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Reducing Adverse Effects of Antenatal Magnesium Therapy for Neuroprotection: Tailoring Treatment to the Intended Recipient

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Abstract

Magnesium sulfate is widely administered to pregnant women at risk of preterm delivery for neuroprotection. However, there are no uniform guidelines in the dosing protocol for magnesium use. While antenatal magnesium therapy reduces the risk of cerebral palsy and gross motor dysfunction, adverse neonatal outcomes related to magnesium have been reported by some, and are the subject of considerable debate. There may be a therapeutic window within which the neuroprotective effects of magnesium sulfate are observed, with adverse neonatal outcomes at levels outside this window.

Magnesium sulfate is one of few drugs currently administered in a "one dose fits all" regimen, without taking into account maternal or fetal parameters. While the mother is monitored and her dose is adjusted as needed, the fetus is not monitored (neither in utero nor in the NICU). Inability to monitor the fetal magnesium concentration while in utero may be countered by identifying variables that influence fetal serum magnesium levels and attempting to adjust the maternal dose accordingly. Further studies with larger sample sizes are needed to determine the optimal dose of maternal magnesium to provide fetal neuroprotection or maternal seizure prophylaxis with minimal neonatal adverse outcomes. It may be possible that monitoring neonatal serum magnesium concentrations and treating neonates with high levels may impact their outcomes and this is an option that needs to be explored.

Keywords: Antenatal magnesium therapy; Immediate neonatal outcomes; Intraventricular hemorrhage; Neuroprotection; Serum magnesium concentration

Introduction

The neuroprotective effect of magnesium sulfate was first suspected following a prospective study by Kuban et al. [1] in 1992 designed to test the hypothesis that maternal preeclampsia was associated with reduced risk of Intraventricular hemorrhage (IVH) in the preterm newborn. This was followed by a case control study by Nelson and Grether [2] which suggested that antepartum magnesium treatment may protect early preterm neonates from cerebral palsy. Since then, there have been several studies on the use of magnesium sulfate for neuroprotection including three large multicenter randomized controlled trials (RCT) [3,4].

Currently, magnesium sulfate is widely administered to pregnant women at risk of preterm delivery for neuroprotection. However, there are no uniform guidelines in the dosing protocol for magnesium use. The American College of Obstetricians and Gynecologists (ACOG) recommends that physicians should develop specific guidelines regarding magnesium treatment regimens in accordance with one of the larger trials. However, the doses used in the three major RCTs on neuroprotection varied from 4 g bolus only to 6 g bolus followed by 2 g/h maintenance [3-5]. The BEAM trial which used the highest dose of magnesium in its protocol required that the infusion be turned off after 12 h if delivery had not occurred and restarted only if there are fresh indicators of imminent delivery. In clinical practice, infusions are usually continued for longer than 12 h if the patient remains undelivered.

While antenatal magnesium therapy reduces the risk of cerebral palsy and gross motor dysfunction [3] adverse neonatal outcomes related to magnesium have been reported by Marret et al. [4] and are the subject of considerable debate. Recently, the FDA changed the safety in pregnancy classification for magnesium sulfate from category A to category D and advised against its use for more than 5-7 days due to concerns regarding fetal and neonatal bone demineralization. In this review, we explore maternal and immediate neonatal adverse outcomes related to magnesium sulfate treatment and possible directions to reduce such adverse outcomes.

Data Supporting the use of Magnesium Sulfate for Neuroprotection

The three large RCTs on the use of magnesium sulfate for neuroprotection (ACTOMgSO_4, PREMAG and BEAM) are summarized in Table 1 along with the two other RCTs (MagNET and MAGPIE) [3-7] that were included in the Cochrane review [7] on magnesium sulfate for neuroprotection. A brief description of these trials follows.

The magnesium and neurological endpoints trial (MagNET)

In this single center study conducted in the United States, 149 women in preterm labor between 25 and 33 weeks of gestation were enrolled into the tocolytic arm (cervical dilatation ≤ 4 cm; n=92) or the neuroprotective (cervical dilatation >4 cm; n=57) arm depending on their cervical dilatation. Women in the tocolytic arm were randomized to magnesium 4 g bolus followed by 2–3 g per h maintenance or an alternate tocolytic and women in the neuroprotective arm were randomized to 4 g magnesium bolus only or placebo. The study was

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	MagNET (2002) Mittendorf et al. [8,9]	ACTOMgSO$_4$ (2003) Crowther et al. [3]	MAGPIE (2002, 2007) Duley et al. [11,12]	PREMAG (2007, 2008) Marret et al. [4,12]	BEAM (2008) Rouse et al. [5]
Intent	Neuroprotection, tocolysis	Neuroprotection	Eclampsia prophylaxis	Neuroprotection	Neuroprotection
Setting	Single center in the United States	16 centers in Australia and New Zealand	International multisite study in 33 countries	18 centers in France	20 centers in the United States
Inclusion	25-33 week in preterm labor	<30 week likely to deliver in 24 h	Severely pre-eclamptic pregnant (any gestation) and postpartum women (within 24 h of childbirth)	<33 week likely to deliver in 24 h	24-31 week at risk of preterm birth (cervix 4-8 cm dilated) or indicated delivery within 24 h)
No. of women (no. of fetuses)	149 (165)	1062 (1255)	N=10141 of whom 8804 women were pregnant and 1544 (1593) were <37 weeks	573 (688)	2241 (2444)
Magnesium dose	Tocolysis (cx<4 cm); 4 g bolus, then 2–3 g/h. Neuroprotection (cx>4 cm); 4 g bolus only	4 g bolus, then 1 g/h up to 24 h	4 g loading, 1 g/h IV maintenance or 5 g every 4 h IM	4 g bolus only	6 g bolus, then 2 g/h for 12 h with retreatment
Primary outcome	Neonatal adverse outcomes (IVH, PVL, death and cerebral palsy)	Pediatric mortality at 2 years, cerebral palsy at 2 years and their combination	Eclampsia and neonatal deaths before discharge (including stillbirth)	Neonatal mortality before discharge, severe WMI and their combination.	Composite infant death at 1 year, stillbirth and CP (moderate/severe) at 2 years
Findings	Children with adverse outcomes had higher umbilical cord magnesium levels (OR 3.7 [1.1-11.9])	Pediatric mortality (13.8% *vs.* 17.1%; RR 0.83 [0.64-1.09]) CP (6.8% *vs.* 8.2%; RR 0.83 [0.54-1.27]) Combined pediatric mortality and CP (19.8% *vs.* 24.0%; RR 0.83 [0.66-1.03]) Substantial gross motor dysfunction (3.4% *vs.* 6.6%; RR 0.51 [0.29-0.91])	Lower risk of eclampsia 58% (95% CI: 40–71) and maternal mortality (RR 0.55 [0.26–1.14]) In the subgroup of 1593 neonates <37 weeks, Mortality (RR 1.11 [0.93–1.31]), CP (RR 0.40 [0.08–2.05]) and substantial motor dysfunction (RR 2.99 [0.12–73.3]) were not different with magnesium treatment	Gross motor dysfunction (OR: 0.65 [0.41-1.02]). CP (RR 0.63 [0.35 to 1.15]) Combined death and CP (OR 0.65 [0.42-1.03]) Combined death and gross motor dysfunction (OR 0.62 [0.41-0.93]) Combined death, CP and cognitive dysfunction (OR 0.68 [0.47-1.00])	Composite death and moderate or severe cerebral (11.3% *vs.* 11.7%, RR 0.97 [0.77-1.23]) Moderate or severe cerebral palsy (1.9% *vs.* 3.5%; RR 0.55 [0.32 to 0.95]) Stillbirth or infant mortality (9.5% *vs.* 8.5%; RR 1.12 [0.85 to 1.47])

MagNET: Magnesium and Neurologic Endpoints Trial; ACTOMgSO$_4$: Australasian Collaborative Trial of Magnesium Sulfate; MAGPIE: Magnesium Sulfate for Prevention of Eclampsia; BEAM: Beneficial Effects of Antenatal Magnesium Sulfate; Cx: Cervix; IV: intravenously; IM: intramuscularly; IVH: Intraventricular hemorrhage; PVL: Periventricular leukomalacia; CP: Cerebral Palsy

Table 1: Details of the major trials for antenatal magnesium administration for fetal neuroprotection.

stopped prematurely following an interim safety monitoring because of concerns about higher pediatric mortality in the magnesium group (risk difference 10.7% [2.9%-18.5%], p=0.02). Children with adverse outcomes (IVH, Periventricular leukomalacia (PVL), cerebral palsy and neonatal death before discharge including stillbirths) had higher umbilical cord magnesium levels (OR 3.7 [1.1-11.9]) and the authors concluded that magnesium use was associated with worse perinatal outcome in a dose-dependent fashion [8,9].

The Australasian collaborative trial of magnesium sulfate study (ActoMgSO$_4$)

This study recruited 1,062 women at less than 30 weeks of gestation in whom birth was anticipated within 24 h from 16 collaborating centers in Australia and New Zealand. The women were randomized to magnesium sulfate (4 g bolus, 1 g/h maintenance up to 24 h) or placebo. The study was powered to detect a 50% reduction in cerebral palsy. There were no significant differences in the primary outcomes which included total pediatric mortality at 2 years corrected age, cerebral palsy at 2 years corrected age, and their combination. Substantial gross motor dysfunction, a secondary outcome, was decreased with magnesium sulfate (RR 0.51 [0.29-0.91]).

The magnesium sulfate for prevention of eclampsia trial (MAGPIE)

This was a multinational RCT on the use of magnesium sulfate to prevent eclampsia in women with severe preeclampsia. Women with severe preeclampsia at all gestational ages and postpartum women within 24 h of childbirth (n=10,141) from 175 centers in 33 countries were randomized to magnesium sulfate (4 g intravenous bolus followed by 1 g/h infusion or 5 g every 4 h intramuscularly for 24 h) or placebo. At the time of enrollment, 8,804 of those women were pregnant and 1,544 women (1,593 fetuses) were less than 37 weeks. Unpublished data were provided from the trial investigators for these 1593 infants less than 37 weeks gestational as reported in the Cochrane Review on neuroprotection. Neonatal mortality (RR 1.11 [0.93–1.31]), cerebral palsy (RR 0.40 [0.08–2.05]) and substantial motor dysfunction (RR 2.99 [0.12–73.3]) were not different with magnesium treatment [10,11].

PREMAG trial: Magnesium sulfate given before very-preterm birth to protect infant brain

This French study randomized 573 women less than 33 weeks of gestation from 18 centers to receive magnesium sulfate (4 g bolus only) or placebo. There were no differences in the primary outcomes reported in 2006 which included neonatal mortality before discharge (OR 0.79 [0.44-1.44]), severe white matter injury (OR 0.78 [0.47-1.31]) and their combination (OR 0.86 [0.55 to 1.34]). In 2008 long term outcomes were reported and there were no significant differences in cerebral palsy, gross motor dysfunction or combined death and cerebral palsy. Combined death and gross motor dysfunction (OR: 0.62 [0.41-0.93]) as well as combined death, cerebral palsy and cognitive dysfunction (OR: 0.68 [0.47-1.00]) were decreased with magnesium sulfate [4,12].

The beneficial effects of antenatal magnesium sulfate trial (BEAM)

This multicenter study conducted by the NICHD in 20 centers across the United States was the largest study on neuroprotection and

recruited 2,241 women between 24 and 31weeks of gestation at risk of preterm birth. Women were randomized to receive magnesium sulfate (6 g bolus, 2 g/h maintenance for 12 h with retreatment) or matching placebo. The primary outcome was composite stillbirth or infant death at 1 year or moderate/severe cerebral palsy at 2 years. The study was powered to detect a 30% reduction in the primary outcome but did not find a significant difference between the two groups. Contrary to previous studies, the rate of moderate or severe cerebral palsy was significantly less frequent in the magnesium treated group (RR 0.55 [0.32 to 0.95]) [5].

The Cochrane review [7] synthesized the data from the above trials and found a reduction in cerebral palsy (RR 0.69 [0.54-0.87]; five trials; 6,145 infants) and substantial gross motor dysfunction (RR 0.61 [0.44-0.85]; four trials; 5,980 infants) with magnesium sulfate without an increase in the risk of pediatric mortality (RR 1.01 [0.82-1.23]; five trials; 6,145 infants).

Maternal Adverse Outcomes

Although life-threatening maternal adverse effects of magnesium sulfate are considered extremely rare in obstetrics, severe consequences of magnesium toxicity including respiratory arrest, cardiac arrest and death have been detailed in case reports [13] and with accidental overdose [14]. Arm discomfort, warmth over the body, dry mouth, mild nausea and sleepiness were the most commonly reported maternal adverse effects in the IRIS trial; an RCT evaluating a slower (compared with a standard) infusion rate of the loading dose of magnesium [15]. Though such maternal adverse effects may be considered comparatively 'minor, they occur frequently (71%, 77% and 89% of women in the BEAM trial, ACTOMgSO_4 trial and IRIS trial, respectively) and have been associated with the need for interruption, dose modification or cessation of magnesium treatment in some mothers (Figure 1).

Magnesium sulfate administration may be associated with lower baseline fetal heart rate, decreased variability, reductions in reactivity or acceleration pattern without an increase in decelerative patterns. However, these changes were small and not associated with adverse clinical outcomes [16,17]. In additions to magnesium related fetal and neonatal bone demineralization; there are also reports of maternal osteopenia, osteoporosis and stress fractures with prolonged use of magnesium sulfate [18-20].

Neonatal Adverse Outcomes Related to Magnesium use

Mortality and neurological morbidity

Interim safety monitoring of the MagNET Trial showed ten pediatric deaths in 75 maternal randomizations to magnesium sulfate and one pediatric death among 75 maternal randomizations to control. With intent to treat analysis, the difference was statistically significant (risk difference 10.7% [2.9%-18.5%], p=0.02) [8,21]. Following this, further enrollment in the trial was halted and the FDA was notified. We previously reported that magnesium exposed neonates with serum magnesium concentration >4.5 mEq/L had increased neonatal mortality (5% *vs.* 16.9%, p<0.05) after correcting for birth weight and gestational age Scudiero et al. reported that exposure to total doses of magnesium sulfate exceeding 48 g was significantly associated with increased perinatal mortality (OR 4.7 [1.1-20.0]; p=0.035) [22] (Figure 1).

Stigson and Kjellmer [23] were the first to report an association between elevated serum magnesium levels and IVH in 1997. Similar findings were reported by Mittendorf et al. [24] who found that higher maternal serum magnesium levels were independently associated with IVH (OR 15.8 [1.4–175.0]) in the MagNET trial. Magnesium induced

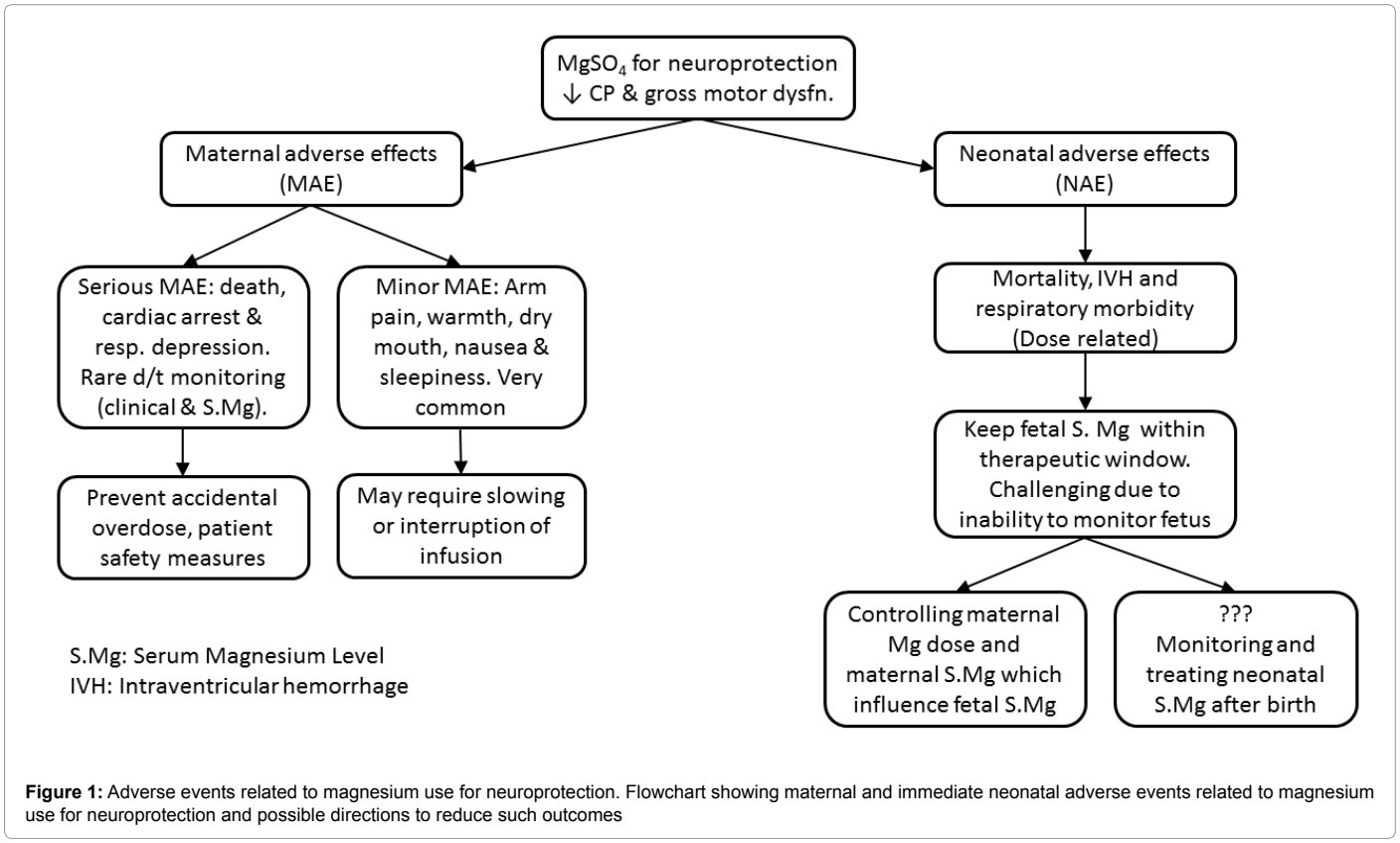

Figure 1: Adverse events related to magnesium use for neuroprotection. Flowchart showing maternal and immediate neonatal adverse events related to magnesium use for neuroprotection and possible directions to reduce such outcomes

cerebral vasodilatation [25] and prolongation of bleeding time may explain the association of elevated magnesium levels with IVH [26,27].

In contrast, the three large RCTs and the Cochrane review on neuroprotection did not show any adverse outcomes among magnesium exposed neonates [3-7]. The Cochrane Review reported on some immediate neonatal outcomes including Apgar scores <7 at 5 min, need for ongoing respiratory support, any IVH, PVL and neonatal convulsions. There were no substantial effects of antenatal magnesium sulfate on any of these immediate neonatal outcomes, but data are limited for some outcomes because they have not been reported for all trials [7]. However, these trials grouped together all magnesium exposed neonates (without considering their neonatal serum magnesium concentrations) and compared them to preterm neonates who were not treated with magnesium; who may have been at a higher risk of IVH due to low serum magnesium concentrations and in accordance with the findings of Kuban et al. [1] who described a decreased risk of IVH with magnesium treatment.

It is important to point out that there were wide variations in the magnesium dosing protocols used in the major RCTs on neuroprotection (Table 2), the PREMAG study used only a bolus of 4 g, the ACTOMgSO$_4$ study used a bolus of 4 g and a maintenance of 1 g/h while the BEAM study used a 6 g bolus followed by a 2 g/h maintenance infusion. The trials that used a maintenance dose had an upper limit for the duration of use; 24 h for the ACTOMgSO$_4$ study and 12 h (with retreatment) for the BEAM study. The median time from randomization to delivery (which correlates with the duration of magnesium treatment) was 1 h and 38 min in the PREMAG study, 3.7 h in the ACTOMgSO$_4$ study and 1.5 weeks in the BEAM study (Table 2). In the BEAM study, 71.5% of women enrolled were eligible for retreatment (which implies that at least 71.5% of the women enrolled were undelivered 12 hours after randomization). The median overall dose of magnesium administered was 6.5 g in the ACTOMgSO$_4$ study and 31.5 g in the BEAM study while most women in the PREMAG study received 4 g except those who delivered before the magnesium loading dose was completed (Table 2).

It is reasonable to conclude that neonatal serum magnesium concentrations would be very different in the PREMAG study which only used a bolus dose of magnesium as compared to the BEAM study where higher doses of magnesium were used for a longer time with retreatment. It is known that there is a therapeutic window for

	ACTOMgSO$_4$ (2003)		PREMAG (2007, 2008)		BEAM (2008)	
	Crowther et al. [3]		Marret et al. [4,12]		Rouse et al. [5]	
	Magnesium	Placebo	Magnesium	Placebo	Magnesium	Placebo
GA at Randomization	27 weeks 3 d (IQR 25 weeks 5 days–28 weeks 5 d)	27 week 2 days (IQR 25 weeks 5 days–28 weeks 5 days)	30 weeks (R 24 weeks–32 weeks 6 days)	30 weeks (R 23 weeks 4 days–32 weeks 6 days)	28.3 weeks ± 2.5 weeks	28.2 weeks ± 2.4 weeks
GA at Delivery	27 weeks 5 days (IQR 26 weeks–29 weeks)	27 weeks 3 days (IQR 25 weeks 6 days–29 weeks)	30 weeks 1 day (R 24 weeks–32 weeks 6 days)	30 weeks 1 days (R 23 weeks 4 days–32 weeks 6 days)	29.8 weeks ± 3.1 weeks	29.7 weeks ± 3.1 weeks
Randomization to delivery interval	3.7 h (IQR 1.4 h - 13.8 h)	3.1 h (IQR 1.3 h - 12.9 h)	1 h 38 min (5 min - 25 h 5 min)	1 h 30 min (8 min - 61 h 30 min)	-	-
Mg bolus dose (grams)	4	N/A	4	N/A	6	N/A
Mg maintenance	1 g/h up to 24 h	N/A	None	N/A	2 g/h for 12 h	N/A
Total Magnesium dose (grams)	6.5 (IQR 4.4-14)	N/A	Most women completed the bolus	N/A	31.5 (IQR 29-44.6)	N/A
Type of pediatric mortality reported	Mortality up to corrected age of 2 years		Neonatal mortality before discharge		Mortality up to corrected age of 1 year	
Pediatric mortality (%)	13.80%	17.10%	9.40%	10.40%	9.50%	8.50%
Type of Neurological disability reported	Cerebral palsy at corrected age of 2 years		severe white matter injury (WMI)		Moderate or severe cerebral palsy at corrected age of 2 years	
Neurological disability (%)	6.80%	8.20%	10%	11.70%	1.90%	3.50%
Composite mortality and neurological disability	19.80%	24%	16.50%	17.90%	11.30%	11.70%
	(mortality+CP)	(mortality+CP)	(mortality+severe WMI)	(mortality+severe WMI)	(mortality+moderate/severe CP)	(mortality+moderate/severe CP)
Grade 1-4 IVH	27.70%	25.30%	20.90%	25.30%	19.60%	21.30%
Grade 3-4 IVH	8.20%	8.50%	2.4% (Grade 4 only)	3.4% (Grade 4 only)	2.10%	3.20%
PVL	3.70%	3.60%	-	-	-	-
Apgar <7 at 5 min	-	-	12.80%	9.20%	18.10%	18.50%

ACTOMgSO$_4$, Australasian Collaborative Trial of Magnesium Sulphate: BEAM: Beneficial Effects of Antenatal Magnesium Sulfate; GA: Gestational Age; IQR: Interquartile Range; R: Range; Mg: Magnesium; WMI: White Matter Injury; CP: Cerebral Palsy; IVH: Intraventricular Hemorrhage; PVL: Periventricular Leukomalacia

Table 2: Heterogeneity among the three major RCTs on neuroprotection and their neonatal outcomes.

maternal serum magnesium concentrations (4.9–8.5 mg/dl) [28] when magnesium is given for eclampsia prophylaxis; it is possible that there is a therapeutic window for neonatal serum magnesium concentrations as well with lower levels being ineffective for neuroprotection and higher levels causing adverse outcomes. When studying outcomes, the RCTs grouped all magnesium exposed neonates together as a single category and this may have been the reason why these RCTs did not find a difference in their primary outcomes despite large sample sizes. It is possible that if these neonates were stratified by their serum magnesium levels, we would find a subgroup of neonates with serum magnesium concentrations within the therapeutic window who had the best outcomes in comparison to untreated neonates and treated neonates with magnesium concentrations outside (too low or too high) of the therapeutic window.

It is notable that most of the studies that found an increase in magnesium related neonatal mortality and neurological morbidity did so in the subgroup of neonates with high concentrations of magnesium [9,10,21-24]. The MagNET trial which used the highest dose of magnesium infusion (2-3 g/h maintenance) found an increase in neonatal mortality, the BEAM trial which also used a high dose found an increase in mortality with magnesium use (9.5% *vs*. 8.5%; RR 1.12 [0.85 to 1.47]), however, this difference was not statistically significant. Since most clinicians in the United States use a magnesium dosing regimen similar to the BEAM study but commonly continue it for longer than 12 h, exposing the preterm neonates to a higher dose of magnesium than that in the BEAM study is concerning. The ACOG and the Society for Maternal-Fetal Medicine support the use of magnesium sulfate for up to 48 h which is much longer than what was studied in the RCTs [29].

Respiratory morbidity

The possibility of an acute depressant effect of magnesium sulfate on neonatal tone and respiratory function is suggested by its mechanisms of action; however, data from a secondary analysis of the BEAM trial studying exposed premature neonates did not support this association [30]. Following concerns that the effects of magnesium sulfate on neonatal acute care needs may have been masked by the larger influence of prematurity, term and late-preterm neonates were studied, and it was found that magnesium exposure was associated with increased NICU admission in a dose dependent fashion, and nearly one-half of the neonates admitted to the NICU after in utero magnesium exposure required respiratory support [31]. Other studies on term neonates have reported that magnesium exposure is associated with Apgar scores <7 at 1 and 5 min (15% *vs*. 11% unexposed, P=0.01 and 3% *vs* 0.7% unexposed, P=0.008) [32]. This suggests that the respiratory morbidity related to magnesium therapy in preterm neonates was indeed masked by the relatively larger respiratory morbidity related to prematurity.

Reducing Magnesium Related Maternal Adverse Outcomes

Serious maternal adverse outcomes related to magnesium sulfate are extremely rare as a result of strict monitoring protocols which include periodic clinical assessments and monitoring serum magnesium levels. Occasionally, magnesium therapy is associated with accidental overdose; fortunately, in most instances, the error is recognized before permanent adverse outcomes occur. Simpson et al have compiled a database of 52 cases involving accidental magnesium sulfate overdose and provide recommendations to promote patient safety and decrease the likelihood of an accidental overdose in their paper, a detailed discussion of which is outside the scope of this review [14].

The IRIS study was a randomized controlled trial that compared a slower (60 min) infusion rate of the loading dose of magnesium sulfate as compared to the standard rate (20 min) for preterm fetal neuroprotection as a strategy to reduce minor but frequent maternal adverse effects. The slower infusion rate did not reduce the occurrence of maternal adverse effects overall, and did not reduce the rate of discontinuation of therapy due to adverse effects; however, maternal flushing and warmth at 20 min into the infusion was reduced with the slower infusion.

Reducing Magnesium Related Neonatal Adverse Outcomes

While the meta-analysis [7] on neuroprotection did not find any difference in adverse maternal outcomes such as death, cardiac arrest, respiratory depression and respiratory arrest, that safety profile may have been achieved, at least in part, because mothers receiving magnesium sulfate are routinely monitored for signs of toxicity clinically, and for serum magnesium concentration with the opportunity to intervene before serious adverse outcomes occur. Since magnesium levels are not routinely measured in preterm neonates whose mothers received magnesium for neuroprotection, if they develop adverse effects, they are generally attributed to prematurity and managed accordingly.

The fetus, whether it is the intended recipient or not, is exposed to magnesium sulfate administered to the pregnant mother. Controversy regarding magnesium-related neonatal adverse outcomes, [3,5,7-9,21-24] combined with an inability to monitor the fetal magnesium concentration while in utero, have led to tailoring treatment to the mother; largely ignoring the possibility of sub-therapeutic or toxic levels in the fetus. While it is not possible to titrate the magnesium infusion to keep the fetal serum magnesium concentrations within the "therapeutic window", an alternate approach is to identify variables that influence those levels and attempt to customize the maternal magnesium dose instead of administering the same dose to all mothers.

Neonatal serum magnesium concentration correlates with maternal magnesium dose [33] and maternal serum magnesium concentrations [34]. Maternal serum magnesium concentrations are usually monitored to prevent maternal toxicity however; there are no specific guidelines on the total dose received by the mother. We suggest that in addition to monitoring maternal serum magnesium levels, the magnesium infusion must be turned off as soon as the clinical situation allows (preferably within 24 h and no later than 48 h) and restarted only if there is a change in clinical condition; such as active preterm labor with cervical changes. Frequently, magnesium is restarted if the mother experiences contractions in the absence of cervical changes due to the concern that if delivery occurs at short notice, there may not be time to restart magnesium. This may be unnecessary as a secondary analysis of the BEAM study showed that the duration of antenatal magnesium sulfate infusion is not associated with risk of death or cerebral palsy [35]. Moreover, in the subgroups of mothers treated with magnesium for less than 12 h, 12-18 h and more than 18 h, the magnesium infusion was on during delivery only in 33.2%, 63.6% and 77.1% of women respectively and the mean number of hours since the last magnesium was 273.5 h, 104.5 h and 45.9 h, respectively. Despite more than two thirds of women being off the magnesium infusion at the time of birth in the first subgroup, they did not have higher rates of cerebral palsy or death compared to the other subgroups. If magnesium use is necessary beyond 48 h, interrupted infusions with cessation of infusion for four or more hours every day may be considered [36].

Variables that influence maternal serum magnesium levels (which in turn influence neonatal serum magnesium levels) while on

magnesium sulfate infusion include body mass index, serum creatinine levels and multiple pregnancies [37-39]. The risk of toxicity is known to be higher with renal dysfunction in the mother although the current concern is for maternal toxicity rather than neonatal adverse effects [28]. A reduced rate of infusion may be considered for mothers who are underweight while an increased rate of infusion may be appropriate for obese women with those with multiple pregnancies.

Future Directions

Magnesium sulfate is one of few drugs currently administered in a "one dose fits all" regimen, without taking into account maternal or fetal parameters. The first step in identifying a solution to any problem is to agree that a problem exists. Currently, there is controversy in literature regarding magnesium related adverse outcomes. Therefore, further multicenter studies with larger sample sizes exploring immediate adverse outcomes in magnesium exposed neonates correlated with their serum magnesium concentrations are needed.

Further, prospective studies must be performed to determine the optimal dose of maternal magnesium for different subgroups of mothers to provide fetal neuroprotection with minimal neonatal adverse outcomes. In the meantime, there is a need for guidelines on use of magnesium sulfate.

While it is not possible to monitor the fetal magnesium concentrations in utero, neonatal serum magnesium concentrations can be monitored. It may be possible that monitoring neonatal serum magnesium concentrations and treating neonates with high levels may impact their outcomes and this is an option that needs to be explored.

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