Hypoxic-Ischemic Encephalopathy and Serum Magnesium Monitoring and Maintenance

Susan Givens Bell, DNP, MABMH, RNC-NIC

ABSTRACT

Magnesium plays important roles in many physiologic functions including protein synthesis, bone development, and cell membrane function. There is some evidence to suggest a role for magnesium sulfate as a therapeutic neuroprotective agent along with therapeutic hypothermia in infants with hypoxic-ischemic encephalopathy, but studies are inconclusive. Ischemic insult and hypothermia may both play a role in altered magnesium levels in this population.

Keywords: hypoxic-ischemic encephalopathy (HIE); magnesium sulfate; magnesium; hypomagnesemia; therapeutic hypothermia

Continuing Nursing Education (CNE) Credit

Attention Readers: The test questions are provided in this issue, but the posttest and evaluation must be completed online. Details to complete the course are provided online at academyonline.org/CNE. A total of 1.5 contact hours may be earned as CNE credit for reading this article and completing the online posttest and evaluation. To be successful the learner must obtain a grade of at least 80% on the test. Test expires three (3) years from publication date. Disclosure: The author/planning committee has no relevant financial interest or affiliations with any commercial interests related to the subjects discussed within this article. No commercial support or sponsorship was provided for this educational activity. ANN/ANCC does not endorse any commercial products discussed/displayed in conjunction with this educational activity.

The Academy of Neonatal Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Provider, Academy of Neonatal Nursing, approved by the California Board of Registered Nursing, Provider #CEP 6261; and Florida Board of Nursing, Provider #FBN 3218, content code 2505.

The purpose of this article is to discuss magnesium and its potential as a neuroprotective agent for infants with hypoxic-ischemic encephalopathy.

Accepted for publication
February 2016.

MAGNESIUM, THE SECOND MOST common intracellular cation, plays important roles in protein synthesis, bone formation, and regulation of potassium and calcium channels in the cell membrane.[1] In addition, magnesium may play a role in neuroprotection for neonates with hypoxic-ischemic encephalopathy (HIE). This article will briefly describe HIE pathophysiology relevant to the potential therapeutic role for magnesium, a brief review of magnesium in clinical practice and research, and monitoring of and target serum levels for magnesium.

PATHOPHYSIOLOGY

Normal serum magnesium levels in preterm and term infants range from 1.6 to 2.4 mg/dL (0.6–1.0 mmol/liter).[2] There are limited data in the literature regarding serum magnesium levels in neonates with HIE. However, normal levels have been reported in two studies of magnesium sulfate infusion in severe perinatal asphyxia. Bhat and colleagues[3] reported a mean serum magnesium level of 1.87 mg/dL (0.77 mmol/liter) in their treatment group prior to administration of a magnesium sulfate infusion. Mean serum magnesium level for the control group was not reported but was noted to be comparable.[3] Ichiba and colleagues[4] reported a similar mean serum magnesium level, 1.94 mg/dL (0.8 mmol/liter), in their treatment group prior to magnesium administration, with comparable results in the control group. Tocco and colleagues[5] reported that 80 percent of the infants in their retrospective study of serum magnesium levels during cooling had serum magnesium levels <1.6 mg/dL (<0.66 mmol/liter) during the 72-hour cooling process. In infants with HIE, hypomagnesemia may be the result of increased magnesium consumption during the ischemic insult or ongoing losses caused by ischemic damage to renal glomeruli and tubules.[5] Diuresis and loss of electrolytes, including magnesium, may occur during therapeutic hypothermia because of decreased solute absorption in the loop of Henle and subsequent osmotic fluid shifts.[6]

The initial event resulting in fetal hypoxia leading to decreased cardiac output and subsequent decreased cerebral blood flow sets off a cascade of events resulting in brain injury. During HIE, an excessive amount of the excitatory amino acid glutamate is released from the presynaptic terminals of nerve cells.[7] Glutamate is an important neurotransmitter that plays a major role in the development of the central nervous system and is

http://dx.doi.org/10.1891/0730-0832.35.3.159

likely involved in normal brain functions including cognition, learning, and memory.[8] However, the release of excessive quantities of glutamate in HIE results in overstimulation of glutamate receptors, 2-aminomethylphenylacetic acid (AMPA), kainite (KA), and *N*-methyl-d-aspartate (NMDA), located on the postsynaptic membrane of nerve cells. This results in excitotoxicity.[7] For the purpose of this discussion, the NMDA receptor is the receptor of interest.

Overstimulation of the NMDA receptor opens the calcium channels in the cell membrane of the postsynaptic neurons, resulting in an influx of calcium ions. Excessive intracellular calcium sets several reactions that result in programmed cell death or apoptosis.[9] Magnesium is an NMDA-receptor antagonist that may block the influx in calcium, therefore minimizing brain injury.[10]

MAGNESIUM IN RESEARCH AND CLINICAL PRACTICE

Magnesium requirements for both preterm and term infants is 0.3–0.5 mEq/kg/day to maintain (or achieve) normal serum levels of 1.6–2.4 mg/dL (0.6–1.0 mmol/liter). Magnesium sulfate is a standard additive in neonatal parenteral nutrition. Tocco and colleagues evaluated serum magnesium levels in a retrospective review of 25 infants ≥36 weeks gestational age (mean age = 38 weeks) who underwent therapeutic hypothermia for moderate to severe HIE.[5] Serum magnesium levels were obtained every 12 hours for 24 hours and then daily for four days. The infants received standard parenteral nutrition (PN) that included 0.5 mEq of magnesium/100 mL. It is not clear from the study at what time point the initial magnesium levels were obtained, nor at what postnatal age PN was initiated. The low threshold for magnesium supplementation over the standard amount in the PN at this center was a plasma magnesium concentration of 1.6 mg/dL (0.66 mmol/liter). Eighty percent of the infants in this retrospective cohort ($N = 25$) were found to have plasma magnesium levels <1.6 mg/dL (0.66 mmol/liter) during the 72-hour cooling period. These infants reportedly received additional supplementation as well as boluses of 25 mg/kg to achieve normal plasma magnesium levels.[5] The authors did not describe the dose of supplementation, the number of boluses per patient, or the number of patients requiring boluses.

In a review of the literature from 2006 to 2015 using the terms *perinatal asphyxia*, *hypoxic-ischemic encephalopathy*, *therapeutic hypothermia*, *total body cooling*, *neonate*, *neuroprotection*, and *magnesium sulfate*, four articles were found that addressed treatment of infants with HIE with magnesium sulfate. Two single-site studies of magnesium sulfate for neuroprotection as a single therapy provide conflicting evidence regarding a neuroprotective role for magnesium sulfate in neonatal HIE.[3,11] Gathwala and colleagues randomized 40 term newborns with severe birth asphyxia to either the study group or the control group.[11] Mean gestational age for the study group was 38.9 ± 0.4 weeks versus 38.7 ± 0.5 weeks in the control group. There was no statistically significant difference in birth weight, mean cord pH, or one- and five-minute Apgar scores between groups. Inclusion criteria were term gestational age and Apgar score of 3 or less at one minute and 6 or less at five minutes. Infants with congenital anomalies and those mothers who received magnesium sulfate or other drugs that could depress the newborn were excluded. The neonates in the study group received 250 mg/kg intravenous (IV) magnesium sulfate in 5 percent dextrose over 30 minutes within 30 minutes of delivery. Subsequent doses of 125 mg/kg were given at 24 and 48 hours per age. No placebo was described. All babies underwent cranial computerized tomography (CT) and electroencephalogram (EEG). The CT scans and EEGs were evaluated by blinded examiners. A detailed neurologic exam was done at the time of discharge. The infants were followed for neurodevelopment assessment until six months of age. The Denver II was used to assess outcome at six months. Two infants in each group died because of complications of their severe HIE; two additional infants in each group died of nosocomial sepsis. Gathwala and colleagues do not describe the timing of these deaths but do note that 16 infants in each group were available for follow-up at six months.[11]

Results revealed that the magnesium sulfate infusions were well tolerated without significant heart rate, oxygen saturations, respiratory rate, or mean arterial blood pressure alterations during either the 250 mg/kg or 125 mg/kg doses. Thirty-five percent of the study group and 50 percent of the control group had seizures. This difference was not statistically significant ($p>.05$). Gathwala and colleagues did not note whether these were clinical seizures or observed only on the EEG.[11] "Slowing of electrical seizure activity and discontinuous pattern"[11(p2)] occurred on EEG in 31.25 percent of the study group and 43.75 percent of the control group ($p>.05$). Focal, multifocal, or diffuse hypodensities were seen on CT scan in 37.5 percent of the study group compared to 62.5 percent of the control group ($p>.05$). At the six-month follow-up, mean head circumference for the 16 study infants was 43.09 ± 0.86 cm. Mean head circumference in the control group was 43.11 ± 1.14 cm. On the Denver II exam, infants were rated as normal, suspect, or abnormal. Among the study group participants, 13 were normal, 2 were suspect, and 1 was abnormal. In the control group, there were 11 normal, 3 suspect, and 2 abnormal. None of these difference reached statistical significance. Gathwala and colleagues concluded magnesium sulfate was well tolerated in their small study sample.[11] They noted that magnesium sulfate does appear to have a beneficial effect in infants with severe HIE.[11] The lack of statistically significant differences between groups on all measures contradicts the assertion of benefit.

Bhat and colleagues[3] studied the effect of postnatal magnesium sulfate infusion on neurologic outcome in a randomized, placebo-controlled study of 40 full-term neonates with HIE. Inclusion criteria for the study were gestational age of

TABLE 1 ■ Criteria for Moderate to Severe Hypoxic-Ischemic Encephalopathy*

Criterion	Moderate	Severe
Level of consciousness	Lethargy	Stupor or coma
Spontaneous activity	Decreased	Absent
Tone	Hypotonia	Flaccidity
Posture	Distal flexion	Decerebrate state
Primitive reflexes	Weak suck or incomplete Moro	Absent suck or absent Moro
Autonomic nervous system	Pupils constricted or bradycardia or periodic breathing	Pupils deviated, dilated, or nonreactive to light or variable heart rate or apnea

*Created from text of article.

≥37 weeks, <6 hours of age at time of admission to the unit, moderate to severe HIE, and severe perinatal asphyxia as evidenced by three of the following four criteria: (1) history of fetal distress defined as late decelerations, loss of beat-to-beat variability, fetal bradycardia, or meconium-stained amniotic fluid; (2) need for positive-pressure ventilation, either bag-valve-mask or bag-to-endotracheal tube for ≥2 minutes after delivery; (3) five-minute Apgar <6; or (4) a base deficit ≥15 mEq/liter or pH ≤7 on a cord blood gases or admission arterial blood gas sample with the first hour after delivery. The HIE was diagnosed if one or more signs was present in three of six categories: level of consciousness, spontaneous activity, tone, posture, primitive reflexes, and autonomic nervous system (Table 1). Exclusion criteria were intrauterine growth restriction, any condition unrelated to asphyxia, >6 hours of age, maternal magnesium administration, metabolic disorder, chromosomal abnormalities, and congenital malformations.[3]

Infants were randomly assigned to receive either magnesium sulfate 250 mg/kg/dose (1 mL/kg/dose) or a normal saline placebo (1 mL/kg/dose) every 24 hours for three doses. Thirty-five percent of the infants in the treatment group and 40 percent of the infants in the placebo group had moderate HIE; 65 percent of infants in the treatment group and 60 percent of the infants in the placebo group had severe HIE. Serum magnesium levels were comparable in both groups at 0 hour but were higher in the treatment group at each assessment (1, 23, 25, 47, 49, and 72 hours). The mean magnesium level in the treatment group remained ≥1.2 mmol/liter during the initial 72 hours after the first infusion. Mean magnesium levels for the placebo group were not reported.[3]

Two infants in each group died during hospitalization. All four of the infants had severe HIE. The two infants in the treatment group died on day of life (DOL) 5 and DOL 6; those in the placebo group died on DOL 3 and DOL 9. Four (22 percent) of the remaining 18 infants in the treatment group had abnormal neurologic examinations at the time of discharge. Ten (56 percent) of the remaining 18 in the placebo group had abnormal neurologic examinations at discharge ($p<.04$). Head CT scans on DOL 14 were abnormal in 3 of 18 (16 percent) of the treatment group and 8 of 18 (44 percent) of the placebo group ($p = .07$). At the time of discharge, 14 of 18 (77 percent) of the infants in the treatment group were taking oral feedings versus 7 of 18 (37 percent) of the infants in the placebo group ($p<.02$).[3] These results indicated improved neurologic outcomes at time of discharge for the infants in the treatment group. Long-term follow-up was not an element of the study design.

In a multicenter trial, Ichiba and colleagues evaluated 30 neonates with HIE and mean gestational age of 39.6 ± 1.5 weeks.[4] Inclusion criteria were clinical history consistent with perinatal asphyxia, gestational age ≥37 weeks, five-minute Apgar ≥6, and failure to initiate spontaneous respiration by ten minutes of age because of asphyxia and signs of encephalopathy. Infants were excluded if their mother received magnesium sulfate and was hypotensive (mean arterial blood pressure ≤35 mmHg) despite pressor or volume expander administration or had major central nervous system malformation or metabolic disorder. They administered 250 mg/kg IV over one hour within six hours of birth in combination with dopamine (5 mcg/kg/min) to prevent hypotension secondary to magnesium-induced vascular smooth muscle relaxation. Two subsequent doses were given at 24-hour intervals.[4] All infants required mechanical ventilation following delivery. Nineteen out of 30 (63 percent) of the infants had mild HIE; 11 of 30 (37 percent) had severe HIE. Clinical seizures were observed in 21 (70 percent) of the infants.[4]

Ichiba and colleagues reported that there were no significant changes in physiologic variables including heart rate and blood pressure during magnesium sulfate infusion.[4] They did note cessation of spontaneous breathing over the ventilator for one to two hours after magnesium sulfate infusion. In addition, all infants were noted to have decreased muscle tone for one to six hours following magnesium sulfate infusion. No other short-term findings were reported. Twenty-eight of the infants were available for follow-up at 18 months of age. Two infants died. The timing of these deaths were not reported. Long-term follow-up results found 6 out of 28 (21 percent) infants with severe neurodevelopmental disability from cerebral palsy, mental retardation, and/or epilepsy. Ichiba and colleagues did not note the degree of encephalopathy (moderate or severe) in these six infants at the time of enrollment.[4] The remaining 22 (79 percent) infants were assessed and had no neurodevelopmental disability.[4]

Rahman and colleagues conducted a multicenter randomized controlled trial of magnesium sulfate combined with therapeutic hypothermia in 60 neonates ≥35 weeks gestational age with moderate to severe HIE.[12] Twenty-nine infants were randomized to receive magnesium sulfate 250 mg/kg/day every 24 hours for three doses in addition to therapeutic hypothermia. The remaining >31 infants received a volume equivalent of normal saline placebo (2.5 mL/kg/day) along with therapeutic hypothermia.[12] Therapeutic hypothermia was discontinued in one infant (group not designated)

because of severe bradycardia. Fifty-five infants were cooled by total body cooling, four with head cooling. Thirty-three (55 percent) of the infants were assessed to have moderate HIE; 27 (45 percent) had severe HIE.[12]

Rahman and colleagues[12] reported no difference between groups for the short-term outcomes of death, seizures, thrombocytopenia, coagulopathy, renal failure, elevated liver enzymes, intracranial hemorrhage, necrotizing enterocolitis, pulmonary hemorrhage, pulmonary hypertension, and pulmonary air leaks ($p>.05$). They concluded that the combination of magnesium sulfate and therapeutic hypothermia is safe in the short term.[12]

Large multicenter randomized, placebo-controlled trials with long-term developmental follow-up are still needed to determine the efficacy of therapeutic hypothermia plus magnesium sulfate for neuroprotection. In addition, if magnesium sulfate is beneficial, research is needed to establish desired serum magnesium levels at which the greatest benefit is realized.

IMPLICATIONS FOR PRACTICE

The current recommendation regarding serum magnesium levels in therapeutically cooled neonates with HIE is to maintain levels within the normal range[a] of 1.6–2.4 mg/dL (0.66–0.99 mmol/liter).[2,13] Clinical presentation of hypomagnesemia and hypermagnesemia (Table 2) may mimic the clinical signs of hypocalcemia and hypercalcemia, respectively.[2] Recommendations may change if conclusive evidence is found to support the use of magnesium sulfate as a "plus" therapy in combination with therapeutic hypothermia. Frequency of monitoring may be unit- or protocol driven. There are currently no published data regarding the frequency of monitoring serum magnesium levels in infants who are therapeutically cooled for moderate to severe HIE. Minimally, a level should be obtained with the initial set of electrolytes on admission and every 24 hours until stable.[13] The IV magnesium sulfate boluses of 25–50 mg/kg may be given for >1–2 hours every 8–12 hours for levels <1.6 mg/dL.[14,15] More frequent laboratory monitoring may be considered if an infant is receiving boluses.

TABLE 2 ■ Signs of Hypomagnesemia and Hypermagnesemia[2]

Hypomagnesemia	Hypermagnesemia
Jitteriness	Hypotonia, hypotension, hyporeflexia, seizures
Apnea	Respiratory depression, hypoventilation, apnea
Feeding intolerance	Bradycardia, hypotension, cardiac arrest*
Seizures	Poor suck, feeding intolerance, decreased GI motility, increased gastric aspirates, abdominal distention, delayed meconium passage
	Meconium plug syndrome, intestinal perforation
	Urinary retention

Abbreviation: GI = gastrointestinal.

*With toxic Mg^{+2} levels (>7.5 mmol/liter).

Clinicians should monitor neonates closely for cardiac arrhythmias, especially bradycardia, and hypotension during bolus infusions. These side effects are more likely to occur if the magnesium bolus is rapidly infused. Magnesium plays an important role in myocardial contractility, acting as a calcium channel blocker, slowing sinoatrial (SA) node impulses and prolonging conduction time potential resulting in bradycardia.[14] Magnesium can also cause vascular smooth muscle relaxation, lowering blood pressure.

SUMMARY

Magnesium is an important electrolyte for normal physiologic function. Small trials of magnesium sulfate as a neuroprotective agent are inconclusive but show promise. Magnesium levels may be affected by both ischemic insult through consumption or renal loss and by therapeutic hypothermia. Diligent monitoring of serum magnesium concentrations, maintenance, and supplemental administration are essential aspects of the care of the infant with HIE.

NOTE

[a]Normal ranges may vary by laboratory and source reference.

REFERENCES

1. Guignard JP, Sulyok E. Renal morphogenesis and development of renal function. In: Gleason CA, Devaskar SU, eds. *Avery's Diseases of the Newborn*. 9th ed. Philadelphia, PA: Elsevier Saunders; 2012:1165-1175.
2. Gomella TL, Cunningham MD, Eyal FG. Magnesium disorders (hypomagnesemia, hypermagnesemia) In: Gomella TL, Cunningham MD, Eyal FG, Tuttle D, eds. *Neonatology: Management, Procedures, On-Call Problems, Diseases and Drugs*. 7th ed. New York, NY: McGraw-Hill; 2013:746-748.
3. Bhat MA, Charoo BA, Bhat JI, Ahmad SM, Ali SW, Mufti MU. Magnesium sulfate in severe perinatal asphyxia: a randomized, placebo-controlled trial. *Pediatrics*. 2009;123(5):e764-e769. http://dx.doi.org/10.1542/peds.2007-3642
4. Ichiba H, Yokoi T, Tamai H, Ueda T, Kim TJ, Yamano T. Neurodevelopmental outcome of infants with birth asphyxia treated with magnesium sulfate. *Pediatr Int*. 2006;48(1):70-75. http://dx.doi.org/10.1111/j.1442-200X.2006.02167.x
5. Tocco NM, Hodge AE, Jones AA, Wispe JR, Valentine CJ. Neonatal therapeutic hypothermia-associated hypomagnesemia during parenteral nutrition therapy. *Nutr Clin Pract*. 2014;29(2):246-248. http://dx.doi.org/10.1177/0884533614522835
6. Luscombe M, Andrzejowski JC. Clinical applications of induced hypothermia. *Contin Educ Anaesth Crit Care Pain*. 2006;6(1):23-27. http://dx.doi.org/10.1093/bjaceaccp/mki064
7. Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. *JAMA Pediatr*. 2015;169(4):397-403. http://dx.doi.org/10.1001/jamapediatrics.2014.3269
8. Danbolt NC. Glutamate uptake. *Prog Neurobiol*. 2001;65(1):1-105. http://dx.doi.org/10.1016/S0301-0082(00)00067-8
9. Johnston MV. Excitotoxicity in neonatal hypoxia. *Ment Retard Dev Disabil Res Rev*. 2001;7(4):229-234. http://dx.doi.org/10.1002/mrdd.1032

10. Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A. Magnesium gates glutamate-activated channels in mouse central neurones. *Nature*. 1984;307(5950):462-465. http://dx.doi.org/10.1038/307462a0
11. Gathwala G, Khera A, Singh J, Balhara B. Magnesium for neuroprotection in birth asphyxia. *J Pediatr Neurosci*. 2010;5(2):102-104. http://dx.doi.org/10.4103/1817-1745.76094
12. Rahman SU, Canpolat FE, Oncel MY, et al. Multicenter randomized controlled trial of therapeutic hypothermia plus magnesium sulfate versus therapeutic hypothermia plus placebo in the management of term and near-term infants with hypoxic ischemic encephalopathy (The Mag Cool study): a pilot study. *J Clin Neonatol*. 2015;4(3):158-163. http://dx.doi.org/10.4103/2249-4847.159863
13. Florida Neonatal Neurological Network. HIE Supportive Care Management Guidelines State Meeting August 1, 2015. https://www.fn3.sites.medinfo.ufl.edu/files/2015/10/HIE-Supportive-Care-Management-Guidelines-08-1-2015-final1.pdf. Accessed January 12, 2016.
14. Gomella TL, Cunningham MD, Eyal FG. Medications used in the neonatal intensive care unit: magnesium sulfate. In: Gomella TH, Cunningham MD, Eyal FG, Tuttle D, eds. *Neonatology: Management, Procedures, On-Call Problems, Diseases and Drugs*. 7th ed. New York, NY: McGraw-Hill; 2013:977.
15. Truven Health Analytics Inc. Magnesium sulfate. In: *Micromedex NeoFax Essential*. 2015;v34_1510031704.

About the Author

Susan Givens Bell, DNP, MABMH, RNC-NIC, has more than 30 years of neonatal nursing experience including roles in staff, education, transport, and management. Currently, she works at Medical Center of Trinity and is in the post-masters NNP certificate program at Vanderbilt University, Nashville. She received a bachelor of science in nursing, a master of science in nursing, a master of arts in bioethics and medical humanities, and a doctor of nursing practice in education leadership from the University of South Florida, Tampa. She is a member of the Academy of Neonatal Nursing (ANN), Sigma Theta Tau, and The Honor Society of Phi Kappa Phi.

For further information, please contact:
Susan Givens Bell, DNP, MABMH, RNC-NIC
Medical Center of Trinity
9330 FL-54
Neonatal Intensive Care Unit
Trinity, FL 34655
E-mail: lilylambbell@gmail.com