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Antenatal Magnesium Sulfate Use for Fetal Neuroprotection: Experience from a Tertiary Care Hospital in Turkey.

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Abstract

Aims: We aimed to demonstrate the effect of magnesium sulfate for fetal neuroprotection on maternal and neonatal outcomes of pregnants delivered before 32 weeks.

Materials and methods: The records of 107 patients who were delivered before 32 weeks of pregnancy were reviewed retrospectively during the period between January 2011-February 2016. Patients who were treated with $MgSO_4$ for fetal neuroprotective effect constituted the study group, and patients who were not received $MgSO_4$ for the fetal neuroprotection represented the control group.

Results: One hundred seven women delivered before 32nd weeks of pregnancy met study criteria and of these patients, 46 were formed the magnesium sulfate group, and the remaining 61 were constituted the control group. The age (28.37 ± 4.97 versus 29.90 ± 5.23 respectively; p=0.129), body mass index (BMI) (26.25 ± 4.12 versus 26.90 ± 5.68 respectively; p=0.342) and gestational age at delivery (28.08 ± 2.66 versus 28.78 ± 2.15 respectively; p=0.136) were similar between the groups. Intraventricular hemorrhage was more common in control group compared with the $MgSO_4$ group [7/61 (11.4%) versus 3/46 (6.5%); p=0.049]. For the periventricular leukomalacia [1 (2.2%) versus 0 (0%) respectively; p=0.430], neonatal convulsion [1 (2.2%) versus 3 (4.9%) respectively; P=0.630] and neonatal encephalopathy [0 (0%) versus 1 (1.6%) respectively; p=0.570], no substantial differences were seen between the groups.

Conclusions: The results of this study suggest that $MgSO_4$ treatment for fetal neuroprotection has a beneficial effect on intraventricular hemorrhage rate. The widespread use of prenatal $MgSO_4$ for the purpose of fetal neuroprotection before 32 weeks of pregnancy at a standard dose protocol could improve the neonatal neurological outcomes.

Keywords: Hemorrhage, Magnesium sulfate, Neuroprotective agents, Periventricular leukomalacia, Pregnancy.

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Introduction

Antenatal magnesium sulfate has been used extensively for the prophylaxis and treatment of eclampsia in obstetric practice as the first line treatment. Use of magnesium sulfate as a maternal neuroprotective agent in preeclampsia has been demonstrated in several studies and systematic reviews [1]. Although magnesium sulfate was used in preterm labor in the past as a tocolytic agent, meta-analysis failed to show the efficacy in this indication [2]. For the first time, Nelson et al. confirmed that magnesium sulfate is associated with reduced cerebral palsy and mortality risk in neonates below 1500 g birthweight in California Cerebral Palsy Project [3]. There were conducted four randomized controlled trials to show the fetal neuroprotective effect of magnesium sulphate [4-7]. The meta-analysis of these studies determined the fetal neuroprotective effect of magnesium sulfate therapy [8]. Intravenous administration of magnesium sulfate can make flushing, sweating and hypotension due to the influence of vasodilation. Although rarely observed, serious side effects are maternal respiratory and cardiac arrest and death. It has not been reported any serious maternal side effects in studies and reviews [1,2,4,8]. The possible side effects for infants include hyporeflexia, hypotonia and rarely mechanical ventilation and respiratory depression. The mechanism of neuroprotective effect of magnesium sulfate is not clear. However, experimental evidence and animal studies described the mechanisms of the protective effect of magnesium's potential neuroprotective effect due to its ability to provide hemodynamic stability against excitotoxic brain damage and antioxidant/ anti-inflammatory effects [9,10]. Magnesium can pass through placenta quickly and can show antagonistic action on N-methyl-D-aspartate (NMDA) and calcium receptors. Animal studies demonstrated that magnesium inhibits neuronal

nuclear calcium influx induced by fetal brain hypoxia thus it protects in utero hypoxia by providing modification of the neuronal nuclear membrane function [11]. Although the existence of the evidence about the use of magnesium sulfate for fetal neuroprotective effect, clinicians couldn't put this treatment into the practice due to the difficulties in identifying the group of patients who should be treated, doses and duration of therapy and absence of a clear protocol. In Turkey, although magnesium sulfate has been licensed for the treatment of severe preeclampsia, eclampsia, and tocolysis, there is no approval for fetal neuroprotection indication. Also, there is still no standard protocol for $MgSO_4$ use for fetal neuroprotective effect at many centers in Turkey. We have established the standard treatment protocol for the purpose of fetal neuroprotection in our clinic since April 2014. In this study, we aimed to demonstrate the effect of $MgSO_4$ for fetal neuroprotection on maternal and neonatal outcomes of pregnants delivered before 32 weeks and compare results with untreated patients.

Materials and Methods

Inonu University Faculty of Medicine Ethics Committee consent was obtained before the study (Ethical Committee Approval no: 2016/3-3). The records of 107 patients who were delivered before 32 weeks of pregnancy were reviewed retrospectively during the period between January 2011-February 2016 at Department of Obstetrics and Gynecology, Inonu University School of Medicine. In these patients, patients who were treated with $MgSO_4$ for fetal neuroprotective effect constituted the study group, and patients who were not received $MgSO_4$ for the fetal neuroprotection represented the control group.

In our clinic $MgSO_4$ treatment protocol for fetal neuroprotection has been established in 2014 as loading dose 6 g $MgSO_4$ in 100 cc 0.9% isotonic sodium chloride solution by intravenous route over 30 minutes and maintenance dose 2 g/h $MgSO_4$ in the isotonic sodium chloride solution until delivery (up to 12 hours) intravenously. Patients who received at least loading dose of the treatment were considered as treated for fetal neuroprotection. Patients who were treated by $MgSO_4$ only for the fetal neuroprotection indication enrolled in this study. Pregnant who were treated $MgSO_4$ for tocolysis or eclampsia prophylaxis were excluded. The heart rate, blood pressure, respiratory rate and urine output of the patients were recorded during the magnesium treatment and the maintenance treatment were discontinued if respiratory rate detected below 12/minute or declined below the 4/min of the baseline respiratory rate or diastolic blood pressure decreased more than 15 mmHg from the baseline or urine output detected below 30 ml/min. Antenatal corticosteroids were administered in the 24^{th} week of pregnancy (two doses of betamethasone 12 mg intramuscularly every 24 hours). If the delivery were anticipated and it was passed at least two weeks from the last dose of betamethasone, rescue dose (a single dose of 12 mg betamethasone, intramuscular) were applied to all patients before delivery. Antibiotics (intravenous ampicillin 4 × 2 g for first 48 hours, per oral ampicillin 2 × 1 g for the next eight days + 1 × 500 mg per oral azithromycin for three days) were administered to all patients diagnosed preterm premature rupture of membrane for ten days. Antenatal care and delivery of patients included in this study were carried out in our clinic according to the standard protocols. All neonates were transferred to the neonatal intensive care unit (NICU). Cranial ultrasonography was performed to all premature infants within the first seven days of life for detecting intraventricular hemorrhage and within the first four weeks for detecting periventricular leukomalacia. Evaluation for retinopathy of prematurity (ROP) was performed to all premature neonates in the postnatal 28th day by an experienced pediatric ophthalmologist. Patients who were met the following criteria enrolled in this study:

1. Maternal age between 18-39
2. Singleton pregnants delivered before 32nd week of pregnancy
3. Treated with $MgSO_4$ for fetal neuroprotection according to the standard protocol because of anticipated delivery within 24 hours.

In the presence of the following situations the patients were excluded from the study:

1. Multiple pregnancies
2. Fetal death
3. Associated fatal congenital anomalies or chromosomal abnormalities.
4. Patients who were administered $MgSO_4$ treatment for any indication during pregnancy period
5. Patients who had contraindications for $MgSO_4$ use.

Data were obtained from the medical records of patients and their neonates. Qualitative data were summarized as mean with standard deviation, and quantitative data were summed up as number and percentile. Eligibility of data to the normal distribution was analyzed with Shapiro-Wilk test. Comparison of independent samples between study and control groups was performed by t test. Pearson's chi-square, Yate's corrected chi-square, and Fisher's exact tests were used for the analysis of categorical variables, where appropriate. $P<0.05$ values were accepted statistically significant. The statistical software package IBM SPSS 22.0 (SPSS Inc., Chicago, Ill., USA) was used for all data analyses.

Results

One hundred seven women delivered before 32^{nd} weeks of pregnancy met study criteria and of these patients, 46 were constituted the magnesium sulfate group, and the remaining 61 were composed the control group. The age (28.37 ± 4.97 versus 29.90 ± 5.23 respectively; p=0.129), BMI (26.25 ± 4.12 versus 26.90 ± 5.68 respectively; p=0.342) and gestational age at delivery (28.08 ± 2.66 versus 28.78 ± 2.15 respectively; p=0.136) were similar between the groups. Although the frequency of vaginal birth was similar between the groups (6/46 (13.0%) versus 12/61 (19.7%); p=0.364), there was

statistically significant difference in the delivery indication between the groups (p=0.002). While the fetal distress was the most common indication for delivery in $MgSO_4$ group, the presence of preterm labour was the most common indication in the control group. Duration of maternal hospitalisation was similar between the groups (2.37 ± 0.97 versus 2.13 ± 0.72 respectively; p=0.06). Other baseline maternal and pregnancy characteristics between the groups are described in Table 1.

Table 1. *Maternal and pregnancy characteristics of groups.*

Maternal characteristics	Magnesium Sulfate (n=46)	Control (n=61)	p value
Age†	28.37 ± 4.97	29.90 ± 5.23	0.129
Gravidy†	2.65 ± 1.66	2.50 ± 1.46	0.636
Parity†	0.84 ± 0.91	0.93 ± 1.09	0.665
BMI(kg/m^2)†	26.25 ± 4.12	26.90 ± 5.68	0.342
Systolic blood pressure (mmHg)†	112.37 ± 13.41	111.54 ± 13.21	0.75
Diastolic blood pressure (mmHg)†	74.95 ± 10.27	73.88 ± 9.32	0.574
Gestational age at delivery (week)†	28.08 ± 2.66	28.78 ± 2.15	0.136
Mode of delivery‡			
Vaginal	6 (13.0)	12 (19.7)	0.364
Cesarean	40 (87.0)	49 (80.3)	
Indication for delivery‡			
Fetal distress	25 (54.3)	14 (23.0)	0.002
Preterm labor with repeat caesarean delivery	17 (37.0)	28 (45.9)	
Malpresentation	2 (4.3)	15 (24.6)	
Placental abruption	1 (2.2)	4 (6.6)	
Chorioamnionitis	1 (2.2)	0 (0)	
Duration of maternal hospitalization† (day)	2.37 ± 0.97	2.13 ± 0.72	0.06

†Data are given as mean ± SD

‡Data are presented as n (%)

The birth weight of the neonates in $MgSO_4$ group was detected lower than the control group (975.50 ± 412.24 versus 1348.46 ± 383.83 respectively; P<0,001). The first minute APGAR score (5.28 ± 1.79 versus 5.80 ± 1.55 respectively; p=0.112), fifth minute APGAR score (7.15 ± 1.86 versus 7.72 ± 1.61 respectively; p=0.094) and the duration of hospitalisation in NICU (23.95 ± 23.16 versus 24.36 ± 23.00 respectively; p=0.929) were similar between the groups. In the $MgSO_4$ group neonates were need more active resuscitation at birth (respiratory support with endotracheal intubation) than the control group [22/46 (47.8%) versus 15/61 (24.7%); p=0.015]. There was statistically significant difference in the respiratory support requirement between the groups (p=0.006). In $MgSO_4$ group, 54.30% of patients needed mechanical ventilation, 37% of patients required nasal continuous positive airway pressure (CPAP), 4.5% of patients needed nasal synchronised intermittent mandatory ventilation (SIMV). In the control group, 32.80% of patients required mechanical ventilation, 32.80% of patients needed nasal continuous positive airway pressure (CPAP), 6.6% of patients needed nasal synchronised intermittent mandatory ventilation (SIMV), 16.4% of patients needed hood oxygenation. Intraventricular hemorrhage was more common in control group compared with the $MgSO_4$ group [7/61 (11.4%) versus 3/46 (6.5%); p=0.049]. There was no statistically significant difference in intraventricular hemorrhage grade between the groups (p=0.910). Neonatal hypotonia [4 (8.7%) versus 0 (0%) respectively; p=0.032], retinopathy of prematurity [12 (26.1%) versus 6 (9.8%) respectively; p=0.040] and neonatal death [17 (37%) versus 9 (14.8%) respectively; p=0.015] were more common in MgSO4 group. For the periventricular leukomalacia [1 (2.2%) versus 0 (0%) respectively; P=0.430], neonatal convulsion [1 (2.2%) versus 3 (4.9%) respectively; p=0.630] and neonatal encephalopathy [0 (0%) versus 1 (1.6%) respectively; p=0.570], no substantial differences were seen between the groups. Neonatal outcomes at birth are shown in Table 2. There was no major maternal adverse effect (death, respiratory arrest, cardiac arrest) in $MgSO_4$ group and only two patients in the $MgSO_4$ group were experienced minor adverse events (nausea,

vomiting, flushing, dry mouth, sweating, dizziness, blurred vision) related to $MgSO_4$ treatment.

Table 2. Neonatal outcomes of groups.

	Magnesium Sulfate (n=46)	Control (n=61)	p value
Birth weight (gr)†	975.50 ± 412.24	1348.46 ± 383.83	<0.001
1. minute APGAR score†	5.28 ± 1.79	5.80 ± 1.55	0.112
5. minute APGAR score †	7.15 ± 1.86	7.72 ± 1.61	0.094
Gender‡			
Male	22 (47.8)	34 (55.7)	0.417
Female	24 (52.2)	27 (44.3)	
Need for active resuscitation at birth (respiratory support with endotracheal intubation)‡	22 (47.8)	15 (24.6)	0.015
Duration of hospitalization in NICU (day) †	23.95 ± 23.16	24.36 ± 23.00	0.929
Need for respiratory support‡	45 (97.8)	54 (88.5)	0.006
Mechanical ventilation	25 (54.3)	20 (32.8)	
Nasal continuous positive airway pressure (CPAP)	17 (37.0)	20 (32.8)	
Nasal synchronized intermittent mandatory ventilation (SIMV)	3 (4.5)	4 (6.6)	
Oxygen hood	0 (0)	10 (16.4)	
Intraventricular hemorrhage‡	3 (6.5)	7 (11.4)	0.049
Intraventricular hemorrhage grade‡			
Grade I	1 (2.2)	2 (3.3)	0.91
Grade II	0 (0)	2 (3.3)	
Grade III	1 (2.2)	2 (3.3)	
Grade IV	1 (2.2)	1 (1.6)	
Periventricular leukomalacia‡	1 (2.2)	0 (0)	0.43
Neonatal convulsion‡	1(2.2)	3 (4.9)	0.63
Neonatal hypotonia‡	4 (8.7)	0 (0)	0.032
Neonatal ensefalopathy‡	0 (0)	1 (1.6)	0.57
Retinopathy of prematurity (ROP) ‡	12 (26.1)	6 (9.8)	0.04
Neonatal death ‡	17 (37)	9 (14.8)	0.015

†Data are given as mean ± SD

‡Data are presented as n (%)

Discussion

Preterm birth is responsible one-third of neonatal mortality and among surviving infants, it is associated with increased risk of white matter damage such as periventricular leukomalacia (PVL), and intraventricular hemorrhage because of the enhanced vulnerability of cerebral white matter [12,13]. In this study, our data showed that administration of magnesium sulfate treatment in pregnants delivered before 32 weeks for the purpose of fetal neuroprotection is associated reduced intraventricular hemorrhage rate. Besides, we demonstrated that there were no substantial differences for the IVH grade and periventricular leukomalacia between the groups. Several studies have shown that maternal administration of magnesium sulfate is associated with a subsequent reduction in the risk of IVH, cerebral palsy, periventricular leukomalacia, and pediatric mortality [14,15]. However, Doyle et al. reported that magnesium sulfate administration to the mother specifically with neuroprotective intent was associated with a 15% relative reduction in the risk of death or cerebral palsy, but they were failed to show any significant decrease in intraventricular hemorrhage or periventricular leucomalacia rate [8]. In this study, we thought that reduction in IVH rate might be due to magnesium sulfate's stabilizing effect of blood flow and

ameliorating effects on hypoxic-ischemic episodes and free radicals in central nervous system cells.

Crowther et al. reported that total pediatric mortality, cerebral palsy in survivors, and combined death or cerebral palsy were all lower in patients received maternal magnesium sulfate treatment before 30 weeks of pregnancy compared with the placebo group [4]. But they were noted that despite the lack of statistical significance, the average sizes of the reductions in these adverse outcomes are potentially clinically relevant. Also, they have demonstrated a statistically significant reduction in substantial motor dysfunction among survivors in the magnesium sulfate group and in the combined outcome of death or substantial motor dysfunction, both of which are considered to be clinically meaningful. In this study higher neonatal hypotonia, retinopathy of prematurity and neonatal mortality rate in the magnesium sulfate group were attributable to the lower birth weight rates in the treatment group.

Although some studies [16,17] were suggested that magnesium exposure may negatively affect immediate neonatal resuscitation and related with increased risk of low Apgar scores, hypotonia, and neonatal intensive care unit admission, not all studies confirm these associations [18,19]. Drassinower et al. were analyzed the data from 1047 patients, of whom 461 neonates (44%) were exposed to magnesium and demonstrated that $MgSO_4$ does not affect immediate neonatal outcomes or neonatal resuscitation efforts including 5-Minute Apgar score <7, oxygen bag, mask, or both, intubation, chest compressions, generalized hypotonicity and mechanical ventilation [20]. In this study, active resuscitation requirement at birth (respiratory support with endotracheal intubation) and respiratory support need in the neonatal intensive care unit were more common in magnesium sulfate treatment group. But first and fifth minute APGAR scores, neonatal convulsion, neonatal hypotonia and neonatal encephalopathy rates were similar between the groups. Prior publications that have described an association between $MgSO_4$ and neonatal depression analyzed populations with prolonged exposure in the context of preeclampsia; although our results are not suitable for this population, our findings are reassuring in the context of $MgSO_4$ administration that is limited to maximum a 12-hour exposure for neuroprotection. Furthermore, there are other factors such as low birth weight that may be implicated in the increased resuscitation in those infants.

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend the short-term (usually less than 48 hours) use of magnesium sulfate in obstetric care for appropriate conditions including fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery but do not state a standard therapeutic protocol for this indication [21]. Due to the heterogeneity of the protocols Reeves et al. proposed a standard treatment regimen as given a loading dose of 6 g of magnesium sulfate over 20-30 minutes and maintenance infusion of 2 g per hour is then continued for 12 hours or until delivery, whichever comes first [22] as we administered in this study. We believe that for adopting maternal magnesium treatment for the purpose of fetal neuroprotection, it is crucial to constitute standard treatment protocols and determine strict eligibility criteria for the treatment.

Conclusion

In conclusion, in this study, we demonstrated the effect of $MgSO_4$ for fetal neuroprotection on maternal and neonatal outcomes of pregnants delivered before 32 weeks. The results of this study suggest that $MgSO_4$ treatment for fetal neuroprotection has a beneficial effect on intraventricular hemorrhage rate, but there was no significant difference in IVH grade and periventricular leukomalacia rate between the groups. The widespread use of prenatal $MgSO_4$ for the purpose of fetal neuroprotection before 32 weeks of pregnancy at a standard dose protocol could improve the neonatal neurological outcomes.

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