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ARAŞTIRMA / RESEARCH

Changes on preterm morbidities with antenatal magnesium

Antenatal magnezyum ile prematüre morbiditelerindeki değişiklikler

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Abstract

Purpose: The effect of magnesium sulphate ($MgSO_4$) to mothers with imminent premature birth at <34 weeks on neonatal morbidities like intraventricular hemorrhage, feeding intolerance, retinopathy or bronchopulmoner dysplasia is not clear. We evaluated the effect of antenatal magnesium sulfate exposure on premature early and late morbidities and mortality retrospectively.

Materials and Methods: 108 infants ≤ 32 gestational age having antenatal magnesium were grouped as Mg (+) and 172 infants ≤ 32 gestational age not having antenatal magnesium were grouped as Mg (-).

Results: Respiratory Distress Syndrome, intraventricular hemorrhage, severe intraventricular hemorrhage (grade 3 and 4), retinopathy of prematurity and bronchopulmonary dysplasia were less in Mg (+) group compared to Mg (-) group but it is not statistically significant, except Respiratory Distress Syndrome.

Conclusion: This retrospective study showed that ante natal exposure to $MgSO_4$ did not have statistically significant beneficial effect on either morbidities or mortality in premature infants.

Keywords: Antenatal magnesium, premature morbidities, intraventricular hemorrhage, feeding intolerance, patent ductus arteriozus

Öz

Amaç: 34 gestasyonel haftadan once doğan bebeklerin annelerine yapılan antenatal magnesiyum sulfatın, bebeklerdeki intraventriküler kanama, beslenme intoleransı, retinopati ya da bronkopulmoner displazi gibi morbiditeler üzerine etkisi henüz tam açıklığa kavuşturulmamıştır. Biz antenatal uygulanan magnezyum sulfatın prematüre bebeklerde erken ve geç morbidite ve mortaliteye etkisini retrospektif olarak araştırmayı amaçladık.

Gereç ve Yöntem: Antenatal magnesiyum alan 108 prematüre bebek Mg (+) grubu, ve antenatal magnesiyum almayan 172 prematüre bebek Mg(-) grubu,oluşturdu.

Bulgular: Respiratuar Distres sendromu, intraventriküler kanama, ağır intraventriküler kanama (evre 3 ve 4), premature retinopatisi, bronkopulmoner displazi Mg (+) grupta daha düşük saptanmasına ragmen sadece Respiratuar Distres sendromu için istatistiksel olarak anlamlı idi.

Sonuç: Bu retrospektif çalışmada antenatal magnesiyum uygulamasının premature bebeklerde morbidite ve mortalite üzerine istatistiksel anlamlı bir yararı gösterilemedi.

Anahtar kelimeler : Antenatal magnesiyum, prematürelik morbiditesi, intraventriküler kanama, beslenme intoleransı, patent duktus arteriozus

INTRODUCTION

Prematurity is the leading cause of infant mortality and morbidity worldwide. Despite marked improvements in survival rates of premature infants, the risk of early preterm morbidities like intraventricular hemorrhage (IVH), feeding intolerance, patent ductus arteriozus (PDA) and late morbidities like retinopathy (ROP), bronchopulmonary dysplasia (BPD) or neurodevelopmental impairment, including cerebral palsy has not decreased over recent years.

Very preterm birth and very low birth weight are principal risk factors for intraventricular hemorrhage (IVH) and cerebral palsy[1-4]. In addition, the incidence of bilateral isolated hearing loss increased in the

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presence of intraventricular hemorrhage[5]. Also, cerebral palsy is usually seen with intraventricular hemorrhage and intraparenchymal hemorrhage[6,7].

Perinatal neuroprotection aims to reduce these outcomes. Administration of magnesium sulphate ($MgSO_4$) to mothers with imminent premature birth at <34 weeks is a neuroprotective strategy to prevent cerebral palsy[8-10]. Although some national guidelines based on relevant clinical evidence present, ongoing controversies about aspects of this therapy remain. The gestational age threshold for optimal $MgSO_4$ benefit in the neuroprotective trials was not clear below <34 weeks also[11].

Maternal administration of $MgSO_4$ may be associated with adverse outcomes in a dose– response manner as adverse neonatal outcomes have been associated with higher ionized magnesium concentrations in umbilical cord blood[12].

Infants who had intraventricular hemorrhage (IVH) were more likely to have been delivered to mothers with higher serum ionized magnesium levels[12]. Extracellular magnesium influences intracellular calcium mobilization of the vascular muscles cells and also endothelial cells, and enhances PGI production; both of the mechanisms can contribute to the delayed closure of the ductus arteriosus[13].

The effect of antenatal administered MgSO4 on the gastrointestinal system still controversial. There are studies concerning the gastrointestinal blood flow of infants who were exposed to antenatal magnesium[14,15]. Pathological blood flow parameters in the superior mesenteric artery were reported to predict problems of intestinal motility and tolerance of enteral feeding[16].

In our unit, $MgSO_4$ has been used as an anti-eclamptic agent, but not as a neuroprotective agent until recently. We evaluated the effect of antenatal magnesium sulfate exposure on premature morbidities and mortality

MATERIALS AND METHODS

Çukurova University Balcalı Hospital is a tertiary perinatal center that accepted referral cases for maternal or fetal indications. After 2013, if there is no contraindication, antenatal magnesium for neuroprotection is administered together with bethamethasone to ≤34 gestational week (GW) pregnant women who have premature birth risk in Çukurova University Balcalı Hospital Obstetric Clinic. $MgSO_4$ is administered with a 6gr/30min loading dose and 2 gr/hour maintenance infusion doses. After 24 hours, if delivery had not occurred and was not determined imminent, the magnesium sulfate was discontinued.

In this study, ≤32 gestational week infants with completed antenatal steroid doses were studied retrospectively. Magnesium sulfate was given as a neuroprotective agent only and not for tocolysis. Inborn infants who were hospitalized in our Neonatal Intensive Care Unit (NICU) were divided into two groups according to antenatal magnesium for neuroprotection. Infants, born between 2011-2012 formed Mg(-) group and infants born between 2014-2016 formed Mg(+) group. Other invasive and non invasive procedures in NICU and obstetric clinic were the same in study periods.

Multifetal pregnancies, except diamniotic twins, and infants with congenital abnormalities were excluded from this study. Neonatal variables included resuscitation at birth, need for mechanical ventilation, duration of mechanical ventilation, infection, symptomatic patent ductus arteriozus (PDA), starting day of enteral feeding, full enteral feeding time, necrotizing enterocolitis, retinopathy, chronic lung disease, duration of hospitalization. Demographic properties of the neonates were collected from hospital data. Newborns with culture-positive sepsis, clinical signs of sepsis with negative blood culture, or meningitis before 72 hour of life were classified as having early onset infection.

The diagnosis of PDA was confirmed by echocardiogram in infants with suspected PDA based on clinical criteria that included cardiac murmur, bounding pulses, respiratory deterioration, increased oxygen requirements, or increased CO_2 retention, wide differential blood pressure, hypotension, decreased urine output and metabolic acidosis.

All babies were evaluated in the first week of life for IVH and then weekly by the same neonatologist. Intraventricular hemorrhage was classified according to Papile classification[17]. Necrotizing enterocolitis was diagnosed according to Bell stage II criteria[18].

Feeding intolerance was diagnosed with at least two of the following criteria: 1) Less than 75 ml/kg/day enteral feeding at the end of the first postnatal week, 2) Gastric residuals (gastric aspirate more than 50% of previous feeding volume), 3) Emesis/Vomiting, 4)

Abdominal distention (increase in abdominal girth), 5) Gastrointestinal bleeding[19,20].

Bronchopulmonary dysplasia (BPD) was defined as oxygen dependency at 36 weeks postconceptional age for those with gestational age ≤ 32 weeks and at 56 days for those with gestational age > 32 weeks[21]. Retinopathy of prematurity (ROP) was diagnosed by direct ophthalmoscope as defined by the International Classification of ROP[22] and babies were evaluated at 52nd postconceptional weeks age and the most severe ROP stage was recorded.

Parental consent was obtained following a protocol approved by the Ethical Committee of the Çukurova University (April 2017/63).

Statistical analysis

The data was analyzed using SPSS 19.0 software package for Windows. Categorical variables were summarized as numbers and percentages and continuous variables were summarized as mean and standard deviation (median and minimum-maximum if necessary). Chi-square test was used to compare groups for categorical variables. Continuous variables were compared using the t-test for normally distributed variables. Mann-Whitney-U test were used for non-normal distributed continuous data. P-values less or equal to 0.05 were accepted as statistically significant..

Table 1. Properties of the neonates

	Mg(+) N=108 Mean± SD Median(min-max)	**Mg(-) N= 172 Mean± SD Median(min- max)**	p
Gestational week(wk)	28.76±2.4 (23-32)	28.58±2.36 (23-32)	0.49
Birth weight(gr)	1197.26±457.36 (500-2780)	1169.18±444.65 (360-2950)	0.71
Starting day of enteral feeding (day)	4.02±4.06 3(1-26)	4.98±5.32 3 (1-36)	0.12
Time of full enteral feeding (day)	24,79±19,07 21(1-109)	24.51±16.25 20(1-105)	0.82
Duration of oxygen therapy (day)	14.76±20.23 6.5 (0-101)	13.42±15.95 8 (0-110)	0,65
Duration of hospitalization (day)	43.33±31.41 (1-138)	41.36±31.59 (1-160)	0.56
Duration of ventilator support (day)	17.24±21.09 10 (1-106)	15.0±16.1 16.1(1-110)	0,82
	Mg(+) n 108 N(%)	**Mg(-) n 172 N(%)**	
Male	56 (51.9%)	93 (54.1%)	0,71
Resuscitation at birth n=162	63 (58.3%)	99 (57.5%)	0.89
Ventilator support n=245	94 (87.0%)	151(87.8%)	0,85
RDS n=177	58 (53.7%)	119 (69.1%)	0.01
PDA (+)	18 (16.7%)	25 (14.5%)	0.63
Early neonatal sepsis n=252	100 (92.5%)	152 (88.3%)	0.25
IVH(+)	32 (26.6%)	73 (42.4%)	0.32
IHV grade 3-4	10 (9.2%)	36 (20.9%)	0,09
Feeding Intolerance(+)	70 (64.8%)	112(65.1%)	0.96
ROP (+)	12 (11.1%)	38 (22.0%)	0.11
BPD (+)	3 (2.8%)	7 (4.1%)	0.36
Death	28 (25.9%)	49(28.5%)	0.64

RESULTS

Total 235 infants in 2011-2012 period and 342 infants in 2014-2016 period were born and hospitalized in NICU. 98 infants did not complete antenatal steroid, 93 infants had congenital anomalies (cardiac, renal, neurologic, and metabolic), 67 infants had antenatal magnesium due to preeclamptic mother and 39 infants sent to other hospitals

During study periods, 280 infants with completed antenatal steroid therapy were enrolled in the study. Mean gestational weeks and birth weights of all infants were 28.91±2.62 (23-34) week and 1220.61±498.25 (360-2980) gr. 101 of the infants were <1000 gr birth weight and 95 infants were <28 GW. 17 infants of the study groups died before 4th day of life due to difficulty in evaluation of MgSO4 effect on morbidities. 108 infants having antenatal magnesium were grouped as Mg (+) and 172 infants not having antenatal magnesium were grouped as Mg (-). Gestational age, birth weight, genders, resuscitation requirement at birth, ventilator support incidence, duration of hospitalization and mortality rate were similar between two groups (Table 1).

18 neonates [7 (6.4%) neonates from Mg (+) group and 11(6.4%) neonates from Mg(-) group] could not start any enteral feeding. 55 neonates [21 (19.4%) neonates from Mg (+) group and 34(19.8%) neonates from Mg (-) group] could not get full enteral feeding. None of the babies had necrotizing enterocolitis. Feeding intolerance, starting day of enteral feeding and time of full enteral feeding were similar between groups (Table 1).

Respiratory Distress Syndrome (RDS), intraventricular hemorrhage, severe intraventricular hemorrhage (grade 3 and 4), ROP and BPD were less in Mg (+) group compared to Mg (-) group but it is not significant statistically ($p>0,05$) except RDS($p<0,05$)

DISCUSSION

This study analyzed the effect of antenatal $MgSO_4$ administration on premature morbidities and mortalities. This retrospective study showed that ante natal exposure to $MgSO_4$ did not have any effect on either morbidities or mortality in premature infants. Investigations for decreasing IVH and neuroprotection in preterm infants continue. Although antenatal steroid is very effective in decreasing IVH, unfortunately still some preterm babies have IVH. Although neuroprotective effect of antenatal magnesium is revealed in animals, exact mechanism of action is not yet understood. In animal models, magnesium sulfate decreases injury after hypoxia- ischemia by decreasing inflammatory cytokines, free radicals, and calcium-induced excitotoxicity[23,24]. The underlying explanation for the neuroprotective effects of magnesium sulfate in premature infants is unclear. Mechanisms suggested to explain the neuroprotective effects of magnesium sulfate include stabilization of rapid fluctuations in blood pressure and increased cerebral blood flow[25].

The effect of $MgSO_4$ on IVH is controversial; many reports support it but on the other hand many reports did not find this effect of magnesium[26-32]. Kuban et al[33] in 1992 reported a decrease from 18.9% to 4.4% in IVH in preeclamptic mothers who had antenatal magnesium administration. Also they found that maternal receipt of magnesium sulfate was associated with decreased risk of germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) even in those babies born to mothers who apparently did not have preeclampsia. Observative studies of Finesmith, Perlman and Wiswell also reported an association between decreasing IVH incidence and antenatal magnesium[26-28]. But many other observative reports did not demonstrated any reduction in IVH after antenatal MgSO4 administration[29-32]. Gano et al[34] reported that antenatal magnesium sulfate was selectively associated with a reduced risk of cerebellar hemorrhage, but not other forms of brain injury, including IVH and white matter injury.

In 2003, Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Colloborative Group did not find any difference in terms of IVH and reported that also neurodevelopment at 2 years of age was not different[35]. In addition Marret et al[36] also reported that they did not find any difference in terms of IVH in infants with and without antenatal magnesium. In 2009 metanalysis demonstrated that there was not any statistical difference in terms of IVH grade >3/4 between babies with and without antenatal magnesium[10]. Zeng et al[37] also could not showed a positive effect of antenatal magnesium on IVH. In our study, we also did not a demonstrated a statistical difference in terms of IVH with transfontanel USG between groups.

There are studies concerning about the dose of antenatal magnesium for neuroprotection. Higher doses might increase mortality while lower doses have neuroprotection effect. There are still discussions about effective and safe dose of magnesium[38]. In the Magnesium and Neurologic Endpoints Trial adverse outcomes were found to be associated with magnesium exposure in a dose-related fashion[12].

In our study $MgSO_4$ is administered with a 6 gr/30min loading dose and 2 gr/hour maintenance infusion doses and stopped if delivery does not occur in 24 hours in our study. A study in mice reported that exposure to high doses of magnesium sulfate resulted in apoptotic cell death in the developing neonatal brain[39]. Effects of antenatal magnesium on infants are still being researched. del Moral et al[40] reported that antenatal exposure to MgSO4 in cohort of extremely low birth (ELBW) infants is associated with a higher risk of PDA with dose-related manner. In our study there was not any statistical difference in terms of PDA between groups.

Infants of mothers who received more than 80 g of intravenous magnesium sulfate prior to delivery were reporreported more likely to develop feeding intolerance[41]. Reduced gastrointestinal motility and limited magnesium sulfate clearance are proposed mechanisms of neonatal enteral feeding intolerance41. In current study, the feeding intolerance, starting day of enteral feeding and duration of full enteral feeding were not different between groups. Less is known about the effect of antenatal administered MgSO4 on the gastrointestinal system. While Robel-Tillig et al16 reported pathological blood flow parameters in the superior mesenteric artery (SMA) to predict problems tolerance of enteral feeding, Gursoy et al42 did not find any difference in blood flow velocity of MgSo4 exposed and unexposed groups.

Ohhashi et al38 reported that the gestational week of the neonate might have role on efficiency of magnesium and it might be less effective in neonates <28 GW, while some better result might be obtained in neonates of 28-32 GW. In our study infants <32 GW were enrolled in the study. As a limitation of our study, small sample size prevented the subgroup analysis. In our study RAS was statistically different between study groups. Elimian et al[43] reported that RDS RDS was not different between magnesium exposed and unexposed groups, while Klauser et al[44] in 2012 also did not find any difference between magnesium, nifedipine and indomethasine group in terms of RDS. Our study is the first study repoting the difference in terms of RDS in MgSO4 exposed group. This result must be supported with other studies including much more cases.

The limitation of the study is the retrospective nature of the analysis. Although the data allowed the computation of the total dose of $MgSO_4$ administered to the mother, no information concerning the time between the last dose of $MgSO_4$ and delivery was available. Differences in this interval may affect the levels of $MgSO_4$ in the newborn. Also magnesium concentrations in the umbilical cord were not assessed in this study.

In conclusion, although improvements of neonatal outcome obtained with $MgSO_4$ are of potential clinical significance, other managements to decrease preterm morbidities are needed. More research is needed to assess the protective effect of $MgSO_4$ alone or in combination with other neuroprotective therapy. Local protocols should be developed with respect to its dosing and indications.

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