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Original Article

Postnatal Preventive Effect of Magnesium Sulfate on Intraventricular Hemorrhage of Preterm Infants

Asharf Mohammadzadeh[1*], Ahmad Shah Farhat[1], Reza Saeidi[1], Marziyeh Roshandel[1], Azin Vaezi[2]

1. Neonatal Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2. Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Background: Germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) are among the causes of morbidity and mortality in very low birth weight (VLBW) neonates. The aim of this study was to determine the postnatal prophylactic effect of magnesium sulfate on GMH-IVH.

Methods: In this double-blind clinical trial, 140 VLBW newborns were selected. The babies with birth weight ≤ 1500 g and gestational age ≤ 32 weeks were included. The babies with major malformation, infection, hemostatic disorders, severe cardio-respiratory failure, as well as asphyxia and resuscitation in the delivery room were excluded. They were randomly divided into two groups using a coin. The case group received 50% magnesium sulfate 4 mg/kg/day as a single dose via intravenous injection over 15-20 min for 3 days. All babies had a head ultrasound (HUS) in 24 to 48 h after birth, and if it was normal they were included in the study. The HUS was repeated in 1, 2, and 3 weeks after birth by a radiologist who did not know about the intervention. The control group received placebo sterile water in a dose similar to magnesium sulfate. The magnesium level was measured on day 4 at the end of the treatment.

Results: Although GMH-IVH was two times more in the control group, the difference was not statistically significant between the two groups (P>0.05). The difference in the grading of IVH was not also significant between the two groups (P=0.25). The level of magnesium sulfate was significantly higher in the case group (P=0.04).

Conclusion: The results of this study showed that the postnatal administration of magnesium sulfate has no effect on the prevention of IVH.

Keywords: Germinal matrix hemorrhage and intraventricular hemorrhage, Magnesium sulfate, Very low birth weight neonate

Introduction

All preterm babies are at high risk of respiratory distress syndrome (RDS) and intraventricular hemorrhage (IVH) (1). In spite of the increased survival of prematurely born infants in an era of increasingly advanced neonatal intensive care units (NICUs), germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) are among the most common causes of significant morbidity and mortality in preterm newborns. The infants, particularly those with high-grade GMH-IVH suffer from the squeal of decreased cerebral perfusion, periventricular leukomalacia, cerebral infarction, posthemorrhagic hydrocephalus, seizure, and increased incidence of handicap later during life.

Many studies reported the incidence of GMH-IVH between 30-40%; even in an advanced NICU, the incidence rate may remain as high as 40% in very low birth weight (VLBW) infants. The more premature and smaller neonates have a higher incidence of IVH, so it may be higher than 60% in infants with birth weight less than 700 g (2, 3). The occurrence of early-onset IVH differs from that of the late-onset IVH. Studies have reported that as much as 50% of IVH occurs during the first day of life, with 19-50% occurring the first 12 h or even immediately after birth. Only approximated 10% of GMH-IVH cases occur after the first week

* *Corresponding author*: Asharf Mohammadzadeh, Neonatal Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +989153146917; Email: Mohamadzadeha@mums.ac.ir

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of life in which late-onset is also common (2).

The etiology of IVH is multifactorial with different risk factors for the early onset and later occurring hemorrhage. Early-onset IVH is more likely to be severe and progress to a high grade, including the risk factors of lower gestational age, lower birth weight, fetal distress, fetal acidosis, need for resuscitation at birth, and mechanical ventilation. Late-onset IVH is related to postnatal risk factors, including RDS, seizure, pneumothorax, airway suctioning, hypothermia, abnormal blood gas, and heparin use.

Reducing the incidence of IVH is an important goal for neonatologists. Germinal matrix (GM) hemorrhage in premature newborn results from the rupture of capillaries in this area. The pathogenesis is principally related to the fragility of the GM vascular, distribution of cerebral blood flow, and coagulation disorders. Many drugs were used for the prevention and treatment of IVH in preterm newborns. Magnesium sulfate ($MgSO_4$) is a unique calcium antagonism that can act on most types of calcium channels in vascular smooth muscle by inhibiting calcium 2+ influx leading to the inactivation of calmodulin-dependent myosin light chain kinase activity and decreased contraction (4).

Magnesium may stimulate the production of prostacyclin by endothelial cells causing vasodilatation or by the inhibition of platelet aggregation. The endothelium appears to potentiate the vasorelaxant effects of antenatal magnesium through the nitric oxide-cyclic guanosine monophosphate and cyclooxygenase systems and prevents preterm labor (4). Several studies were conducted on the prenatal prophylactic effect of magnesium sulfate on IVH. In this study, we explored whether the administration of magnesium sulfate immediately after birth can reduce the rate of IVH in preterm neonates postnatally.

Methods

This double-blind clinical trial (IRCT ID: IRCT201307181162N21) was performed on 140 VLBW newborns. The study was approved by the Research Committee of Mashhad University of Medical Sciences in Mashhad, Iran. The babies with birth weight ≤ 1500 g and gestational age ≤ 32 weeks were included. The babies with major malformation, infection, hemostatic disorders, severe cardiorespiratory failure, antenatal magnesium sulfate, as well as asphyxia and resuscitation in the delivery room, were excluded. They were randomly divided into two groups using a coin. The case group received 50% magnesium sulfate 4 mg/kg/day via intravenous injection over 15-20 min for 3 days.

The control group received placebo sterile water in a dose similar to magnesium sulfate. All the babies underwent a head ultrasound (HUS) in 24 to 48 h after birth, and if it was normal they were included in the study. The HUS was repeated in 1, 2, and 3 weeks after birth by a radiologist who did not know about the intervention. It was performed by only one radiologist and confirmed by the Radiology Department. Informed consent was obtained from the neonates' parents. Demographic and clinical information, including gestational age, birth weight, gender, five-minute Apgar score, surfactant usage, blood sugar, anemia, seizure, infection, acidosis, hypoxia, pneumothorax, and hypertension, were recorded. The magnesium level was measured on day 4 at the end of the treatment.

Gestational age was based on obstetric estimate combining with the date of the last menstrual period and Ballard scale (5). The GMH-IVH was diagnosed by the HUS image. In our hospital, the standard practice is to perform 1 or 2 HUS during the first week after birth and weekly for the following 2 weeks. The grade of GMH-IVH was reported based on the criteria of Volpe (6). The analysis was performed using the student's t-test, Chi-square test, and multiple logistic analyses as appropriate. Multinomial logistic regression was constructed to quantify the relationship between the leading causes of preterm delivery and occurrence of IVH before and after adjustment. Odds ratio and 95% confidence interval were estimated. P-value less than 0.05 was considered statistically significant. The data were analyzed using SPSS software (version 11).

Results

In this study, a total of 140 preterm newborns were studied. Two groups were the same regarding the demographic factors and prenatal complications (Table 1). The mean values of birth weight in the case and control groups were 1,343±161 and 1,243±224 g, respectively. The results of the student's t-test showed that the mean value of birth weight was significantly higher in the case group (P=0.003). The logistic regression line showed no difference between the two groups except for the sodium bicarbonate administration, which was more in the control group (Table 2).

The mean numbers of risk factors in the case and control groups were 5.0±2.0 and 4.07±2.06,

Table 1. Demographic factors and prenatal complications

Characteristics	Case (n=70)	Control (n=70)	P-value
Maternal age (year) Mean±standard deviation	27.9±5.4	27.04±4.83	0.34
Gestational age (week) Mean±standard deviation	27.9±5.02	27.04±4.83	0.67
Birth weight (g) Mean±standard deviation	1,343±161	1,243±224	0.003
Male n (%)	30 (42.9)	25 (35.7)	0.01
PPROM* n (%)	18 (25.7)	14 (20)	0.42
Antenatal corticosteroids n (%)	7 (10)	0 (0)	0.01
Antenatal antibiotics n (%)	9 (12.9)	6 (8.6)	0.41
Maternal diabetes mellitus n (%)	5 (7.1)	2 (2.9)	0.44
Maternal hypertension n (%)	7 (10)	5 (7.1)	0.55

*PPROM: Preterm premature rupture of membranes

Table 2. Risk factors of intraventricular hemorrhage

Characteristics		Case (n=70)	Control (n=70)	P-value
Newborn disease n (%)	RDS*	12 (17.1)	18 (25.7)	0.45
	TTN**	23 (32.9)	19 (27.1)	
	Asphyxia	1 (1.4)	0	
	No disease	34 (48.6)	33 (47.1)	
Blood gas state n (%)	Hypoxia	54 (77.1)	44 (62.9)	0.06
	Acidosis	9 (12.9)	16 (22.9)	0.12
	Minimum oxygen saturation Mean±standard deviation	80.5±11.35	78.61±10.22	0.08
	Sodium bicarbonate administration	3 (4.3)	11 (15.7)	0.02
Ventilatory support n (%)	Intubation	10 (14.3)	14 (20)	0.37
	CPAP***	46 (65.7)	39 (55.7)	0.23
Pneumothorax n (%)		2 (2.9)	4 (5.7)	0.69
Temperature	Hypothermia	3 (4.3)	1 (1.4)	0.62
	Hyperthermia	0 (0)	(1.4)	

* RDS: Respiratory distress syndrome
** TTN: Transient tachypnea of the newborn
*** CPAP: Continuous positive airway pressure

Table 3. Distribution of intraventricular hemorrhage in two groups after intervention

	Magnesium (n=70)	Control group (n=70)	P-value
First HUS* (n)	0	3	0.25
Second HUS (n)	6	10	0.29
Third HUS (n)	5	10	.017

*Head ultrasound

Table 4. Intraventricular hemorrhage grade distribution in two groups after intervention

	Magnesium (n=70)	Control group (n=70)	P-value
Grade one (n)	5	9	0.25
Grade two (n)	3	3	
Grade three (n)	0	0	
Grade four (n)	0	1	

respectively (P=0.33). The mean values of serum magnesium sulfate in the case and control groups were 0.999±0.30 and 0.948±032 mg/dl, respectively, which was significantly higher in the case group (P=0.04). The frequency distribution of GMH-IVH was not significant in the two groups (Table 3). The difference in the grade of GMH-IVH was not also significant between the two groups (Table 4; P=0.25). We found no drug side effects in the case group.

Discussion

Preterm birth is associated with a significant developmental disability, and numerous studies have identified IVH as a major cause of adverse birth outcomes in VLBW preterm babies. The poor sequels of IVH have promoted the development of pharmacologic prevention strategies for this injury in the developing brain of preterm newborns for recent decades. These reagents include phenobarbital, pavulon, vitamin E, ethamsylate, indomethacin, ibuprofen, and recombinant activated factor VIIa. Pavulon, vitamin E, and ethamsylate have been studied many years ago, but these agents currently are not widely used (3, 7).

Prenatal and postnatal pharmacologic prophylaxes have shown various incidences of GMH-IVH. The basic reduction is generally associated with the improvement of neonatal care without the use of any drug. The NICU characteristic is essential to reduce the incidence and severity of GMH-IVH. In NICUs with a high number of patients and high neonatologist- to patient- ratio, a lower rate of severe GMH-IVH is observed. Antenatal steroids are the most specific prophylactic drugs. A systemic review published in 2007 on 4,000 babies showed a significant reduction in the risk of GMH-IVH (3).

In spite of more usage of prenatal steroids in the case group in our study, no difference was observed in the IVH prevalence. Maternal vitamin K administrations have shown no significant reduction in the overall rate and severity of GMH-IVH (3). Antenatal phenobarbital was shown to be protective in some studies, but the quality of all these studies was not good (3). Phenobarbital as the first drug used for the postnatal prevention of GMH-IVH appears to stabilize blood pressure and potentially offer protection from free radicals. Whitelaw and Odd reviewed the literature regarding the preventive effect of phenobarbital. In 8 of the 10 trails, they found no significant difference in the risk of IVH between the phenobarbital-treated and control groups. They also showed the rates of severe IVH and hydrocephalus in 4 of the 10 trials, but there was no significant difference between the two groups (8).

Indomethacin decreases prostaglandin synthesis via the nonspecific inhibition of the constitutive and inducible isoforms of cyclooxygenase. Indomethacin is thought to prevent IVH through the effects on blood flow and basement membrane maturation. The results of experimental and human studies have shown that indomethacin had a decreasing effect on both the incidence and severity of IVH (3, 9). Ment et al. studied the effect of indomethacin on the basis of gender. They found that the rate of IVH significantly decreased in male infants, and the grade of IVH was also significantly low in males treated with indomethacin (10).

Aranda and Thomas reviewed the use of ibuprofen in neonates and found that it was ineffective in the prevention of GMH-IVH (3). A meta-analysis of 27 studies about the administration of ibuprofen did not show a reduction in the incidence of IVH in a subgroup of 571 infants (11). Recombinant activated factor VII, which was used for hemophilia, is thought to act in the clotting cascade.

Other agents evaluated postnatally for treatment of GMH-IVH include pavulon, vitamin E, and ethamsylate. Ethamsylate promotes platelet adhesion and increases the stability of the basement membrane of the capillary by causing hyaluronic acid polymerization. In clinical trials, ethamsylate decreased the rate of IVH in VLBW infants with no effect on severe IVH, death, and neurological abnormality. Vitamin E as an antioxidant also decreases the rate of IVH, but the effect on the rate of high-grade IVH was not significant (3, 5).

Magnesium sulfate is widely used in obstetrics for seizure prophylaxis in preeclampsia or tocolysis. It might be neuroprotective by the stabilization of fetal cerebral circulation and reduction in the area of ischemia-reperfusion injury. Magnesium sulfate also reduces palate and adhesiveness (12, 13). Garnier et al. found that increasing magnesium sulfate in cerebrospinal fluid (CSF) during oxygen-glucose deprivation has a neuroprotective role (14). Magnesium may influence blood pressure via the modulation of structural and vascular tone. It acts on various biochemical reactions that control vascular contraction/dilation, growth/apoptosis, differentiation, and inflammation.

Magnesium is physiologically important in blood pressure regulation (4). It appears that magnesium sulfate has potential vasorelaxant in endothelium; therefore, it may protect the rupture of vessels in GM. Damage to the endothelial cells and altered brain hemostasis due to the immaturity of the preterm infant's antioxidant system and increased susceptibility to reactive oxygen species that increases the risk of IVH can be mitigated by excess magnesium in cerebrospinal fluid.

There are different results in the antenatal administration of magnesium sulfate. The results of a systemic review published in 2009 conducted on 6,000 babies showed that the risk of cerebral palsy reduced substantially. The incidence of either a small or large GMH-IVH had no reduction in a large randomized multicenter study. No significant reduction was found in a recent multicenter randomized control trial for the incidence of a large GMH-IVH. Moderate or severe cerebral palsy occurred significantly less frequently in the magnesium sulfate group, compared to that reported for the control group (3). In a study conducted by Elimian et al., the administration of magnesium sulfate was not associated with increased both mortality and morbidity in neonates (15).

Di Renzo et al. studied the combined antenatal administration of magnesium sulfate and aminophylline. They found a substantial reduction in the IVH rate (13). Anna Petrova and R Mehta studied the magnesium sulfate as a tocolytic agent and found that antenatal exposure may have a preventive effect on GM-IVH (16). Although magnesium sulfate is the first-line treatment for preeclampsia in pregnant women, it increases the risk of fetal abnormalities (17, 18).

In our project, we studied the prophylactic effect of magnesium sulfate on preterm neonates postnatally probably for the first time. The results showed no preventive effect of magnesium sulfate on the rate and severity of GMH-IVH. Although the rate of IVH was two times higher in the control group, it was not statistically significant. Birth weight was higher in the case group in spite of no difference in the prevalence of IVH.

The results of studies showed that small preterm newborns have a high incidence of IVH (2). It means that birth weight did not support the prevalence of IVH probably because of different races. On the other hand, the frequency of diabetic mothers was higher in the case group leading to more birth weight. The findings of some studies have shown that the male gender is associated with a high incidence of IVH and an increased rate of severe IVH (19, 20).

However, in our study, as the frequency of the male subjects in the case group was higher than the control group, the rate of IVH was not different. However, we controlled known confounding factors using logistic regression. We found that the administration of intravenous sodium bicarbonate was more in the control group, but no significant difference was observed in the prevalence of IVH.

Conclusion

In conclusion our study showed postnatal magnesium sulfate has no preventive effect. It may be due to the lower rate of GMH-IVH in our NICU, compared to that reported worldwide because we looked after the newborns using kangaroo mother care, low sample size, and the limited use of MRI. We recommend performing a multicentre study, with larger sample size, prolonged duration of treatment with the detection of CSF level of magnesium, and combination of magnesium sulfate with other drugs to justify the effect of magnesium sulfate on the prevention of postnatal GMH-IVH. We found no drug side effect for magnesium sulfate in the case group.

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Conflicts of interests

All the authors declare that there is no conflict of interest.

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