Neonatal Magnesemia in Preterm Neonates Unexposed to Maternal MgSO4 Administration and in Neonates Exposed for Fetal Neuroprotection or Maternal Eclampsia Prevention.

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Abstract

Objective - To compare neonatal magnesemia in the first fifteen days of neonatal life between three groups: a control group not exposed to $MgSO_4$, a neuroprotection group, and an eclampsia prevention group, and to explore its' associations with child outcomes.

Design - Retrospective single-centre cohort study.

Setting - Tertiary care setting.

Population - Infants admitted at the neonatal intensive care unit born between 24 and 32 weeks' gestation, regardless of etiology of preterm birth.

Methods - Linear mixed regression of neonatal magnesemia on exposure group and day of life. Generalised estimating equations models of child outcomes on neonatal magnesemia according to exposure group and day of life.

Main outcome measures - Neonatal magnesemia (mmol/l).

Results - Neonatal magnesemia is significantly higher in the preeclampsia group compared to the control and neuroprotection group. On the day of birth, this is irrespective of maternal magnesemia (preeclampsia vs control group), and the maternal total dose or duration of $MgSO_4$ administration (preeclampsia vs neuroprotection group). No differences were found in short-term composite outcome between the three groups.

Conclusions - We found mean differences in neonatal magnesemia between children not exposed to $MgSO_4$ antenatally, children exposed for fetal neuroprotection, and children exposed for maternal eclampsia prevention. A 4g loading and 1g/h maintenance dose, for fetal neuroprotection and eclampsia prevention, appears to be safe on the short term for the neonate.

What Is Known

Magnesium sulfate is a valuable medicine in obstetrics. The main indications are prevention of eclampsia and fetal neuroprotection. The most used dosage is a 4 or 6 grams loading dose and a 1 or 2 grams per hour maintenance dose. It reduces neuromotor disabilities in extreme to moderate preterm born children.

What is new - Maternal concentrations are supraphysiological and the maternal total dose can be high. Concentrations in neonates appear to remain in safe ranges. A dosage of 4 grams loading and 1 gram/hour seems safe for the preterm neonate on the short term.

Introduction

For several decades now, the administration of magnesium sulphate (MgSO4) is current practice in obstetrics. Historically $MgSO_4$ was used as a tocolytic agent. However, the utility of magnesium sulphate in this context is questionable [1]. Current guidelines recommend the use of MgSO4 for prevention or treatment of seizures in women with (pre)eclampsia or for fetal neuroprotection when extreme or early preterm birth is imminent. $MgSO_4$ administered for fetal neuroprotection reduces the risk of gross motor dysfunction and moderate to severe cerebral palsy [2–8].

While severe adverse effects (such as respiratory depression, cardiac arrest, coma and eventually death) due to an iatrogenic overdose are reported, most maternal adverse effects are minor and well tolerated [9]. Despite widespread use by obstetricians, controversy over unintended adverse neonatal outcomes following maternal magnesium therapy remains. Higher maternal serum magnesium concentrations have been significantly associated with neonatal complications, including low Apgar scores at 1 and 5 minutes, respiratory depression, hypotension, hypotonia, hyporeflexia, neonatal intensive care unit admission, intraventricular hemorrhage, and spontaneous intestinal perforation [10–14]. On the other hand, a recently published systematic review concluded that antenatal $MgSO_4$ administration was not associated with neonatal morbidities or perinatal death [15]. A limitation of most trials examining adverse neonatal effects of maternal MgSO4 administration is grouping all magnesium-exposed neonates together, regardless of its indication. The indication however may have an influence on maternal and neonatal magnesemia.

The primary aim of this study was to compare neonatal magnesemia in the first fifteen days of neonatal life between three groups of infants born before 32 weeks' gestation: a control group that was not exposed to $MgSO_4$ antenatally, a neuroprotection group of neonates whose mothers received $MgSO_4$ for fetal neuroprotection, and a preeclampsia group of neonates whose mothers received $MgSO_4$ to prevent eclampsia.

Secondary aims were to explore correlations between neonatal magnesemia and maternal serum magnesium concentration, maternal total dose of magnesium, and duration of exposure to magnesium before delivery. We also explored if neonatal magnesemia was associated with adverse short-term outcomes.

Materials And Methods

Study design, data source and collection

We conducted a retrospective single-centre cohort study in Ghent University Hospital, a referral centre for high-risk pregnancies in Belgium. Data on neonates born at a gestational age between 24^{+0} and 31^{+6} weeks' gestation from January 2012 to December 2015 were extracted from the hospital preterm birth register. The preterm birth register was created in 2016 and provides maternal and neonatal data on demographics, procedures/interventions, diagnoses, short- and long-term morbidities and mortality for preterm births between 24^{+0} and 33^{+6} weeks' gestation. Obstetrical data were retrospectively entered in the database by senior clinicians. Neonatal data were extracted from an already operational neonatal database and imported into the register. The database was built and managed using the REDCap® electronic data capture tool. The preterm birth register was registered at clinicaltrials.gov (NCT03405116). Patient involvement was limited to consenting in registration and use of the data for scientific purposes. The funding body played no role in the creation of the manuscript.

Population

Neonates born at a gestational age between 24^{+0} and 31^{+6} weeks' gestation, regardless of the etiology of preterm birth, admitted at the neonatal intensive care unit were included in this study. Neonates with major congenital malformations are not included in the preterm birth register. A major congenital malformation is defined as a malformation with higher neonatal morbidity or mortality.

Intervention and comparison

In Ghent University Hospital, the dosage of $MgSO_4$ for fetal neuroprotection is the same as the dosage for eclampsia prevention. A four gram loading dose is given over 15 to 20 minutes and is followed by a maintenance dose of one gram per hour (Zuspan's regimen)[15]. In the setting of fetal neuroprotection, the infusion is stopped when delivery does not occur within 24 hours after start and preterm birth is no longer threatening. If an imminent risk of preterm delivery re-emerges, $MgSO_4$ administration is repeated. In the setting of (pre)eclampsia, $MgSO_4$ infusion is stopped 48 hours after delivery. $MgSO_4$ administration for fetal neuroprotection was introduced in 2014, all neonates not exposed to $MgSO_4$ make up the control group. $MgSO_4$ was not given to the neonates.

Endpoints

The primary endpoint is neonatal magnesemia, measured repeatedly at unfixed time points in the first fifteen days of neonatal life. If more than one serum magnesium value was available on one day, the first value of that day was taken.

Short-term neonatal core outcome includes neonatal intensive care unit mortality, intraventricular hemorrhage (IVH) and/or periventricular leukomalacia (PVL). IVH and PVL were detected on routine brain ultrasound and respectively scored according to Papille classification criteria and the four-grade classification by de Vries et al [16, 17].

Statistical analysis

Maternal and neonatal characteristics were compared across the three exposure groups. Continuous variables were compared between groups with one-way ANOVA and pairwise significant differences were identified using the Tukey honest significant differences test. Categorical data on the level of the mother were compared using a Chi-square or Fisher's exact test. Correlations between two continuous variables were assessed using the Pearson correlation coefficient.

To account for clustering due to multiple pregnancies and repeated outcome assessments over days, linear mixed models (LMMs) with two random intercepts were fitted for log-transformed neonatal magnesemia. For the main research question, neonatal day of life (day of birth (= day 0) until day 14), exposure group, and their two-way interaction were included in the fixed effects part of the model. For the other research questions, the models included a three-way interaction between neonatal day of life, exposure group, and maternal magnesemia / total maternal dose of $MgSO_4$ / duration of $MgSO_4$ administration, and all underlying effects. The estimated marginal means with their 95% confidence interval (CI) are plotted by neonatal day of life according to exposure group. No indication of multi-collinearity was found based on the variance inflation factor (< 2.5).

Generalised estimated equation (GEE) models with an independence correlation structure, Gaussian distribution and identity link function were used to assess the association between neonatal magnesemia and a composite short-term outcome.

Neonatal and maternal magnesemia, total maternal dose of $MgSO_4$, and duration of $MgSO_4$ administration were log-transformed for all analyses. Regression coefficients from analyses with log-transformed dependent outcome were exponentiated to infer associations regarding the geometric mean. With log-transformed independent variables, the estimated % change in geometric mean neonatal magnesemia for each 10% increase in the independent variable was reported.

Subgroup analyses were performed according to exposure group. No analyses regarding maternal magnesemia were performed in the neuroprotection subgroup, due to the limited number of measured maternal magnesemia values (n = 6). Evidently, no analyses regarding total maternal dose of $MgSO_4$ and duration of $MgSO_4$ administration were performed in the control subgroup.

All hypothesis testing was performed at the two-sided 5% significance level. No adjustment for multiple testing was done. All analyses were performed using R version 4.0.5. The package “lme4” was used to construct the LMMs and the “geepack” package to fit the GEE models.

Ethical considerations

The preterm birth register was approved by the Medical Ethics Committee of Ghent University Hospital on May 5th 2017 with registration number BE670201732322. This study was approved on February 26th 2018 with registration number BE670201835532. Data were gathered after informed consent was obtained and were handled with professional confidentiality. Withdrawal from the study was possible at any time.

Results

Demographics and characteristics of the study cohort

Between 2012 and 2015, 345 neonates were born alive before 32 weeks’ gestation and admitted to the neonatal intensive care unit. One hundred and three neonates (29.9%) were part of a twin and five of a triplet (1.4%). Two hundred and ninety six mothers were included.

There are 218 neonates in the control group (63.2%), 68 in the neuroprotection group (19.7%), and 59 in the preeclampsia group (17.1%). Demographics and characteristics are summarised in Table 1. In the preeclampsia group, maternal body mass index (BMI) is, on average, higher compared to the other groups (+3.1 kg/m^2 [95% confidence interval (CI) 1.3, 4.9] versus the control group, and + 2.7 kg/m^2 [95%CI 0.5, 4.8] versus the neuroprotection group) and neonatal birth weight is, on average, lower (-283.0 g [95%CI -390.0, -176.0] versus the control group and -210.7 g [95%CI -348.0, -73.2] versus the neuroprotection group). There is a difference in number of multiple pregnancies, with less multiple pregnancies in the preeclampsia group (-22.7% [95%CI -36.5, -0.9] versus the control group, and -17.3% [95%CI -35.2, 0.5] versus the neuroprotection group). There are no other significant differences between groups found in our sample.

Table 1
Demographics and characteristics of the study cohort

	No MgSO4 (N=218)	Neuroprotection (N=68)	Preeclampsia (N=59)	Overall (N=345)
Maternal age (years)				
Mean (SD)	30.5 (5.1)	30.2 (5.8)	30.4 (4.8)	30.4 (5.2)
Median [Min, Max]	30.0 [16.0, 42.0]	30.0 [16.0, 43.0]	30.0 [17.0, 44.0]	30.0 [16.0, 44.0]
Pre-pregnancy BMI (kg/m^2)				
Mean (SD)	23.9 (4.3)	24.4 (5.1)	27.0 (7.3)	24.5 (5.2)
Median [Min, Max]	23.3 [15.2, 37.2]	23.4 [16.5, 42.8]	26.0 [16.2, 64.5]	23.6 [15.2, 64.5]
Parity				
Nulliparous	129 (59.2%)	46 (67.6%)	37 (62.7%)	212 (61.4%)
Primiparous	53 (24.3%)	11 (16.2%)	13 (22.0%)	77 (22.3%)
Multiparous	36 (16.5%)	11 (16.2%)	9 (15.3%)	56 (16.2%)
Conception				
Spontaneous	156 (71.6%)	49 (72.1%)	47 (79.7%)	252 (73.0%)
Assisted	62 (28.4%)	19 (27.9%)	12 (20.3%)	93 (27.0%)
Antenatal corticosteroids				
No	17 (7.8%)	2 (2.9%)	4 (6.8%)	23 (6.7%)
Yes	201 (92.2%)	66 (97.1%)	55 (93.2%)	322 (93.3%)
Number of fetuses				
Singleton	139 (63.8%)	47 (69.1%)	51(86.4%)	237 (68.7%)
Twin	74 (33.9%)	21 (30.9%)	8 (13.6%)	103 (29.9%)
Triplet	5 (2.3%)	0 (0.0%)	0 (0.0%)	5 (1.4%)
Sex				
Male	120 (55.0%)	32 (47.1%)	27 (45.8%)	179 (51.9%)
Female	98 (45.0%)	36 (52.9%)	32 (54.2%)	166 (48.1%)
Gestational age at birth (weeks)				
24-27+6w	43 (19.7%)	21 (30.9%)	12 (20.3%)	76 (22.0%)
28-31+6w	175 (80.3%)	47 (69.1%)	47 (79.7%)	269 (78.0%)
Birth weight (grams)				
Mean (SD)	1340 (356)	1260 (396)	1050 (356)	1270 (378)
Median [Min, Max]	1360 [565, 2200]	1280 [620, 2120]	980 [538, 2500]	1290 [538, 2500]

There is a moderately positive correlation between the total maternal dose of $MgSO_4$ and the maternal magnesemia in the whole population (pearson = 0.64) and in the preeclampsia group (pearson = 0.60). The neonatal magnesemia is, for all days and in all groups, correlated with the neonatal magnesemia of the subsequent day. Table 2 provides a summary of the observed maternal and neonatal magnesium values.

Table 2
Observed maternal and neonatal (day of birth - neonatal day 7) magnesium values

	No MgSO4 (N=218)	Neuroprotection (N=68)	Preeclampsia (N=59)	Overall (N=345)
Maternal magnesemia (mmol/l)				
Mean (SD)	1.00 (0.59)	1.23 (0.37)	1.91 (0.64)	1.49 (0.75)
Median [Min, Max]	0.75 [0.63, 2.97]	1.24 [0.76, 1.64]	1.85 [0.74, 3.08]	1.52 [0.63, 3.08]
Missing	177 (81.2%)	62 (91.2%)	8 (13.6%)	247 (71.6%)
Maternal total Mg dose (grams)				
Mean (SD)	-	2610 (5250)	9190 (12200)	5640 (9640)
Median [Min, Max]	-	838 [4, 33600]	3570 [4, 52300]	1480 [4, 52300]
Missing	-	1 (1.5%)	2 (3.4%)	221 (64.1%)
Duration MgSO4 infusion (minutes)				
Mean (SD)	-	688 (722)	6240 (6820)	3240 (5400)
Median [Min, Max]	-	336 [39, 3020]	3600 [15, 31200]	1020 [15, 31200]
Missing	-	1 (1.5%)	2 (3.4%)	221 (64.1%)
Neonatal magnesemia, day of birth (mmol/l)				
Mean (SD)	0.82 (0.25)	1.12 (0.20)	1.65 (0.51)	1.02 (0.43)
Median [Min, Max]	0.77 [0.55, 2.86]	1.12 [0.73, 1.81]	1.61 [0.79, 3.17]	0.84 [0.55, 3.17]
Missing	28 (12.8%)	10 (14.7%)	8 (13.6%)	46 (13.3%)
Neonatal magnesemia, day 1 (mmol/l)				
Mean (SD)	0.92 (0.20)	1.13 (0.17)	1.51 (0.45)	1.06 (0.33)
Median [Min, Max]	0.89 [0.53, 2.55]	1.12 [0.77, 1.63]	1.52 [0.76, 2.78]	0.95 [0.53, 2.78]
Missing	21 (9.6%)	6 (8.8%)	8 (13.6%)	35 (10.1%)
Neonatal magnesemia, day 2 (mmol/l)				
Mean (SD)	1.04 (0.15)	1.17 (0.14)	1.39 (0.31)	1.13 (0.23)
Median [Min, Max]	1.02 [0.73, 2.00]	1.17 [0.87, 1.58]	1.34 [0.89, 2.26]	1.07 [0.73, 2.26]
Missing	16 (7.3%)	4 (5.9%)	5 (8.5%)	25 (7.2%)
Neonatal magnesemia, day 3 (mmol/l)				
Mean (SD)	1.10 (0.13)	1.16 (0.14)	1.28 (0.24)	1.15 (0.17)
Median [Min, Max]	1.09 [0.77, 1.88]	1.15 [0.88, 1.47]	1.23 [0.92, 1.77]	1.11 [0.77, 1.88]
Missing	24 (11.0%)	5 (7.4%)	5 (8.5%)	34 (9.9%)
Neonatal magnesemia, day 4 (mmol/l)				
Mean (SD)	1.09 (0.12)	1.13 (0.11)	1.17 (0.21)	1.11 (0.14)
Median [Min, Max]	1.09 [0.62, 1.59]	1.12 [0.92, 1.47]	1.15 [0.76, 1.60]	1.10 [0.62, 1.60]
Missing	34 (15.6%)	8 (11.8%)	10 (16.9%)	52 (15.1%)
Neonatal magnesemia, day 5 (mmol/l)				
Mean (SD)	1.04 (0.12)	1.06 (0.09)	1.06 (0.17)	1.05 (0.13)
Median [Min, Max]	1.04 [0.38, 1.46]	1.05 [0.91, 1.26]	1.04 [0.79, 1.48]	1.04 [0.38, 1.48]
Missing	47 (21.6%)	16 (23.5%)	6 (10.2%)	69 (20.0%)

	No MgSO4 (N=218)	Neuroprotection (N=68)	Preeclampsia (N=59)	Overall (N=345)
Neonatal magnesemia, day 6 (mmol/l)				
Mean (SD)	1.00 (0.10)	1.02 (0.09)	1.00 (0.16)	1.00 (0.11)
Median [Min, Max]	0.98 [0.72, 1.39]	1.02 [0.81, 1.27]	0.98 [0.79, 1.41]	0.99 [0.72, 1.41]
Missing	68 (31.2%)	14 (20.6%)	11 (18.6%)	93 (27.0%)
Neonatal magnesemia, day 7 (mmol/l)				
Mean (SD)	0.96 (0.09)	0.96 (0.08)	0.93 (0.13)	0.95 (0.10)
Median [Min, Max]	0.95 [0.71, 1.28]	0.96 [0.80, 1.10]	0.91 [0.72, 1.27]	0.95 [0.71, 1.28]
Missing	72 (33.0%)	30 (44.1%)	22 (37.3%)	124 (35.9%)

Primary aim (Online Resource S1)

The distribution of neonatal magnesemia according to neonatal day of life (day 0-14) and indication for $MgSO_4$ administration is visualised in Figure 1.

There is a significant difference in geometric mean neonatal magnesemia between the three groups from the day of birth up to the fourth day of life (day 0-3). No significant differences in neonatal magnesemia between the three exposure groups beyond day four of neonatal life could be found in our sample. The estimated geometric mean neonatal magnesemia (with 95% CI) per neonatal day of life and group is depicted in Figure 2a and numerically summarised in Online Resource Table S1.

In all three groups, there is no indication of an association of maternal BMI and neonatal birth weight with neonatal magnesemia.

Maternal magnesemia (Online Resource S1)

In our cohort, there is a significant association between maternal magnesemia and neonatal magnesemia during the first four days of life (day 0-3) in both the control and the preeclampsia group. The association remains significant until the eight day of life (day 0-7) in the preeclampsia group (Online Resource Table S3).

Maternal magnesemia is, on average, higher in the preeclampsia group versus the control group (+0.70 mmol/L [95%CI 0.50, 0.89])(Online Resource Figure S1a).

The estimated geometric mean neonatal magnesemia per neonatal day of life per exposure group for a maternal magnesemia corresponding to the overall geometric mean of 1.30 mmol/l is depicted in Figure 2b and numerically summarised in Online Resource Table S2. Only on the first day of neonatal life (day 0), independent of the maternal magnesemia, neonatal magnesemia is significantly higher in the preeclampsia group compared to the control group.

Total maternal dose of $MgSO_4$ (Online Resource S1)

Most women in the neuroprotection group received $MgSO_4$ for less than 24 hours; only 12 out of 68 women in the neuroprotective group received the maximum dose of 28 grams.

There is a significant association between total maternal dose and neonatal magnesemia during the first four days of life (day 0-3) in both the neuroprotection and the preeclampsia group. The association is significant until the seventh day of life (day 0-6) in the preeclampsia group (Online Resource Table S3).

The geometric mean maternal total dose is, on average, 4.62 times higher in the preeclampsia group versus the neuroprotection group (x4.62 [95% CI x3.13, x6.82])(Online Resource Figure S1b).

The estimated geometric mean neonatal magnesemia per neonatal day of life per exposure group for a total maternal dose of $MgSO_4$ corresponding the overall geometric mean in these two exposure groups of 23.82 grams, is depicted in Figure 2c and numerically summarised in Online Resource Table S2. In our cohort, on the two first days of neonatal life (day 0-1) neonatal magnesemia is significantly higher in the preeclampsia group compared to the neuroprotection group, independent of the total maternal $MgSO_4$ dose.

Duration of $MgSO_4$ exposure (Online Resource S1)

There is a significant association between the duration of $MgSO_4$ administration and the neonatal magnesemia during the first three days of life (day 0-2) in both the neuroprotection and the preeclampsia group. The association remains significant until the seventh day of life (day 0-6) in the preeclampsia group (Online Resource Table S3).

The duration of maternal $MgSO_4$ administration is, on average, 6.96 times higher in the preeclampsia group versus the neuroprotection group (x6.96 [95% CI x3.97, x12.18])(Online Resource Figure S1c).

The estimated geometric mean neonatal magnesemia per neonatal day of life per exposure group for a duration of $MgSO_4$ administration corresponding to the overall geometric mean of 850 minutes in these two exposure groups is depicted in Figure 2d and numerically summarised in Online Resource Table S2. In our cohort, on the two first days of neonatal life (day 0-1) neonatal magnesemia is significantly higher in the preeclampsia group compared to the neuroprotection group, independent of the duration of $MgSO_4$ administration.

Short-term outcome (Online Resource S1)

Ninety three neonates (27.0%) experienced the composite short-term neonatal outcome (mortality, IVH and/or PVL). No significant differences in short-term neonatal outcome between the three exposure groups were identified in our cohort.

Discussion

Main findings

We used LMMs to explore the association of neonatal magnesemia with antenatal $MgSO_4$ exposure. In our cohort, neonatal magnesemia is significantly higher in the preeclampsia group compared to the neuroprotection and control group, and in the neuroprotection group compared to the control group, during the first four days of life. There was an association between maternal and neonatal magnesemia during the first four days in the control and preeclampsia group (too few maternal magnesemia values in neuroprotection group). Within the preeclampsia and neuroprotection groups, there was an association between total maternal $MgSO_4$ dose and neonatal magnesemia during the first four days and between duration of administration and neonatal magnesemia during the first three days. Corrected for maternal magnesemia, total dose or duration of administration, the neonatal magnesemia was higher in the preeclampsia group compared to the neuroprotection group on the day of birth. No group differences were found in short-term outcome.

Strengths and limitations

This is the first study exploring neonatal magnesemia in three distinct groups during the first fifteen days of life. Most studies only take into account the day of birth and/or the day after. Furthermore, few studies compare neonates not exposed to $MgSO_4$ to neonates primarily exposed for neuroprotection or preeclampsia.

We recognise the limitations of a single-centre retrospective study design with a relatively small sample size. Maternal pre-delivery magnesemia levels were missing in the majority of neuroprotection group patients. We could not explore long-term outcomes due to considerable loss to follow-up (Online Resource S2).

Since few women in the neuroprotection group received the maximum dose (28 grams), caution is warranted in making safety statements about ‘neuroprotective dosage’. However, results from the preeclampsia group, with higher doses in more pathological circumstances, were reassuring.

A considerable amount of comparisons were made: four research questions, three exposure subgroups, 15 days of life. A risk of false positive significant associations exists. No correction for multiple testing was done, partly because it is not clear at what level the corrections should be done. On the other hand, a lack of power might be present due to small sample sizes, resulting in less associations found than truly present. Our analyses should be considered exploratory.

Interpretation

Higher levels of neonatal magnesemia in the neuroprotection group compared to unexposed neonates have been reported [11, 18, 19]. The mean neonatal magnesemia in the neuroprotection group of our cohort on day 0 and 1 is comparable to the findings by Garcia et al. (1.10 mmol/L), but considerably lower than in the study of Basu et al. (1.75 mmol/L), which had a different protocol (6g loading dose, 2g/h maintenance)[11, 18]. Sherwin et al. explored the correlation between maternal and neonatal magnesemia in a group with any indication for $MgSO_4$ [20]. Mean neonatal and maternal magnesemia were significantly associated. It is not clear when neonatal magnesemia was measured. We found an association between neonatal and maternal magnesemia from day 0 to 3 in both control and preeclampsia group. Choi et al. explored the association between maternal BMI and maternal and umbilical cord magnesemia in children born at less than 32

weeks. Maternal and adjusted umbilical cord magnesemia were not significantly different between BMI categories [21]. In our cohort, there was no association between BMI and neonatal magnesemia.

Two studies found a correlation between the total maternal dose and neonatal magnesemia on day 0 when $MgSO_4$ is given for neuroprotection, as we did [18, 22]. Borja-Del-Rosario et al. excluded patients with preeclampsia [18]. They did not detect a correlation between maternal and neonatal magnesemia, nor between total $MgSO_4$ dose and maternal magnesemia [18, 22]. We have too few values in the neuroprotection group to confirm or refute these findings.

Nassar et al. reported a higher neonatal magnesemia in a group exposed more than 48 hours to $MgSO_4$ as tocolysis compared to shorter exposure [23].

We cannot explain why neonatal magnesemia was higher in the preeclampsia on the day of birth. It might be due to placental dysfunction, or could be multifactorial.

In general, antenatal $MgSO_4$ is considered to be safe for the neonate [15, 24, 25]. However, there are reports of an association between high neonatal magnesemia and neonatal morbidity and mortality [11, 12, 26, 27]. Basu et al. found that neonatal mortality, in children born between 24 and 32 weeks, increased with increasing neonatal magnesemia. Mortality was highest when neonatal magnesemia exceeded 2.25 mmol/L during the first day of life [11]. In our cohort, none of the neonates in the neuroprotection group had a value exceeding 2.25 mmol/L. In the preeclampsia group, five neonates had a higher magnesemia. There were no cases of neonatal mortality. They found no association with survival without IVH and/or PVL. In the meta-analysis of Shepherd et al., no differences in perinatal death were identified between exposed and unexposed neonates [15]. Only in one (of 11 non-randomised trials) cohort study, with moderate to high bias risk, an increased risk of perinatal death was observed when the dose was more than 48 grams. Possible harms were mostly seen in studies not correcting for confounders, studies with small sample sizes, or in subgroup analyses [15]. Mittendorf et al. concluded that exposure to 50 grams or more of tocolytic $MgSO_4$ is indirectly associated with IVH [28]. We didn't find any between group differences in the proportions of our short-term outcome, which included IVH. In the preeclampsia and neuroprotection group, respectively 36 and two women received a dose of 50g or more. Garcia-Alonso et al. studied outcomes in exposed and unexposed children born before 29 weeks. Eighteen per cent of exposed neonates had preeclamptic mothers. They found a significant correlation between $MgSO_4$ dose and neonatal magnesemia on day 0 in the whole group, as we did in the preeclampsia and neuroprotection group. They reported a lower mortality in the exposed group and no differences in neonatal morbidity [29].

Conclusion

We found mean differences in neonatal magnesemia between children not exposed to $MgSO_4$, children exposed for fetal neuroprotection, and children exposed for maternal eclampsia prevention. After correction for maternal magnesemia, a higher neonatal magnesemia was still present in the preeclampsia group compared to the control group on the day of birth (no comparison with neuroprotection group). After correction for total dose or duration of administration, a higher neonatal magnesemia was still present in the preeclampsia compared to the neuroprotection group till day two of life. When considering neonatal magnesemia per day of neonatal life by exposure group, there was an association with maternal magnesemia, total dose, and duration of administration the first days. A 4g loading and 1g/h maintenance dose, for fetal neuroprotection and eclampsia prevention, appears to be safe on the short term for the neonate.

Abbreviations

ACS	antenatal corticosteroids
BMI	body mass index
IVH	intraventricular hemorrhage
MgSO4	magnesium sulfate
PVL	periventricular leukomalacia

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contribution

ID: conception, planning, carrying out, analysing, writing. **TVS**: conception, planning, carrying out, analysing, writing. **KDC**: conception, planning, writing. **SDB**: analysing, writing. **JDC**: writing. **KS**: writing. **KR**: conception, planning, writing.

Ethics approval

The preterm birth register was approved by the Medical Ethics Committee of Ghent University Hospital, Belgium, on May 5th 2017 with registration number BE670201732322. This study was approved on February 26th 2018 with registration number BE670201835532.

Consents to participate

Written informed consent was obtained from the parents.

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Tables

Table 1: Demographics and characteristics of the study cohort

	No MgSO4 (N=218)	Neuroprotection (N=68)	Preeclampsia (N=59)	Overall (N=345)
Maternal age (years)				
Mean (SD)	30.5 (5.1)	30.2 (5.8)	30.4 (4.8)	30.4 (5.2)
Median [Min, Max]	30.0 [16.0, 42.0]	30.0 [16.0, 43.0]	30.0 [17.0, 44.0]	30.0 [16.0, 44.0]
Pre-pregnancy BMI (kg/m^2)				
Mean (SD)	23.9 (4.3)	24.4 (5.1)	27.0 (7.3)	24.5 (5.2)
Median [Min, Max]	23.3 [15.2, 37.2]	23.4 [16.5, 42.8]	26.0 [16.2, 64.5]	23.6 [15.2, 64.5]
Parity				
Nulliparous	129 (59.2%)	46 (67.6%)	37 (62.7%)	212 (61.4%)
Primiparous	53 (24.3%)	11 (16.2%)	13 (22.0%)	77 (22.3%)
Multiparous	36 (16.5%)	11 (16.2%)	9 (15.3%)	56 (16.2%)
Conception				
Spontaneous	156 (71.6%)	49 (72.1%)	47 (79.7%)	252 (73.0%)
Assisted	62 (28.4%)	19 (27.9%)	12 (20.3%)	93 (27.0%)
Antenatal corticosteroids				
No	17 (7.8%)	2 (2.9%)	4 (6.8%)	23 (6.7%)
Yes	201 (92.2%)	66 (97.1%)	55 (93.2%)	322 (93.3%)
Number of fetuses				
Singleton	139 (63.8%)	47 (69.1%)	51(86.4%)	237 (68.7%)
Twin	74 (33.9%)	21 (30.9%)	8 (13.6%)	103 (29.9%)
Triplet	5 (2.3%)	0 (0.0%)	0 (0.0%)	5 (1.4%)
Sex				
Male	120 (55.0%)	32 (47.1%)	27 (45.8%)	179 (51.9%)
Female	98 (45.0%)	36 (52.9%)	32 (54.2%)	166 (48.1%)
Gestational age at birth (weeks)				
24-27+6w	43 (19.7%)	21 (30.9%)	12 (20.3%)	76 (22.0%)
28-31+6w	175 (80.3%)	47 (69.1%)	47 (79.7%)	269 (78.0%)
Birth weight (grams)				
Mean (SD)	1340 (356)	1260 (396)	1050 (356)	1270 (378)
Median [Min, Max]	1360 [565, 2200]	1280 [620, 2120]	980 [538, 2500]	1290 [538, 2500]

Table 2: Observed maternal and neonatal (day of birth - neonatal day 7) magnesium values

	No MgSO4 (N=218)	Neuroprotection (N=68)	Preeclampsia (N=59)	Overall (N=345)
Maternal magnesemia (mmol/l)				
Mean (SD)	1.00 (0.59)	1.23 (0.37)	1.91 (0.64)	1.49 (0.75)
Median [Min, Max]	0.75 [0.63, 2.97]	1.24 [0.76, 1.64]	1.85 [0.74, 3.08]	1.52 [0.63, 3.08]
Missing	177 (81.2%)	62 (91.2%)	8 (13.6%)	247 (71.6%)
Maternal total Mg dose (grams)				
Mean (SD)	-	2610 (5250)	9190 (12200)	5640 (9640)
Median [Min, Max]	-	838 [4, 33600]	3570 [4, 52300]	1480 [4, 52300]
Missing	-	1 (1.5%)	2 (3.4%)	221 (64.1%)
Duration MgSO4 infusion (minutes)				
Mean (SD)	-	688 (722)	6240 (6820)	3240 (5400)
Median [Min, Max]	-	336 [39, 3020]	3600 [15, 31200]	1020 [15, 31200]
Missing	-	1 (1.5%)	2 (3.4%)	221 (64.1%)
Neonatal magnesemia, day of birth (mmol/l)				
Mean (SD)	0.82 (0.25)	1.12 (0.20)	1.65 (0.51)	1.02 (0.43)
Median [Min, Max]	0.77 [0.55, 2.86]	1.12 [0.73, 1.81]	1.61 [0.79, 3.17]	0.84 [0.55, 3.17]
Missing	28 (12.8%)	10 (14.7%)	8 (13.6%)	46 (13.3%)
Neonatal magnesemia, day 1 (mmol/l)				
Mean (SD)	0.92 (0.20)	1.13 (0.17)	1.51 (0.45)	1.06 (0.33)
Median [Min, Max]	0.89 [0.53, 2.55]	1.12 [0.77, 1.63]	1.52 [0.76, 2.78]	0.95 [0.53, 2.78]
Missing	21 (9.6%)	6 (8.8%)	8 (13.6%)	35 (10.1%)
Neonatal magnesemia, day 2 (mmol/l)				
Mean (SD)	1.04 (0.15)	1.17 (0.14)	1.39 (0.31)	1.13 (0.23)
Median [Min, Max]	1.02 [0.73, 2.00]	1.17 [0.87, 1.58]	1.34 [0.89, 2.26]	1.07 [0.73, 2.26]
Missing	16 (7.3%)	4 (5.9%)	5 (8.5%)	25 (7.2%)
Neonatal magnesemia, day 3 (mmol/l)				
Mean (SD)	1.10 (0.13)	1.16 (0.14)	1.28 (0.24)	1.15 (0.17)
Median [Min, Max]	1.09 [0.77, 1.88]	1.15 [0.88, 1.47]	1.23 [0.92, 1.77]	1.11 [0.77, 1.88]
Missing	24 (11.0%)	5 (7.4%)	5 (8.5%)	34 (9.9%)
Neonatal magnesemia, day 4 (mmol/l)				
Mean (SD)	1.09 (0.12)	1.13 (0.11)	1.17 (0.21)	1.11 (0.14)
Median [Min, Max]	1.09 [0.62, 1.59]	1.12 [0.92, 1.47]	1.15 [0.76, 1.60]	1.10 [0.62, 1.60]
Missing	34 (15.6%)	8 (11.8%)	10 (16.9%)	52 (15.1%)
Neonatal magnesemia, day 5 (mmol/l)				
Mean (SD)	1.04 (0.12)	1.06 (0.09)	1.06 (0.17)	1.05 (0.13)
Median [Min, Max]	1.04 [0.38, 1.46]	1.05 [0.91, 1.26]	1.04 [0.79, 1.48]	1.04 [0.38, 1.48]
Missing	47 (21.6%)	16 (23.5%)	6 (10.2%)	69 (20.0%)
Neonatal magnesemia, day 6 (mmol/l)				
Mean (SD)	1.00 (0.10)	1.02 (0.09)	1.00 (0.16)	1.00 (0.11)

	No MgSO4 (N=218)	Neuroprotection (N=68)	Preeclampsia (N=59)	Overall (N=345)
Median [Min, Max]	0.98 [0.72, 1.39]	1.02 [0.81, 1.27]	0.98 [0.79, 1.41]	0.99 [0.72, 1.41]
Missing	68 (31.2%)	14 (20.6%)	11 (18.6%)	93 (27.0%)
Neonatal magnesemia, day 7 (mmol/l)				
Mean (SD)	0.96 (0.09)	0.96 (0.08)	0.93 (0.13)	0.95 (0.10)
Median [Min, Max]	0.95 [0.71, 1.28]	0.96 [0.80, 1.10]	0.91 [0.72, 1.27]	0.95 [0.71, 1.28]
Missing	72 (33.0%)	30 (44.1%)	22 (37.3%)	124 (35.9%)

Figures

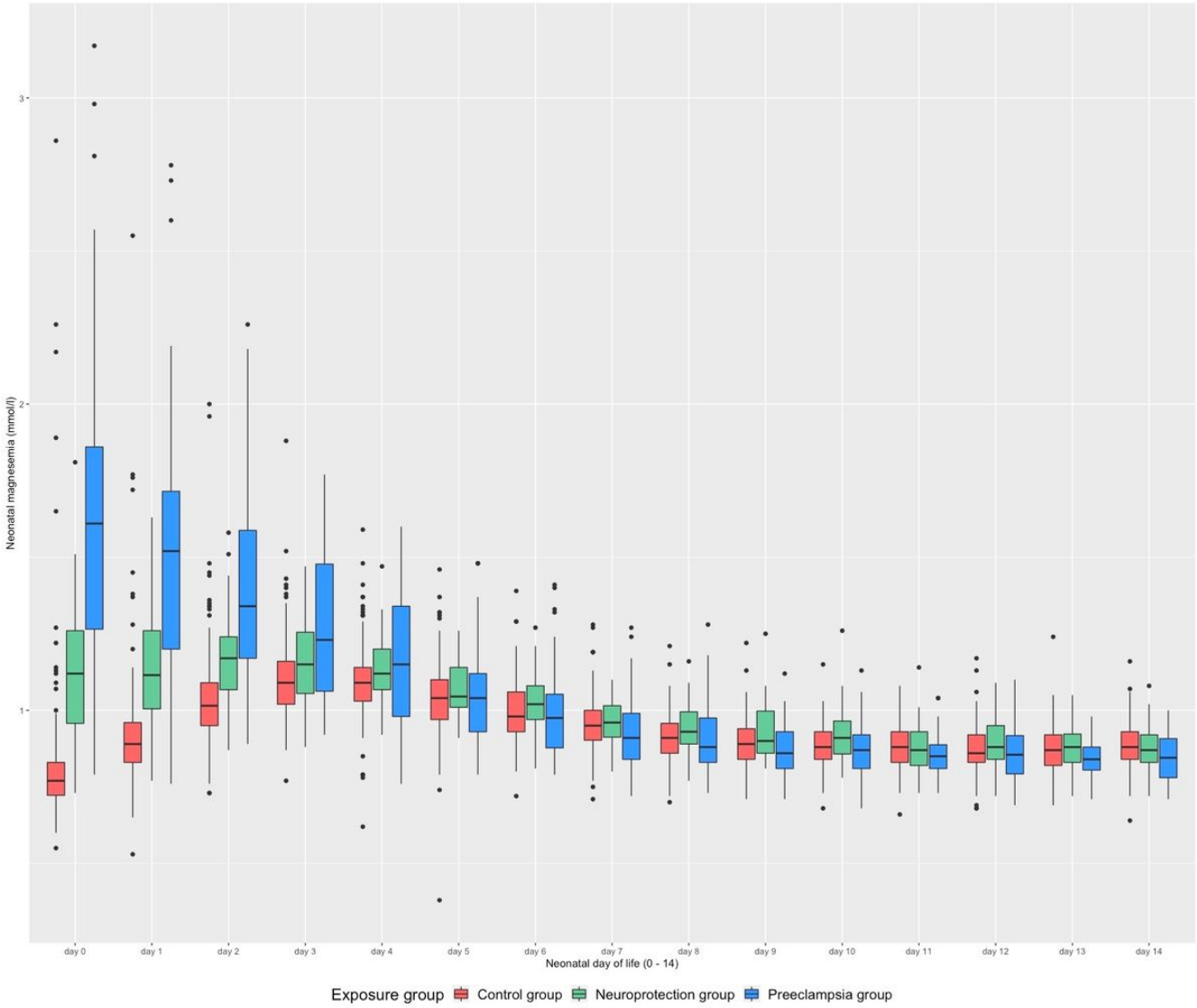

Figure 1

Observed neonatal magnesemia according to indication for MgSO4.

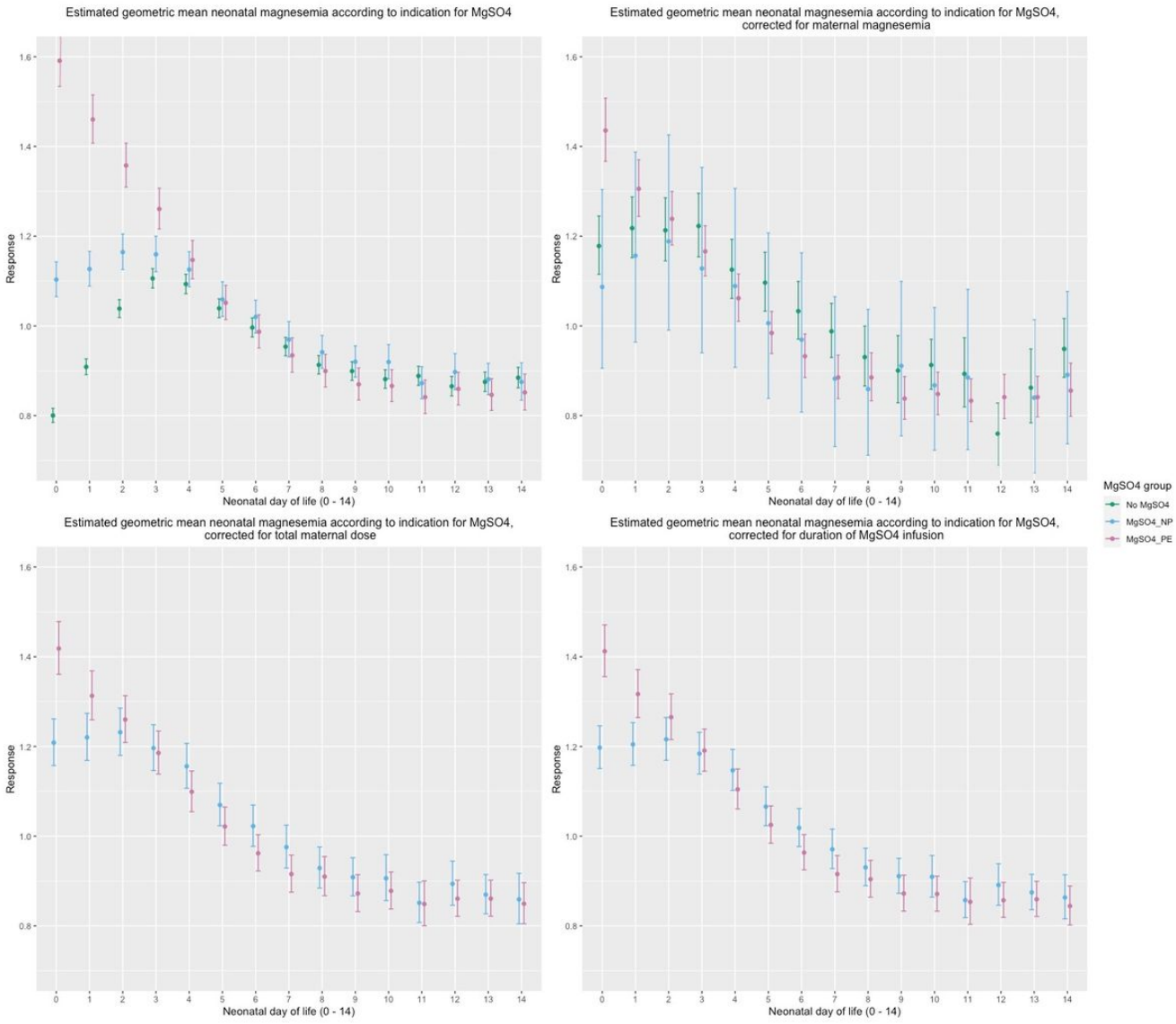

Figure 2

Estimated geometric mean neonatal magnesemia according to indication for MgSO4.

Supplementary Files

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