Original Investigations

Does Antenatal Magnesium Sulphate improve hearing function in premature newborns?

Kasapoğlu et al. Magnesium for hearing impairement

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Abstract

Objective: To evaluate whether antenatal magnesium sulphate (MgSO4) exposure has a neuroprotective effect against hearing impairment in premature newborns.
Materials and Methods: Retrospective cohort study performed with prematurely (<37 weeks) delivered newborns at a tertiary university hospital. Newborns of 92 women who received MgSO4 infusions (study group) for various indications were compared to newborns of 147 women who did not receive MgSO4 infusions (control group). Every eligible premature newborn underwent hearing screening by auditory brainstem response (ABR) testing before being discharged from the hospital.
Results: The fail rate in ABR hearing screening was 3.3% (n=3) in the study group and 10.9% (n=16) in the control group (p=0.034). The rate of concurrent use of betamethasone was higher in the study group (72.8%; n= 67) compared to control group (29.2%; n=43) (p<0.001). Other neonatal parameters such as the number of neonates who are small for gestational age and the rate of microcephaly were similar between the groups (p=0.54, p=0.48, respectively). After adjusting for co-variates including the use of betamethasone and gestational age at delivery, we did not find any statistically significant association between antenatal administration of MgSO4 and fail rates in hearing screening by ABR testing (p=0.07).
Conclusion: Our results do not suggest a clear and definite benefit from antenatal MgSO4 infusion in respect of hearing impairment in premature newborns.
Keywords: Magnesium sulphate, prematurity, hearing screening, hearing loss, ototoxicity, neuroprotection.

Introduction

Currently, magnesium sulphate (MgSO4) is widely used in obstetric care for various indications to improve obstetric outcomes, mainly to reduce the risk for eclampsia and as a tocolytic agent, although its efficacy as a tocolytic agent is still controversial. A recent indication have been established to provide neuroprotection for immature fetal central nervous system and to reduce the incidence of major neurological morbidity, particularly cerebral palsy in premature newborns (1,2).

The earliest data on the use of MgSO4 for neuroprotection have been published in 1980s and 1990s (3,4). Data were collected from infants who were exposed to MgSO4 in utero. In those cases, perinatal morbidity including intracranial events and cerebral palsy were observed to be less severe (3,4). According to those preliminary findings, magnesium has been investigated widely for its neuroprotective effects and furthermore, guidelines have been created especially for antenatal administration of MgSO4 (AAM) in premature deliveries (1). In this regard, MgSO4 infusions address protecting fetal central nervous system in preterm infants as well as reducing the rate of preterm births in patients presenting with threatened preterm labor.

Recent advances in in intensive care techniques are associated with improved survival rates in premature infants (5). However, the rate of preterm birth complications has not been reduced yet (6). Currently, prematurity is the sole factor addressed as the leading cause of the central nervous system morbidities (7). Major neurological disorders accompanying prematurity include cerebral palsy (CP), mental retardation, sensorineural hearing loss (SNHL), and blindness (8,9). In spite of decreased rates of prematurity-related mortality, the incidence of SNHL has remained high, in a range varying from 0.2% to 6.4% (10). Hearing loss, which also impairs speech and language development, is a major disability closely associated with social and physical development of the newborn, and has a significant impact on the quality of life. Congenital hearing loss is a universal health problem and is one of the health measurements which are used to determine health-related quality of life (11). Early recognition and adequate treatment regimens can mitigate adverse outcomes. This is the reason why hearing screening programs in newborns are essential and hearing screening is recommended in all infants during the first month after delivery (12).

There is lack of evidence-based data on the efficacy of AAM in preventing hearing loss in preterm infants. Most of the previous studies assessing magnesium usage for neuroprotection have evaluated CP as the primary outcome (2), but there are insufficient data on cochlear functions. There are only limited studies which suggest beneficial effects of magnesium administration on noise induced hearing loss in adults (13). However the mechanism of noise induced hearing loss and the mechanism of congenital hearing loss are different. Considering widespread use of AAM in obstetric care, we aimed at assessing potential neuroprotective effect of antenatal MgSO4 on auditory nerve development and sensorineural hearing in premature newborns.

Materials and Methods

This study was performed in a tertiary University Hospital in Turkey, within a period of 2 years (January 2015-2017). The study protocol was approved by the Local Research Ethics Committee at the beginning of the study (2017-14/12). Each participant was informed about the study and provided their written consent.

All preterm infants (< 37^{th} gestational weeks) born within this period of 2 years were included in the study. Medical records of study subjects were retrospectively reviewed. Neonates born from mothers who were administered antenatal MgSO4 for at least 8 hours, before the delivery for various indications (prophylaxis for eclampsia,

tocolysis or neuroprotection for prematurity) were enrolled in the *study group*. Neonates whose mothers did not receive MgSO4 constituted the *control group*. Among them, newborns who had a history of intrauterine infections, lethal congenital abnormalities, craniofacial anomalies, and who died after birth were excluded from the study.

Antenatal MgSO4 (Magnesium Sulfate 15%; Biofarma) was administered as continuous intravenous infusion at a rate of 2 grams per hour, for at least 8 hours following 4.5 grams of a loading dose, as recommended, for any indications including neuroprotection, tocolysis or prophylaxis for eclampsia. Antenatal administration of corticosteroids consisted of 2 courses of 12 mg betamethasone, when indicated.

Main neonatal outcome measurement was the effect of fetal magnesium sulphate exposure on fail rates in ABR hearing screening in newborns.

As all of the newborns were premature and had risk factors for hearing loss, all eligible newborns underwent auditory brainstem response (ABR) hearing screening during the first month after delivery before being discharged from the neonatal intensive care unit (NICU). The results of ABR tests were evaluated in these two groups , since ABR allows neurophysiologic assessment of brainstem maturation and auditory pathway in newborns.

The ABR tests were performed using Madsen Accuscreen (Otometrics, Denmark). The ABR is done with 30 dB click stimulus with disposable, hydrogel electrodes and the standard for the device was, EN-60645-7, Type-2.

Based on the results of screening ABR test, newborns were considered to have 'passed the test', if the hearing level did not exceed 30 decibels (dB NHL) of normal hearing level in *both* ears, if not, they were considered to have 'failed the test', according to the suggested algorithm of hearing screening of newborns.

Maternal characteristics which could affect neonatal outcomes such as maternal age, parity, use of antenatal corticosteroids, presence of preeclampsia, premature rupture of membranes, delivery route and neonatal characteristics including gestational age at birth, birth weight, Apgar scores, and umbilical cord arterial power of hydrogen (pH) values were also retrieved. In addition, other neonatal parameters evaluated within the first 28 days, such as microcephaly and the incidence of postnatal morbidities including requirement for mechanical ventilation, neonatal sepsis and exposure to ototoxic agents, meningitis, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), respiratory distress syndrome (RDS), phototherapy requirement, bronchopulmonary dysplasia were analyzed as composite outcomes. The rate of pathological electroencephalography (EEG), visual evoked potentials and early Denver Developmental Screening test results were also analyzed.

Statistical Analysis

SPSS (Released in 2012. IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY) version 21.0 was used to analyze study data. The distribution pattern of the data was examined for normality with the Shapiro–Wilk test. Variables were reported as mean ± standard deviation or median (minimum–maximum) values. According to the normality test result, the independent samples t-test or Mann-Whitney U test were used for intergroup comparisons. The Chi-square test or Fisher's exact test was used for the comparisons of categorical variables. Binary logistic regression analysis was performed in order to determine independent risk factors that could possibly affect fail rates in the screening test . The level of significance was set at α=0.05.

Results

During a period of two years 285 eligible women were administered MgSO4 and/or

gave birth before 37th weeks of gestation. Newborns who died after birth (n=37, 12.9%) and whose hearing screening results were not available (n=9, 3.1%) were excluded from the study. A total of 239 newborns were included in further statistical analysis. Mothers of 92 out of 239 newborns (38.5%) received MgSO4 whereas mothers of 147 (61.5%) newborns did not.

The mean maternal age at delivery was similar between the study group and the control group (30.5±5.9 years and 30.7±5.7 years respectively, p=0.83). Cesarean delivery rate was significantly higher in the study group (80.4%) compared to the control group (68.8%) (p=0.048) (Table 1).

The median gestational age at delivery was significantly lower in the study group compared to the control group (32 weeks [range: 26 – 36^{+3} weeks] and 35 weeks [range 26^{+5} – 36^{+5} weeks], respectively; p<0.001). The incidence of premature rupture of membranes was comparable between the two groups (2.4% versus 5.1%, p= 0.29). The prevelance of preeclampsia was statistically significantly higher in the study group compared to the control group (41.3% versus 3.4%, p<0.001). The mean birth weight was lower in the study group compared to the mean birth weight in the control group (1733±586 g and 2336±668 g, respectively; p<0.001). Apgar scores at one and five minutes were lower in the newborns in study group than those in control group (p=0.017 and p=0.03, respectively). There was no significant difference between two groups in the umbilical cord pH measurements (p=0.23) (Table 1).

19 newborns failed the screening ABR test, in total. Fail rates significantly differed between the two groups (3.3% [n=3] for the study group and 10.9% [n=16]) for the control group, respectively (p=0.034) (Table 2). Seven (36.8%) out of 19 infants who failed in the ABR test had unilateral hearing loss and 12 (63.2%) had bilateral loss .

The rate of antenatal administration of betamethasone (AAB) was significantly higher in the study group (72.8%) compared to control group (29.2%) (p<0.001). No statistically significant association was found between AAB and the result of ABR hearing screening in the analysis of screening test results by the rate of AAB (p=0.31).

The rates of small for gestation age neonates and the incidence of microcephaly did not significantly differ between the two groups (p=0.54, p=0.48, respectively). Composite neonatal outcome except RDS was similar in these 2 groups (Table 3). Additionally, the rate of pathological EEGs, visual evoked potentials and the results of early Denver Developmental Screening test and being treated in NICU (neonatal intensive care unit) did not significantly differ between the two groups (Table 3).

Adjustments were analyzed using a logistic regression model for AAM, AAB, and gestational age (day) as major variables significantly differ between groups and that could be associated with ABR hearing screening outcomes. In this final model, none of the variables was found to be an independent variable for ABR results (Table 4).

Discussion

The use of magnesium sulphate is mainly recommended for the prophylaxis of eclampsia and recently, for the protection of fetal central nervous system in preterm labor before 32 weeks (1). In our study, we aimed at evaluating whether AAM exposure had a neuroprotective effect on hearing in premature newborns. Our results showed that the fail rate in the ABR screening test was lower in group of newborns exposed to antenatal MgSO4 than the fail rate in the group of neonates who were not exposed to antenatal MgSO4 (p=0.034). Nevertheless, after adjustment for co-variates including betamethasone and gestational age at delivery (day), we did not find any statistically significant association between antenatal administration of MgSO4 and the fail rate in the ABR screening test (p=0.07).

Magnesium is one of the mandatory elements for many physiological processes for the systems in the body (14), and it participates in preserving cell membrane polarization by regulating calcium channels (15). In this context, magnesium contributes to cochlear physiology and has a role in hearing process. Despite its known neuroprotective effects and protective effects against cerebral palsy (CP), data on the effect of magnesium on sensorineural hearing is limited. In a study conducted with guinea pigs, a negative correlation was observed between cochlear magnesium levels and hearing loss. It was demonstrated that magnesium content of the inner ear has a regulatory function and hinders reactive oxygen species (ROS) formation after noise exposure (16,17). Furthermore, there is evidence of cellular damage due to oxidative stress associated in magnesium deficiency (18). Withal, in adults, protective effects of oral magnesium supplementation have been demonstrated in hearing loss due to acoustic trauma (13). Most of the studies mentioned above, were conducted with animals or adults and particularly evaluated noise-induced cochlear damage. Based on those studies, we aimed at evaluating possible protective effects of magnesium on sensorineural hearing in premature newborns. We specifically evaluated premature newborns, because of higher incidences of SNHL in this population (19), which is related to delayed neurodevelopment (12,19).

In line with previous studies, we found a high percentage of hearing impairment as assessed by the ABR screening test (7.9%), in our population of premature newborns. Although, various mechanisms could be suggested for the development of hearing loss in premature newborns, prematurity alone is one of the established major risk factors (19) as fetal audiological development mainly occurs between 20 and 33 weeks of gestation. Therefore, the risk for labyrinth pathologies of the inner ear is also increased in premature newborns (20). This is the reason why we included premature newborns in this study.

Other etiologic factors include hypoxic damage, mechanical ventilation, hemorrhage, and increased levels of bilirubin and administration of ototoxic drugs (e.g. aminoglycoside antibiotics). In a previous study, which investigated risk factors for hearing loss in preterm newborns, it was suggested that the etiology of hearing loss was multifactorial rather than a single factor that has a prominent effect on ototoxicity (21). Regarding possible clinical risk factors for hearing loss, clinical factors were evaluated in two groups separately in this study . Intergroup comparisons indicated that newborns in the study group who received antenatal MgSO4 had significantly lower birth weights and lower at the one minute and five minute Apgar scores. But they performed better in the hearing screening test than newborns who did not received antenatal MgSO4.

A recent Cochrane review, which evaluated potential neuroprotective effect of antenatal magnesium in preterm newborns, included limited number of studies (2). Furthermore, most of these studies evaluated mortality, gross motor disability or CP as primary outcomes. Mortality rates did not differ with magnesium pretreatment (RR 1.04 [95% CI 0.92–1.17]) (2). In our study population, we also found a very high mortality rate (12.9%), supporting that prematurity was a risk factor.

To date, there are not enough data yet to interpret protective effect of magnesium administration on sensorineural hearing . Only one study, which was included in the above review evaluated neurological impairment in 1047 participant (22). In that study, hearing loss was not separately evaluated, instead it was accepted as a component of moderate neurological disability. The authors did not report significant difference between groups of patients who received magnesium and who did not, with respect to sensorineural disability (22).

Only a retrospective study, evaluated the outcomes of hearing screening for any possible associations between these outcomes and antenatal maternal medications. None of the medications including magnesium and corticosteroids was reported to be associated with a reduced risk for hearing loss (23). It should be emphasized that in most of the studies, which evaluated neuroprotective effects of magnesium, participants also received corticosteroids. In another recent study, which only evaluated the effects of antenatal steroid administration on hearing function in newborns, no associations were found between corticosteroids and hearing screening results (24). Moreover repeated antenatal administration of steroids rather than a single dose did not add benefit based on ABR evaluations in newborns, in another study (25). Moreover in another study, it was indicated that steroid dosage made no difference in hearing function of newborns born after the 34th gestational week (26). In our study population, we also used betamethasone to improve neonatal outcomes. In line with those studies, we did not find any direct association between antenatal betamethasone administration and neonatal ABR hearing screening test results ($p=0.31$) in univariate, as well as further multivariate analyses.

Preliminary results of this study on AAM indicated improved hearing screening test results in premature newborns in our cohort. However, further analysis (multivariate) of data did not support the initial results. Therefore, we could not gather a robust data indicating a clear benefit from AAM in terms of hearing impairment in premature newborns. This study has significant implications for hearing loss in premature newborns as a a high-risk population for SNHL and also points out that AAM is a possible adjuvant therapy that may reduce the incidence of SNHL in this group.

In our study population we detected a higher incidence of impaired hearing based on screening outcomes in neonates born after 34 weeks of gestation compared to preterm infants who had received antenatal magnesium. A possible explanation for this result might be the potential protective effect of magnesium on cochlear functions or on the fetal brain, which might still remain important in neonates born after 34 weeks of gestation. However possible confounders cannot be excluded. Any discrepancy in such association needs to be elucidated with further studies.

Although this study included all premature newborns (<37 weeks) within a period of 2 years, relatively small study population and retrospective nature of the study were the limitations of this study. Additionally, for the newborns who were treated in neonatal intensive care units before undergoing the ABR test, we could not exclude the possible external confounding factors.

Conclusion

Our results do not suggest a clear and definite benefit from antenatal MgSO4 infusion in respect of hearing impairment in premature newborns. For the usage of MgSO4 as a neuroprotective medication against hearing impairment in premature newborns, further research is warranted to reach a definite conclusion.

Declaration of interest statement

All authors state that, there is no conflict of interest or funding.

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Table 1. Demographic and clinical characteristics of the cohort groups

	Study Group (n=92)	**Control Group (n=147)**	***p* value**
Maternal age (years)	30.5±5.9	30.7±5.7	0.830
Cesarean delivery	74 (80.4%)	99 (68.8%)	**0.048**
Gestational age (weeks)	32 (26–36^{+3})	35 (26^{+5}–36^{+5})	**<0.001**
Incidence of early membrane rupture (%)	5.1%	2.4%	0.29
Birth weight (grams)	1.733±586	2.336±668	**<0.001**
Presence of preeclampsia	38 (41.3%)	5 (3.5%)	**<0.001**
Apgar at one minute	7 (1–10)	8 (1–10)	**0.017**
Antenatal administration of betamethasone	67 (72.80%)	43 (29.20%)	**<0.001**
Umbilical arterial pH	7.30 (6.8–7.4)	7.31 (7–7.53)	0.230

Data were presented as median (minimum-maximum), mean ± standard deviation and n(%)

Table 2. ABR Hearing screening outcomes with respect to antenatal administration of MagnesiumSulphate

	Study Group	**Control Group**	***p* value**
Infants who passed ABR (n=220)	89 (96.7%)	131 (89.1%)	**0.034**
Infants who failed ABR (n=19)	3 (3.3%)	16 (10.9%)	

Data were presented as n (%)

Table 3. Neonatal parameters and postnatal morbidities in the study and control groups

Variable(n)	Study group	Control group	p value
	(n=92)	(n=147)	
Being treated in NICU	38(41.3%)	61(41.5%)	0.97
Small for gestational age (SGA)	7(7.6%)	12(8.2%)	0.543
Microcephaly	4 (4.3%)	8(5.4%)	0,48
Intubation	19(20.7%)	32(21.8%)	0,48
Sepsis	18(19.6%)	20(13.6%)	0,46
Phototherapy requirement	18(19.6%)	28 (19%)	0,52
Meningitis	3 (3.3%)	4(2.7%)	0,54
Bronchopulmonary dysplasia	4 (4.3%)	9 (6.1%)	0,39
Intraventricular hemorrhage	6(6.5%)	9(6.1%)	0.55
Retinopathy of prematurity	4 (4.3%)	4(2.7%)	0.37
Respiratory distress syndrome	25(27.2%)	24(16.3%)	**0.03**
Pathological electroencephalography finding	2(2.2%)	3(2%)	0.63
Pathological visual evoked potentials finding	2(2.2%)	3(2%)	0.63
Pathological Denver finding	4(4.3%)	7(4.8%)	0.57
Data were presented as n (%)			

Table 4. Logistic regression model of variables associated with the ABR hearing screening test results

Factor	OR (95 %CI)	p value
Antenatal administration of magnesium sulphate	0,23 (0,05-1,19)	0,08
Antenatal administration of betamethasone	1.59 (0.39-6.43)	0.51
Gestational age at delivery (day)	1.01 (0.98-1.04)	0.34
Being treated in NICU	1.52(0.46-4.99)	0.48
OR: Odds ratio CI: Confidence interval		