากสายสะดือ

สโรชา ปริยานนท์, ปรุฬห์ สนุ่นรัตน์

บทคัดย่อ

วัตถุประสงค์: *เพื่อประเมินความสัมพันธ์ระหว่างปริมาณทั้งหมดและระยะเวลาในการให้ยาแมกนีเซียมซัลเฟตของมารดากับระดับแมกนีเซียมในเลือดสายสะดือ และเพื่อหา Cutoff ที่มีความหมายทางคลินิกที่สัมพันธ์กับระดับแมกนีเซียมทารกแรกเกิดที่สูง*

วัสดุและวิธีการ: *การศึกษาแบบตัดขวาง รวมหญิงตั้งครรภ์ 47 ราย อายุครรภ์ ≥ 24 สัปดาห์ซึ่งได้รับแมกนีเซียมซัลเฟตตามแนวทางการให้ยาปริมาณเริ่มต้น 4 กรัม และให้คงระดับขนาด 1 กรัมต่อชั่วโมงทางหลอดเลือดดำที่โรงพยาบาลราชวิถี เลือดมารดาสำหรับวัดแมกนีเซียมถูกเก็บภายใน 1 ชั่วโมงก่อนคลอด และเลือดสายสะดือถูกเก็บทันทีหลังรกคลอด มีการบันทึกขนาดยารวม ระยะเวลาให้ยา และพารามิเตอร์ทางชีวเคมี มีการวิเคราะห์สหสัมพันธ์ การถดถอย และ receiver operating characteristic (ROC) curve*

ผลการศึกษา: *ปริมาณทั้งหมดของแมกนีเซียมซัลเฟตและระยะเวลาในการให้ยา แสดงความสัมพันธ์เชิงบวกอย่างมีนัยสำคัญ กับระดับแมกนีเซียมในเลือดสายสะดือ ($r = 0.65$, $p < 0.001$) ระดับแมกนีเซียมในเลือดของมารดา แสดงความสัมพันธ์ที่สูงที่สุด ($r = 0.73$, $p < 0.001$) และยังคงเป็นปัจจัยทำนายอิสระในแบบจำลองหลายตัวแปร ร่วมกับระดับครีอะตินีนของมารดา การวิเคราะห์ ROC ระบุ cutoff ที่มีความหมายเชิงคลินิกสองค่า สำหรับการทำนายระดับแมกนีเซียมในสายสะดือที่ ≥ 5 mg/dL ได้แก่ ขนาดยารวม 12.8 กรัม (ความไวร้อยละ 100 ความจำเพาะร้อยละ 71.4) และระยะเวลาให้ยา 280 นาที (ความไวร้อยละ 100 ความจำเพาะร้อยละ 68.6) ระดับการได้รับยาที่สูงกว่า ซึ่งเทียบเท่ากับขนาดยารวม 31.3 กรัม หรือระยะเวลาให้ยา 855 นาที ให้ค่าความจำเพาะร้อยละ 100*

สรุป: *ทั้งขนาดยาแมกนีเซียมซัลเฟตรวมและระยะเวลาให้ยา เป็นตัวทำนายที่สำคัญของระดับแมกนีเซียมสายสะดือทารก ค่า cutoff ที่ระบุได้ให้แนวทางที่สามารถใช้จริงในคลินิก สำหรับประเมินความเสี่ยงของแมกนีเซียมสูงในทารก และสนับสนุนการเฝ้าระวังทารกแรกเกิดอย่างเฉพาะเจาะจงหลังมารดาได้รับแมกนีเซียมซัลเฟตของ*

คำสำคัญ: *แมกนีเซียมซัลเฟต, เลือดจากสายสะดือ, การตั้งครรภ์*

Introduction

Magnesium sulfate ($MgSO_4$) has been widely utilized in obstetrics for various clinical indications. It is most commonly administered for the prevention of seizures in pregnant women with hypertensive disorders or preeclampsia. Additionally, it is used as a tocolytic agent to inhibit uterine contractions and as a neuroprotective agent for preterm neonates[1-3].

The use of magnesium sulfate during the peripartum period has become increasingly common, as magnesium ions can cross the placenta and are rapidly absorbed into fetal tissues[4]. A previous study, however, found that maternal administration of magnesium sulfate is the most common cause of neonatal magnesium toxicity. Following intravenous administration in pregnant women, approximately 40% of circulating magnesium ions bind to plasma proteins, while the unbound fraction distributes into the extravascular extracellular compartment or, various maternal tissues, crossing the placenta into the fetal tissues and amniotic fluid[5, 6].

Magnesium exerts its pharmacologic effect primarily by inhibiting acetylcholine release at the neuromuscular junction, particularly affecting the respiratory muscles, although it does not have a direct central nervous system effect. Specifically, magnesium sulfate reduces the amount of acetylcholine released, decreases the sensitivity of the postsynaptic membrane, and inhibits muscle membrane excitability, resulting in muscle weakness and respiratory depression[7].

Neonatal outcomes following maternal magnesium sulfate administration warrant close monitoring, even though, the effects of magnesium sulfate on neonates remain unclear. Several studies have reported elevated serum magnesium levels in neonates whose mothers received magnesium sulfate during pregnancy[8-10]. Furthermore, neonates exposed to antenatal magnesium sulfate may develop hypermagnesemia, respiratory depression, apnea, cyanosis, decreased muscle tone (hypotonia), low apgar scores and increased rates of neonatal intensive care unit (NICU) admission and length of stay (LOS)[9, 11-14]. Neonatal magnesium sulfate levels above 2.5 mmol/L (~ 6.08 mg/dL) may increase the risk of hypotonia, respiratory depression, and NICU admission[15, 16]. Umbilical cord blood magnesium levels exceeding 4.5 mEq/L (~5.4 mg/dL) are associated with a higher risk of immediate neonatal death.

A recent study demonstrated a significant positive correlation between the cumulative dose of magnesium sulfate and maternal serum magnesium levels with cord blood magnesium levels in neonates[17]. Cord blood samples may be collected from either the umbilical artery or vein, as the magnesium concentrations in both vessels have been shown to be comparable[18]. In this study, samples were collected from the umbilical vein due to its larger size and ease of identification.

The primary objective of this research was to investigate the correlation between the total dose and duration of magnesium sulfate administration during pregnancy before delivery and the umbilical cord blood magnesium levels in neonates. The secondary objective was to find the cutoff of cumulative dose $MgSO_4$ and the duration of $MgSO_4$ administration that will cause cord blood magnesium level ≥ 5mg/dL which our research assumed that this value may cause poor neonatal outcomes. The findings aim to support neonatal surveillance and preparedness for potential complications associated with hypermagnesemia after birth.

Materials and Methods

This was a cross-sectional study conducted at Rajavithi Hospital between July 2024 and June 2025. The study was registered with the Research Ethics Committee of Rajavithi Hospital (Reference number 131/2567, issue on June 25th, 2024) before data collection started. The inclusion criteria were women with singleton pregnancy ≥ 24 weeks gestation who

received intravenous magnesium sulfate before delivery, were aged ≥ 18 years, and had an understanding of written or spoken Thai. The exclusion criteria were pregnant people who had renal impairment (serum creatinine > 1.0 mg/dL) and failure to collect cord blood. All participants provided informed consent. $MgSO_4$ was used for treatment according to obstetric indications (such as prevention of eclampsia, inhibition of labor, and fetal neuroprotection). All patients received a standard loading dose of $MgSO_4$ 4 g, followed by a continuous infusion at 2g/h until delivery. The cumulative dose of $MgSO_4$ before delivery was calculated as the sum of the loading dose and the total amount given during the maintenance infusion, using the following formula: Cumulative dose (g) = loading dose (g) + [infusion rate (g/h) x infusion duration (h)]. The duration of $MgSO_4$ infusion was defined as the time from administration of the loading dose until delivery. In cases with interruptions or multiple infusion segments, each segment was calculated separately and summed. Any additional bolus doses were also included in the total cumulative dose. Maternal bloods for magnesium levels were collected within 1 hour before delivery[23]. Umbilical cord bloods were collected immediately from the umbilical vein, in the part that connects to the placenta, after placental delivery, and amounts of 4-6 ml were then immediately sent for magnesium level testing. All magnesium serums were analyzed using the Alinity ci-series Operation Manual. Baseline characteristics, including obstetric data, total dosage, and duration of $MgSO_4$ were recorded, along with neonate data.

The sample size was calculated based on the formula for correlation coefficient analysis. A previous study by Ahmed Altraigey et al[17] was used as a reference, in which the correlation coefficient (r) was reported as 0.65. With a significance level (α) set at 0.01 and a statistical power of 99%, the sample size was determined to be 47 participants.

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 26.0; IBM Corporation, Armonk, NY). Descriptive statistics, including mean, standard deviation, number, and percentage were used to describe baseline characteristics and related data. Pearson's correlation and linear regression were used to determine the correlation between total dosage of $MgSO_4$ and cord blood magnesium, and a p value < 0.05 was considered to be statistically significant.

Results

Forty-seven pregnant women were enrolled. Table 1 shows the baseline characteristics of the participants, whose mean maternal age was 30.5 ± 7.6 years. The average gestational age at delivery was 35.1 ± 3.4 weeks, indicating that the majority of participants (61.7%) delivered preterm (< 37 weeks). Mean BMI was 30.6 ± 5.8 kg/m², and the mean birth weight was 2,201.3 ± 738.8 grams, reflecting the high proportion of preterm births.

More than half of the women (55.3%) were nulliparous, and the vast majority (87.2%) delivered via cesarean section.

Table 2 shows that the median total dosage of $MgSO_4$ was 12.3 grams and the median duration of $MgSO_4$ infusion was 280 minutes. Maternal serum magnesium levels at delivery averaged 5.3 ± 1.6 mg/dL, while umbilical cord blood magnesium levels were slightly lower, with a mean of 4.4 ± 1.1 mg/dL (range 2.9-7.2 mg/dL).

As shown in Table 3, the total dosage of $MgSO_4$ and duration of $MgSO_4$ infusion showed a strong positive correlation with umbilical cord blood magnesium levels ($r = 0.65$, $p < 0.01$). Maternal serum magnesium levels were highly predictive of cord blood levels ($r = 0.73$, $p < 0.01$). Fig. 1 and Fig. 2 illustrate significant positive linear correlations between maternal $MgSO_4$ exposure and umbilical cord blood magnesium levels. Increasing total $MgSO_4$ dosage (Fig. 1) and longer infusion duration (Fig. 2) were both associated with higher cord magnesium concentrations.

Table 1. Baseline characteristics of pregnant women and neonates (n = 47).

Characteristics	mean ± SD (min-max)
Maternal age (years)	30.5 ± 7.6 (18 - 45)
Gestational age (weeks)	35.1 ± 3.4 (26.4 - 40.0)
Body mass index (kg/m^2)	30.6 ± 5.8 (21.9 - 49.6)
Parity, n (%)	
Nulliparity	26 (55.3)
Multiparity	21 (44.7)
Indication for $MgSO_4$ administer, n (%)	
Hypertension in pregnancy	47 (100)
Route of delivery, n (%)	
Vaginal delivery	6 (12.8)
Cesarean delivery	41 (87.2)
Neonate characteristics	
Birth weight (g)	2,201.3 ± 738.8
Preterm (GA < 37 weeks), n (%)	29 (61.7)
Term (GA ≥ 37 weeks), n (%)	18 (38.3)

$MgSO_4$: magnesium sulfate, SD: standard deviation

Table 2. Characteristics of magnesium sulfate administration and serum biochemical levels.

	median (IQR)	min - max
Total dosage of $MgSO_4$ (g)	12.3 (8.64 - 17.98	5.6 - 143.8
Duration of $MgSO_4$ administration (minutes)	280 (162.5 - 444.5)	78 - 4212
	mean ± SD	min - max
Maternal serum magnesium (mg/dL)	5.3 ± 1.60	1.8 - 12.2
Cord blood magnesium (mg/dL)	4.4 ± 1.1	2.9 - 7.2
Maternal serum creatinine (mg/dL)	0.63 ± 0.19	0.4 - 1.1

$MgSO_4$: magnesium sulfate, IQR: interquartile range, SD: standard deviation.

Table 3. Correlation between umbilical cord blood magnesium and total dosage of $MgSO_4$ as well as duration of $MgSO_4$ infusion.

Parameters	Correlation (r)	p value
Total dosage of $MgSO_4$	0.65	< 0.01
Duration of $MgSO_4$ infusion	0.65	< 0.01
Maternal serum magnesium	0.73	< 0.01

$MgSO_4$: magnesium sulfate

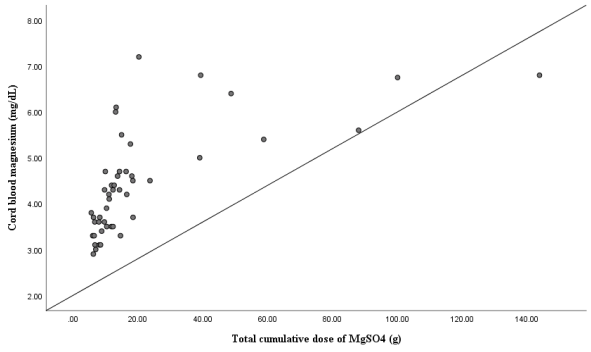

Fig. 1. Scatter plot with regression line showing the relationship between total dosage of $MgSO_4$ and cord blood magnesium levels.

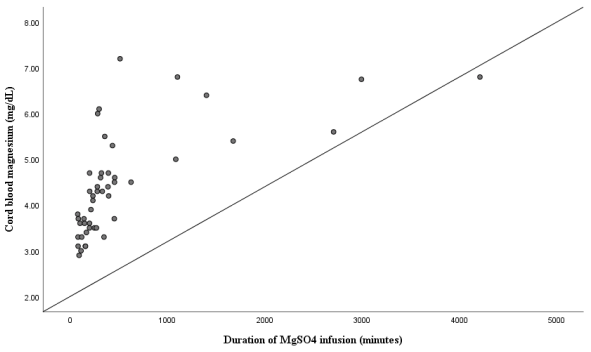

Fig. 2. Scatter plot with regression line showing the relationship between duration of $MgSO_4$ administration and cord blood magnesium levels.

Table 4 presents that total dosage of $MgSO_4$, duration of $MgSO_4$ administration, maternal serum magnesium levels, and maternal serum creatinine were significantly associated with cord blood magnesium level in univariable analysis ($p < 0.01$).

In the multiple linear regression model after adjusting for maternal serum magnesium, birth weight, and creatinine, total dosage of $MgSO_4$ remained a significant predictor of cord blood magnesium levels (Adjusted $\beta = 0.02$, 95% CI 0.01, 0.03, $p < 0.01$), maternal serum magnesium (Adjusted $\beta = 0.28$, 95% CI 0.14, 0.42, $p < 0.01$) and maternal serum creatinine (Adjusted $\beta = 1.98$, 95% CI 0.92, 3.03, $p = 0.001$) remained significantly associated with cord blood magnesium level.

Table 4. Univariable and multivariable linear regression for risk factors for cord blood magnesium level.

Variables	Univariable analysis			Multivariable analysis		
	Crude β	95% CI	p value	Adjusted β	95% CI	p value
Total dosage of $MgSO_4$ (g)	0.03	0.02, 0.04	< 0.001*	0.02	0.01-0.03	< 0.01*
Duration of $MgSO_4$ (hours)	0.05	0.04, 0.07	< 0.001*			
Maternal serum Mg level (mg/dL)	0.52	0.37, 0.66	< 0.001*	0.28	0.14-0.42	< 0.01*
Serum Cr (mg/dL)	2.79	1.17, 4.40	0.001*	1.98	0.92-3.03	0.001*
Maternal BMI (kg/m^2)	-0.02	-0.08, 0.04	0.501			
Birth weight (g)	-0.00	-0.00, 0.00	0.018*	0.00	0.00-0.00	0.790

Adjusted for duration of $MgSO_4$, maternal Mg level and maternal creatinine.

$MgSO_4$: magnesium sulfate, Mg: magnesium, Cr: creatinine, BMI: body mass index, CI: confidence interval

*Significant at $p < 0.05$

Receiver operating characteristic (ROC) analysis demonstrated that both total dose and duration of $MgSO_4$ administration were strong predictors of elevated cord magnesium levels (≥ 5 mg/dL). The ROC curve for total $MgSO_4$ dose demonstrated excellent discriminative ability, with an area under the curve (AUC) of 0.926 (95% CI 0.850, 1.000, $p < 0.001$). The optimal cutoff point, based on the Youden Index, was identified at 12.80 grams (a sensitivity of 100% and specificity of

71.4%) and 31.37 grams (a sensitivity of 58.5% and specificity of 100%) (Fig. 3, Table 5). The ROC curve for duration of $MgSO_4$ infusion also showed strong predictive performance, with an AUC of 0.919 (95% CI 0.836, 1.000, $p < 0.001$). The optimal cutoff point was 280 minutes (a sensitivity of 100% and specificity of 68.6%) and 855 minutes (a sensitivity of 58.6% and specificity of 100%) (Fig. 3, Table 6). These findings suggested that both total dose and duration of $MgSO_4$ administration were accurate predictors of elevated neonatal magnesium exposure.

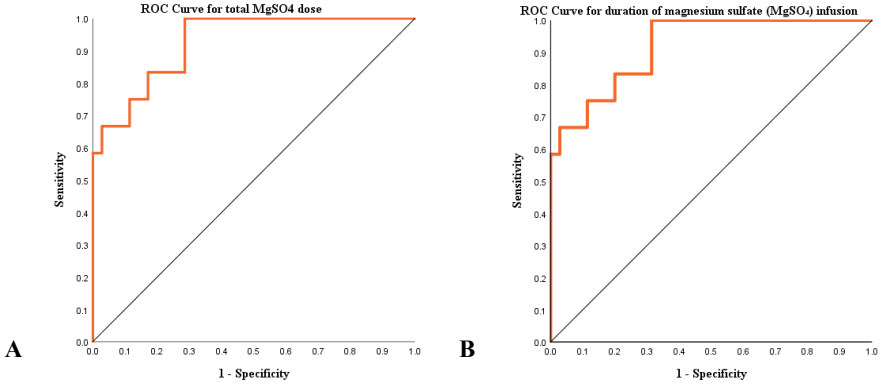

Fig. 3. Cutoff values of total dosage of $MgSO_4$ for predicting cord blood magnesium ≥ 5 mg/dL.

Table 5. Cutoff values of total dosage of $MgSO_4$ for predicting cord blood magnesium ≥ 5 mg/dL.

Cutoff (g)	Sensitivity	Specificity	Positive likelihood ratio
12.80	100.0	71.4	3.50
31.37	58.5	100.0	∞

Table 6. Cutoff values of duration of $MgSO_4$ infusion for predicting cord blood magnesium ≥ 5 mg/dL.

Cutoff (minutes)	Sensitivity	Specificity	Positive likelihood ratio
280	100.0	68.6	3.18
855	58.6	100.0	∞

ROC curves for (A) total dosage of $MgSO_4$ and (B) duration of $MgSO_4$ infusion in predicting elevated umbilical cord serum magnesium level ≥ 5 mg/dL. Both parameters demonstrated excellent predictive performance, with AUC values of 0.919 and 0.926 respectively.

Discussion

This study demonstrated a strong positive correlation between both the total dosage and duration of $MgSO_4$ administration and umbilical cord blood magnesium levels. These findings were consistent with those of previous studies in the literature, including the work by Ahmed Altraigey et al[17], which reported similar trends in elevated cord magnesium concentrations in neonates exposed to antenatal $MgSO_4$ therapy.

Our data further support the hypothesis that transplacental transfer of magnesium is dose-dependent and influenced by the duration of maternal

exposure[4,17].

In this study, the mean cord blood magnesium concentration was 4.4 ± 1.1 mg/dL, aligning with prior reports of neonates exposed to antenatal magnesium sulfate. Large-scale studies, including the BEAM trial, have documented average levels of between 3.7 and 4.4 mg/dL, particularly in the context of neuroprotection for preterm birth[19, 17]. Clinically, serum magnesium concentrations up to 2.0 mmol/L (~ 4.8 mg/dL) in neonates are generally considered safe and well tolerated[3, 21]. Although there is no universally accepted cutoff to define hypermagnesemia in neonates, several studies suggest that levels above 2.5 mmol/L (~ 6.08 mg/dL) may increase the risk of hypotonia, respiratory depression, and NICU admission[15,16]. One study by Basu et al[22] found that cord blood magnesium levels exceeding 4.5 mEq/L (~ 5.4 mg/dL) were associated with a 16.9-fold increased risk of immediate neonatal death. Considering the standard deviation in our data, it is plausible that a subset of neonates had magnesium concentrations exceeding this threshold, warranting attention. Therefore, this study adopted a cutoff value of cord blood magnesium ≥ 5 mg/dL as a potential threshold associated with adverse neonatal outcomes, based on both prior clinical evidence and the distribution of cord blood magnesium levels observed in our own cohort.

This study demonstrated that both the total dose and the duration of antenatal magnesium sulfate ($MgSO_4$) infusion were strongly associated with elevated cord blood magnesium levels (≥ 5 mg/dL), which may potentially increase the risk of adverse neonatal outcomes. ROC curve analysis revealed excellent discriminatory performance of both predictors.

With regard to the total $MgSO_4$ dose, AUC was 0.926, indicating high accuracy in predicting elevated cord magnesium levels. Similarly, the duration of $MgSO_4$ infusion yielded an AUC of 0.919, which also reflects excellent predictive ability. These findings suggested that both cumulative exposure and infusion time were reliable indicators of fetal magnesium transfer.

Our findings indicated that a cutoff value of approximately 12.80 grams for the total $MgSO_4$ dose and 280 minutes for infusion duration may serve as an early threshold for clinical consideration. Furthermore, when maternal cumulative exposure exceeds 31.3 grams or the infusion duration reaches 855 minutes or longer, neonatal serum magnesium level monitoring becomes necessary. These thresholds hold clinical significance, especially in contexts where prolonged $MgSO_4$ exposure is anticipated or when there is a concern regarding neonatal hypermagnesemia, emphasizing the importance of postnatal biochemical surveillance in infants identified as at risk.

Furthermore, within the scope of our research, umbilical cord magnesium levels equal to or exceeding 5 mg/dL can be predicted using the following equation:

Calculated umbilical cord magnesium = 1.268 + [1.976 x serum creatinine (mg/dL)] + [0.729 x serum magnesium (mg/dL)] + [0.019 x total magnesium dosage (grams)]

The calculated umbilical cord magnesium showed a robust positive correlation with the actual measured umbilical cord magnesium ($r = 0.83$, $p < 0.01$). ROC curve analysis indicated that a calculated umbilical cord magnesium threshold of 7.4 can effectively identify cases with true umbilical cord blood magnesium levels of 5 mg/dL or higher, with a sensitivity of 91.7% and a specificity of 94.3% (AUC of 0.96).

A key strength of this study lies in its prospective design and the use of direct biochemical measurements from both maternal serum and umbilical cord blood. The analysis comprehensively evaluated total dosage and duration of magnesium sulfate administration, alongside maternal renal function, as potential predictors of cord blood magnesium levels. The inclusion of both univariate and multivariate regression models enhances the robustness of the findings by accounting for potential confounders.

The limitation of this study was the relatively

small sample size, which restricted our ability to demonstrate a definitive association between maternal $MgSO_4$ dose or duration of infusion and neonatal outcomes. Nevertheless, the study provides meaningful preliminary guidance for clinical practice and highlights the need for future studies with larger cohorts to validate and refine these observations.

Conclusion

Total dose and duration of magnesium sulfate infusion were strong predictors of neonatal cord blood magnesium levels. Importantly, our study identified preliminary clinically meaningful thresholds: 12.8 g total dose and 280 minutes of infusion as early indicators, and 31.3 g or 855 minutes as critical points warranting neonatal monitoring. These findings provide practical guidance for clinicians and highlight the need for future studies with larger cohorts to validate and refine these cutoffs for safer perinatal management.

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Author Contribution

CK: protocol/project development, Data collection or management, Data analysis, Manuscript writing

KK: protocol/project development, Data analysis, Manuscript editing

TH: protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing

Potential conflicts of interest

The authors declare no conflicts of interest.

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