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Effects of antenatal magnesium sulfate use for neuroprotection on cardiorespiratory complications during the early neonatal period in preterm infants

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Antenatal magnesium sulfate ($MgSO_4$) treatment is widely used for fetal neuroprotection in women at risk of preterm delivery. Possible adverse effects of $MgSO_4$ include respiratory depression and delay in closure of ductus arteriosus by antagonism of calcium channels. The aim of this study was to investigate the effects of antenatal $MgSO_4$ exposure on cardiorespiratory complications during the early neonatal period in premature infants.

Methods: A retrospective cohort study was performed on 340 preterm infants born between 23 and 32 weeks of gestational age. Patients were divided into two groups according to antenatal $MgSO_4$ exposure: The $MgSO_4$ group (n=186) and the no-$MgSO_4$ group (n=154). Outcomes were acute cardiorespiratory events (intubation at birth, respiratory support, and hypotension in first day of life), and hemodynamically significant patent ductus arteriosus (HsPDA).

Results: Mothers in the $MgSO_4$ group were more likely to have preeclampsia and antenatal steroid treatment, while their infants were younger in gestation and weighed less (P<0.05). Multivariate regression analysis showed that antenatal $MgSO_4$ exposure was significantly associated with decreased mechanical ventilation (odds ratio [OR] 0.45 95% confidence interval [CI] 0.25-0.81, P=0.008), hypotension (OR 0.47, 95% CI 0.24-0.90, P=0.023) and HsPDA (OR 0.52, 95% CI 0.28-0.97, P=0.039). There was no significant association between antenatal $MgSO_4$ exposure and intubation at birth (OR 1.06 95% CI 0.62-1.82, P=0.828).

Conclusion: Among the preterm infants ≤32 weeks, antenatal $MgSO_4$ was not associated with increased risk for acute cardiorespiratory events during the early neonatal period. It might have a protective role in helping with ductal closure.

Keywords: Antenatal magnesium sulfate, Neonatal resuscitation, Patent ductus arteriosus, Preterm infants, Neuroprotection

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Introduction

Recent advances in perinatal medicine have markedly increased the survival rates of premature infants. However, long-term neurodevelopmental outcomes, particularly cerebral palsy, and cognitive deficits, remain important health challenges [1, 2].

Magnesium sulfate ($MgSO_4$) therapy has long been widely used for tocolysis in preterm labor and seizure prevention in preeclampsia [3]. Large randomized controlled trials and systematic reviews have reported that antenatal $MgSO_4$ exposure reduces the risk of gross motor dysfunction and cerebral palsy in surviving infants [4-7]. Based on the available evidence, some national guidelines have recommended antenatal $MgSO_4$ for fetal neuroprotection [8].

However, several studies raised concerns about the possible adverse effects of antenatal $MgSO_4$ in terms of neonatal morbidities [9]. In the Magnesium and Neurological Endpoints Trial [10], antenatal $MgSO_4$ was associated with a higher risk for adverse neonatal outcomes. Previous studies reported that antenatal $MgSO_4$-exposed infants had an increased risk for hypotonia, delivery room intubation, and significant patent ductus arteriosus (PDA) compared with infants not exposed to antenatal $MgSO_4$ [11-13]. However, the cardiorespiratory effect of antenatal $MgSO_4$ in preterm infants is still controversial [14, 15].

In our unit, $MgSO_4$ is administered for fetal neuroprotection in preterm deliveries. This study aimed to investigate the effects of antenatal $MgSO_4$ exposure on cardiorespiratory complications during the early neonatal period in premature infants.

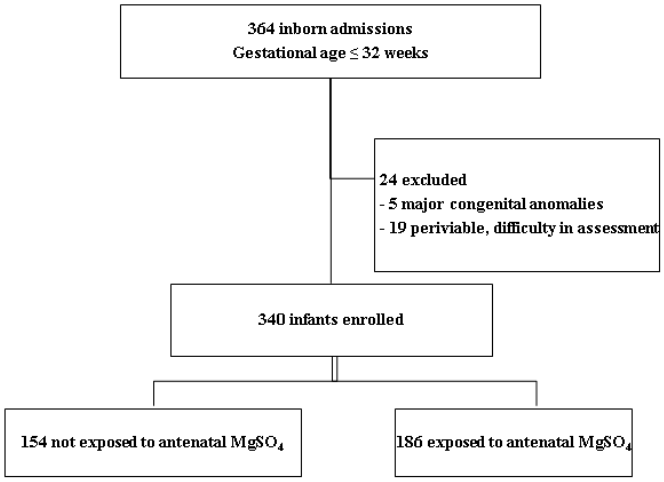
Materials and methods

This retrospective study was performed in the neonatal intensive care unit (NICU) of a university hospital. It was approved by Istanbul Medeniyet University, Goztepe Training and Research Hospital Ethics Committee (Number: 2021/0287, date: 21.06.2021) and conducted per the principles of the 2008 Declaration of Helsinki. Informed consent was obtained from the families of the patients included in the study for all interventional procedures during admission to the NICU. The STROBE checklist was used in the study design and drafting of the manuscript [16].

All inborn infants with a gestational age of 32 weeks or less admitted to our NICU during the study period were evaluated. Data were obtained from the electronic records and patients' files. Infants with major congenital anomalies were excluded from the study. We also excluded the periviable infants who died within the first day of life due to the difficulty in determining the effects of $MgSO_4$ on neonatal outcomes.

A total of 364 preterm infants were assessed for eligibility for the study. Of these, 24 infants were excluded based on our criteria, leaving 340 infants in the cohort for analysis. Patients were divided into two groups according to antenatal $MgSO_4$ exposure as the $MgSO_4$ group and no-$MgSO_4$ group. Of the 340 infants in the study, 186 (54.7%) were exposed to antenatal $MgSO_4$ (Figure 1).

Figure 1: Flow diagram of the study



In our center, antenatal $MgSO_4$ therapy for neuroprotection is standard practice for preterm deliveries ≤ 32 weeks since 2014 and consists of a loading dose of 4 g, followed by a 2 g per hour continuous infusion. It is discontinued if the delivery has not occurred in 12 hours. Antenatal care and delivery of patients were carried out according to the unit protocols.

We reviewed hospital electronic records and patients' files and collected the following data: Maternal age, complications during pregnancy (preeclampsia, preterm prolonged rupture of membrane, and chorioamnionitis), whether mothers received antenatal steroid (ANS) and $MgSO_4$ therapy, delivery mode, gestational age, birth weight, gender, 1- and 5-minute APGAR scores and neonatal outcomes. Antenatal steroid treatment was defined as the completion of 2 doses of 12 mg betamethasone before delivery. Gestational age determination was based on the last menstrual period confirmed by ultrasonography during the first half of pregnancy or Ballard score.

Primary outcomes were acute cardiorespiratory events such as intubation at birth, respiratory support, and hypotension (treated with volume resuscitation, pressors, or steroids) within the first day of life, and hemodynamically significant PDA (HsPDA) (non-restrictive left-to-right shunt identified by echocardiography that was medically or surgically treated). Intubation for surfactant administration followed by immediate removal was not considered as intubation at birth. Types of respiratory support included invasive mechanical ventilation, nasal intermittent positive pressure ventilation or continuous positive airway pressure (CPAP). Data on intraventricular hemorrhage (IVH), duration of invasive ventilation, age at full enteral feeds, necrotizing enterocolitis (NEC) (stage ≥2) [17], moderate to severe bronchopulmonary dysplasia (BPD) [18], retinopathy of prematurity (ROP) [19], length of NICU stay and mortality were also collected.

All infants were evaluated by echocardiography performed by a pediatric cardiologist within the first 3 days of life, as per our unit protocol. The management of PDA was based on the Turkish Neonatal Society PDA guidelines [20]. These infants were also screened for IVH at least weekly by a neonatologist.

Statistical analysis

SPSS 23.0 for Windows program was used for data analysis. The distribution of continuous variables was checked

by the Shapiro-Wilk test. Non-normally distributed numerical variables were presented as median and interquartile range (IQR) and compared with the Mann-Whitney U test. Chi-square and Fisher's exact tests were used for the comparison of categorical variables. Baseline characteristics with $P<0.1$ (gestational age, ANS treatment, preeclampsia, and 5-minute Apgar score) were selected and included in the multivariate model. Stepwise binary logistic regression was used to identify the association between antenatal $MgSO_4$ exposure and primary outcomes. Results were presented as odds ratio (OR) and 95% confidence interval (CI). *P*-values <0.05 were considered statistically significant.

Results

The mean gestational age and birth weight of the infants in the study were 28.9 (2.6) (range: 23-32) weeks and 1228.9 (441.5) (range: 400-2290) g, respectively. The female to male ratio was 0.9.

Baseline characteristics of the groups are presented in Table 1. Women in the $MgSO_4$ group were more likely to have preeclampsia (37.6% vs. 13.6%, $P<0.001$) and received ANS treatment (83.9% vs. 70.1%, $P=0.002$). Infants in the $MgSO_4$ group had lower gestational age and birth weight ($P<0.001$ for both).

Table 1: Comparison of baseline characteristics among the study groups

	$MgSO_4$ (n=186) Median (IQR)	No-$MgSO_4$ (n=154) Median (IQR)	*P*-value
Maternal age (y)	29 (26-32)	29 (25-31)	0.218
Gestational age (wk)	29 (26-30)	30 (28-32)	<0.001
Birth weight (g)	1096 (788-1400)	1348 (998-1655)	<0.001
Apgar score at 1 min	5 (4-6)	5 (4-6)	0.227
Apgar score at 5 min	7 (7-8)	7 (6-8)	0.096
	n (%)	n (%)	
Preeclampsia	70 (37.6)	21 (13.6)	<0.001
Prolonged rupture of membrane	32 (17.2)	34 (22.1)	0.258
Chorioamnionitis	11 (5.9)	13 (8.4)	0.361
Antenatal steroid	157 (84.4)	105 (68.2)	<0.001
Cesarean delivery	149 (80.1)	113 (78.6)	0.142
Male sex	94 (50.5)	81 (52.6)	0.705
Multiple gestation	19 (10.2)	17 (11)	0.806
Small for gestational age	29 (15.6)	16 (10.4)	0.159

IQR, interquartile range

There were no significant differences in the rates of intubation at birth, respiratory support, hypotension treatment in the first day of life, and HsPDA between the groups (Table 2). Other morbidities, and the length of mechanical ventilation or hospital stay, and age at full enteral feeds were also similar (Table 3).

Table 2: Comparison of primary outcomes among the study groups

	MgSO4 (n=186) n (%)	No MgSO4 (n=154) n (%)	*P*-value
Intubation at birth	75 (40.3)	47 (30.5)	0.061
Respiratory support [a]	138 (74.2)	110 (71.4)	0.568
Mechanical ventilation	100 (53.8)	82 (53.2)	0.924
Hypotension	42 (22.6)	36 (23.4)	0.862
HsPDA	50 (26.9)	37 (24.0)	0.548

a: Respiratory support included invasive mechanical ventilation and nasal intermittent positive pressure ventilation or continuous positive airway pressure (CPAP). HsPDA: hemodynamically significant patent ductus arteriosus

After adjustment for covariates including gestational age, preeclampsia, ANS status, and 5-minute Apgar score, antenatal $MgSO_4$ was significantly associated with reduced risk for mechanical ventilation (OR 0.45 95% CI 0.25-0.81, $P=0.008$), hypotension treatment (OR 0.47 95% CI 0.24-0.90, $P=0.023$) and HsPDA (OR 0.52 95% CI 0.28-0.97, $P=0.039$). There was no significant association between antenatal $MgSO_4$ exposure and the need for intubation at birth (OR 1.06 95% CI 0.62-1.82, $P=0.828$) (Table 4).

Table 3: Comparison of neonatal mortality and morbidity among the study groups

	MgSO4 (n=186) n (%)	No MgSO4 (n=154) n (%)	*P*-value
IVH	46 (24.7)	33 (21.4)	0.473
IVH (Grade ≥3)	8 (4.3)	7 (4.5)	0.913
PVL	2 (1.3)	2 (1.1)	0.849
NEC (Stage ≥2)	13 (7)	7 (4.6)	0.340
Sepsis (culture proven)	42 (22.6)	24 (15.8)	0.117
Moderate to severe BPD	47 (25.3)	28 (18.2)	0.117
ROP	16 (8.6)	10 (6.5)	0.466
Mortality	30 (16.1)	19 (12.3)	0.322
	Median (IQR)	Median (IQR)	
Length of mechanical ventilation (d)	5 (0-18)	4 (0-13)	0.512
Time to full enteral feed (d)	24 (17-35)	21.5 (15-32)	0.243
Length of hospitalization (d)	66 (35-89)	58.5 (34-84)	0.408

IVH: intraventricular hemorrhage, PVL: periventricular leukomalacia, NEC: necrotizing enterocolitis, BPD: bronchopulmonary dysplasia, ROP: retinopathy of prematurity; IQR: interquartile range

Table 4: Multivariate logistic regression analysis estimating effects of antenatal magnesium exposure and risk of cardiorespiratory complications

Outcomes	OR	95% CI	*P*-value
Intubation at birth	1.06	0.62 – 1.82	0.828
Respiratory support	0.61	0.34 – 1.11	0.108
Mechanical ventilation	0.45	0.25 – 0.81	0.008
Hypotension	0.47	0.24-0.90	0.023
HsPDA	0.52	0.28 – 0.97	0.039

Covariates: gestational age, antenatal steroids, preeclampsia. 5 min Apgar score, OR: odds ratio, CI: confidence interval, HsPDA: hemodynamically significant patent ductus arteriosus

Discussion

In this retrospective analysis of very premature infants, we demonstrated that antenatal $MgSO_4$ exposure was not associated with increased risk for resuscitation at the delivery room, neonatal morbidities, delayed feeding, mortality, or longer hospital stay. Moreover, the rates of invasive mechanical ventilation, hypotension and HsPDA of infants exposed to antenatal $MgSO_4$ were significantly less compared to non-exposed infants.

There are limited data on the effect of antenatal $MgSO_4$ exposure on neonatal cardiorespiratory complications. Magnesium given to the mother was associated with hypotonia, hyporeflexia, and respiratory depression in neonates [21, 22]. Abbassi-Ghanavati et al. [11] reported hypotonia, lower APGAR scores, increased intubation at the delivery room with antenatal MgSO4 exposure. However, in a clinical trial, Johnson et al. [23] did not find any correlation between antenatal magnesium exposure and the need for resuscitation among preterm infants exposed to antenatal $MgSO_4$ for neuroprotection. In the current study, there was no association between antenatal $MgSO_4$ and risk for intubation at birth.

A study from Turkey reported a significantly lower rate of respiratory distress among antenatal $MgSO_4$ exposed infants than antenatal $MgSO_4$ unexposed infants, though mechanical ventilation rates were similar [24]. In our study, antenatal $MgSO_4$ was significantly associated with a reduced need for invasive mechanical ventilation, but there was no significant association between antenatal $MgSO_4$ exposure and total respiratory support. In preterm infants, invasive mechanical ventilation can lead to lung injury resulting in chronic lung disease. Therefore, ventilation strategies were changed to use more non-invasive modes to prevent lung injury [25, 26]. The change in ventilation practices can explain the differences in the rates of invasive ventilation between studies. In our study, more infants in the $MgSO_4$ group received ANS treatment, which reduces the severity of RDS and need for mechanical ventilation

[27], which again might result in a lower need for mechanical ventilation among infants in the $MgSO_4$ group.

Reports on the association of antenatal $MgSO_4$ with hypotension are limited. Two clinical trials reported no significant relationship between antenatal $MgSO_4$ exposure and the risk of hypotension [4, 5]. In our study, infants exposed to antenatal $MgSO_4$ had significantly less hypotension treatment, consistent with the study by De Jesus et al. [14]. They evaluated 1544 infants <29 weeks' gestational age and reported a significant decrease in hypotension treatment related to antenatal $MgSO_4$ exposure. Magnesium ions regulate vascular tone and contribute to the stabilization of blood pressure and improvement of cardiac function in the first days of life [28]. Hypotension in preterm infants is associated with lower gestational age, and higher mean airway pressure. Also, ANS treatment improves systemic blood pressure in preterm infants [29]. In our study, more ANS exposure and less invasive MV in these infants may explain our finding of less hypotension in infants exposed to antenatal $MgSO_4$.

Magnesium ions antagonize the effects of intracellular calcium and modulate prostacyclin synthesis in the vascular smooth muscle cell. Both mechanisms lead to vasodilatation and can cause a delay in ductus arteriosus closure in preterm infants [30]. Previous studies reported an increased risk for symptomatic PDA in extremely preterm infants who were exposed to antenatal $MgSO_4$ [12, 13]. However, in a study on cardiovascular effects of antenatal $MgSO_4$, Paradisis et al. [31] reported an incidental finding of significantly smaller PDA in the exposed group. Qasım et al. [15] recently showed a decreasing trend of HsPDA with antenatal $MgSO_4$ exposure. In our study, antenatal $MgSO_4$ was associated with significantly decreased HsPDA. Although there were more infants treated with ANS in the antenatal $MgSO_4$ exposed group, ANS treatment did not show an association with HsPDA in multivariate analysis. The variations in the study results can be explained by the differences in PDA management. Most previous studies evaluated PDA after clinical symptoms were encountered. In our study, all infants were routinely screened by echocardiography for evaluation of PDA. Our finding of reduced risk for HsPDA with antenatal $MgSO_4$ exposure indicates that magnesium might affect ductal closure by different complex intracellular actions rather than antagonizing the calcium channels responsible for mediating ductal constriction. Further studies are needed to explore the effects of antenatal $MgSO_4$ on PDA.

In our center, antenatal $MgSO_4$ therapy consisted of a 4 g loading dose followed by an infusion of 2 g per hour and stopped if delivery did not occur in 24 hours. However, there is no consensus on an effective and safe dose of antenatal $MgSO_4$. Studies using higher doses of $MgSO_4$ have shown a trend towards increased perinatal mortality [5, 9]. McPherson et al. [32] reported similar effectivity on neuroprotection between higher and lower doses of antenatal $MgSO_4$. In addition to dose, gestational age, birth weight, maternal characteristics are related to the effects of antenatal $MgSO_4$. Ohhashi et al [33] found that antenatal $MgSO_4$ was more effective in infants born at 28-32 weeks of gestation with a low dose regimen (<50 g). In this study, we could not perform subgroup analysis due to the small sample size. In addition, we were unable to investigate the association between total magnesium dose received and change in neonatal outcomes.

Another limitation of this study includes the lack of data on neonatal serum magnesium concentration. In preterm infants, higher neonatal serum magnesium concentrations were associated with an increased risk for mortality [9, 10]. As this was a retrospective study, possible confounding factors might be missed. However, being a single center study in which all patients were managed using the same standard protocols regarding maternal and newborn follow-up can be considered a strength. In our center, antenatal $MgSO_4$ for neuroprotection is a standard practice in all women at risk of preterm birth before 33 weeks of gestation. However, 45.3% of eligible women did not receive antenatal MgSO4 and the rate of receiving ANS treatment was also low. These women probably do not have enough time between admission to the hospital and delivery. To account for the effects of ANS and maternal factors, we performed a multivariate analysis and found that antenatal MgSO4 has significant reducing effects on mechanical ventilation, hypotension, and HsPDA independent of ANS and other confounders.

Conclusions

The use of antenatal $MgSO_4$ for neuroprotection was not associated with an increase in cardiorespiratory complications in preterm infants born ≤ 32 weeks of gestation. Moreover, infants exposed to antenatal $MgSO_4$ had significantly less invasive mechanical ventilation, and hypotension treatment in the first day of life. Antenatal Mg appears to have a protective role in helping with ductal closure. Further studies with a larger population are needed to clarify the effect of antenatal MgSO4 on acute cardiorespiratory events and HsPDA.

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