The Effects of Hypermagnesemia on Gastrointestinal Motility in Newborns

Magnesium (Mg\(^{2+}\)) is the 4th most abundant cation and 2nd most common intracellular electrolyte found in the human body. The homeostasis of Mg\(^{2+}\) and Calcium (Ca\(^{2+}\)) require a complex interaction of hormonal and non-hormonal factors. Homeostasis involves the use of the renal, gastrointestinal and skeletal systems. Ca\(^{2+}\) and Mg\(^{2+}\) levels in the body also depend on dietary intake and medication use.

Only the free form of Mg\(^{2+}\) can be measured with the serum level. Intracellular Mg\(^{2+}\) is located in membrane structures (60-90%) and 10% is free unbound. Free intracellular Mg\(^{2+}\) has a critical role in cellular physiology, catalyzing enzymatic processes concerned with transfer, storage and use of energy. Different cell types maintain different intracellular concentrations of Mg\(^{2+}\) by regulating the influx and efflux based on metabolic needs. As the extracellular concentration of Mg\(^{2+}\) rises there is a linear increase of intracellular Mg\(^{2+}\) until the saturation point is reached indicating an active transport process.

Fetal distribution of Mg\(^{2+}\) in the 3rd trimester is primarily in the bone (60%), less in the muscle (20%) and intracellular space of other tissues (20%). 70% of serum Mg\(^{2+}\) is unbound. Mg\(^{2+}\) transport across the placenta occurs in the 3rd trimester with the fetus having higher levels than the mother due to active transport. However, in maternal hypomagnesemia, fetal Mg\(^{2+}\) levels are lower than the mother. Maternal hypomagnesemia results in vasocostriction of the placental vasculature leading to a drop in uteroplacental blood flow and a decrease in the production of growth factors causing IUGR and SGA. Magnesium Sulfate (MgSO\(_4\)) is used for seizure prevention in pre-eclampsia, tocolysis (shown to be a poor tocolytic agent), and for fetal neuroprotection (in all 23-32 week gestations). Studies of prolonged administration of MgSO\(_4\) (>5-7 days for tocolysis) found an association with osteopenia and fractures in the fetus. Maternal hypomagnesemia inhibits the maternal secretion of parathyroid hormone leading to increased Ca\(^{2+}\) reabsorption and decreased Ca\(^{2+}\) in the blood. Maternal hypocalcemia leads to decreased transport of Ca\(^{2+}\) to the fetus causing osteopenia. Consequently the U.S. Food and Drug Administration (FDA) advises against use of MgSO\(_4\), injection for more than 5-7 days to stop preterm labor in pregnant women and changed the drug classification from Category A to Category D as well as a labeling change that include this new warning information. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine continue to support the short-term (usually less than 48 hours)
Risk of gross underestimation exists because nearly every study regards candidemia as the only diagnostic parameter of fungal sepsis. Reports usually fail to account meningitis, UTI or peritonitis. Candida UTI account for 3-4% in extremely low birth weight (ELBW) infants. Interestingly, this has the same associated mortality as Candida blood stream infection. Bowel perforations and stage III Necrotizing Enterocolitis (NEC) contribute 1-2% of IFI.

Several randomized controlled trials had been done to show whether anti-fungal prophylaxis is effective in preventing IFI. The population of these studies are VLBWs who are enrolled prior to 72h of life. They perform surveillance fungal cultures of sites like ears, umbilicus, stool, etc. Fluconazole is the most frequently used agent. The dosing is similar on these studies.

The study by Kaufman et al (2001) showed that there is lesser colonization in the treatment group compared to placebo group. There was no IFI in the treatment group, while the placebo group had 20%. This means that their unit has a high incidence of IFI. Review of the demographics showed that their unit had a high use of antibiotics. Seventy four percent of their population was on cephalosporin, 98% was on ampicillin & gentamicin, 62% was on vancomycin. All of the babies in their study were also intubated. Despite the decreased incidence of IFI with prophylaxis, there was no difference in mortality, or other secondary outcomes like bacterial infections, NEC, etc., in both arms. They also found out that there was no association between fungal colonization and incidence of invasive fungal infection, meaning, once a baby is colonized, that baby may develop or may not develop IFI. This is the reasoning behind antifungal prophylaxis, that it prevents IFI by decreasing candida colonization. However, there was an association between the occurrence of IFI and the number of sites that had been colonized at the last screening. The higher the number of sites colonized, the more likely the baby would progress into IFI. Babies in the prophylaxis group have lesser sites that were colonized compared to the placebo arm.

Subsequent studies by Mansoni et al, (2007), and Aydemir et al. (2011) showed similar results as Kaufman’s, i.e., IFI was significantly higher in placebo than in treatment group. Although colonization was higher in the placebo than in treatment group, progression from colonization to invasive fungal infection was similar in both groups. This supports the finding of Kaufman that, to prevent IFI, we have to prevent colonization. Death from any cause before hospital discharge or death attributable to fungal infection were similar in both groups.

Meta-analysis of 7 studies with 498 babies in the prophylaxis group and 382 babies in the placebo group by Austin and McGuire (2013) showed that treatment decrease IFI; however, it does not affect death prior to hospital discharge. These results are consistent with the 3 studies mentioned above.

The emergence of resistance is always possible with prophylaxis. With wide use of fluconazole (as in prophylaxis for all VLBWs), we encourage resistance of C. albicans, which is the most common and most virulent fungal infection in these VLBWs. However, C. albicans is also the most susceptible to fluconazole among the Candidal sp. With prophylaxis, we encourage the emergence of C. glabrata and C. parapsilosis, which are resistant to, and are more capable of, developing resistance to fluconazole. The randomized controlled trials (RCTs) have reported that there was no change in predominance of flora in their units. However, these studies reviewed their candidal flora less than five years after institution of fungal prophylaxis unit wide. There is no study that has shown that surveillance was done after more than five years of fungal prophylaxis. Before instituting unit wide prophylaxis, there should be a long term surveillance study of the candidal flora, and it should show that prophylaxis did not change this flora.

Before implementing unit-wide prophylaxis, the benefit-to-risk ratio has to be studied well, the number needed to treat should be known, and these should be significant. Average incidence of invasive fungal infection was 16% in the RCTs, compared to <5% generally reported from other large cohort studies. There should also be better ways to accurately reflect the burden of infection, e.g.: B-glucan assay, D-arabinitol assay or PCR, not only by blood culture.

To summarize, fungal prophylaxis decreases the incidence of colonization, and thus IFI. However, mortality due to any cause is not changed with fungal prophylaxis. There are no good studies showing a better neurodevelopmental outcome for the prophylaxed group. There are no good studies showing that prophylaxis will not change the candidal flora to the more resistant species. With these things in mind, we recommend that VLBWs should not be routinely placed on fungal prophylaxis. We should identify risk factors like extreme prematurity, extreme low birth weight, central venous catheter use, multiple and/or broad spectrum antibiotics, prior bacterial bloodstream infection, duration of mechanical ventilation and abdominal surgery. If there are several of these factors in a baby, fungal prophylaxis should be considered. Instead of a non-selective fungal prophylaxis, we should focus on modifiable risk factors such as early feeding practices, prudent use of H2 antagonists, and judicious use of antibiotics.

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References:

Congratulations

Anita Mohan, MD, 3rd year Fellow of Neonatology at Westchester Medical Center, Maria Fareri Children’s Hospital has been appointed to the American Academy of Pediatrics (AAP) section of Young Physicians Subcommittee on Leadership skills/Development. The Leadership Subcommittee is committed to fostering leadership skills for Section of Young Physicians members. As a member of this committee Dr. Mohan will assist young physicians to strive to reach the highest rung of their desired career ladder both at their institutions and within the AAP via dissemination of articles, participation in leadership conferences and collaboration with leaders in the field around the country.

Jonathan Blau, MD, former Neonatal Fellow at the Regional Neonatal Intensive Care Unit at The Maria Fareri Children’s Hospital at Westchester Medical Center & graduate of New York Medical College has been promoted to the position of Associate Director of the Division of Neonatology in the department of Pediatrics at Staten Island University Hospital after serving there 2 years as an attending neonatologist and Director of Neonatal Performance Improvement.
use of MgSO₄ in obstetric care for appropriate conditions and for appropriate durations of treatment, which include the following: a) Prevention and treatment of seizures in women with preeclampsia or eclampsia; b) Fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery; c) Short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids in pregnant women between 24 weeks of gestation and 34 weeks of gestation who are at risk of preterm delivery within 7 days. Regardless of maternal and fetal indications, dose and duration for all MgSO₄ therapy is the same with a therapeutic goal of a maternal serum Mg²⁺ level between 4-6 mg/dl. Extrapolating from normal placental physiology, maternal level of 4-6 mg/dl will lead to similar or higher fetal levels significantly more than the normal serum Mg²⁺ range of 1.5-2.4 mg/dl.³

Mg²⁺ is involved in regulating the production and secretion of Parathyroid Hormone (PTH) and as a cofactor for the production of 1,25 (OH)₂ Vitamin D. Neuromuscular effect of Mg²⁺ is twofold: a) decreasing nerve conduction by blockage of Ca²⁺ reuptake, inhibiting presynaptic release of acetylcholine (ACh) and b) decreasing the sensitivity of the postsynaptic ACh receptor. In addition, Mg²⁺ affects the muscle directly by dephosphorylating adenosine triphosphate (ATP) and relaxing the muscle during the contractility cycle. Higher concentrations of Mg²⁺ lead to a longer muscle relaxation cycle (skeletal, smooth, and cardiac).

The side effects of hypermagnesemia are well documented in adults and include nausea, vomiting, respiratory depression, hypotension, bradycardia, arrhythmias, cardiac arrest, and neuromuscular disturbances such as hypotonia, hyporeflexia, weakness, and decreased gastrointestinal (GI) motility.⁴ Adult neuromuscular depression and hypotension occur with Mg²⁺ levels >4-6 mg/dl, difficulties in urination >5 mg/dl, CNS depression >6-8 mg/dl and respiratory depression and coma >12-17 mg/dl.⁵ In terms of the GI effects, Golzarlan et al.⁶ reported two cases of females over the age of 65 years with hypermagnesemia-induced paralytic ileus after the use of Mg²⁺ containing medications (Mg²⁺ citrate, milk of Mg²⁺ and Epsom salt (contains 40mg/g of MgSO₄). They presented with abdominal distention, tenderness, hypoactive bowel sounds, constipation and paralytic ileus with Mg²⁺ levels of 5.1 and 8.1 mg/dl on admission. After four days Mg²⁺ levels decreased to 1.6 and 2.7 mg/dl respectively with resolution of symptoms. Although these parameters are well documented in adults there is limited published data in infants. Sokal et al.⁷ published the first neonatal case report of hypermagnesemia with meconium plug syndrome in two late preterm neonates, born to eclamptic mothers treated with MgSO₄. The neonates presented with respiratory depression, hypotonia, hyporeflexia, hypoactive bowel sounds, abdominal distention, bilious vomiting and no passage of meconium. In both cases clinical and radiographic studies excluded aganglionic megacolon and cystic fibrosis induced meconium ileus. Mg²⁺ levels ranged from 6.6-7.3 mg/dl. All patients passed meconium plug after barium enema was performed. Mg²⁺ levels normalized and the symptoms resolved. The authors attributed the symptoms of hypotonia and ileus to the excessive Mg²⁺ level.

Brazyl et al.⁸, published a comparison of 28 preterm infants born to hypertensive mothers and 28 matched controls born to normotensive mothers. All hypertensive mothers were treated with IV MgSO₄. Maternal Mg²⁺ levels prior to delivery ranged from 4.8-6.7 mg/dl, but neonatal levels were not recorded. Infants of hypertensive mothers were found to have decreased GI motility with delayed passage of stool (50% vs 21%, p<0.05), delayed time to first stool (31 vs 14 hours, p<0.01), ileus (25% vs 4%, p<0.05), and hypotonia (18% vs 0%, p<0.05). The authors concluded that GI dysfunction and hypotonia were related to hypermagnesemia.

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The retrospective case series by Yu et al.⁹, reviewed 12 very low birth weight infants with gestational age (GA) 27.8±2.3 weeks, birth weight 1080±243 grams, delayed stooling (2.75±1.2 days) and meconium obstruction, born to pre-eclamptic mothers, of which 33% were treated with MgSO₄. NEC, gastrochisis, intestinal atresia, Hirschsprung’s disease, microcolon, malrotation, volvulus, motility disorders, sepsis, hypothyroidism, and congenital anomalies were excluded. The infants initially had frequent small stools followed by abdominal distention. The authors concluded that premature infants of mothers with a history of hypertension with or without administration of MgSO₄ have an increased risk of meconium obstruction. In the most recent publication by Greenberg et al.¹⁰, NICU admission rates in 264 term infants born to mothers with pre-eclampsia with and without antenatal exposure to MgSO₄ were compared. 78% were exposed to MgSO₄ (total dose 23.±17.4 grams (range 4-120 grams)) with length of exposure 10.2±8.9 hours (range 0.5-56 hours), and serum Mg²⁺ levels of 4.1±1.6 mg/dl. Mg²⁺ exposure of any amount was associated with an increased risk of admission to the NICU (15% vs 5%, p=0.04), hypotonia (21% vs 0%, p=0.06), hypermagnesemia (7% vs 0%, p=0.06) and fluid and nutritional support (60% vs 0%, p=0.04). A multivariate regression analysis controlling for potential confounders (GA, public insurance, birth weight, cesarean delivery, chronic hypertension and severe pre-eclampsia) found an association between antenatal MgSO₄ exposure and NICU admission in otherwise healthy term neonates of pre-eclamptic mothers in a dose-response manner.

Given the known distribution and function of Mg²⁺ there is a physiologic rational for hypermagnesemia induced GI hypomotility supported by a limited number of publications in the neonatal literature. With the current recommendations for MgSO₄ for neuroprotection in all 23-32 week gestation deliveries a larger number of neonates are expected to present with hypermagnesemia. Extrapolating from adult literature Mg²⁺ levels greater than 3 mg/dl may be associated with decreased GI motility. Maternal MgSO₄ therapy should be an indication for investigation of neonatal serum Mg²⁺ levels, especially if the neonate exhibits signs and symptoms of hypermagnesemia. MgSO₄ should not be added to the parenteral nutrition until serum level is normalized.

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Maternal Morbidity & Mortality

Two to three women die every day in the United States from complications that occur while giving life. Approximately half of these maternal deaths have been determined to be preventable. African American women have 3-4 times more deaths than women of all other racial/ethnic groups.

Deaths are just the tip of the iceberg.

Every 10 minutes a woman in the United States almost dies of pregnancy-related complications. Postpartum hemorrhage is a leading cause of these complications, with an estimated 2.9% of the women who give birth in the U.S. will bleed too much. This means about 125,000 women a year are affected. In addition, in the last 10 years, there was a 183% increase in the number of women who had a blood transfusion around the time they gave birth.

In 1998-1999 compared to 2008-2009 there was a 75% increase in the number of women who suffered serious injuries while giving birth.

The US is one of the only countries where maternal deaths and injuries have increased.

We must act now to eliminate preventable deaths and injuries since women are the cornerstone of a healthy and prosperous world.

Imagine a world where no mother needlessly dies or is injured when giving birth and where all women can make informed choices about their health. AWHONN is working to make this vision a reality.

Stay tuned for more information on our efforts and how you can join the effort, feel free to contact us customerservice@awhonn.org.

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