Antenatal Exposure to Magnesium Sulphate and Neonatal Outcomes in Very Low Birth Weight Infants: a multicenter study.

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Abstract

Objective

To explore the association between antenatal magnesium sulphate (MgSO₄), mortality and incidence of intraventricular hemorrhage (IVH) in very low birth weight (VLBW) infants.

Study design

Retrospective, cohort study of infants < 32 weeks’ GA born at centers of NEOCOSUR Network between January 2015 and December 2020. Subjects were categorized as exposed vs non-exposed to antenatal MgSO₄. Primary outcomes were death, incidence of severe IVH (Grade III-IV) and severe IVH/death. Secondary outcomes included relevant morbidities.

Results

7418 VLBW infants were eligible. Antenatal MgSO₄ was associated with a significantly decreased death rate after admission (aOR 0.59 [95% CI, 0.46–0.74]) and severe IVH/death (aOR 0.63 [95% CI, 0.49–0.83]). No significant reduction in severe IVH was observed (aOR 0.89 [95% CI, 0.63–1.25]). No differences between groups were observed in rates of morbidities.

Conclusion

Antenatal MgSO₄ was associated with a decreased death rate after admission and in severe IVH/death.

1- Background

Survival of very low birthweight (VLBW) infants has increased in high- and middle-income countries over the last 4 decades. However, there is concern about long term sequelae in survivors, particularly in neurodevelopment compromise.

Intraventricular hemorrhage (IVH), a possible complication in preterm infants, that consists of bleeding inside the ventricles or in the brain parenchyma, can cause long term disability and cerebral palsy (CP) in VLBW [1, 2, 3, 4, 5, 6, 7]. The risk of IVH and CP increases considerably by decreasing gestational age (GA) at birth. [1, 2, 3, 4, 5, 6]

The NEOCOSUR Neonatal Network reported for the South American region an increase in survival without major morbidities of VLBW infants during 2001–2016 period, however, no reduction in the rates of severe IVH was observed during the study period [8]. This has raised the interest in analyzing neuroprotective strategies to reduce IVH incidence.

Antenatal magnesium sulfate (MgSO₄) is currently widely use in obstetric practice for preeclampsia, and fetal neuroprotection in women at risk of preterm delivery. Recent studies have shown that antenatal
MgSO$_4$ exposure is associated with favorable neurodevelopmental outcomes in preterm infants under 32 weeks’ gestation, mostly assessing CP, gross motor dysfunction, cerebellar hemorrhage, and white matter injury [2, 4, 5, 6, 7, 9, 10, 11, 12] However, there is scarce evidence regarding antenatal MgSO$_4$ exposure and IVH.

The latest RCT published in 2008 demonstrated that MgSO$_4$ has a neuroprotective effect in preterm infants and reduced the odds of CP, however, no effect was observed in the combined outcome of severe CP or death [5, 13]. A recently published meta-analysis concluded that antenatal MgSO$_4$ for fetal neuroprotection prevents CP and reduces the combined risk of death or CP, regardless of the cause for preterm birth (NNT 41)[14].

Neuroprotective effects are thought to be mediated via NMDA receptor excitotoxicity, reduced brain injury by blocking glutamate release in the calcium channel, reduced proinflammatory cytokine levels, and oxidative stress [5, 15]. PK/PD data suggest neuroprotective effects can be achieved with serum magnesium levels between 3.7 and 4.4 mg/dL [15].

There are non-consistent findings regarding prenatal administration of MgSO$_4$ and the incidence of IVH in preterm infants [4, 5, 7, 13]. Although there is considerable evidence supporting antenatal MgSO$_4$ efficacy and safety in terms of mortality and major morbidities [1, 2, 5], there have been concerns regarding possible unintended adverse outcomes of MgSO$_4$ exposure in the vulnerable population of VLBW infants. These concerns are mainly related to possible undesired neonatal effects such as hypotonia, respiratory depression, low Apgar scores at birth and feeding intolerance [5, 16, 17, 18, 19].

The purpose of this study was to assess the association between antenatal MgSO$_4$ exposure and neonatal mortality, the incidence of severe IVH and composite outcome IVH grade III-IV/ death in VLBW infants. Secondarily, explore potential in-hospital undesired effects of MgSO$_4$ administration in this cohort.

2- Materials and Methods

2.1 Study design

This is a retrospective, multicenter cohort study, with prospective data entry of VLBW infants ≤ 32 weeks GA and ≤ 1500 g, born at any of the 26 centers of the NEOCOSUR Neonatal Network between January 1, 2015, and December 31, 2020. Infants born before 24 weeks’ GA or ≤ 500 grams, as well as those born with any major congenital abnormality were excluded from the study sample.

NEOCOSUR Neonatal Network is a voluntary non-profit association between NICUs from six South American countries (Argentina, Brazil, Chile, Paraguay, Perú and Uruguay) who’s main purpose is to improve regional neonatal outcomes, fostering collaborative work between the participating centers. All NEOCOSUR centers provide tertiary care and are university affiliated. Data on VLBW infants born at the
participating centers is prospectively collected at each site by trained nurses and physicians using predefined diagnostic criteria and an online registry system that is periodically validated by local statisticians.

The cohort sample was categorized as infants exposed to antenatal MgSO$_4$ and non-exposed to antenatal MgSO$_4$. Primary outcomes were death in delivery room (DR) and after admission, severe IVH (grade III-IV), diagnosed by cranial ultrasound and classified according to Papile´s criteria, and the combined outcome grade III-IV HIV/death. Secondary outcomes were intubation, mask ventilation and cardiac massage in DR; 5-minute Apgar score $\leq$ 3; surfactant; rate of mechanical ventilation; rate of patent ductus arteriosus requiring treatment (PDA); necrotizing enterocolitis (NEC), defined clinically and radiologically by Bell´s criteria, surgical NEC, age at start of enteral feeds, age at 100 ml/kg/day of enteral feeds; periventricular leukomalacia (LPV) by cerebral ultrasound examination; late-onset sepsis (LOS), defined as any positive blood or cerebrospinal fluid culture after 72 hours of life; bronchopulmonary dysplasia (BPD), defined as need of supplementary oxygen at 36 weeks postmenstrual age; and global retinopathy of prematurity (ROP), defined according to the international classification.

A subgroup analysis was performed to evaluate primary outcomes in four cohorts categorized by gestational age: infants born between 24 + 0/7 to 25 + 6/7 weeks’ gestation, between 26 + 0/7 to 27 + 6/7 weeks’, 28 + 0/7 to 29 + 6/7 weeks’ and between 30 + 0/7 to 31 + 6/7 weeks’. Gestational age in completed weeks was defined as the best estimate of GA based on the last menstrual period together with an early prenatal ultrasound.

This study was approved by the Ethics Committee and Institutional Review Board of Pontificia Universidad Católica de Chile, School of Medicine (ID 230223002) that serves as central Review Board for all 26 NEOCOSUR Neonatal Centers. The study was performed in accordance with the declaration of Helsinki.

2.2 Statistical Analysis

Standard descriptive statistics were used for continuous variables expressed as mean and standard deviation, minimum and maximum values. Categorical variables are shown as number of cases and percentages. Continuous variables were compared between infants exposed to MgSO$_4$ and those not exposed to Mgso4 by independent samples t-test. Pearson’s chi-square test was used to assess differences for proportions.

Adjusted odd ratio (a OR) and 95% confidence intervals (CI) were calculated by logistic regression analyses and controlled for birth weight, GA at birth, sex, multiple birth, small for gestational age (SGA), mode of delivery, antenatal corticosteroids, 1 minute Apgar score $\leq$ 3, chorioamnionitis and pregnancy hypertensive disorders. All p values were two-tailed, and a value of < 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS 17.0 software (Chicago, IL, USA).

3- RESULTS
3.1 Characteristics of the general study population.

A total of 7418 VLBW infants were eligible and followed until death or hospital discharge, whichever came first. Main perinatal characteristics are shown in table 1. From the total cohort, 4 019 were not exposed and 3 399 were exposed to antenatal MgSO\(_4\). Non-exposed infants were delivered at a significantly lower GA compared to exposed infants (27.8 ± 2.1 vs 28.2 ± 2.1 weeks, p < 0.001). Similarly, non-exposed infants showed a significantly lower rate of controlled pregnancy (at least one prenatal visit) (88.2% vs 92.6%, p < 0.001), a lower incidence of pregnancy hypertensive disorders (21.6% vs 41.3%, p < 0.001), lower antenatal exposure to corticosteroids and rate of C-Section (77.1% vs 95.4%, p < 0.001 and 72.8% vs 81.1%, p < 0.001 respectively). Non-exposed infants were less prone to be SGA and showed higher 1 minute Apgar scores at birth (Table 1).

3.2 Neonatal interventions and outcomes.

Multivariate analysis showed that infants exposed to antenatal MgSO\(_4\) had a significantly decreased death rate after admission (aOR 0.59 [95% CI, 0.46-0.74]) (Table 2). However, for the exposed cohort, reduction in severe IVH did not reach significance (aOR 0.89 [95% CI, 0.63–1.25]). Nonetheless, our analysis showed that for the combined outcome severe IVH/ death, MgSO\(_4\)-exposed infants had a significant reduction (aOR 0.63 [95% CI, 0.49-0.83]).

Regarding secondary outcomes, exposed infants showed a significant reduction in the need for intubation in the DR (aOR 0.74 [95% CI, 0.60-0.91]), although they received more mask ventilation at birth (aOR 1.24 [95% CI, 1.05-1.47]) as can be depicted from table 2.

No differences between groups were observed regarding tolerance to enteral feeds. Neither age at starting feeds nor days to 100 ml/kg/day reached statistical significance (1.52 ±1.8 vs 1.55 ± 1.9 [p value 0.94] and 14.29 ±11.5 vs 14.18 ±10.8 [p value 0.90], respectively).

In addition, rates of other major neonatal morbidities such as LOS, PDA, global IVH (any grade IVH), NEC, PVL, ROP, and BPD were no different for MgSO\(_4\) exposed versus non-exposed infants (Table 2).

In the subgroup analysis, MgSO\(_4\) exposure in the 24+ 0/7 to 25+6/7 weeks´ gestation subpopulation was associated to a decreased incidence of severe IVH, death and combined IVH/death. Statistical significance was not achieved after controlling for confounders in severe IVH and severe IVH/death (Table 3). Among 26+0/7 to 27+6/7 week's gestation infants, no significant differences were found. For the 28+0/7 to 29+6/7 weeks’ gestation infants, death after admission, as well as severe IVH / death showed a significant reduction for the MgSO\(_4\) exposed group. In the upper subsets of 30+0/7 to 31+6/7 weeks´ GA, both death after admission and severe IVH/death showed a decreased incidence for the exposed group, however, after adjusting no statistically significant reduction was observed (Table 3).

Discussion
Results from this analysis reveal that antenatal exposure to MgSO\textsubscript{4} in preterm birth before 32 weeks’ GA significantly reduces the death rate after admission and the composite outcome severe IVH/death. However, no statistically significant reduction was observed in severe IVH or death in DR in the MgSO\textsubscript{4} exposed group. In the more immature 24+ 0/7 to 25+6/7 weeks infants’ antenatal exposure to MgSO\textsubscript{4} was associated to a decrease in all primary outcomes including severe IVH. These findings are reassuring, not only in terms of mortality, but also regarding other important short- and long-term morbidities such as need for intubation in DR, low 5-minute Apgar scores, need for surfactant, necrotizing enterocolitis, PVL, BPD, ROP or LOS, which did not show any increased risk in the MgSO\textsubscript{4} exposed group. Interestingly, results show a significant reduction in the need for intubation in DR, differing with the common perception among clinicians that MgSO\textsubscript{4} exposed infants more frequently need resuscitation in the DR and exposure is associated with respiratory depression at birth as a side-effect. However, we did find a significant increase in need of mask ventilation in the DR, probably related to the decrease in need for intubation. MgSO\textsubscript{4} exposure has also previously been associated with a rise in the incidence of low Apgar scores, hypotonia, and neonatal intensive care unit (NICU) admission. Other studies demonstrated that exposure to antenatal MgSO\textsubscript{4} in preterm infants did not affect the need for resuscitation at birth or other short-term outcomes such as hypotonia, respiratory distress syndrome (RDS), need of mechanical ventilation, gastrointestinal-related morbidities, IVH or death [16,18,19,20]. These outcomes are aligned with our findings.

Although no statistically significant reduction was observed in death in DR in exposed infants, we would like to highlight the low rates of death being only 1.1% vs 6.8% in the non-exposed group. We believe these results might be of clinical relevance.

After adjusting for main confounders, no statistically significant reduction was observed in severe IVH in the MgSO\textsubscript{4} exposed group. Similarly, in a study published in 2015 by Hirtz et al, authors found a non-statistically significant reduction in the overall risk of any grade IVH, PVL or ventriculomegaly in prenatally exposed vs not exposed infants. They did show a significant reduction in echodensity and echolucency that only partially explains the MgSO\textsubscript{4} effect on CP [4]. In 2018, Stockley et al did not find any statistically significant reduction in the odds of any grade of IVH in MgSO\textsubscript{4} prenatally exposed SGA [11]. Nevertheless, they found a statistically significant reduction in the risk of death or neurodevelopmental impairment at 18-36 weeks’ gestation in infants born < 29 weeks’ gestation. Similarly, in a meta-analysis published in 2020, Moradi et al showed a protective but not statistically significant effect of MgSO\textsubscript{4} in IVH [7]. The aforementioned results agree with our primary findings, as we did not find a statistically significant reduction in any grade IVH. However, in the subgroup analysis, we observed that in the more immature cohort, 24+ 0/7 to 25+6/7 weeks gestational age, antenatal exposure to MgSO\textsubscript{4} was also associated to a decrease in the incidence of severe IVH.

The findings of this study should be interpreted with caution because they also may be associated with an improved overall antenatal care in the MgSO\textsubscript{4} exposed infants: higher rates of controlled pregnancy and antenatal corticosteroids (95.4 vs 77%), having a greater influence in the more immature infants. On
the other hand, if we compare antenatal steroid versus MgSO₄ administration in our VLBW population (85.5 vs 45.8%), we believe we should aim to decrease this gap. In this respect, high regional variations in MgSO₄ uptake have been reported (49%-79%), indicating inequalities in perinatal practices [21].

Our results support current FIGO and ACOG recommendations that highly encourage antenatal MgSO₄ administration when preterm birth < 30 weeks’ gestation is anticipated and propose considering administration from 30 to 31+6/7 weeks’ gestation [2,17]. Moreover, in a quality improvement (QI) initiative to increase uptake of MgSO₄ in preterm deliveries in an English cohort, authors report the QI programme was effective and cost-effective [21].

Evidence shows that the number needed to treat (NNT) increases at higher gestational ages [2].

We believe one of the strengths of this study is the inclusion of a robust large population cohort of VLBW infants from a multicenter middle-income region network. Our results add evidence regarding the effectiveness and safety of antenatal MgSO₄ administration in these high-risk pregnancies. The power of our study can be estimated by the large sample size and by the width of the calculated confidence intervals.

Because of the retrospective design of this study, potential methodological limitations should be considered. As an example, we were not able to evaluate the administrated dose, or treatment duration, neither did we assess the reason for indicating it, being that for neuroprotective purposes, as tocolytic or as part of severe preeclampsia syndrome treatment. This information was not available in our database. Also, information regarding mother’s body mass index and serum creatinine at time of administration was not available, being this a determinant of volume of distribution and clearance, therefore, having an impact in its effects [15]. MgSO₄ crosses the placenta and plasma concentration in the newborn correlates consistently with plasma levels in the mother and, therefore, the effects are dose dependent [15].

While multicenter studies are challenging because of inherent intercenter variations in the practice of clinical care, all centers participating in the NEOCOSUR Network fulfil standardized entry criteria in relation to the level of care and technology in an attempt to ameliorate such variability. Finally, we do not have the data to report long-term follow-up neurological outcomes for these patients.

There are currently a wide variety of plans for indicating MgSO₄. Both the 2021 FIGO and 2015 National Institute for Health and Care Excellence (NICE) practice recommendation on MgSO₄ administration for preterm fetal neuroprotection suggest that MgSO₄ should be administered from viability to 30 weeks’ gestation when early preterm birth is expected within 24 hours. The optimal regimen is a 4 g loading dose (administered over 20-30 minutes), followed by 1 g per hour as a maintenance dose until birth, but should be stopped if delivery does not occur after 24 hours [2,21]. SOGC currently recommends for women with imminent preterm birth under 33+ 6/7 weeks’, antenatal MgSO₄ administration should be considered for fetal neuroprotection [17].
Future research should help elucidate the optimal dosing and interval for fetal neuroprotection.

**Conclusions**

In this large multicenter study, antenatal MgSO$_4$ was associated with a decreased death rate after admission and combined severe IVH/ death in VLBW infants. However, these results must be interpreted with caution as they may represent an overall improved antenatal care in the MgSO$_4$ exposed group.

**Abbreviations**

C-section  
caesarean section  
GA  
gestational age  
SGA  
small for gestational age.

**Declarations**

**Conflict of interest**

The authors declare no known competing financial interests or personal relationships that could influence the work reported in this paper.

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**Author contributions**

Catalina Vaz Ferreira: Conceptualization, investigation, writing- original draft and visualization. José Caro: Conceptualization, methodology, investigation, writing- review and editing. Luis Villarroel: Methodology, software, formal analysis, and validation. Sergio Muñoz: Investigation. Patricia Alvarez: Investigation. Gerardo Flores: Investigation. Tamara Herrera: Investigation. Alberto Toso: Conceptualization, investigation, writing- review and editing and supervision.

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Tables

Tables 1 to 3 are available in the Supplementary Files section

Supplementary Files

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- Table3.pdf