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ORIGINAL ARTICLE

Prenatal treatment with magnesium sulphate: Initial clinical outcomes in pre-term infants less than 29 weeks and correlation with neonatal magnesium levels☆

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KEYWORDS
Magnesium sulphate;
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Abstract
Introduction: Antenatal magnesium sulphate ($MgSO_4$) administration has shown to be effective in minimising cerebral palsy and severe motor dysfunction at the age of 2 years.

The aim of this study is to analyse the initial clinical outcome of preterm neonates less than 29 weeks who have received prenatal $MgSO_4$, as well as to determine the relationship between the magnesium dose delivered to the mother and the magnesium concentration in the neonates.
Material and methods: A prospective cohort study was conducted on neonates of less than 29 weeks gestation admitted to the Neonatal Intensive Care Unit (NICU) of Hospital Universitario de Vigo from December 2012 to July 2015. Comparative analysis was performed on the perinatal outcomes, neonatal morbidity, mortality, and magnesium levels between the groups of neonates exposed to magnesium sulphate and the control group.
Results: A total of 42 neonates were included in the study. The mothers of 28 of them had received $MgSO_4$ as a neuroprotective agent.

Statistical significance was obtained in the mortality variable. There were no significant differences in the rest of studied variables. There was a significant correlation between the full dose of $MgSO_4$ received by the mother and the levels of magnesium in the neonate in the first 24 h of life (r^2 0.436; $P < 0.001$).

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Conclusions: A lower mortality was observed in the group that had been exposed to $MgSO_4$. No significant side effects were found as a result of administering of $MgSO_4$. The $MgSO_4$ dose received by mother has a linear relationship with the magnesium levels obtained in neonates.

PALABRAS CLAVE
Sulfato de magnesio;
Neuroprotección;
Mortalidad

Terapia prenatal con sulfato de magnesio: evolución clínica de los recién nacidos pretérmino menores de 29 semanas y correlación con la magnesemia neonatal

Resumen
Introducción: La administración prenatal de $MgSO_4$ ha mostrado su eficacia en reducir la parálisis cerebral y la disfunción motora severa a los 2 años de edad.

El objetivo de este trabajo es estudiar la evolución clínica inicial de los neonatos menores de 29 semanas, que han recibido prenatalmente $MgSO_4$ con indicación neuroprotectora y dilucidar la asociación entre la dosis de magnesio administrada a la madre y las concentraciones de magnesio en suero neonatal.

Material y métodos: Estudio prospectivo de cohortes en el que se incluyó a los neonatos menores de 29 semanas ingresados en la Unidad de Cuidados Intensivos Neonatales del Hospital Universitario de Vigo desde diciembre del 2012 hasta julio del 2015. Análisis comparativo de resultados perinatales, de morbimortalidad neonatal y magnesemia entre el grupo expuesto prenatalmente al sulfato de magnesio y un grupo control.

Resultados: Se incluyó a un total de 42 recién nacidos, en 28 de los cuales sus madres habían recibido $MgSO_4$.

Se encontró significación estadística en la variable mortalidad. No hubo diferencias significativas en el resto de las variables estudiadas. Se obtuvo una correlación significativa entre la dosis total de $MgSO_4$ recibida por la madre y los niveles de magnesio del recién nacido en las primeras 24 h de vida (r^2 0,436; $p < 0{,}001$).

Conclusiones: Se ha obtenido una menor mortalidad en el grupo expuesto a $MgSO_4$. No se han encontrado efectos secundarios significativos derivados de la administración de $MgSO_4$. La dosis de $MgSO_4$ recibida por las madres tiene una relación lineal con los niveles de magnesio obtenidos en los recién nacidos.

Introduction

Although the survival rates of preterm newborns have increased significantly in the past 20 years, the incidence of cerebral palsy (CP) in children has remained stable through time, probably due to the increased survival of extremely preterm NBs and the associated morbidity and neurosensory impairment.[1,2]

The main risk factor for CP in children is preterm birth, and 35% of cases occur in children born at less than 34 weeks' gestation.[3] Cerebral palsy is 70 times more frequent in children born at less than 28 weeks and 40 times more frequent in children born at 28–32 weeks compared to children born to term.[4–7] The risk is inversely proportional to gestational age.

A Cochrane systematic review[8] published in 2009 concluded that administration of magnesium sulphate ($MgSO_4$) to women at risk of preterm birth, regardless of its purpose or route of administration, significantly reduces the incidence of cerebral palsy and severe motor dysfunction at age 2 years in children born before 32 weeks' gestation.

Two metaanalyses[9,10] published in 2009 suggest that the number needed to treat to prevent one case of CP is 63 pregnant women.

However, few studies have assessed the initial outcomes of newborns exposed to $MgSO_4$ before birth or described their clinical course during admission in the neonatal period. Studies in the literature have reported an increased incidence of hypotonia, intubation in the delivery room, a higher need for mechanical ventilation and patent ductus arteriosus, among other respiratory, haemodynamic,[11] neurologic and gastrointestinal[7,12] adverse effects.

On the other hand, there is currently no consensus regarding the dose, standard regimen, therapeutic window and safety of the use of $MgSO_4$ for neuroprotection. The cumulative dose of magnesium received by the mother that

is safe to the newborn is not known, as its association with the serum levels of magnesium in the newborn has not been sufficiently studied.[13] Thus, although there is a therapeutic window in which the neuroprotective effects of magnesium are observed, it is known that neonatal morbidity and mortality increase after serum magnesium exceeds certain levels in the newborn.[14]

The main aim of our study was to assess the initial clinical outcomes of patients admitted to a tertiary level neonatal intensive care unit (NICU) that received prenatal $MgSO_4$ for neuroprotection, to analyse the potential side effects of its administration, and last of all to determine the association between the dose of magnesium given to the mother and the serum levels of magnesium in the newborn.

Materials and methods

We conducted a prospective cohort study from December 2012 to July 2015. We included newborns delivered at less than 29 weeks' gestation to mothers that were given $MgSO_4$ for neuroprotection admitted to the NICU of the Complejo Hospitalario Universitario de Vigo. We compared these preterm newborns to a control group of the same gestational age born during the same period. We excluded newborns with other risk factors leading to immediately poor outcomes, which in our series included one patient with polymalformation syndrome and one that died a few hours after birth following placental abruption. We chose newborns of less than 29 weeks of gestational age because this group is more likely to require advanced resuscitation measures in the delivery room or respiratory support with invasive mechanical ventilation, and is at higher riskof neurologic sequelae.[1,5]

We collected data for the following perinatal variables: gestational age, weight, small for gestational age (defined as birth weight below the 10th percentile), sex, twin pregnancy, caesarean delivery, exposure to prenatal corticosteroids, chorioamnionitis (diagnosed by histological examination), preeclampsia, gestational diabetes and timing of rupture of membranes.

We analysed the need in the first hour of life of advanced or intensive cardiopulmonary resuscitation (CPR) (defined as any of the following: intubation,chest compressions, administration of epinephrine), the Apgar score at 1 and 5 min, and the umbilical artery pH.

We studied a series of haemodynamic, respiratory, neurologic, gastrointestinal, ophthalmologic and infectious variables.

The haemodynamic analysis included the sonographic assessment for patent ductus arteriosus, the need for volume expansion and the administration of inotropic agents for low blood pressure.

To assess the impact of $MgSO_4$ from a respiratory perspective, we took into account the need for invasive mechanical ventilation, surfactant administration, the total duration of oxygen therapy (in days), the presence of bronchopulmonary dysplasia (BPD) and its severity (based on the definition given by the Standards Committee of the Sociedad Española de Neonatología [Spanish Society of Neonatology], 2013)[15] and administration of intravenous corticosteroids for BPD.

The study of gastrointestinal variables included the presence of necrotising enterocolitis (NEC),[16] the day since birth at which enteral feedings were initiated, and the day when exclusive enteral feeding without need for any type of parenteral supplementation was achieved.

We also analysed neurologic outcomes (development of intraventricular haemorrhage [HIV] and periventricularleukomalacia), ophthalmologic outcomes (retinopathy of prematurity), infectious outcomes (nosocomial sepsis, defined as elevated acute phase reactants combined with clinical manifestations of sepsis) and mortality.

In our hospital, the $MgSO_4$ regimen used for neuroprotection is the same that has been used for the treatment of preeclampsia and/or prevention of eclampsia.[13] Treatment with $MgSO_4$ is initiated with a loading dose of 4 g delivered over half an hour and continues with infusion of 1 g/hour until delivery. Administration of $MgSO_4$ should be discontinued if delivery does not occur within 24 h of initiating infusion. If the risk of imminent preterm birth recurs after discontinuation, treatment with $MgSO_4$ should be resumed. If less than 6 h have elapsed from discontinuation, treatment should resume with the maintenance dose, and otherwise should be reinitiated with a loading dose.

To study the association between the cumulative dose of magnesium received by mothers and the levels of magnesium in the newborn, we measured these levels in the first 24 h from birth in all preterm newborns whose mothers had received $MgSO_4$ by adding this parameter to blood tests performed for other reasons.

We analysed the data with SPSS version 21. We used the Kolmogorov–Smirnov test to analyse distribution of the variables, and based the analysis of quantitative variables on its results, using Student's *t* test and ANOVA for normally distributed variables and the Mann–Whitney *U* test for nonparametric variables. We analysed differences between nominal variables by means of the chi square test. We conducted linear regression analysis to determine the statistically significant correlations between qualitative variables. We considered differences to be statistically significant when the *p*-value obtained in any of the tests mentioned above was less than 0.05.

Results

The total sample consisted of 42 newborns of less than 29 weeks of gestational age, of whom 28 were exposed to $MgSO_4$ prenatally, and 14 were not.

Both groups had similar perinatal characteristics, which allowed the comparison of the treatment and control groups. The percentage of caesarean deliveries (85.7%) and twin pregnancies (46.4%) was higher in the group treated with $MgSO_4$ (Table 1), and these differences were statistically significant.

We did not find any differences in the outcomes of the two groups in terms of need for advanced CPR, Apgar score, umbilical artery pH, respiratory variables, neurologic variables, retinopathy (grade >2),and nosocomial sepsis (Table 2). However, the mortality was greater in the group that was not treated with $MgSO_4$ (21.4%), a difference that was statistically significant. Furthermore, while the incidence of BPD was similar in both groups, the subset of patients born

Table 1 Perinatal variables.

	$MgSO_4$	No $MgSO_4$	*P*
Frequency (%)	28 (66.7)	14 (33.3)	
Weight in g (mean ± SD)	869.68 ± 207.19	951.43 ± 244.07	NS
Gestational age in weeks (mean ± SD)	27.26 ± 1.18	26.84 ± 1.93	NS
Male sex (%)	14 (50)	8 (57.1)	NS
Small for gestational age (%)	6 (21.4)	2 (14.3)	NS
Prenatal corticosteroids (%)	28 (100)	13 (92.9)	NS
Chorioamnionitis (%)	13 (48.1)	9 (69.2)	NS
Preeclampsia (%)	5 (17.9)	0	NS
HBP (%)	2 (7.1)	0	NS
Twin (%)	13 (46.4)	1 (7.1)	0.016
Caesarean (%)	24 (85.7)	7 (50)	0.022
Gestational diabetes (%)	2 (7.1)	3 (21.4)	NS

HBP, high blood pressure; $MgSO_4$, prenatal treatment with magnesium sulphate; No $MgSO_4$, no prenatal treatment with magnesium sulphate; NS, not significant; SD, standard deviation.

before 29 weeks' gestation and not treated with $MgSO_4$ had a higher incidence of moderate-to-severe BPD (five cases of moderate-severe BPD compared to 2).

All newborns and their mothers were included in the analysis of the association between maternal magnesium dose and neonatal magnesium levels. In the group treated with $MgSO_4$, the prenatal exposure was of 4 g in eight newborns, more than 8 g in twelve newborns, and between 4 and 8 g in the rest. The mean cumulative dose of $MgSO_4$ given to mothers was 10.09 g, with a median of 7.5 g.[14] The mean serum levels of magnesium in exposed newborns was 2.68 mg/dL (median, 2.65 mg/dL), which differed significantly from magnesium levels measured the first day of life in newborns that were not treated with

Table 2 Neonatal outcomes.

	$MgSO_4$	No $MgSO_4$	*P*
Serum magnesium (mg/dL) (mean ± SD)	2.68 ± 0.10	1.89 ± 0.66	<0.001
Serum calcium (mg/dL) (mean ± SD)	4.87 ± 0.88	5.2 ± 0.98	NS
Advanced CPR (%)	18 (64.3)	10 (71.4)	NS
Umbilical artery pH (mean ± SD)	7.27 ± 0.11	7.21 ± 0.17	NS
Apgar 1 (mean ± SD)	7.03 ± 1.15	6.36 ± 1.15	NS
Apgar 5 (mean ± SD)	8.34 ± 0.72	8.00 ± 0.88	NS
IMV (%)	23 (82.1)	13 (92.9)	NS
Surfactant (%)	23 (82.1)	12 (85.7)	NS
Total days of O_2 (mean ± SD)	42.10 ± 21.25	47.09 ± 25.50	NS
BPD (%)	21 (75)	8 (72.7)	NS
Moderate-severe BPD (%)	2 (9)	5 (62.5)	0.007
IV corticosteroids (%)	6 (20.7)	0	NS
Inotropes (%)	15 (53.6)	9 (64.3)	NS
PDA (%)	12 (42.9)	7 (50)	NS
Initiation enteral nutrition (days) (mean ± SD)	2.41 ± 0.98	3.38 ± 1.80	NS
Full enteral nutrition (days) (mean ± SD)	20.48 ± 15.55	25.09 ± 13.59	NS
Death (%)	0	3 (21.4)	0.029
IVH (%)	7 (25)	6 (42.9)	NS
IVH grade III–IV (%)	5 (17.9)	5 (35.7)	NS
NEC (%)	5 (17.9)	4 (30.8)	NS
PVL (%)	4 (14.3)	0	NS
ROP > 2 (%)	10 (35.7)	2 (18.2)	NS
Nosocomial sepsis (%)	17 (60.7)	8 (61.5)	NS

BPD, bronchopulmonary dysplasia; CPR, cardiopulmonary resuscitation; IMV, invasive mechanical ventilation; IV, intravenous; IVH, intraventricular haemorrhage; $MgSO_4$, prenatal treatment with magnesium sulphate; No $MgSO_4$, no prenatal treatment with magnesium sulphate; NS, not significant; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP > 2, retinopathy of prematurity grade > 2; SD, standard deviation.

Table 3 Mean levels of magnesium, and levels by cumulative maternal dose.

	$MgSO_4$	No $MgSO_4$	*P*
Newborns (*N*)	28	14	
Mg (mg/dL) (mean ± SD)	2.68 ± 0.10	1.89 ± 0.66	<0.001

	No $MgSO_4$	$MgSO_4 \leq 4$ g	$MgSO_4 > 4$ g and <8 g	$MgSO_4 \geq 8$ g
Newborns (*N*)	14	8	8	12
Neonatal Mg (mg/dL) (mean ± SD)	1.89 ± 0.66	2.39 ± 0.13	2.40 ± 0.11	3.07 ± 0.16
	$p = 0.002$			

$MgSO_4$ (Table 3). We found a statistically significant linear correlation between the $MgSO_4$ dose received by mothers and the magnesium serum levels measured in newborns in the first 24 h of life ($r^2 = 0.436$; $p < 0.001$). In our series, the highest serum level of magnesium was 4.04 mg/dL and corresponded to a newborn whose mother had received 20 g of $MgSO_4$.

Using the cumulative dose of magnesium received by the mother and the serum levels of magnesium in the newborn (Table 3), we conducted an analysis to assess the correlation between birth weight and serum magnesium levels, but found no statistically significant differences.

We also compared the levels of magnesium in preterm newborns whose mothers had only received the loading bolus with 4 g of $MgSO_4$ with the levels in newborns of mothers that were not treated with $MgSO_4$. The group with mothers that received the loading dose of 4 g of $MgSO_4$ had a mean serum level of magnesium of 2.39 mg/dL (median, 2.3 mg/dL), while the group that was not exposed to magnesium had a mean serum level of magnesium of 1.89 mg/dL (median, 1.86 mg/dL), a difference that was statistically significant.

Discussion

When it came to the initial outcomes in the delivery room, we found no significant differences in the need for advanced CPR, Apgar score or umbilical artery pH. These results were consistent with those of other cohort studies that already supported the safety of the use of $MgSO_4$ under these circumstances.[17]

From a respiratory perspective, there were no differences in the need for invasive mechanical ventilation, use of surfactant and total days of oxygen therapy, so we could not attribute any respiratory side effects to $MgSO_4$, contrary to what has been assumed historically, as treatment with $MgSO_4$ was associated with an increased incidence of respiratory depression.[18] Bronchopulmonary dysplasia was less severe in the treated group.

From a haemodynamic perspective, the absence of adverse effects was also consistent with the finding of other studies, as we did not observe an increased prevalence of patent ductus arteriosus or increased use of inotropic agents.[19] We did not find differences in the remaining outcome variablesduring the stay in the NICU, and we observed that, at the neurologic level, the incidence of IVH and leukomalacia were similar in both groups. In this regard, it would be interesting to conduct a long-term followup of these patients to study their psychomotor development. We also found no differences at the gastrointestinal level in either the development of NEC, initiation of enteral nutrition or the number of days post birth at which full enteral nutrition was achieved. Furthermore, we observed similar outcomes in relation to the development of retinopathy of prematurity from an ophthalmologic perspective, and of nosocomial sepsis from an infectious perspective.

We did find differences in mortality in the group treated with $MgSO_4$. Once again, the small sample size requires that we interpret this result with caution and continue collecting data for future comparisons. We must keep in mind that the Cochrane systematic review of 2009[13] established that when $MgSO_4$ was administered for the sole purpose of neuroprotection, there was a reduction in the composite outcome of death and cerebral palsy at age 2 years in exposed children.[9,20]

It would be worth exploring whether the association of $MgSO_4$ exposure with a decrease in childhood mortality starts as early as the neonatal period. Other studies in the literature have also found a lower mortality in the group treated with $MgSO_4$,[17] although its mechanism of action remains unclear. Studies conducted in recent years have found an association between antenatal $MgSO_4$ and decreased oxygen consumption in the newborn brain, with a decreased cerebral fractional tissue oxygenation extraction (cFTOE).[21]

When it came to the dose of $MgSO_4$ administered to the mothers, we found a linear correlation between the cumulative dose and magnesium levels in newborns of less than 29 weeks of gestational age in the first 24 h post birth. This finding allows the establishment of safe maternal doses to prevent the development of side effects in preterm newborns.

The mean level of magnesium in the newborns was 2.68 mg/dL, below the 4.5 mg/dLthreshold potentially associated with the development of side effects and poor clinical outcomes in the neonatal period.[22] It is very likely that the absence of side effects from the use of $MgSO_4$ in our series was due to the generally low doses administered to the mothers. In the group of exposed children in our study, the highest level of magnesium was 4.04 mg/dL and corresponded to a boy whose mother had received 20 g of $MgSO_4$. Therefore, we could establish

a safety threshold of 20 g for the cumulative dose and 16 h of continuous infusion, after which the dose would come dangerously close to levels associated with worse outcomes.

In eight out of the twenty-eight newborns of mothers treated with $MgSO_4$, the mother was only given the loading bolus with 4 g due to the short time elapsed to delivery. Even these newborns had a statistically significant increase in magnesium levels compared to the newborns of mothers that had not received $MgSO_4$. For this reason, we recommend that at least the loading dose of 4 g be given to mothers at risk of giving birth at less than 29 weeks' gestation, even if the birth is imminent.

We also recommend the measurement of magnesium levels in all newborns of mothers treated with $MgSO_4$ before birth. The reasons for this are, first, the increased mortality detected in association with serum levels of magnesium greater than 4.5 mg/dL[22] and, second, the adjustments that need to be made in the composition of the parenteral feeds administered to these newborns in the first days of life until their magnesium levels normalise.

In conclusion, our study found that $MgSO_4$ was safe at the administered dose, with a linear correlation between serum levels of magnesium in the newborn in the first 24 h of life and the cumulative dose of magnesium received by the mother.

Long-term follow-up studies of the patients included in this study are requiredto assess the impact of $MgSO_4$ therapy on future neurodevelopmental outcomes.

Conflict of interests

The authors have no conflict of interests to declare.

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