The Role of Magnesium Sulfate in the Prevention of Cerebral Palsy

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MAGNESIUM SULFATE ($MgSO_4$) has been widely used in the perinatal arena for many decades. It has been used for tocolysis in the U.S. for more than 60 years. Estimations of $MgSO_4$ use for preterm labor (less than 34 weeks of gestation) run as high as 80 percent. Magnesium sulfate is a smooth, skeletal, and cardiac muscle depressant. It is used for preterm labor because of its potential to decrease muscle contractility by interfering with calcium uptake in the cells. Thousands of moms and babies have been exposed to this medication even though tocolysis remains an off-label use, the exact mechanism of action is not completely understood, and there are studies that show that it is ineffective for this indication, and no evidence that it improves perinatal outcomes.[1–3] Additionally, it is a high alert medication because of its narrow therapeutic window and the risk of causing an immediate life-threatening condition (acute respiratory failure) if an error in administration occurs.[4]

A second perinatal use for $MgSO_4$ is for treatment and prevention of eclampsia. Magnesium sulfate is commonly administered peripartum for seizure prophylaxis in preeclampsia. When administered parenterally in doses sufficient to produce hypermagnesemia (serum magnesium concentrations greater than 2.5 meq/dL), $MgSO_4$ reduces the seizure threshold by depressing central nervous system's irritability. Magnesium sulfate produces its anticonvulsant effects by slowing neuromuscular conduction, depressing the vasomotor center, and causing neuromuscular blockade of peripheral neuromuscular transmission.[2]

Cerebral Palsy (CP) is the most common cause of severe motor disability in childhood, with an incidence of 1 in 323 children.[5] Cerebral palsy is defined as permanent, nonprogressive abnormal gross and fine motor functioning that is attributed to disturbances that occurred in the developing fetal or infant brain.[6] It is 80 times more common in premature infants born at less than 27 weeks of gestation.[7] Preterm labor prediction and prevention still eludes us, but advances in neonatal care have increased the survival of very preterm infants; those at the greatest risk of CP.[8]

CP extracts an enormous economic and emotional burden. The Centers for Disease Control and Prevention (CDC) estimates the lifetime costs including direct medical (physician visits, hospital stays, medications, assistive devices, long-term care), direct nonmedical (home and automobile modifications, special education), and indirect (productivity losses) for all people born with CP in 2000 to be $11.5 billion.[5]

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MAGNESIUM SULFATE AND CP: A REVIEW OF THE EVIDENCE

As with many practice changes, the process of developing a base of evidence for the use of $MgSO_4$ for neuroprotection in children was a lengthy one. Early observational reports in the 1990s described cohorts of children with and without CP born at very low birth weights (VLBWs).[9] Those with CP were significantly less likely to have been exposed to $MgSO_4$ in utero during delivery than those without CP, suggesting $MgSO_4$ had a protective effect of some sort.[9]

Subsequent observational studies both confirmed and refuted this finding. In all these studies, $MgSO_4$ was administered for either tocolysis or prevention of eclamptic seizures, not neuroprotection.[10–11]

Over the next 10 years, researchers on several continents searched for the link between $MgSO_4$ and neuroprotection and reduction in CP (Table 1). Several preterm, prenatal prophylactic $MgSO_4$ randomized controlled trials were conducted with favorable outcomes.[12–14] Finally, the results of three meta-analyses show convincingly that $MgSO_4$ given prior to premature birth reduces the risk of CP by 30 percent without increasing the risk of infant death or significant perinatal morbidity.[15] In 2007, a Cochrane review was completed and concluded antenatal $MgSO_4$ therapy as a neuroprotective agent for the preterm fetus could not be recommended based on the data available at the time.[16] In the 2009 update of this review, with the weight of the new studies—including 6,145 babies of moms given $MgSO_4$ for preterm labor at less than 37 weeks—the authors conclude that the neuroprotective role of this drug had been established.[17]

THEORIES ON THE MECHANISM OF ACTION

Although there is evidence that the use of $MgSO_4$ decreases the incidence and severity of CP, the mechanism of action is not entirely clear. Volpe describes several effects of magnesium including blocking of glutamate receptors and other excitatory neurotransmitters, decreasing cytokine production, antiplatelet properties, and antioxidant properties.[19] These properties may decrease cell apoptosis.[8] Volpe also describes increased uterine blood flow and a potential for improved cerebral blood flow in the neonate, which may help to prevent hypoxia and tissue damaging ischemia.[19] It has also been postulated that $MgSO_4$ has an effect on

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TABLE 1 ■ Summary of the Evidence of Magnesium Sulfate and Neuroprotection

Author and Year	Number of Mothers/Babies Inclusion Criteria	Type of Study/Treatment Regimen	Primary Outcomes or Conclusions
Nelson & Grether, 1995[9]	155,636 children born 1983–1985	Retrospective case-control study VLBW children with CP compared with randomly selected VLBW control survivors. Mothers received $MgSO_4$ for preeclampsia or tocolysis.	In utero exposure to $MgSO_4$ was more frequent in controls than in children with CP, suggesting a protective effect of $MgSO_4$ against CP in VLBW infants.
Paneth et al., 1997[10]	1,105 infants < 2,000 g Mothers received $MgSO_4$ (no specific indication)	Retrospective chart review.	Reduction of neonatal brain lesions or CP in low birth not statistically supported in this study, although a modest reduction in risk of CP cannot be excluded; suggestion that magnesium may be associated with reduction in risk of CP in low birth weight infants who have late-onset brain lesions.
Grether et al., 2000[11]	458 infants < 1,500 g & 1,500–1,999 g < 33 weeks gestation 1988–1994 without preeclampsia, delivered > 3 hours after admission	Retrospective case-control study	Magnesium exposure not associated with lower risk of cerebral palsy in infants born prematurely to women without preeclampsia.
Marret et al., 2008[16]	573 women/688 fetuses < 33 weeks expected to deliver within 24 hours	RCT 4 g loading dose only	Protective against "severe motor dysfunction or death" (OR 0.62, 95% CI 0.41–0.93).
Crowther et al., 2003[13]	1,062 women; < 30 weeks	RCT at 16 tertiary hospitals in Australia and New Zealand. 4 g loading dose/ 1 g/hr or placebo.	Magnesium group had lower rates of pediatric mortality (13.8% vs. 17.1%; RR: 0.83; 95% CI 0.64–1.09); CP (6.8% vs. 8.2%; RR: 0.83; 95% CI 0.54–1.27), combined outcome of death or CP (19.8% vs. 24.0%; RR: 0.83; 95% CI 0.66–1.03).
Rouse et al., 2008[14]	2,241 mothers/2,444 fetuses; 24–31 weeks of gestation at risk for imminent delivery	Multicenter placebo controlled trial. 6 g loading dose/2 g/hr or placebo.	Moderate to severe CP significantly lower in the magnesium group (1.9% vs. 3.5%; RR 0.55; 95% CI 0.32–0.95). Only < 28 weeks of gestation showed a significant reduction in moderate or severe cerebral palsy.
Marret et al., 2007[12]		Meta-analysis of 4 RCTs	Neuroprotective role not demonstrated
Doyle et al., 2009[17]	6,145 fetuses $MgSO_4$ for preterm labor under 37 weeks	Meta-analysis of 5 eligible RCTs	Neuroprotective role is now established. Neuroprotective against motor disorders in childhood for the preterm fetus.
Conde-Agudelo & Romero, 2009[18]	5,357 babies $MgSO_4$ prior to 34 weeks	Meta-analysis	Significant reduction in risk of CP, moderate or severe CP and substantial gross motor dysfunction.
Costantine, Weiner; for Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, 2009[15]	5,235 fetuses/infants	Meta-analysis of 5 RCTs	Significantly reduces risk of cerebral palsy without increasing risk of death.

Note: VLBW = very low birth weight; CP = cerebral palsy; $MgSO_4$ = magnesium sulfate; RCT = randomized controlled trial.

the fetal inflammatory response syndrome (FIRS), which is a risk factor for perinatal mortality and morbidities such as bronchopulmonary dysplasia and brain injury.[20]

The same mechanism that alters cerebral blood flow may affect other body systems and perfusion. Side effects of magnesium exposure have been reported, which include an increase in patent ductus arteriosus and alterations in bowel blood flow. There were no significant differences between the exposed and unexposed groups in intestinal blood flow velocities, but trials that prospectively evaluate intestinal blood flow velocities are recommended to further study potential effects of antenatal $MgSO_4$ on the gastrointestinal tract of preterm infants and resultant clinical outcomes such as necrotizing enterocolitis.[21,22] Magnesium at levels of 8–12 mg/dL results in the loss of deep tendon reflexes and muscle weakness—including the diaphragm and other respiratory muscles—leading to acute respiratory failure. Cardiac arrest may occur at levels of 20–35 mg/dL. Because fetal levels approximate maternal levels, fetal sedation and respiratory depression are potential side effects of therapy.[2,3]

Intravenous $MgSO_4$ has an immediate onset and duration of 30 minutes. Nursing implications of this therapy include the monitoring of newborns for hypotension, hyporeflexia, and respiratory depression.[23]

In spite of the potential side effects of maternal $MgSO_4$ therapy, Elliott et al. concluded in their review of the literature that there is no association of magnesium exposure in an appropriate dose with excess risk for neonatal death or morbidity.[24]

FURTHER STUDIES

Despite the current body of knowledge about $MgSO_4$, questions remain. It is unclear which group of infants might benefit most from this therapy: patients 34 weeks and lower, 30 weeks and lower, or 28 weeks. The number needed to treat—the number of mothers that would need to be treated to prevent one child from developing CP—ranges from 15 (for infants at 22–27 weeks of gestation) to 333 (at 32–36 weeks).[8] This would indicate that younger gestational ages derive more benefit from magnesium prophylaxis. Additional information is needed about strategies to reduce maternal side effects during administration of $MgSO_4$ therapy, as well as the short- and long-term side effects in the neonate.

Further research is needed to delineate the most efficacious dose and timing of $MgSO_4$ administration. The dosage of $MgSO_4$ used in the trials ranged from loading doses of 4–6 g with maintenance infusion of 0–2 mg per hour. It may be possible to use a much smaller dose and therefore reduce side effects but this has not been investigated. Additional questions include whether maintenance dosing is needed or not and whether repeated treatment is indicated when preterm labor is arrested, but reoccurs at a later date. It appears that having the $MgSO_4$ in the fetal blood stream at birth may be important, but more research is needed to determine how long it needs to be in the nervous system to accomplish the beneficial effect and the most effective levels to achieve. An additional question is whether in emergencies, or in order to spare side effects to the mother, $MgSO_4$ could be administered directly to the baby at birth, as has been reported to be beneficial in term asphyxiated neonates.[8,25]

NEXT STEPS

In March 2011, the American College of Obstetrics and Gynecology (ACOG) issued a committee opinion on the use of $MgSO_4$ for neonatal neuroprotection. The ACOG supports administration of a loading dose of $MgSO_4$ followed by maintenance therapy when imminent delivery seems likely. Specific guidelines for dosing and gestational age are not specified; providers are encouraged to develop these based on the clinical trials. The committee report recommends $MgSO_4$ to be given before an indicated preterm delivery or prior to a scheduled cesarean delivery. In order to decrease maternal exposure to the medication, the ACOG also recommends delaying administration until cervical ripening is achieved and delivery is expected within 24 hours. The ACOG does not support delaying emergent delivery for the administration of $MgSO_4$. At this point, no retreatment is recommended. The $MgSO_4$ is discontinued when the baby is delivered, unless it is indicated for a maternal condition such as preeclampsia. The dosing recommended by the ACOG is similar to those used for tocolysis and preeclampsia, but as discussed earlier, future studies may find other dosing regimens that are safer and more efficacious.[26]

INTERNATIONAL IMPLICATIONS

The potential benefits of $MgSO_4$ extend worldwide. While we debate the perfect dose of $MgSO_4$ to administer, nurses in other parts of the world may debate whether they can afford to administer it at all. Many of the trials were conducted in developed countries, but the pathophysiology of CP and its sequelae are universal to all countries. In developed countries, as well as in developing countries, resources for caring for children with disabilities may be limited and difficult to access and have consequences on resource allocation. It may be tempting to jump to the use of a panacea for a known problem, especially when it is easily accessible.

Magnesium sulfate itself is not expensive, but as a high-alert medication, it has a very narrow safe dosage range, and overdose can cause serious complications, including acute respiratory failure and cardiac arrest.[4] It may be that in some under-resourced settings, there may not be people and equipment available to administer $MgSO_4$ with the monitoring needed to prevent and manage the potential complications. In these situations, weighing the risks to the mother and benefits of neuroprotection of infants will have to occur, and resource allocation decisions made.[27]

SUMMARY

A commonly administered perinatal medication, $MgSO_4$, has a new use that can affect families all over the world. Few effective strategies exist for prevention of preterm birth

and the associated complication of CP, so the emergence of $MgSO_4$ as an easily accessible, low-cost intervention is exciting. Questions remain about dosing, timing, side effects, and resource use, and research is needed to elucidate these points. The neonatal nurse needs to be abreast of practice changes in obstetrics that may affect her patients. The use of antenatal prophylactic $MgSO_4$ to reduce the emotional and economic burden of cerebral palsy is one of these practice changes.

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