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Original article

Neonatal outcomes after *in-utero* exposure to magnesium sulphate: a retrospective analysis

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Abstract

Background: Magnesium sulphate ($MgSO_4$) is routinely administered to pregnant women as a tocolytic and as a neuroprotective agent against cerebral palsy and motor impairment in preterm neonates. However, concerns have recently been arising regarding its effects in the neonate, including cardiovascular, intestinal, and neurological adverse effects. Our goal is to analyse prenatal $MgSO_4$ administration and neonatal outcomes.

Methods: We conducted a retrospective study that included all neonates born under 32 weeks of gestational age admitted to our Neonatal Intensive Care Unit between January 2016 and December 2019. Patients with life-threatening congenital malformations were excluded. Gestational, perinatal and outcome data were collected and statistically analysed.

Results: One hundred and eighteen infants were included, of which 61 (51.7%) had been exposed to $MgSO_4$ *in utero*. Mothers treated with $MgSO_4$ were more likely also to have received corticosteroids for lung maturation and/or perinatal antibiotics. All but 5 (95.8%) infants needed post-natal resuscitation manoeuvres. Neonates that were prenatally exposed to $MgSO_4$ were less likely to require such manoeuvres ($p = 0.039$), and immediate oxygen therapy ($p = 0.015$) was less frequently required. The

median neonatal serum magnesium was higher in those exposed to $MgSO_4$ (2.51 mEq/L) than in non-exposed (1.87 mEq/L) ($p < 0.001$). Neonatal serum magnesium values had a positive correlation with maternal prenatal values, with a Spearman's value of 0.78 ($p < 0.001$). Neonates prenatally exposed to $MgSO_4$ were less likely to require surfactant treatment or aminergic support as well as less likely to have a persistent ductus arteriosus. No other statistically significant differences were found when comparing both groups for other outcomes.

Conclusion: Prenatal exposure to $MgSO_4$ is apparently safe for preterm infants. However, the conduction of a larger, prospective study must confirm these data.

Keywords

Magnesium sulphate, cerebral palsy, necrotizing enterocolitis, preterm birth, persistent ductus arteriosus.

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Introduction

Optimization of neonatal care in the past decades has led to significant improvement in the survival of preterm infants [1, 2]. However, this has consequently led to higher incidences of prematurity-related morbidity [1, 2]. One of such complications is cerebral palsy, a condition whose main risk factor is preterm birth and whose prevalence and severity are inversely related to gestational age [1, 3, 4].

Magnesium sulphate ($MgSO_4$) may be administered to pregnant women as a tocolytic or as a treatment for pre-eclampsia (to prevent progression) or eclampsia [5, 6]. It may also be used antenatally as a neuroprotective agent to prevent cerebral palsy and motor impairment in preterm infants [3, 7-10]. It acts as a neurotransmitter regulator, reduces neural inflammation and oxygen free radicals, and optimizes brain perfusion by regulating cerebral haemodynamics [3, 11]. However, concerns have arisen regarding its adverse effects in neonates [12], including: changes in intestinal blood flow resulting in the late passage of stools and feeding intolerance [13], intestinal perforation [14] and necrotizing enterocolitis (NEC) [15]; neurologic outcomes including intraventricular haemorrhage [16], hypotonia and hyporeflexia [17]; a higher need for intubation, and higher prevalence of persistent ductus arteriosus (PDA) [18].

The goal of our study is to assess neonatal outcomes that may be related to *in-utero* $MgSO_4$ exposure by comparing exposed and non-exposed infants and exploring the outcomes' correlations with neonatal serum magnesium concentration levels.

Methods

Our hospital is a public tertiary facility in the north of Portugal and a reference centre for most neonatal conditions. The Neonatal Intensive Care Unit (NICU) is a level 3 Unit that admits neonates of all gestational ages, including those with surgical conditions and congenital heart defects.

We conducted a retrospective analysis in which we included all neonates born at less than 32 weeks of gestational age admitted in our NICU between January 2016 and December 2019. We selected this gestational age threshold due to the $MgSO_4$ administration protocol in use in our institution, detailed below. Patients with life-threatening congenital malformations were excluded. Gestational and perinatal data were collected, as were data on neonatal outcomes, including pulmonary, neurological, cardiovascular, and gastrointestinal comorbidities. In our institution, $MgSO_4$ is routinely administered to all pregnant women with a gestational age between 24 and 31 weeks and 6 days, who are either admitted in preterm labour (when there is a high likelihood of birth in the following 2 to 12 hours) or when emergent birth is indicated [19]. A laboratory workup, including serum magnesium assessment, is routinely requested on admission to our NICU, for all infants. Bronchopulmonary dysplasia was defined as a need for supplemental oxygen for at least a total of 28 days, up until 36 weeks post-menstrual age or discharge [20]. Neonatal respiratory distress syndrome was diagnosed and managed in accordance with the 2016 *European*

Consensus Guidelines [21]. PDA was considered as an outcome only when there was an indication for pharmacological or surgical closure [22]. NEC was diagnosed and staged according to Bell's criteria [23]. Intraventricular haemorrhage was diagnosed by cranial ultrasound according to Volpe's and Whitelaw's criteria [24, 25]. Selected infants were screened for retinopathy of prematurity in accordance with established institutional protocols, which are in line with international guidelines [26].

Statistical analysis was conducted using IBM® SPSS® Statistics version 26, using Chi-square test to compare categorical variables, Student's t-test to compare binominal categorical to parametric continuous variables, one-way ANOVA to compare multinomial categorical to parametric continuous variables, Mann-Whitney U test to compare binominal categorical to non-parametric continuous variables and Kruskal-Wallis test multinomial to compare categorical to non-parametric continuous variables. Correlation between continuous variables was determined with Pearson's and Spearman's coefficients. We assumed a p-value under 0.05 to determine statistical significance.

This study was approved by our institution's Health Ethics Committee.

Results

One hundred and eighteen newborns were included, of which 61 (51.7%) were prenatally exposed to $MgSO_4$. Eighteen parturients (15.3%) presented with pre-eclampsia. The median gestational age was 29.7 weeks (interquartile range 27.9-30.9 weeks) – no significant difference between the groups was found in this parameter (p = 0.990).

Tab. 1 compares prenatal and perinatal data between exposed and non-exposed infants. Perinatal antibiotic therapy (p = 0.011) and lung maturation with corticosteroids (p < 0.001) were more frequently practiced in pregnant women to whom $MgSO_4$ was administered. All but 5 (95.8%) infants required post-natal resuscitation manoeuvres. Neonates who had been exposed to $MgSO_4$ were less likely to require such manoeuvres (p = 0.039) or immediate oxygen therapy (p = 0.015). No difference was found when comparing both groups regarding any other specific reanimation manoeuvre. Neonates presented a medium serum magnesium of 2.22

Table 1. Prenatal and perinatal data comparison between exposed and non-exposed neonates.

	Total (n = 118)	No $MgSO_4$ (n = 57 [48.3%])	$MgSO_4$ (n = 61 [51.7%])	p-value
Multiple gestation	52 (44.1%)	27 (47.4%)	25 (41.0%)	0.485
Foetal growth restriction	12 (10.2%)	4 (7.0%)	8 (13.1%)	0.273
Olygoamnios	3 (2.5%)	2 (3.5%)	1 (1.6%)	0.609
Maternal fever	7 (5.9%)	4 (7.0%)	3.00 (4.9%)	0.710
Corioamnionitis	11 (9.3%)	7 (12.3%)	4 (6.6%)	0.285
Pre-eclamplsia	18 (15.3%)	3 (5.3%)	15 (24.6%)	**0.004**
Perinatal corticosteroids	97 (82.9%)	40 (70.2%)	57 (95.0%)	**< 0.001**
Perinatal antibiotic	45 (38.1%)	15 (26.3%)	30 (49.2%)	**0.011**
Distocic labour	91 (77.1%)	42 (73.7%)	49 (80.3%)	0.391
Gestational age, weeks, median [IQR]	29.7 [27.9-30.9]	29.4 [27.6-30.4]	29.7 [28.1-31.1]	0.990
Apgar at first minute ≥ 7	56 (47.5%)	24 (42.1%)	32 (52.5%)	0.260
Apgar at fifth minute ≥ 7	98 (83.1%)	45 (78.9%)	53 (86.9%)	0.251
Birthweight, grams, mean [SD]	1,234.1 [± 347]	1,198.4 [± 353]	1,267.5 [± 342]	0.283
Male sex	59 (50%)	29 (50.9%)	30 (49.2%)	0.854
Resuscitation	113 (95.8%)	56 (98.2%)	57 (93.4%)	**0.039**
Oxygen	102 (88.7%)	52 (96.3%)	50 (82.0%)	**0.015**
Positive pressure	92 (78%)	47 (83.9%)	45 (73.8%)	0.181
Chest compressions	4 (3.4%)	2 (3.5%)	2 (4.3%)	1
Intubation	42 (35.6%)	22 (38.6%)	20 (32.8%)	0.510

Data are expressed as n (%), if not otherwise stated.
Statistical tests: Chi-square test to compare categorical variables, Mann-Whitney U test to compare binominal categorical to non-parametric continuous variables, Student's t-test to compare binominal categorical to parametric continuous variables.
IQR: interquartile range; $MgSO_4$: magnesium sulphate; SD: standard deviation.

mEq/L. Infants exposed to $MgSO_4$ had higher levels of serum magnesium (2.51 mEq/L) when compared with non-exposed neonates (1.87 mEq/L) ($p < 0.001$). Neonatal serum magnesium values presented a positive correlation with maternal prenatal values, with a Spearman's value of 0.78 ($p < 0.001$).

Different perinatal parameters and the corresponding median neonatal serum magnesium concentrations for each group are listed in **Tab. 2** – neonates who underwent corticosteroid lung maturation presented higher serum magnesium ($p = 0.044$) and neonates who required resuscitation presenter lower values ($p = 0.044$).

Tab. 3 lists the analysed neonatal outcomes' frequencies in exposed and non-exposed as well as in the totality of the studied newborns. Neonates exposed to $MgSO_4$ had a lower incidence of PDA (24.6% vs 50%, $p = 0.004$) as well as a lower frequency of surfactant treatment (47.5% vs 73.2%, $p = 0.005$) and aminergic support (9.8% vs 26.3%, $p = 0.019$). No statistically significant differences were found when comparing the frequencies of other outcomes between both groups, including non-invasive ($p = 0.179$) and invasive ($p = 0.543$) ventilation, pulmonary diseases including bronchopulmonary dysplasia ($p = 0.985$) and neonatal respiratory distress syndrome ($p = 0.124$), parenteral nutrition dependency ($p = 0.473$), NEC ($p = 1.0$), neurologic comorbidities, and mortality ($p = 0.051$).

Tab. 4 compares median serum magnesium between infants with and without the analysed comorbidities. Serum magnesium was lower in neonates who developed NEC (1.97 mEq/L) compared to that of infants who did not develop the condition (2.29 mEq/L) ($p = 0.021$); however, this result was not confirmed through logistic regression as it revealed a Wald test p-value of 0.059, with a non-significant Hosmer and Lemeshow test ($p = 0.955$), confirming the model's adequacy. Due to sample size, logistic regression with multiple co-variates while avoiding overfitting was not possible.

Tab. 5 describes the correlations between the neonates' serum magnesium concentrations and continuous variables related to comorbidity management. We found a weak negative correlation between serum magnesium and duration of exclusive parenteral nutrition (Spearman's rho -0.234, $p = 0.016$), but no other significant correlations were found, including when assessing the duration of NICU stay.

Table 2. Prenatal and perinatal parameters and the corresponding median neonatal serum magnesium concentrations.

		Median serum Mg (mEq/L) [IQR]	p-value
Multiple gestation	**No**	2.17 [1.82-2.95]	0.518
	Yes	2.29 [1.94-2.61]	
Foetal growth restriction	**No**	2.24 [1.83-2.70]	0.976
	Yes	2.14 [1.97-2.77]	
Olygoamnios	**No**	2.26 [1.85-2.75]	0.483
	Yes	1.90 [1.79-2.00]	
Maternal fever	**No**	2.22 [1.83-2.65]	0.659
	Yes	2.56 [1.87-2.75]	
Chorioamnionitis	**No**	2.22 [1.83-2.65]	0.719
	Yes	2.39 [2.14-2.75]	
Pre-eclampsia	**No**	2.26 [1.82-2.62]	0.829
	Yes	2.18 [1.95-3.07]	
Perinatal corticosteroid	**No**	2.13 [1.83-2.43]	**0.044**
	Yes	2.31 [1.82-2.77]	
Perinatal antibiotic	**No**	2.22 [1.82-2.76]	0.791
	Yes	2.27 [1.86-2.69]	
Dystocic labour	**No**	2.31 [1.82-2.63]	0.171
	Yes	2.22 [1.84-2.76]	
Apgar at first minute ≥ 7	**No**	2.13 [1.86-2.49]	0.113
	Yes	2.37 [1.80-2.88]	
Apgar at fifth minute ≥ 7	**No**	1.99 [1.71-2.41]	0.143
	Yes	2.29 [1.87-2.76]	
Sex	**Male**	2.24 [1.82-2.75]	0.926
	Female	2.22 [1.87-2.65]	
Resuscitation	**No**	2.88 [2.82-3.08]	**0.044**
	Yes	2.22 [1.82-2.62]	
Oxygen	**No**	2.53 [2.11-2.88]	0.238
	Yes	2.17 [1.80-2.62]	
Positive pressure	**No**	2.39 [2.16-3.05]	0.213
	Yes	2.14 [1.82-2.57]	
Chest compressions	**No**	2.22 [1.80-2.76]	0.126
	Yes	1.86 [1.84-1.93]	
Intubation	**No**	2.28 [1.93-2.77]	0.362
	Yes	2.14 [1.77-2.61]	

Statistical test: Mann-Whitney U.
IQR: interquartile range; Mg: magnesium.

Table 3. Frequency of comorbidities in exposed and non-exposed neonates.

Comorbidity	Total (n = 118)	No $MgSO_4$ (n = 57 [48.3%])	$MgSO_4$ (n = 61 [51.7%])	p-value
NIV	106 (89.8%)	49 (86.4%)	57 (93.4%)	0.179
NIV days, median [IQR]	13 [6-29.5]	13 [7-30]	13 [6-28]	0.901
IMV	67 (56.8%)	34 (59.6%)	33 (54.1%)	0.543
IMV days, median [IQR]	6.5 [2-17]	7 [3-21]	5 [2-12]	0.332
Total ventilation days, median [IQR]	16 [6-34]	17 [8-35]	14 [5-34]	0.227
Bronchopulmonary dysplasia	27 (22.9%)	13 (22.8%)	14 (23.0%)	0.985
Neonatal respiratory distress syndrome	81 (68.6%)	43 (75.4%)	38 (62.3%)	0.124
Surfactant need	70 (59.8%)	41 (73.2%)	29 (47.5%)	**0.005**
PDA	43 (36.8%)	28 (50.0%)	15 (24.6%)	**0.004**
AS	21 (17.8%)	15 (26.3%)	6 (9.8%)	**0.019**
AS duration, days, median, [IQR]	2 [1-5.25]	3 [1-6]	2 [1-3]	0.638
PN duration, days, median [IQR]	18 [10.25-29.75]	20 [11-30]	16 [10-27]	0.473
Exclusive PN duration, days, median [IQR]	3 [1-7]	3 [1-7]	2 [1-6]	0.503
Gastroesophageal reflux	17 (12.7%)	6 (10.5%)	9 (14.8%)	0.491
NEC	7 (5.9%)	3 (5.3%)	4 (6.6%)	1
Intraventricular haemorrhage	29 (24.8%)	16 (28.6%)	13 (21.3%)	0.364
Periventricular leukomalacia	10 (8.5%)	6 (10.7%)	4 (6.6%)	0.517
Hypotonia	3 (2.6%)	2 (3.6%)	1 (1.6%)	0.603
Seizures	3 (2.6%)	2 (3.6%)	1 (1.6%)	0.060
Retinopathy of prematurity	47 (40.2%)	20 (35.7%)	27 (44.3%)	0.346
Deceased	12 (10.2%)	9 (15.80%)	3 (4.90%)	0.051

Data are expressed as n (%), if not otherwise stated.
Statistical tests: Chi-square test to compare categorical variables, Mann-Whitney U test to compare binominal categorical to non-parametric continuous variables, Student's t-test to compare binominal categorical to parametric continuous variables.
AS: aminergic support; IMV: invasive mechanical ventilation; IQR: interquartile range; $MgSO_4$: magnesium sulphate; NEC: necrotizing enterocolitis; NIV: non-invasive ventilation; PDA: persistent ductus arteriosus; PN: parenteral nutrition.

Table 4. Median serum magnesium concentrations in infants with and without comorbidities.

Comorbidity		Median serum Mg (mEq/L) [IQR]	p-value
NIV	**No**	2.09 [1.82-2.18]	0.104
	Yes	2.28 [1.85-2.75]	
IMV	**No**	2.33 [1.89-2.82]	0.226
	Yes	2.16 [1.80-2.62]	
Bronchopulmonary dysplasia	**No**	2.28 [1.87-2.70]	0.407
	Yes	2.11 [1.80-2.76]	
Hyaline membrane disease	**No**	2.28 [1.89-2.75]	0.494
	Yes	2.21 [1.80-2.65]	
Treatment with surfactant	**No**	2.33 [1.97-2.82]	0.222
	Yes	2.16 [1.77-2.62]	
PDA	**No**	2.30 [1.92-2.87]	0.278
	Yes	2.13 [1.80-2.59]	
AS	**No**	2.29 [1.86-2.69]	0.143
	Yes	2.14 [1.75-2.76]	
Reflux	**No**	2.22 [1.86-2.64]	0.971
	Yes	2.31 [1.79-2.90]	
NEC	**No**	2.29 [1.86-2.76]	**0.021**
	Yes	1.97 [1.75-2.12]	
Intraventricular haemorrhage	**No**	2.32 [1.85-2.76]	0.096
	Yes	2.14 [1.82-2.59]	
Periventricular leukomalacia	**No**	2.27 [1.87-2.75]	0.335
	Yes	1.96 [1.75-2.45]	
Hypotonia	**No**	2.26 [1.85-2.76]	1
	Yes	1.87 [1.39-2.41]	
Seizures	**No**	2.24 [1.86-2.70]	0.988
	Yes	1.77 [1.75-3.03]	
Retinopathy of prematurity	**No**	2.18 [1.93-2.75]	0.518
	Yes	2.29 [1.78-2.59]	
Deceased	**No**	2.26 [1.82-2.75]	0.763
	Yes	2.16 [1.93-2.76]	

Statistical test: Mann-Whitney U.
AS: aminergic support; IMV: invasive mechanical ventilation; IQR: interquartile range; Mg: magnesium; NEC: necrotizing enterocolitis; NIV: non-invasive ventilation; PDA: persistent ductus arteriosus.

Table 5. Correlations between the neonates' serum magnesium concentrations and continuous variables related to comorbidity management.

Outcome	Spearman's rho	p-value
NIV days	-0.025	0.811
IMV duration	0.041	0.745
Total ventilation	-0.069	0.472
AS duration	-0.489	0.054
PN duration	-0.081	0.398
Exclusive PN duration	-0.234	**0.016**
NICU stay duration	-0.103	0.273

AS: aminergic support; IMV: invasive mechanical ventilation; NICU: Neonatal Intensive Care Unit; NIV: non-invasive ventilation; PN: parenteral nutrition.

Discussion

As previously reported in the literature [27, 28], we found a correlation between maternal and neonatal values. As expected, prenatal $MgSO_4$ exposure positively correlated with higher serum magnesium concentrations.

Previous studies have described lower Apgar scores and higher NICU admission rates in term and late preterm neonates who were prenatally exposed to $MgSO_4$ [12, 29]. However, other studies, focusing exclusively on preterm infants of less than 32 weeks of gestational age, in line with our results, found no difference when comparing Apgar scores between exposed and non-exposed neonates [10, 30].

Mothers to whom $MgSO_4$ was administered were more likely to have been given prenatal corticosteroids and antibiotics. We theorize that some of the women had a more abrupt, spontaneous labour, resulting in a lack of time to apply prenatal medication protocols. This could explain the higher rates of resuscitation and oxygen requirements in non-exposed infants.

When assessing respiratory outcomes, we observed that, despite presenting a similar incidence of neonatal respiratory distress syndrome, exposed infants were less likely to require surfactant treatment. This is possibly explained by the accompanying higher administration rates of prenatal corticosteroid for lung maturation.

Previous studies have described higher intubation rates in neonates exposed to $MgSO_4$ [17]. However, in accordance with our study, this was not the case when studying preterm infants in particular [18, 27, 31]. We also found no differences when comparing the duration of invasive and non-invasive ventilation. Despite respiratory depression being described as a side effect of $MgSO_4$ in pregnant women, it does not appear to be a comorbidity in exposed neonates – the aforementioned, accompanying, higher prenatal corticosteroid exposure rates may also play a protective part against severe respiratory outcomes.

A correlation between $MgSO_4$ exposure and an increased incidence of PDA has been reported, probably in relation to increased prostaglandin production secondary to calcium mobilization [18, 31, 32]. Surprisingly, we found the opposite association: our exposed neonates presented lower PDA incidence. This could be explained by different inclusion criteria, as we only considered PDA cases that required medical or surgical intervention. Our results could also be explained by higher corticosteroid exposure rates or the neonates' enhanced clinical stability.

Aminergic support requirement, as a whole, was less frequent in exposed than non-exposed neonates, but no differences were found when comparing for the treatment's duration in those who required it. Shokry et al. [32] described lower cerebral flow fluctuations in preterm infants exposed to $MgSO_4$ – since cerebral perfusion may be used as a surrogate for perfusion in preterm infants, it is likely that $MgSO_4$ reduces the risk of haemodynamic instability. These authors also described a decreased cerebral blood flow and higher PDA incidence [32]. Imamoglu et al., on the other hand, described higher cerebral vascular velocities in exposed infants, with no differences in PDA incidence [11]. Neither found differences in aminergic support requirements. These studies and our results reflect how little is presently known regarding vascular effects of $MgSO_4$ in preterm infants.

We found no differences in cerebral co-morbidities, namely intraventricular haemorrhage and periventricular leukomalacia incidence. However, there is conflicting evidence regarding the influence of $MgSO_4$ exposure in the incidence of intraventricular haemorrhage in preterm neonates. Evidence suggests that the improvement of focal blood flow and the consequent prevention of ischemic lesions may play a part in neuroprotection [11].

No differences were found when comparing exposed and non-exposed infants regarding parenteral nutrition dependency or NEC incidence. Despite $MgSO_4$'s theoretically impairment of mesenteric blood flow and intestinal peristalsis, our findings are in line with results described in current literature, namely a recent study by Mikhael et al. [33], describing a lack of relationship between $MgSO_4$ exposure and NEC or intestinal perforation in preterm infants less than 28 and 26 weeks of gestational age. When comparing the incidence of NEC with neonatal serum magnesium concentration, we found that infants with NEC had lower serum magnesium values; however, this was not confirmed in the logistic regression.

When comparing median neonatal serum magnesium levels with the presence of the selected outcomes or the management requirements, we found no statistically significant differences or correlations (except for a weak negative correlation with exclusive parenteral nutrition duration), including when comparing surfactant need, aminergic support and PDA incidence. This could remove some significance to the aforementioned findings; however, similar results have been described in other studies [18]. It is also possible that the small sample size and the large range of serum magnesium levels could limit our results due to type II errors.

Our study presents several limitations, including those inherent to a retrospective study, and presents a small sample size, which made it impossible to conduct a multivariable analysis while avoiding overfitting. Data collecting errors, which could be significant in a small sample study, should also be considered. Another possible bias is the timing of neonatal serum magnesium concentration assessment. Despite our Unit's protocol to collect blood samples for magnesium assessment at 24 hours of life, there is considerable variation secondary to the Unit's daily practices; the median time of blood sample collection was 24 hours, with an interquartile range of 9.8 hours.

Despite its limitations, we consider our study to be relevant due to the small number of similar studies, especially when considering the conflicting available data regarding several outcomes.

In conclusion, neonatal exposure to $MgSO_4$ appears to be safe in preterm infants. However, there is a clear need for larger, prospective studies to avoid previously described biases.

Declaration of interest

The Authors declare that there is no conflict of interest.

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