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Original Article

Neonatal Magnesium Levels Between 24 and 48 Hours of Life and Outcomes for Epilepsy and Motor Impairment in Premature Infants

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ABSTRACT

OBJECTIVE: Elevated rates of epilepsy and motor impairments including cerebral palsy are observed in children who were born prematurely. Maternal antenatal magnesium supplementation has been associated with decreased rates of cerebral palsy in infants born prematurely. Our objective was to determine whether the neonatal serum magnesium level between 24 and 48 hours after birth is associated with better long-term neurodevelopmental outcomes (epilepsy, motor impairment) in premature infants. **METHODS:** We performed a retrospective cohort analysis in infants born less than 37-weeks gestation over a ten-year period. Prenatal, perinatal, and postnatal clinical and demographic information was collected. Crude and adjusted odds ratios were estimated under generalized linear models with generalized estimating equations to examine the association of the neonatal serum magnesium level between 24 and 48 hours after birth with the risk of epilepsy and/or motor impairment (spasticity; hypotonia; cerebral palsy). **RESULTS:** The final cohort included 5461 infants born less than 37-weeks gestation from 2002 to 2011. The adjusted relative risk ratio for the combined outcomes of epilepsy and/or motor impairment, controlling for gestational age, current age, maternal magnesium supplementation, maternal steroid administration, five-minute Apgar score, neonatal infection, need for vasopressor use, and birth weight and with serum magnesium level as the main independent variable, was 0.85 ($P = 0.24$). Stratified analyses by gestational age less than 32 or greater than 32 weeks were not significantly associated with adverse neurodevelopmental outcome (risk ratio = 0.79 and 1.2, $P = 0.12$ and 0.49, respectively). A multivariate analysis for the risk of motor impairment alone had a risk ratio of 0.94 ($P = 0.72$). **CONCLUSION:** This study demostrates that the neonatal magnesium level between 24 and 48 hours of life in premature infants is not significantly associated with the risk for developing epilepsy or motor impairment.

Keywords: magnesium, prematurity, neurological, neuroprotection, neonate

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Introduction

Premature birth is a significant public health problem affecting 11.4% of births each year in the United States.[1] Children who were born prematurely are at increased risk for developing a range of adverse neurodevelopment outcomes including cerebral palsy, epilepsy, autism spectrum disorder, intellectual disability and school difficulty, and behavioral and neuropsychiatric problems including attention-deficit hyperactivity disorder.[2-5]

The pathophysiology leading to the neurodevelopmental problems of ex-premature infants and children is complex.[6,7] There is increasing evidence that both developing neurons and oligodendrocytes are at risk in the premature brain,[8,9] with potential to cause gross structural damage or more subtle disruptions in measures of connectivity.[10-12]

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There are few proven therapeutic options for preventing the adverse neurodevelopmental outcomes of premature birth, although antenatal maternal steroid administration, antenatal magnesium sulfate, N-acetylcysteine, erythropoietin, melatonin, and stem cell transplants are under active investigation.[13-15] In particular, antenatal magnesium sulfate has been found to reduce rates of subsequent cerebral palsy in multiple studies and in meta-analyses, although a large randomized trial did not find association between antenatal magnesium sulfate administration and rates of cerebral palsy or abnormal motor function.[16-19] Maternal antenatal magnesium sulfate was also found to decrease abnormal echogenicities on head ultrasounds in infants born at less than 32-week gestation.[20] Experimental evidence from tissue culture and animal models ranging from mouse to zebrafish support potential mechanisms of magnesium to exert neuroprotective effects.[21-24] However, concerns have been raised that magnesium sulfate can have adverse effects,[25-27] and therefore an improved understanding of dose and timing of administration and levels are important.[28-30] Furthermore, it is unknown if the neuroprotective effects are limited to prenatal or perinatal exposure or whether postnatal levels and roles in the postnatal brain are important. If magnesium continued to play neuroprotective effects in premature infants after delivery, then serum levels of magnesium in these infants would potentially correlate with their neurodevelopmental outcomes. For example, a small pilot study from our group suggested that higher *postnatal* serum magnesium levels in premature infants were associated with decreased risks for motor impairment.[31]

We tested the hypothesis that the neonatal serum magnesium level after birth was associated with better long-term neurodevelopmental outcomes in premature infants. The outcomes of interest were for epilepsy, for motor impairment including cerebral palsy, spasticity, or hypotonia, or for a composite including both epilepsy and motor impairment. To test our hypothesis, we performed a retrospective analysis in which we evaluated serum magnesium levels in premature infants between 24 and 48 hours after birth and related the levels to subsequent diagnoses of epilepsy and/or motor impairment in a cohort of 5461 infants.

Materials and Methods

This study was approved by institutional review boards of the University of Utah and Intermountain Healthcare (IH). Data were anonymously collected and analyzed with no identifying information, and a waiver of informed consent was obtained. IH is a vertically integrated not-for-profit health care system in the Intermountain West encompassing 23 hospitals including the sole children's hospital. Antenatal, perinatal, and follow-up data were obtained from the Enterprise Data Warehouse (EDW) maintained by IH.

Data extraction and analysis were performed retrospectively in premature infants born at an IH hospital between January 1, 2002, and December 31, 2011. Follow-up for all outcomes was through December 31, 2014. Inclusion criteria were a gestational age less than 37 weeks and linkage to mother's records. Exclusion criteria were infants with known or likely genetic conditions or chromosomal abnormalities; infants with bacterial or viral meningitis during their initial postbirth hospitalization; infants with congenital hydrocephalus; infants with epileptic encephalopathies; infants with a chromosomal abnormality or genetic syndrome; infants with a congenital brain malformation; infants with congenital heart disease; and infants who developed meningitis, encephalitis, stroke, or traumatic head injury.

Using unique identifiers assigned to each of the cohort infants, we queried the EDW for the study and follow-up periods, using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify outcomes. Data collected from the EDW included name, date of birth, gender, ethnicity, birth weight, gestational age, presence of multiple gestation, administration of corticosteroids before delivery, administration of magnesium sulfate before delivery, length of hospitalization, neonatal total serum magnesium levels drawn between ages 24 and 48 hours of life, days requiring mechanical ventilation, and the presence of seizures.

A total of 6874 potential patients were identified. We excluded subjects that did not have a serum magnesium level obtained between 24 and 48 hours after birth (n = 1370) and subjects missing gestational age or birth weight (n = 43); leaving 5461 infants for the final cohort (Fig 1).

The main exposure variable was defined as the serum magnesium level (mg/dL) obtained between 24 and 48 hours after birth. In subjects where multiple serum magnesium levels were drawn in this time frame, only the first observation was used. Covariates included gestational age at delivery, current age (years), maternal magnesium supplementation, maternal steroids, five-minute Apgar score, neonatal infection, need for vasopressors, and birth weight. Maternal magnesium supplementation was included as a covariate because we wished to evaluate the relationship between the outcomes and variation in neonatal magnesium levels that was not accounted for by maternal supplementation.

The two primary outcome variables were (1) motor impairment, defined as the presence of at least one of the following: use of a wheelchair, Baclofen prescription, or Botox injection (all identified using charge codes); dorsal rhizotomy (03.1); heel-cord release (83.11; 83.85); hypotonia (342.x); or spasticity or cerebral palsy (333.71; 343.x) and (2) epilepsy, defined by ICD-9 codes 345.x. For the diagnosis of epilepsy, diagnoses of seizures at any time during the neonatal intensive care unit (NICU) hospitalization were excluded (779.0), as was a diagnosis of febrile seizures.

The relationships of the neonatal magnesium level with the outcomes were represented using discrete proportional hazards regression models to relate the age of occurrence (categorized into age intervals of one to two years) of the outcomes to the neonatal magnesium exposure variables, with adjustment for gestational age at delivery, maternal

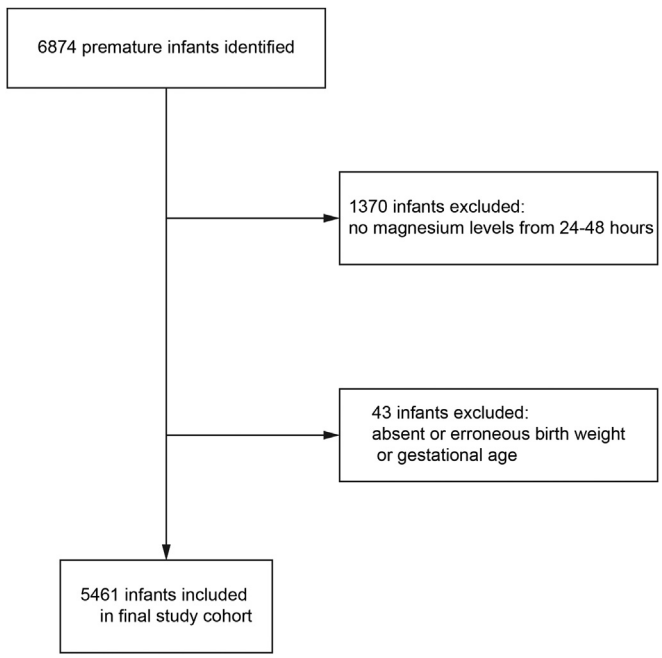

FIGURE 1.
Patient enrollment. Potential patients were identified from a computer-based ICD-9-CM code search of the Intermountain Healthcare Enterprise Data Warehouse for the study time period.