Original Research Article

Maternal and fetal serum concentrations of magnesium after administration of a 6-g bolus dose of magnesium sulfate (MgSO₄) to women with imminent preterm delivery

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Abstract

Introduction: Magnesium sulfate is used world-wide to treat pregnant women at imminent risk of preterm delivery in order to protect the brain of the premature infant. Previous research has shown that magnesium sulfate decreases the risk of cerebral palsy by ~30% in infants born preterm. Despite this, the dosage required for optimal neuroprotection remains unknown. We aimed to investigate whether 6 g magnesium sulfate given as a single bolus dose was tolerable for the women and infants and whether the desired target concentration in the mother’s blood was reached and non-toxic level in the infant could be ensured.

Material and methods: In total, 49 women who were at risk of delivery prior to 32 weeks of gestation were recruited. They received a bolus dose of 6 g magnesium sulfate intravenously between 1 and 24 h prior to giving birth and were closely monitored during and after infusion. Blood samples from the patients were analyzed at different time-points (20–30 min after start of infusion, 1, 2, 6 and 24 h) post-administration. Blood samples from the umbilical cord were also taken directly after birth to assess the concentration of magnesium in the infant.

Results: None of the women who received magnesium sulfate reached serum magnesium concentrations >3.3 mmol/L. In all, 72% of the women showed serum magnesium levels within the therapeutic interval (2.0–3.5 mmol/L) and no adverse events were observed during the infusion. The serum magnesium levels in the mothers declined to pre-bolus levels within 24 h after delivery. Serum magnesium levels in the umbilical cord samples ranged from 0.87 to 1.4 mmol/L, which means that all but two were within the normal expected range for a newborn premature infant.

Conclusions: A bolus dose of 6 g magnesium sulfate was well tolerated and without any serious side effects in either mother or infant. Most of our women reached the targeted concentration range of serum magnesium levels after infusion was completed.

Abbreviations: APGAR, Appearance Pulse Grimace Activity Respiration; BMI, body mass index; CP, cerebral palsy; MgSO₄, magnesium sulfate; RCT, randomized controlled trial; s-Mg, serum magnesium.
1 | INTRODUCTION

Cerebral palsy (CP) and other neurodevelopmental conditions are serious outcomes among infants born preterm. Around 11% of all infants worldwide are born preterm (<37 weeks of gestation). Those who survive have an increased risk of neurological impairment, such as CP, deafness or cognitive disability. The risk of CP increases with decreasing gestational age. Magnesium sulfate (MgSO₄) has long been used to treat eclampsia and passes easily across the placenta barrier. In addition, since 2015, World Health Organization has recommended the administration of MgSO₄ as neuroprophylaxis when there is an immediate risk of preterm birth. The neuroprotective effect of MgSO₄ is relatively well documented and previous research has shown that MgSO₄, given to women at imminent risk of preterm birth, reduces the risk of intraventricular/periventricular hemorrhage and CP. There are as yet no international guidelines concerning the optimal dose of MgSO₄ for neuroprotection in infants born preterm. Internationally, the dose varies; published randomized controlled trials have all different regimens of dosage, ranging from a single bolus dose (4 g) or a bolus dose between 4 and 6 g followed by an infusion ranging from 1 to 2 g/h. There are also different opinions about when to administer the dose and for how long; hence, Crowther et al. concludes in their meta-analyses that there is insufficient data to inform about the optimal dose and how to best provide magnesium sulfate to mothers prior to preterm birth.

Our aims were to evaluate whether 6 g MgSO₄ given as a bolus dose to women at risk of preterm birth would (1) reach the presumed therapeutic level of serum magnesium (s-Mg; 2.0–4.0 mmol/L) based on the concentrations required for seizure prophylaxis and the neuroprotective concentrations in experimental models; (2) be tolerable for the women and that no extra clinical controls were necessary during the administration; (3) lead to non-toxic Mg concentrations in neonatal blood after birth.

2 | MATERIAL AND METHODS

Between November 2018 and February 2020, pregnant women in gestational weeks 23–32, and expected to give birth within 24 h (preterm labor, rupture of membranes and a cervix dilated of 3 cm or more), were recruited from the delivery unit at Sahlgrenska University Hospital. All women who met the inclusion criteria as stated above were asked to participate in the study. Some women declined to participate in the study and some women were transferred to another hospital before delivery and hence were excluded from the study. Women were not eligible if they met any of the following exclusion criteria: severe kidney disease (creatinine >100 μmol/L), myasthenia gravis, known congenital anomalies of the fetus, allergy to MgSO₄, severe preeclampsia or eclampsia that needed MgSO₄ as a part of treatment.

In total 49 women were recruited. The twenty first included women were given MgSO₄ as a part of treatment. Written instructions were available for both methods of drug administration. Blood samples for analysis of creatinine and magnesium were taken from all the included women before starting the infusion to ensure normal kidney function and a normal baseline of s-Mg. The analyses were performed using enzymatic photometry at the accredited laboratory of Sahlgrenska University Hospital.

2.1 | Monitoring

Women were included by the responsible physician, who made an overall assessment of the women. The midwife noted the woman's...
general condition, respiratory rate and knee reflexes in a case report form before, during and after the infusion. Any adverse events due to the administration of MgSO$_4$ were recorded. Baseline data (weight and body mass index [BMI]) for each patient were collected. An antidote to MgSO$_4$, calcium gluconate 9 mg/mL, was always available in case of an unexpected adverse event.

After infusion of MgSO$_4$, blood samples were collected from the pregnant mother at different time-points (directly after = 20–30 min after start of infusion, 1 h, 2 h, 6 h and 24 h after start of infusion) to assay the levels of s-Mg. A blood sample from the umbilical cord of the infant was also taken directly after birth to allow analysis of s-Mg levels. The infants were monitored according to clinical routine.

2.2 Statistical analyses

Data analysis was done using the GraphPad PRISM 8 version 8.1.1. t-test, Mann–Whitney test, simple linear regression analysis and Spearman rank were applied as appropriate. Pearson’s test was used for normal distribution analysis. A two tailed p-value <0.05 was considered statistically significant.

2.3 Ethical Approval

The Regional Ethical Review Board in Gothenburg approved the study (Registration number 385-17 and 2020-07258), on 24 January 2018 and 30 January 2021. The Swedish Medical agency approved the study (EudraCT nr 2017-004-898-14 – 180 403, Dnr 5.1-2018-12 254). The study was overseen by an external monitor according to GCP guidelines and regulations for clinical studies. The database was coded and registered in accordance with the Personal Data Act and approved by the Data Protection Officer at Sahlgrenska University Hospital (2017-00496). The work described in this article was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

3 RESULTS

Two multiparous and 47 nulliparous women were included. One woman was pregnant with duplex and one woman was pregnant with triplex. The age ranged between 20 and 39 years. BMI was used and calculated as the last weight found in the woman’s medical chart or the weight that was recorded when she was enrolled in the study. The women ranged between 17.6–40 kg/m$^2$. The women included were between gestational weeks 23+0 and 32+0 and were relatively equally distributed between the different weeks.

Blood pressure, respiratory rate and knee reflexes were normal in all women, both before and during the administration of MgSO$_4$. All women had normal creatinine levels (38–55 μmol/L) prior to administration of MgSO$_4$.

None of the 49 women reached an s-Mg concentration >3.3 mmol/L in the first blood sample taken directly after completion of the infusion (Figure 1). The therapeutic range was considered to be 2.0–4.0 mmol/L. A statistical analysis was calculated and our material was considered normally distributed. Due to this, the total number of women is considered to be enough statistically and hence no further observations would change the statistical outcome or give us any further unexpected outcomes in s-Mg levels. In those women who received MgSO$_4$ through an
infusion pump, the range in s-Mg concentration in the first blood sample was 1.4–2.8 mmol/L. The women who received MgSO₄ manually had higher levels of s-Mg (1.8–3.3 mmol/L), suggesting that MgSO₄ given manually gives the women a better chance of reaching a therapeutic interval irrespective of gestational age. The first blood sample was taken 18–36 min after start of infusion of MgSO₄. Three women gave birth shortly after completed infusion (23, 34 and 75 min, respectively). These women had an s-Mg concentration of 2.7, 3.2 and 2.6 mmol/L, respectively, and two of MgSO₄ could not be analyzed. A total of 72% of the included women from the infant born within 23 min after completed infusion (23, 34 and 75 min, respectively). These women had an s-Mg value >2 mmol/L. Factors associated with not reaching >2.0 mmol/L included that blood was not sampled within the stated time frame or that BMI was 30 kg/m² or higher.

BMI in correlation with s-Mg for the women included in the study is shown in Figure 2. There was a moderate but significant correlation between s-Mg and BMI (p = 0.035, r = −0.31) using Spearman rank test and Pearson’s test for normal distribution, suggesting that the s-Mg levels were inversely proportional to BMI.

The blood levels from the umbilical cord of the infants (in total 36 blood samples) ranged between 0.87 and 1.4 mmol/L. All three triplex infants were sampled but only one sample from the duplex infants was retrieved. Blood samples from 12 infants were not retrieved, and the volume of two blood samples was too small to be analyzed.

The lowest analyzed concentration (0.81 mmol/L) was taken from the umbilical cord of a twin infant, who was diagnosed with intrauterine growth restriction. We had one case of triplex, delivered 16 h after completed infusion, where the blood levels from the umbilical cord were in line with normal intervals for all of the three infants (0.91, 1.2 and 0.92 mmol/L, respectively). The infant with a concentration of 1.2 had a restricted blood flow in the umbilical artery diagnosed as blood flow class 3a (normal range class 0), defined as intrauterine growth restriction.

In total, 36 blood samples from the umbilical cord were analyzed. Time in hours from start of infusion till end of delivery ranged between 1 and 24 h.

We found a negative correlation showing that s-Mg declines over time. MgSO₄ has a half time of 2.7–4 h in patients with normal kidney function (non-preeclamptic patients). According to our data, the infants who were born 6–8 h after the mother was given the bolus dose of MgSO₄ tended to have higher s-Mg than did those born later after maternal administration of Mg. The correlation was statistically significant using Spearman rank test (p = 0.009, r = −0.44).

There was no correlation between infant s-Mg (blood from the umbilical cord taken directly after birth) and maternal s-Mg (first blood sample taken directly after completed infusion of MgSO₄) (p = 0.18, r = 0.056; Spearman Rank test).

In total, 44 infants were given an APGAR score in their medical file. Nine infants of 44 had a score <7 at 5 min. Most of these infants received one point (instead of two full points) in APGAR score at 5 min using the criteria grimace (reflex), appearance (color) and activity (tonus). A few infants received a zero point using the criteria grimace and respiratory.

4 | DISCUSSION

The 6 g bolus of MgSO₄ given over 20–30 min resulted in a transient elevation of s-Mg up to >2.0 mmol/L in most women, but none reached levels higher than 3.3 mmol/L. All women tolerated the treatment well and no adverse events were noted. As MgSO₄ easily crosses the placenta barrier, we expect a similar transient increase of s-Mg in fetal blood during the maternal administration, but at the time of delivery the Mg levels in umbilical blood were within the normal range and no side effects were found in the newborns.

The presumed therapeutic level for MgSO₄ (2–4 mmol/L) is based primarily on the effective prophylactic dose in eclampsia. In addition, experimental studies in newborn rats show that a bolus of MgSO₄ resulting in a transient elevation of s-Mg to 2–4 mmol/L offered a marked neuroprotection if administered >6 h prior to the insult. However, at present there is no clinical information on the degree or duration of s-Mg elevation that is required to provide effective neuroprophylaxis.

Our data support that a majority of women at risk of preterm birth regardless of week of gestation, BMI or single/multiple birth and their infants are exposed to a potentially therapeutic level of s-Mg over at least a limited time period. We do not know whether infants exposed to Mg over a longer period is better or worse, but according to Crowther et al. the protective effect was not improved by bolus-s-infusion vs only bolus. In the study by Marret et al. women received 4 g of MgSO₄ as a single bolus dose without a subsequent infusion. This regime tended to improve outcome but...
did not result in any significant difference in white matter injury as compared with controls. Even though the study was underpowered, the results may indicate that a dose of 4 g MgSO4 is too low to prevent brain injury in infants born preterm. On the other hand, high dose MgSO4 regimens have been associated with increased adverse events in preterm infants, eg one study showed that mortality in preterm born infants was higher if s-Mg exceeded 2.25 mmol/L during the first 24 h of life. Several studies have shown that Mg passes easily across the placenta barrier and nearly the same concentrations of s-Mg are detected in fetal as in maternal blood. Renal clearance is reduced in neonates, especially in preterm infants, during the first days of life, causing s-Mg levels to remain high, which is important to keep in mind when administering MgSO4 infusions over longer periods. Previous research has shown difficulties in compliance when prescribing MgSO4 for neuroprotection. Chollat et al. highlighted that compliance was lower if a bolus was combined with infusion, especially if treatment required long-lasting maternal monitoring, which can be problematic as shortness of staff are the case in many delivery wards.

Vilchez et al. showed that MgSO4 for fetal neuroprotection was effective in non-obese, but not in obese women, suggesting that obese women may need a higher dose. In our study, six of 10 obese women reached an s-Mg concentration of 2.0 mmol/L in the first blood sample taken 20 min after completed infusion. These women had a BMI between 30 and 40 kg/m2 and s-Mg levels of 2.0–2.7 mmol/L. However, BMI at 30 kg/m2 or higher was a factor associated with increased risk of not reaching s-Mg levels >2.0 mmol/L. At the moment there are no international guidelines supporting a bolus dose of >6 g MgSO4, but obese women and their offspring may benefit from a higher dose of MgSO4: further research in this area is needed.

An important conclusion from our study is that 6 g MgSO4 can safely be administered manually as a bolus dose and is well tolerated by the women, with no extra surveillance needed during or after the infusion. This is in agreement with the individual participant data meta-analysis, where Crowther et al. did not find any serious adverse outcomes in the women. The side effects from MgSO4 increase with higher dosage and it is important for the health of the women and neonates to administer the lowest effective dose.

Increased levels of Mg in infants (>2.5 mmol/L) are associated with adverse outcomes and admission to intensive care unit, but levels up to 2.5 mmol/L seem to be well tolerated. In our study, the offspring received MgSO4 treatment before birth and all of the 37 infants at birth had umbilical blood levels of Mg in the normal range regardless of the mothers’ BMI, gestational week, parity, estimated birthweight or a reduced blood flow in the umbilical artery. Fenton et al. showed there was a mean s-Mg of 0.79 mmol/L (0.65–0.94) in the umbilical cord at gestational weeks 23–27 and 0.79 mmol/L (0.58–0.99 mmol/L) at gestational weeks 28–31.

A major limitation with this study is that when analyzing subgroups, in terms of BMI, gestational week, single or multiple birth, intrauterine growth restriction and restriction in blood flow in the umbilical artery, there were too few women to draw any firm conclusions.

MgSO4 treatment is inexpensive and easy to administer and the results of several randomized controlled trials (RCTs) implies that the treatment would reduce the burden of healthcare because of a decreased number of cases with CP. To evaluate whether a 6-g bolus dose of MgSO4 has the desired effect, in terms of reducing CP among preterm born infants, in our population and in line with what Doyle et al. showed, we aim to conduct a “real world” population-based cohort study to compare the outcomes for infants receiving a 6-g bolus dose of MgSO4 compared with a cohort prior to the Swedish national implementation of MgSO4 treatment in February 2020. The study will compare a 3-year cohort prior to implementation to a 3-year cohort after implementation, using registers and medical journals. Study design is based on a priori power-analysis with the primary outcome of death and moderate to severe CP at 2 years, corrected age, similar to the outcome in the published RCTs.

5 | CONCLUSION

This study shows that 6 g MgSO4 given to women at imminent risk of preterm birth for fetal neuroprotection is likely to result in therapeutic levels of Mg and appears to be safe for the mother and the offspring.

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CONFLICT OF INTEREST

None.

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REFERENCES

1. Marlow N. Neurocognitive outcome after very preterm birth. Arch Dis Infant Fetal Neonatal Ed. 2004;89:F224-F228.
2. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379:2162-2172.
3. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371:261-269.
4. Himpes E, Van den Broeck C, Oostra A, Calders P, Vanhaevertbrock P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. Dev Med Infant Neurol. 2008;50:334-340.
5. WHO fact sheets about preterm birth. https://www.who.int/newsroom/fact-sheets/detail/preterm-birth
6. Rouse DJ, Hirtz DG, Thom E, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. N Engl J Med. 2008;359:895-905.
7. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulfate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev*. 2009;1:CD004661.

8. Crowther CA, Middleton PF, Voysey M, et al. Assessing the neuroprotective benefits for infant of antenatal magnesium sulfate: an individual participant data meta-analysis. *PLoS Med*. 2017;14:e1002398.

9. Kuban KC, Leviton A, Pagano M, Fenton T, Strassfeld R, Wolff M. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature infant. *J Infant Neurol*. 1992;7:70-76.

10. Wolf HT, Huusom LD, Henriksen TB, Hegaard HK, Brok J, Pinborg A. Magnesium sulfate for fetal neuroprotection at imminent risk for preterm delivery: a systematic review with meta-analysis and trial sequential analysis. *BJOG*. 2020;127:1180-1188.

11. Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. *Clin Pharmacokinet*. 2000;38:305-314.

12. Koning G, Leverin AL, Nair S, et al. Magnesium induces preconditioning of the neonatal brain via profound mitochondrial protection. *J Cereb Blood Flow Metab*. 2019;39:1038-1055.

13. Marret S, Marpeau L, Zupan-Simunek V, et al. Magnesium sulfate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial*. *BJOG*. 2007;114:310-318.

14. Brookfield KF, Su F, Elkomy MH, Drover DR, Lyell DJ, Carvalho B. Pharmacokinetics and placental transfer of magnesium sulfate in pregnant women. *Am J Obstet Gynecol*. 2016;214:737.e1-9.

15. Basu SK, Chickajajur V, Lopez V, Bhutada A, Pagala M, Rastogi S. Immediate clinical outcomes in preterm neonates receiving antenatal magnesium for neuroprotection. *J Perinat Med*. 2011;40:185-189.

16. Chollat C, Marret S. Magnesium sulfate and fetal neuroprotection: overview of clinical evidence. *Neural Regen Res*. 2018;13:2044-2049.

17. Gatik K, May R, Crowther C. Survey on use of antenatal magnesium sulphate for fetal neuroprotection prior to preterm birth in Australia and New Zealand - Ongoing barriers and enablers. *Aust N Z Obstet Gynaecol*. 2020;60:44-48.

18. Vilchez G, Dai J, Lagos M, Sokol RJ. Maternal side effects & fetal neuroprotection according to body mass index after magnesium sulfate in a multicenter randomized controlled trial. *J Matern Fetal Neonatal Med*. 2018;31:178-183.

19. Rigo J, Pieltain C, Christmann V, et al. Serum magnesium levels in preterm infants are higher than adult levels: a systematic literature review and meta-analysis. *Nutrients*. 2017;9:1125.

20. Fenton TR, Lyon AW, Rose MS. Cord blood calcium, phosphate, magnesium, and alkaline phosphatase gestational age-specific reference intervals for preterm infants. *BMC Pediatr*. 2011;11:76.

21. Doyle LW, Spittle AJ, Olsen JE, et al. Translating antenatal magnesium sulphate neuroprotection for infants born <28 weeks’ gestation into practice: a geographical cohort study. *Aust N Z J Obstet Gynaecol*. 2021;61:513-518.

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